January 2012

BioSupply Trends

Special Focus: PLASMA

Quarterly

IG Therapy:

The Investigational Frontier

Individual IG Dosing: Analyzing the Strategies

IG Reimbursement: A Healthcare Crisis

The State of Acquired Hemophilia

Next Steps in Cancer Treatment & Care

Myths & Facts About Stroke

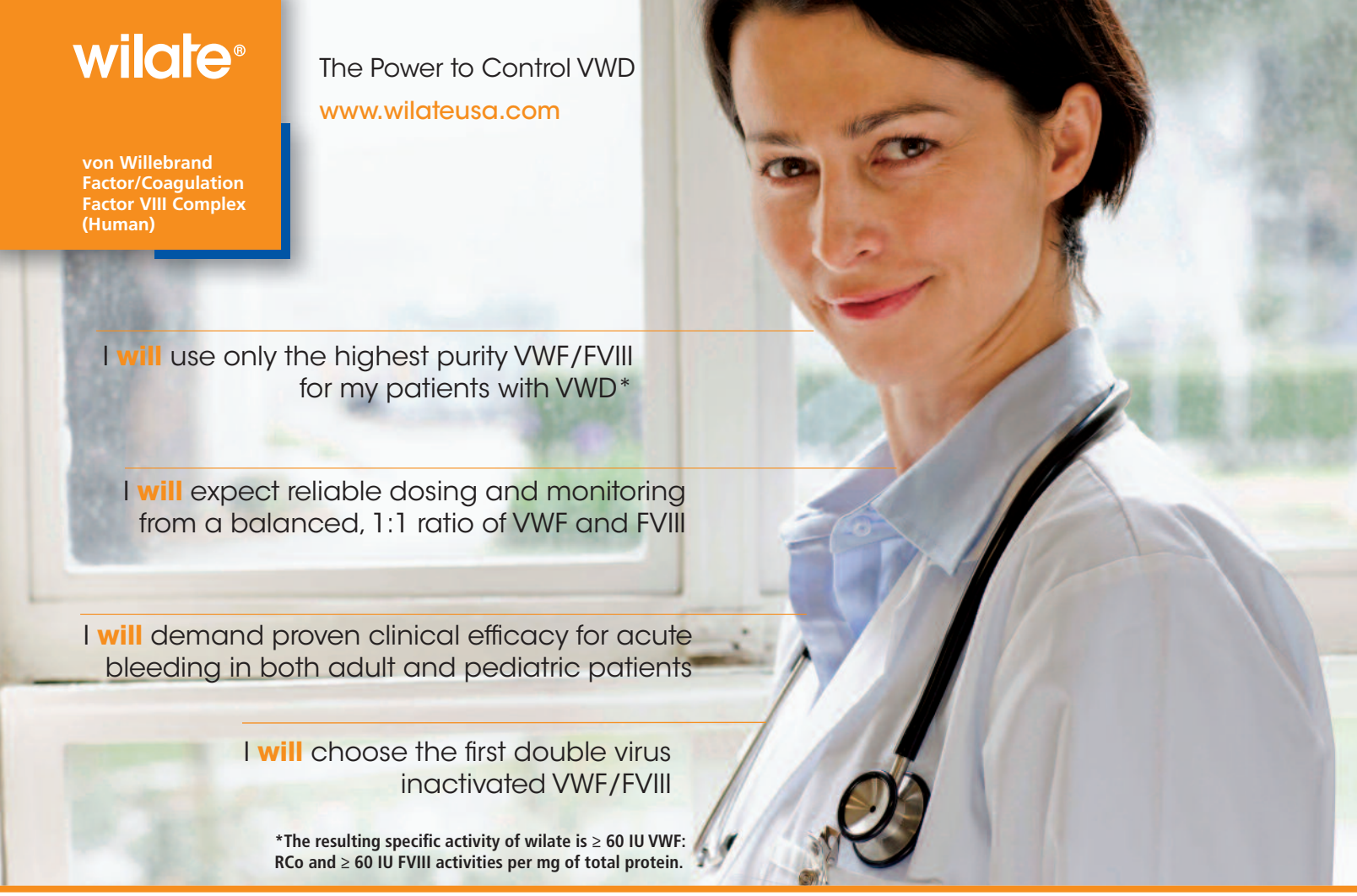
New Against the Flu — Page 62

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

The Power to Control VWD

www.wilateusa.com



I **will** use only the highest purity VWF/FVIII for my patients with VWD*

I **will** expect reliable dosing and monitoring from a balanced, 1:1 ratio of VWF and FVIII

I **will** demand proven clinical efficacy for acute bleeding in both adult and pediatric patients

I **will** choose the first double virus inactivated VWF/FVIII

***The resulting specific activity of wilate is ≥ 60 IU VWF: RCo and ≥ 60 IU FVIII activities per mg of total protein.**

I **will** help my patients take control of VWD

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

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To report suspected adverse reactions,
Contact Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

Important safety information:
wilate® is contraindicated for individuals with a history of anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container. Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement therapies. FVIII activity should be monitored to avoid sustained excessive FVIII levels. wilate® is made from human plasma. The risk of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease agent, cannot be completely eliminated. The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions. Patients with VWD, especially type 3 patients, may potentially develop neutralizing antibodies (inhibitors to VWF).

Please see Highlights of Prescribing Information on adjacent page

Date of preparation: December 2011

octapharma
For the safe and optimal use of human proteins

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Wilate safely and effectively. See full prescribing information for Wilate.

Wilate, von Willebrand Factor/Coagulation Factor VIII Complex (Human), Powder for Solution, for Intravenous Use Only. Initial U.S. Approval: 2009

INDICATIONS AND USAGE

- Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.
- Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients.
- Wilate is also not indicated for Hemophilia A

DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:
  - 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
  - 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL

CONTRAINDICATIONS

- Hypersensitivity with known anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container.

WARNINGS AND PRECAUTIONS

- Hypersensitivity reaction
- Thromboembolic events associated with von Willebrand factor/Coagulation Factor FVIII (VWF/FVIII) products: plasma levels of FVIII activity should be monitored to avoid sustained excessive FVIII levels, which may increase the risk of thrombotic events
- Potential for inducing antibodies to Factor VIII (inhibitors) and antibodies to VWF, especially in VWD type 3 patients
- Theoretical risk of infectious agents transmission as the product is made from human plasma

ADVERSE REACTIONS

The most common adverse reactions in clinical studies on VWD were urticaria and dizziness (each 2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

- Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.
- Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay.
- The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma).

Dosage in von Willebrand Disease

The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1.

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

Dosing Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 1.

The careful control of replacement therapy is especially important in life-threatening hemorrhages. **When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity.**

Shelf life

- Store Wilate for up to 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Do not freeze.
- Do not use after the expiration date.
- Store in the original container to protect from light.
- Reconstitute the Wilate powder only directly before injection. Use the solution immediately after reconstitution. Use the reconstituted solution on one occasion only, and discard any remaining solution.

PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician.

Table 1 Guide to Wilate Dosing for Treatment of Minor and Major Hemorrhages

Type of Hemorrhages	Loading Dosage (IU VWF:RCo/kg BW)	Maintenance Dosage (IU VWF:RCo/kg BW)	Therapeutic Goal
Minor Hemorrhages	20-40 IU/kg	20-30 IU/kg every 12 – 24 hours*	VWF:RCo and FVIII activity through levels of >30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12 – 24 hours*	VWF: RCo and FVIII activity through levels of >50%

Treatment guidelines apply to all VWD types

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible, appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

In the unlikely event that a patient who is actively bleeding should miss a dose, it may be appropriate to adopt a dosage depending on the level of coagulation factors measured, extent of the bleeding, and patient's clinical condition.

NDC Number	Size	Protein Amount
67467-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
67467-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

HOW SUPPLIED/STORAGE AND HANDLING

- Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs.
- Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.
- Components used in the packaging of Wilate contain no latex.
- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities.
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded.

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For the safe and optimal use of human proteins

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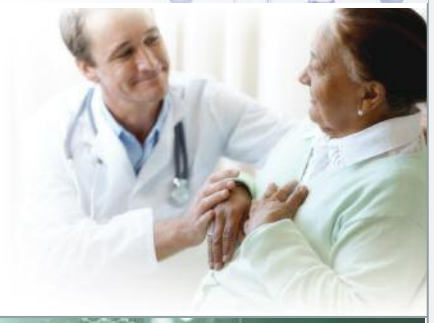
January 2012

Features

Special Focus: Plasma



Up Front

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About BioSupply Trends Quarterly
BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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IG: The Challenge, the Promise, the Future

THERE ARE NO shortages of challenges and opportunities in the world of healthcare. From new technologies in flu vaccine to exciting advances in cancer treatment and the extraordinary strides with plasma therapies, the future is indeed promising. But with these promises come challenges, and in the world of immune globulin (IG), the demonstrated potential of these miraculous proteins to save and sustain lives is often thwarted by the complex and intertwined encumbrances that continually create barriers to access.

This third plasma-themed issue of *BioSupply Trends Quarterly* takes a close, magnifying glass look at IG — from the on- and off-label diseases it treats, to dosing strategies and a complex reimbursement model that, coupled with the high cost of this fragile lifesaving therapy, has created what many are calling a perfect storm.

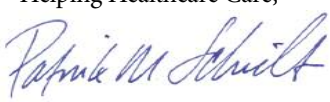
In our feature Immune Globulin Therapy: The Investigational Frontier, it is gratifying to see that IG is showing promise in the treatment of more diseases than ever, despite having FDA on-label approval for only five. And while the number of off-label diseases IG is used to treat may exceed 60, according to the Medscape reference website, the majority of these are relatively new to the IG treatment frontier. The promise of this new landscape is hindered only by the challenges in supply and access. Our feature Immune Globulin Reimbursement explores the healthcare crisis that a complex reimbursement model has been instrumental in creating. Navigating this regulatory maze is all the more difficult because of the numerous obstacles and continually changing healthcare landscape. Healthcare providers and their patients are repeatedly challenged to not only find a therapy for what are usually rare and often misunderstood diseases, but then to manage therapy access and cost. The good news is that there are individuals and groups now collaborating to propose universally accepted criteria and standardization of processes to help prescribing physicians maintain continuity of care when treating patients with IG.

Another standardization challenge clinicians face with IG therapy is the lack of dosing guidelines. Dosing strategies are often unique to individual patients. Our feature Individual IG Dosing Strategies examines ongoing research and studies that could result in establishing national guidelines for IG dosing in the U.S. The impact of evidence-based guidelines would be the development of treatment protocols that result in a higher quality of life for a large portion of primary immune deficiency disease (PIDD) patients, among other IG patient populations.

Access is at the center of the mission of this issue's featured leader, Nebraska State Senator Abbie Cornett, a PIDD patient, and also chair and president of The Alliance for Biotherapeutics of which she is a founding member. The Alliance works on behalf of patient groups and providers to help ensure that all individuals in need receive access to and adequate reimbursement for lifesaving biotherapeutics. Given the dynamic nature of the industry and its complex challenges, her leadership and commitment to working with all stakeholders is appreciated by those who share this vision.

As we bring in a new year, we look forward to new strides in both the development of and access to these miraculous proteins that are both lifesaving and life-enhancing to the patients we serve. We hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it both relevant and helpful to your practice. ❖

Helping Healthcare Care,



Patrick M. Schmidt, Publisher

BioSupply Trends Quarterly

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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HHS Releases ACO Final Regulations

Responding to concerns about the initial Accountable Care Organization (ACO) rules, the U.S. Department of Health and Human Services (HHS) has made several concessions. Under the final ACO regulations:

• Providers will be able to participate in an ACO and share in savings with Medicare without risk of losing money. And, ACOs will be able to start sharing in the savings earlier rather than letting Medicare retain it all initially.

• ACOs will have to meet fewer quality measures — 33 versus the original 65 — to qualify for performance bonuses.

• Rather than waiting until their contract ends, ACOs will be told when they form which Medicare beneficiaries are likely to be a part of their system.

• Community health centers and rural health clinics, which were initially left out of the proposal, will be allowed to lead ACOs.

• And, the timetable for the launch of the ACOs was relaxed, allowing groups to apply throughout 2012.

ACOs are a key provision in the health law to slow rising healthcare costs while delivering high-quality care to Medicare beneficiaries. They are designed to change the incentives that influence how doctors and hospitals operate by rewarding providers for holding down costs and meeting certain quality measures, such as reducing hospital readmissions or emergency room visits. ❖

HHS Launches Initiative for Primary Care Practices

The U.S. Department of Health and Human Services (HHS) has launched a new initiative made possible by the Affordable Care Act to help primary care practices deliver higher-quality, more coordinated and patient-centered care. Under the Comprehensive Primary Care Initiative, Medicare will work with commercial and state health insurance plans to offer additional support to primary care doctors who better coordinate care for their patients. The initiative is modeled after innovative practices developed by large employers and leading private health insurers in the private sector that show patients are healthier and avoid having to seek care in more complex and expensive settings when primary care practices have the resources to better coordinate care, engage patients in their care plan, and provide timely preventive care.

The voluntary initiative will begin as a demonstration project available in five to seven healthcare markets across the U.S. Primary care providers will be enrolled in the initiative by Medicare and its partners who will support doctors to help patients with serious or chronic diseases follow personalized care plans; give patients 24-hour access to care and health information; deliver preventive care; engage patients and their families in their own care; and work together with other doctors, including specialists, to provide better coordinated care. Primary care practices will be paid a monthly fee by the Centers for Medicare and Medicaid for these activities, in addition to the usual Medicare fees that these practices would receive for delivering Medicare-covered services.

More information can be found about the Comprehensive Primary Care Initiative at innovations.cms.gov/areas-of-focus/seamless-and-coordinated-care-models/cpci. ❖

Supreme Court to Rule on Healthcare Law Constitutionality

In September, the Justice Department said it would forgo an appeal to the full U.S. 11th Circuit Court of Appeals in Atlanta, which ruled 2-1 in August that the healthcare reform law's requirement that people buy health insurance is unconstitutional. The suit before a three-member panel of the court was brought by 26 states, the National Federation of Independent Business and several individuals. Opponents of the law had expected the government to ask for the so-called en banc hearing to delay a ruling by the U.S. Supreme Court until at least 2013. The decline of the appeal and the subsequent request by the Obama administration for

the Supreme Court to hear the case clears the way for arguments on the constitutionality of the healthcare law in the spring and a decision by June, in time to land in the middle of the 2012 presidential campaign. ❖

Twelve New Diagnoses Added to Compassionate Allowances List

In July, 12 new medical diagnoses were added to the Social Security Administration's Compassionate Allowances program. Established in 2008 with a list of 50 diseases, the program expedites review of applications for disability benefits by quickly identifying those that meet Social Security's standards. These additions are important for people with rare diseases who, historically, have encountered problems when applying for assistance because those making decisions are not familiar with their diseases. With patient advocates submitting diseases for consideration, along with input from medical experts at the National Institutes of Health and leading medical centers, there are now 100 diseases on the list. For a complete list of compassionate allowances, go to http://www.ssa.gov/compassionateallowances/conditions.htm. ❖

New Pioneer ACO Model Proposed

The U.S. Department of Health and Human Services has announced a new pioneer accountable care organization (ACO) model, which officials say "will provide a faster path for mature ACOs" and save Medicare as much as $430 million over three years. The new ACO comes on the heels of strong criticism from hospital and doctor groups who complain that ACOs create more financial risks than rewards and impose onerous reporting requirements. ACOs are a new delivery model created under the Affordable Care Act that offers providers financial incentives to work together to provide high-quality care to Medicare beneficiaries while keeping down costs.

Under the new ACO model, existing integrated-care organizations, such as Geisinger Health System, the Cleveland Clinic and Intermountain Healthcare, will be able to pocket more of the expected savings in exchange for taking on greater financial risk. For less-mature health systems, the Centers for Medicare and Medicaid Services (CMS) announced it is considering helping cash-strapped provider groups form ACOs by giving them some of their share of anticipated savings up front. CMS also will offer four free "learning sessions" for providers interested in finding out more about starting an ACO. ❖

$40M in Funds Available for Chronic Disease Prevention

The Centers for Disease Control and Prevention will award a total of $40 million in grants to all 58 U.S. states and territories for three-year coordinated chronic disease programs. Created by the Affordable Care Act, the initiative targets the nation's five leading chronic disease-related causes of death and disability: heart disease, cancer, stroke, diabetes and arthritis. State and territorial health activities will focus on reducing age-adjusted mortality due to chronic diseases and reducing the prevalence of disabling chronic diseases. It also will aim to improve health and quality of life by promoting environmental and policy changes related to nutrition, physical activity and clinical preventive services, and by promoting education and management skills for people diagnosed with or at high risk for chronic diseases. ❖

Vaccines

CDC to Launch Streamlined Vaccine Tracking System

In April, the Centers for Disease Control and Prevention (CDC) will launch the final deployment of a system to transform the way the agency distributes vaccines to more than 100,000 U.S. doctors and clinicians. The CDC is responsible for providing almost 60 percent of the pediatric vaccines used in the country each year. In the past, distribution was handled through 64 different state, local and territorial health departments, each of which handled its own inventories, had its own methods of tracking those supplies, and had its own way of getting vaccines to health providers. According to Anjella Vargas-Rosales, management officer for the CDC's National Center for Immunization and Respiratory Diseases (NCIRD): "You're basically talking about 64 grantees doing business their way. Of course, with more touches, you increase the likelihood of wasted product, of wasted vaccine. And, there was no visibility into the amount of vaccine that was in the pipeline at any one time."

In December 2010, the first deployment of the new Vaccine Tracking System (VTrckS) was implemented by the NCIRD with six grantee pilot programs. The final deployment of that implementation in April will integrate all the pieces of the vaccine supply chain, from the CDC's purchase of vaccine from manufacturers, through the ordering by the grantees and the final distribution of the vaccine to health providers. In addition to simplifying the way vaccines are ordered and distributed, VTrckS provides NCIRD more visibility into the process and enables it to use more controls and apply business rules. All grantees will be required to report the levels of inventory they have on hand through VTrckS and that, together with the ordering data, will give the NCIRD a continual update on the state of the supply pipeline. "When I explain it to people, I say that VTrckS completes the vaccine life cycle," says Vargas-Rosales. ❖

Disease Risk

Teens/Young Adults Have Increase in Stroke Prevalence

Ischemic stroke hospitalization rates in adolescents and young adults ages 15 to 44 increased up to 37 percent between 1995 and 2008, according to a study conducted by researchers at the Centers for Disease Control and Prevention (CDC). The findings, which are available in *Annals of Neurology*, report an increase in the prevalence of hypertension, diabetes, obesity, lipid disorders and tobacco use among this age group during the 14-year study period.

CDC researchers used hospital discharge data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project to identify patients hospitalized for ischemic stroke, as well as stroke risk factors and comorbidities among those hospitalized with stroke. Of the patients hospitalized for ischemic stroke, the study found that nearly one in three patients ages 15 to 34 years and more than half ages 35 to 44 years also were diagnosed with hypertension. One-fourth of patients ages 35 to 44 years also had diabetes. One in four females ages 15 to 34, one in three females ages 35 to 44 and one in three males ages 15 to 44 were tobacco users. Other common co-existing conditions included obesity and lipid disorders. ❖

Medicines

FDA Approves First MS Oral Treatment

The U.S. Food and Drug Administration (FDA) has approved Gilenya, the first oral treatment for multiple sclerosis (MS). For years, the only treatments for patients with MS had to be injected. In MS, the body's immune system attacks myelin, a substance that protects nerves. Gilenya works by holding certain immune cells in the lymph nodes so they can't reach the myelin. In clinical studies, Gilenya reduced MS relapses by 54 percent compared with a placebo and by 52 percent compared with another common injectable drug. However, because there are not many patients yet on the drug, the long-term effects are unknown. And, Gilenya can cause serious side effects such as slowed heart rate, liver problems, headaches and a buildup of fluid in the eye. Currently, four other oral medications are in the final phase of clinical testing that could soon become FDA approved. ❖

Insurance

Medicare Part B Premiuns Lower Than Projected for 2012

The U.S. Department of Health and Human Services (HHS) announced that Medicare Part B premiums in 2012 will be $15.50 lower ($99.90 vs. $106.60) than previously projected and the Part B deductible will decrease by $22 to $140. In addition, because of the Affordable Care Act, people with Medicare also receive free preventive services and a 50 percent discount on covered prescription drugs when they enter the prescription drug "doughnut hole." In 2010, 1.8 million people with Medicare received cheaper prescription drugs, while nearly 20.5 million Medicare beneficiaries received a free annual wellness visit or other free preventive services.

The majority of people with Medicare have paid $96.40 per month for Part B since 2008, due to a law that freezes Part B premiums in years when beneficiaries do not receive a cost-of-living adjustment (COLA) in their Social Security checks. In 2012, these people with Medicare will pay the standard Part B premiun of $99.90, amounting to a monthly charge of $3.50 for most people with Medicare. But this increase will be offset for almost all seniors and people with disabilities by the additional income they will receive for COLA. The average COLA for retired workers is about $43 per month.

HHS also announced a $1 increase in Medicare Part A monthly premiums, as well as a $24 increase in the Part A deductible. For more information about Medicare premiums and deductibles for 2012, go to https://www.csm.gov/apps/media/fact_sheets.asp. ❖

Healthcare

HealthWell Foundation Launches SLE Fund

HEALTHWELL FOUNDATION®

The HealthWell Foundation, a non-profit organization providing financial assistance to insured patients facing a variety of chronic and life-altering illnesses, has launched a new fund to support treatment of systemic lupus erythematosus (SLE), the most common form of lupus. The fund provides copayment assistance to people who are living with SLE who cannot afford the high-cost medication. "Critical to taking advantage of the latest therapeutic option for any disease is the ability to afford that option," said HealthWell Foundation President Mary P. Sundeen. "As a direct result of the generosity of our donors, the HealthWell Foundation stands ready to reduce the cost-sharing obligations that many insured patients face when trying to access gold-standard and recently approved medications." Application information for the SLE fund, as well as information on making a financial donation to support this and other funds, can be found at www.HealthWellFoundation.org. ❖

Vaccines

Modified Vaccine May Prevent Malaria

Michigan State University researchers have created a new malaria vaccine — one that combines the use of a disabled cold virus with an immune system-stimulating gene — that appears to increase the immune response against the parasite that causes the deadly disease. They also discovered that another immune-system stimulating agent — which was created at MSU and has been successful in improving immune response in vaccines for diseases such as HIV — made for a less-effective malaria vaccine. The findings, which are published in the September issue of *PLoS One*, will help researchers develop more effective vaccine platforms in general, and malaria vaccines specifically.

In mouse models, the researchers used two gene adjuvants (rEA and EAT-2), both of which aimed to elicit improved immune responses to the malaria CSP gene. Surprisingly, the rEA agent developed at MSU did not produce the desired result and instead worsened the animal's ability to generate an immune response to CSP. However, the EAT-2 gene-adjuvant stimulated the immune system in a different way, increasing the ability of the immune system to respond to CSP to a level that surpassed currently available malaria vaccine systems. ❖

Did You Know?

"Fifty percent of all antibiotics prescribed for nonhospitalized patients are unnecessary because they are prescribed for nonbacterial infections.

— American College of Physicians

Vaccines

Nobel Medicine Prize Awarded to Tumor Vaccine Developers

The Nobel Foundation has awarded Ralph Steinman of Canada, American Bruce Beutler and Jules Hoffmann of France the Nobel Medicine Prize for their discoveries concerning the body's immune responses. The work of all three scientists has been pivotal to the development of improved types of vaccines against infectious diseases and novel approaches to fighting cancer, and has helped lay the foundations for a new wave of therapeutic vaccines that stimulate the immune system to attack tumors.

Beutler and Hoffmann discovered in the 1990s that receptor proteins act as a first line of defense (innate immunity) by recognizing bacteria and other microorganisms. Steinman's work explained how, if required, dendritic cells in the next phase (adaptive immunity) kill off infections that break through. Understanding dendritic cells led to the launch of the first therapeutic cancer vaccine in 2010, Dendreon's Provenge, which treats men with advanced prostate cancer.

Unfortunately, Steinman died of pancreatic cancer three days before he could be told of his award and after using his own discoveries about dendritic-cell-based immunotherapy to extend his life. The Nobel Committee at Sweden's Karolinska Institute said it does not typically make posthumous awards, but Steinman's selection will stand because the committee was unaware of his death at the time of its announcement. Steinman's prize money will go to his heirs, while Beutler and Hoffmann will share the other half of the 10 million Swedish crown ($1.46 million) prize. ❖

People and Places in the News

FDA APPROVAL

Accentia Biopharmaceuticals Inc. and its majority-owned subsidiary, Biovest International Inc., has been granted orphan drug designation for **Revimmune** for the prevention of graft-versus-host disease following bone marrow transplant.

APPOINTMENTS

Abbie Cornett, Nebraska state senator and current board of trustee chairperson for the Alliance for Biotherapeutics, has assumed the additional role of president for the Alliance. The Alliance was formed in 2007 under the name The Alliance for Plasma Therapies to advocate for patients in need of specialty biotherapeutics.

Kathleen M. Metters, PhD, former senior vice president and head of worldwide basic research at Merck, has been named president and chief executive officer and a member of the board of directors at Lycera Corp., a biopharmaceutical company pioneering innovative approaches to developing novel oral medicines to treat autoimmune diseases.

Rebecca H. Buckley, MD, has been elected as a member of the National Academy of Sciences for her life-saving research in pediatric immunological diseases. Dr. Buckley is the J. Buren Sidbury Professor of Pediatrics and professor of immunology at Duke University Medical Center.

ACQUISITIONS/ALLIANCES

Shire Human Genetic Therapies Inc. announced its Firazyr (icatibant injection), for treating hereditary angioedema in adults 18 years of age and older, received FDA approval in August.

Merck Serono has acquired worldwide exclusive rights to a Phase II-ready multiple sclerosis candidate, PI-2301, originally developed by **Peptimmune Inc**. after it filed for Chapter 7 bankruptcy in 2011.

Zymeworks Inc. and **Merck** are collaborating to develop novel bi-specific antibody therapeutic candidates designed to bind to two different drug targets for broad use in clinical applications such as oncology or autoimmune disease.

Kineta has been awarded its second National Institutes of Health (NIH) contract of $1.4 million to identify new drug targets for infectious, cardiovascular, neurological, metabolic and autoimmune diseases.

GlaxoSmithKline has entered into a strategic alliance with **Fondazione Telethon** and **Fondazione San Raffaele** to research and develop novel treatments to address rare genetic disorders using gene therapy carried out on stem cells taken from the patient's bone marrow (ex vivo).

Sanofi-aventis has established a research collaboration with **Harvard University** to advance knowledge in translational biomedical research in multiple therapeutic areas, including cancer, diabetes and inflammation.

Cangene Corp. has merged its indirect, wholly owned subsidiaries **Mid-Florida Biologicals Inc.**, which operates plasma-collection facilities in Florida and Maryland, and **Biotherapeutic Laboratories Inc.**, which operates a plasma-collection center in California.

Research

COPD Patients Have Higher Risk of Shingles

Patients with chronic obstructive pulmonary disease (COPD) are at greater risk of shingles compared with the general population, according to a study published in the *Canadian Medical Association Journal*. And, the risk is greatest for patients taking oral steroids to treat COPD.

The study, which used data from the Taiwan Longitudinal Health Insurance Database, included 8,846 patients with COPD and 33,944 subjects from the comparison cohort. Of the total 42,430 patients, 1,080 had an incident of shingles (or herpes zoster, which is a reactivation of the chicken pox virus) during the follow-up period. Of those, there were 321 cases of shingles identified among COPD patients, which is 16.4 cases per 1,000 person years, and 759 cases in the comparison cohort, which is 8.8 per 1,000 person years.

Because there is increasing evidence that COPD is an autoimmune disease and other autoimmune diseases, such as "rheumatoid arthritis and inflammatory bowel disease, have been reported to be associated with an increase of herpes zoster, it is reasonable to hypothesize that immune dysregulation found in COPD may put patients at higher risk of developing herpes zoster," says Dr. Hui-Wen Lin of the Taipei Medical University. ❖

Baxter International Inc. has agreed to acquire all of the hemophilia-related assets of **Archemix**, a privately held biopharmaceutical company, and has entered into an exclusive license agreement for certain related intellectual property assets.

Amgen is partnering with **Xencor** to jointly develop XmAb587, an Fc-engineered monoclonal antibody dually targeting the CD19 and CD32b pathways that is currently in Phase II testing. XmAb587 is a potentially promising new treatment for auto-immune diseases.

MolMed SpA has signed an agreement with **GlaxoSmithKline** under which MolMed will develop a production process for an investigational gene therapy for adenosine deaminase deficiency-severe combined immune deficiency (ADA-SCID).

The **David H. Murdock Research Institute** has acquired the **Immune Tolerance Institute Inc**. to accelerate the discovery and development of breakthrough treatments for the range of immune-related diseases.

Dyadic, **Sanofi Pasteur** and **Engen Bio** are partnering on research that will utilize Dyadic's C1 fungus platform for certain vaccine applications.

Thermo Fisher Scientific is acquiring **Phadia**, a global leader in allergy and autoimmunity diagnostics, from European private equity firm Cinven. The transaction is expected to be completed in the fourth quarter of 2011.

Debiopharm is working with researchers at **Yale University** to develop Debio 1036, a first-in-class inhibitor for autoimmune and inflammatory diseases. Debio 1036 is an orally available small molecule that antagonizes a key mediator in the inflammation process.

RxMD, a global therapeutics development company, has entered into an agreement with **GlycoRegimmune Inc.** (GRI) to develop new treatments for inflammatory, autoimmune and neurodegenerative conditions based on GRI's novel natural killer T cell-targeted technologies. ❖

Insurance

Uninsured Unable to Pay Hospital Bills

A new report by the U.S. Department of Health and Human Services (HHS) examines the issues surrounding hospital stays for the uninsured. According to the report, families without health insurance can afford to pay in full for only approximately 12 percent of hospital stays. Hospital stays for which the uninsured cannot pay in full account for 95 percent of the total amount hospitals bill the uninsured. It is estimated that this uncompensated cost of care is up to $73 billion a year, a significant portion of which is shifted into higher costs for Americans with insurance and their employers.

"One of the most enduring myths in American healthcare is that people without health insurance can get care with little or no problem. Nothing could be further from the truth," said HHS Secretary Kathleen Sebelius. "The result is families going without care — or facing healthcare bills they can't hope to pay. When the uninsured cannot afford the care they receive, that cost must be absorbed by other payers. This is why expanding access to affordable health insurance under the Affordable Care Act is so important." ❖

Insurance

Insurance Premiums Up 9 Percent in 2011

Average annual insurance premiums for employer-sponsored family health coverage increased to $15,073 in 2011, up 9 percent from 2010, according to the Kaiser Family Foundation/Health Research & Educational Trust (HRET) 2011 Employer Health Benefits Survey. On average, workers paid $4,129 and employers paid $10,944 toward those annual premiums. The study also found 31 percent of covered workers were in high-deductible health plans, with deductibles for single coverage of at least $1,000, including 12 percent with deductibles of at least $2,000. Covered workers in smaller firms (three to 199 workers) were more likely to face such high deductibles, with half of workers in smaller firms with deductibles of at least $1,000, including 28 percent with deductibles of $2,000 or more.

The 13th annual Kaiser/HRET survey of small and large employers provides a detailed picture of trends in private health insurance costs and coverage. Last year's survey also looked at employers' experiences with several already implemented provisions of the 2010 health reform law affecting employer coverage. In particular, the survey estimated that employers added 2.3 million young adults to their parents' family health insurance policies as a result of the health reform provision that allows young adults up to age 26 without employer coverage on their own to be covered as dependents on their parents' plan. ❖

Research

"Bouncer" Protein Halts Rheumatoid Arthritis

Researchers at the Feinberg School of Medicine have figured out how the immune cells of rheumatoid arthritis (RA) patients become hyperactive and attack their joints and bones. They found that the cells lose their "bouncer," a burly protein that keeps immune cells from going into their destructive mode through the cartilage and bone. When the scientists developed and injected an imitation of the protein into an animal model of RA, it halted the disease progress. The findings were reported on in *Arthritis & Rheumatism*. ❖

Medicines

Octagam 5% Returns to Market in U.S. and Europe

The U.S. Food and Drug Administration (FDA) and the Committee for Medicinal Products for Human Use in Europe have approved the return of Octagam 5% (human normal immunoglobulin 50 mg/ml) to the market. Marketing authorization was suspended in August 2010 in the U.S. and in September 2010 in Europe after a massive voluntary recall by Octapharma due to an increase of thromboembolic events (TEEs). To determine the biochemical root cause(s) of the TEEs in concerned Octagam batches, Octapharma conducted a number of tests, which identified FXIa as the major procoagulant activity. In response, FXIa was successfully removed through corrective and preventive measures in the manufacturing process.

Octapharma then conducted a 10-month product analysis of its Octagam 5% and Octagam 10% that confirmed an enhanced level of safety. "Industry-wide, immune globulin products can lead to TEEs in approximately one individual or less for every 10,000 treatments," said Octapharma Chairman Wolfgang Marguerre. "But our analysis indicates that Octagam 5% and Octagam 10% outperformed this industry benchmark with no reported TEEs in approximately 60,000 patient treatments."

Octapharma has now implemented post-marketing studies to ensure product safety. "Our collaboration with the FDA over the last year has enhanced awareness of the industry-wide concerns regarding procoagulant activity and TEEs," said Octapharma USA President Flemming Nielsen. "Octapharma has always believed that patient safety comes first, so the Octagam 5% that we will return to the U.S. market … will enjoy the highest level of safety scrutiny available today and the same level of tolerability that our patients have come to expect from Octapharma therapies." ❖

Research

Urine Test Could Warn About Cognitive Decline

The presence of albuminuria — too much albumin, or protein, in urine — detected by a urine test could be used as an independent predictor of cognitive decline. Researchers at Brigham and Women's Hospital in Boston tracked more than 1,200 women ages 70 and older in the Nurses' Health Study for six years who were tested on general cognition, verbal/word memory, speed in making word associations and short-term memory. They found that the women with albuminuria at the start of the study experienced cognitive decline at a rate two to seven times faster than those who had cognitive decline due to aging but did not have albuminuria. The findings were presented at Renal Week held by the American Society of Nephrology. ❖

Vaccines

Flu Vaccine Production to Double by 2015

Global production of seasonal flu vaccine is expected to double to 1.7 billion doses by 2015, with 11 new manufacturers expected in developing countries, according to the World Health Organization. This means that if a new influenza pandemic occurs, the world's projected 37 vaccine makers could potentially triple their annual production of trivalent seasonal vaccine to make 5.4 billion doses of pandemic vaccine. However, the actual amount would depend on the yield of the virus grown in the egg, which was low for the H1N1 pandemic, as well as on how much adjuvant (which stretches the active ingredient) is used in the pandemic vaccine. GlaxoSmithKline and Sanofi are among the major producers of influenza vaccine. ❖

Research

Top-Line Results for Phase III Study of HyQ in PIDD Patients

A Phase III study of HyQ, an investigational facilitated subcutaneous immune globulin (SCIG) product for use in patients with primary immunodeficiency (PIDD), has produced top-line results. In the open-label study by Baxter International Inc. and Halozyme Therapeutics Inc., 89 patients with PIDD were enrolled in 15 centers in the U.S. and Canada to evaluate the effectiveness of HyQ in the prevention of infections and to measure other secondary endpoints, including tolerability. Patients were infused with a three-week or four-week dose of 10% HyQ in a single infusion site. Results showed that the acute serious bacterial infection rate was .025 per patient per year, which is below the required efficacy threshold of 1.0. The tolerability assessment showed that the most frequently reported adverse reactions were infusion site reactions (20 percent), headache (3 percent), fatigue (1 percent) and fever (1 percent).

The data from this trial confirm the interim results presented in late 2010 and support the recent submission of a biologics license application to the U.S. Food and Drug Administration. The trial also established a foundation for the HyQ extension study that will further evaluate HyQ administration in patients through March 2012. In addition to the recent regulatory submission in the U.S., Baxter expects to file in Europe and Canada, and will present results from the Phase III study by the end of 2011. ❖

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

The rising cost of healthcare continues to be a hot-button issue for the healthcare industry and patient advocacy groups. Chronic diseases, in particular, appear to be targets for cost-saving measures. As a result, several groups are focusing their advocacy efforts on reimbursement issues that they believe threaten patients' access to care. Following is a summary of some of these issues and the viewpoints of key opinion leaders.

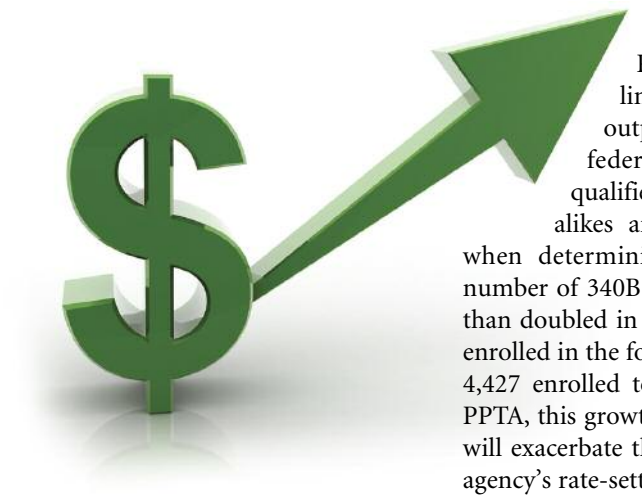
Medicare IVIG Access Act

The current Medicare Part B reimbursement methodology does not allow equal access to care in all settings. In the case of intravenous immune globulin (IVIG), Medicare Part B pays for the drug only for patients with primary immunodeficiency diseases (PIDD). In addition, Medicare Part B does not reimburse for the supplies, nursing or infusion pump unless the patient is certified homebound.

The American Academy of Allergy, Asthma and Immunology (www.aaaai.org), the Clinical Immunology Society (www.clinimmsoc.org/educational-resources/ivig/medicare-ivig-access-act-summary) and the Immune Deficiency Foundation (primaryimmune.org/idf-advocacy-center/ivig-reimbursement) support and advocate for legislation currently under consideration. House Bill 1845 and Senate Bill 960 direct that a three-year demonstration project be conducted to study the benefits of providing coverage and payment for items and services necessary to administer IVIG in the home.

Drug Reimbursement Under the CMS OPPS

The Centers for Medicare and Medicaid Services (CMS) has proposed to set the payment level of separately payable non-pass-through drugs and biologicals at the average sales price (ASP) plus 4 percent, which is less than the current outpatient prospective payment system (OPPS) level of ASP plus 5 percent.



The Plasma Protein Therapeutic Association (PPTA) (www.pptaglobal.org/news/news.aspx?nid=90) believes the payment rate should be no less than ASP plus 6 percent to help ensure that hospital outpatient departments remain a viable option for beneficiaries to receive therapies such as alpha-1 proteinase inhibitor, blood clotting factors and IVIG. "PPTA has long advocated for parity between the statutory physician office rate of ASP plus 6 and the OPPS rate," said Julie Birkofer, senior vice president, North America, PPTA. "This inequality between sites of service has been problematic in the past for patient access to plasma protein therapies."

The PPTA also commented on the use of the 340B Drug Pricing Program, which limits the cost of covered outpatient drugs to certain federal grantees, federally qualified health center look-alikes and qualified hospitals, when determining ASP pricing. The number of 340B hospital sites has more than doubled in three years, from 2,213 enrolled in the fourth quarter of 2008 to 4,427 enrolled today. According to the PPTA, this growth of the 340B program will exacerbate the flawed nature of the agency's rate-setting calculation.

Although PPTA advocates for removing 340B sales from the CMS rate-setting calculation, it cautioned against establishing two payment rates — one for 340B hospitals and one for non-340B hospitals. "Reducing Medicare payments to 340B hospitals [through a separate payment rate] for separately paid drugs would undermine the purpose of the 340B program to reach more eligible patients and provide more comprehensive services," said Birkofer.

The Affordable Care Act

Many sources continue to fund political action committees representing the special interests of patient advocacy groups and medical associations. All are concerned that changes in policy could impact reimbursement, which could have a negative impact on patient care.

Enhancing life's defenses

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

Positive efficacy outcomes
For PI patients receiving Gammaplex there were:

> No reports of Acute Serious Bacterial Infection[1]
> Just 0.75 days per year of subjects hospitalized[1]
> Only 8.73 days per subject year out of work/school/day care[1]

Low IgA levels
> The content of IgA is <10 µg/mL[1]

Convenient infusion schedule
> Infusion rate can be increased every 15 minutes to a maximum rate of 0.08 mL/kg/min[1]

Robust 3-step virus reduction
> An extremely low risk of viral transmission

Room temperature storage
> Gammaplex can be stored between 2°C and 25°C (36°F to 77°F) unopened for 2 years

Effective January 1, 2012, the permanent HCPCS "J" code for Gammaplex is **J1557**

For more information visit **www.gammaplex.com**

IMPORTANT SAFETY INFORMATION
Gammaplex is indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

WARNING: Renal dysfunction, acute renal failure, osmotic nephropathy and death may be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable. See full prescribing information for complete boxed warning.

Gammaplex is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to human immune globulin and in patients with selective IgA deficiency and in patients with a history of hypersensitivity.

In patients at risk of developing renal failure, monitor urine output and renal function including blood urea nitrogen (BUN) and serum creatinine. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. Thrombotic events may occur following treatment with Gammaplex and other IGIV products. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known/suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. Hemolysis and hemolytic anemia can develop subsequent to IGIV treatments. Noncardiogenic pulmonary edema may occur in patients following IGIV treatment (i.e. transfusion-related acute lung injury [TRALI]). Monitor patients for pulmonary adverse reactions (TRALI). Test product and patient's serum for anti-neutrophil antibodies.

Gammaplex is derived from human plasma. The risk of transmission of infectious agents, including viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies, the most common adverse reactions with Gammaplex were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain and vomiting.

Report adverse reactions to adr@bpl.co.uk

REFERENCES
1. BPL. US Prescribing Information, VSUS1PI, Sept. 2009.

Please see the Brief Summary of Prescribing Information, including boxed warning, on the reverse.

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Bio Products Laboratory
a commitment for life

For product information and inquiries, please call **(866) 398-0825** or email BPLinfo@LashGroup.com

December 2011 GPX/11/61 Printed in USA

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION PRIOR TO USE

INDICATIONS AND USAGE
Gammaplex®, Immune Globulin Intravenous (Human), 5% Liquid, is indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

CONTRAINDICATIONS
Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, is contraindicated in patients who have had an anaphylactic or severe systemic reaction to human immune globulin and in IgA-deficient patients with antibodies to IgA.

WARNINGS

Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy and death. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those who are overweight or are receiving known nephrotoxic drugs. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable.

See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections in the Package Insert for important information intended to reduce the risk of acute renal failure.

Because this product is made from human plasma, it may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob [CJD] agent that can cause disease. The risk has been reduced by screening plasma donors for prior exposure, testing donated plasma and inactivating or removing viruses during manufacturing. Despite these measures, Gammaplex carries an extremely remote risk of transmission of viral diseases. The physician should discuss the risks and benefits of this product with the patient, before prescribing it to the patient.

All infections suspected by a physician possibly to have been transmitted by this product should be reported to (866) 398-0825 or email BPLinfo@LashGroup.com on behalf of Bio Products Laboratory Ltd.

Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, should only be administered intravenously.

PRECAUTIONS
General
The product should be used promptly after piercing the cap. Any partially used or unused product should be discarded. Visually inspect each bottle before use. Do not use if the solution is cloudy or turbid. Solution that has been frozen should not be used.

Hypersensitivity
Severe hypersensitivity reactions may occur. In case of hypersensitivity, discontinue Gammaplex infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Renal dysfunction/failure
Ensure that patients with pre-existing renal deficiency are not volume depleted before infusion of IGIV. Periodic monitoring of renal function and urine output is particularly important in patients considered to be at increased risk of developing acute renal failure. Renal function, including blood urea nitrogen (BUN) and serum creatinine, should be assessed before administering Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

Information for patients: Patients should be instructed to report the following signs and symptoms to their healthcare professional: decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage).

Hyperproteinemia, increased serum viscosity, and hyponatremia
Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV therapy. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion practicable.

Thrombotic events
Thrombotic events may occur following treatment with IGIV products. Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), hyperproteinemia or monoclonal gammopathies (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion possible.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome (AMS) may occur infrequently with Immune Globulin Intravenous (IGIV) treatment, usually beginning within several hours to 2 days after IGIV. AMS may occur more frequently with high doses (2 g/kg) and/or rapid infusion of IGIV. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis
IGIV products can contain blood group antibodies (hemolysins) that coat red blood cells (RBCs) in vivo with immune globulin, resulting in a positive direct antiglobulin test (DAT). Acute hemolysis has been reported with IVIG. Delayed hemolytic anemia can develop due to RBC sequestration. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests).

Transfusion-related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema [Transfusion-related Acute Lung Injury (TRALI)] may occur in patients following IGIV treatment. Symptoms (fever, severe respiratory distress, pulmonary edema, hypoxemia but normal left ventricular function) typically appear within 1 to 6 hours following treatment. If TRALI is suspected, test for anti-neutrophil antibodies in both the product and the patient's serum (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). Management includes oxygen and appropriate ventilatory support.

Laboratory Tests
For appropriate monitoring, see previous sections on Renal, Hyperproteinemia, Hemolysis and TRALI.

Drug Interactions: Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella (SEE PATIENT COUNSELING INFORMATION IN PACKAGE INSERT).

Pregnancy Category C: Animal reproduction studies have not been conducted with Gammaplex. It is not known whether Gammaplex can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Gammaplex should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS
General
Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, contains no reducing carbohydrate stabilizers (e.g. sucrose, maltose) and no preservative.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of IGIV products.
Infusion reactions: hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia and changes in blood pressure.
Renal: Acute renal dysfunction/failure, osmotic nephropathy.
Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm.
Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension.
Neurological: Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome.
Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, dermatitis (e.g., bullous dermatitis).
Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test.
Gastrointestinal: Hepatic dysfunction, abdominal pain.
General/Body as a Whole: Pyrexia, rigors.

Primary Humoral Immunodeficiencies (PI)
In a multicenter, open-label, non-randomized clinical study, 50 subjects with primary humoral immunodeficiency received 703 infusions with Gammaplex. Doses ranged from 279 to 799 mg/kg every 21 days (mean dose 465 mg/kg) or 28 days (mean dose 458 mg/kg), for up to 12 months. At some time during the study, all 50 subjects had an adverse event (AE) and in twenty-four subjects (48.0%) it was considered product-related.

The temporally associated AEs that occurred in more than 5% of subjects during a Gammaplex infusion or within 72 hours after the end of an infusion, *irrespective of causality* are given in the table below:

Adverse Event	Subjects (%) [n=50]	Infusions (%) [n=703]
Headache	18 (36%)	53 (7.5%)
Sinusitis	8 (16%)	9 (1.3%)
Pyrexia	7 (14%)	10 (1.4%)
Nausea	6 (12%)	7 (1.0%)
Pain	5 (10%)	5 (0.7%)
Chills	3 (6%)	5 (0.7%)
Fatigue	3 (6%)	9 (1.3%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Nasal congestion	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)

Five subjects (10%) experienced seven serious AEs. Two of these serious AEs were considered related to Gammaplex treatment (thrombosis and chest pain). Three other subjects withdrew from the study due to the following AEs: paresthesia, bronchospasm and pregnancy.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or Parvovirus B19.

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December 2011 US/Gx/1211/0001

The American Academy of Neurology (AAN) (www.aan.com/advocacy/issues/?event=home.showIssue&id=29) and the AAN Professional Academy support legislation to replace the current CMS formula based on the Sustainable Growth Rate (SGR) with one based on the Medical Economic Index, which measures annual practice cost increases. Paying physicians according to the actual costs associated with treating patients is necessary to maintain consistent access to providers. Additionally, they would like to see neurologists recognized as "principal care providers" for patients with complex neurological conditions.

The National Hemophilia Foundation (NHF) (www.hemophilia.org/NHFWeb/MainPgs/MainNHF.aspx?menuid=333&contentid=1350&rptname=advocacy) remains committed to making sure the gains that patients made under the Affordable Care Act remain intact. Although NHF has not endorsed any specific legislative proposal, its public policy team is working to shape the policies that most affect the bleeding disorders community. Specifically, it is working to ensure that health reform legislation recognizes the specialized needs of individuals with rare diseases and includes:

- private market insurance reforms, including the elimination of lifetime caps and pre-existing conditions clauses;
- provisions to ensure the affordability of insurance coverage such as limits on out-of-pocket costs; and
- access to specialists and the full range of therapies.

Specialty Tiers

Several advocacy groups support the growing popularity for state legislation to limit the use of specialty drug tiers. Instead of paying a fixed copayment, specialty tiers require patients to pay as much as a 33 percent coinsurance. The concern is that the increased use of specialty tiers will result in unaffordable out-of-pocket expenses for patients with chronic diseases. Therefore, advocacy groups would like to see limits in place to cap the out-of-pocket liability patients must pay for their medications.

According to Dominick Spatafora, president of the Neuropathy Action Foundation (www.neuropathyaction.org) and member of the Alliance for BioTherapeutics (www.bioalliance.org), "The specialty tier formulary simply makes treatment for these costly yet life-saving and life-enhancing therapeutics unaffordable for most patients." Tina Tockarshewsky, president and CEO of the Neuropathy Association, adds that "patients shouldn't fear for their lives or their livelihoods because a life-sustaining treatment is being taken away."

The Alliance for Biotherapeutics is particularly concerned that specialty tiers are limiting affordable access for patients with chronic diseases. Abbie Cornett, president and chair of the Alliance for BioTherapeutics and Nebraska state senator, said: "The Alliance is actively pursuing state legislation to address these very serious issues. We are working closely with patient and industry allies to find solutions at the state and federal level."

Drug Shortages

Drug shortages compromise care and safety, disrupt medical trials and increase the cost of healthcare. Unless a manufacturer is the sole source provider of a drug, no current law exists that allows the U.S. Food and Drug Administration (FDA) to require mandatory reporting of impending shortages. In response to concerns, H.R. 2245, titled Preserving Access to Life-Saving Medications Act of 2011, was introduced. If passed, it would give the FDA authority to impose civil monetary penalties if a manufacturer fails to give notice of a discontinuation or disruption of a drug that results in a drug shortage.

The American Society of Health-Systems Pharmacists (ASHP) (www.ashp.org/menu/AboutUs/ForPress/PressReleases/PressRelease.aspx?id=643) supports H.R. 2245. "The rapid increase in the number of drug shortages in recent years is akin to a public health crisis and is the cause of serious patient harm," said ASHP President Stan Kent, MS, FASHP. "We are pleased to see that Congress is working to address this critical issue and will advocate strongly for its passage." ❖

Reimbursement Unraveled

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KRIS MCFALLS *is the patient advocate for* IG Living *magazine, directed to patients who rely on immune globulin and their caregivers.*

Editor's Note: The content of this column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

Immune Globulin Therapy:
The Investigational Frontier

By Ronale Tucker Rhodes, MS

IG is being successfully studied to treat more diseases than ever before, especially for hematological, neurological and autoimmune conditions.

Despite immune globulin (IG) being approved by the U.S. Food and Drug Administration (FDA) to treat only five diseases, the number of diseases treated off label by IG (those not FDA-approved) continues to grow. According to the Medscape Reference website, that number exceeds 60 disease states. A few of these off-label treatments have become accepted use, while many others are under investigation and are relatively new to the IG treatment frontier.

For all off-label uses, IG is currently considered a second line of treatment after first-line treatments have proved ineffective. Because this is often the case, IG is a lifesaving therapy that offers hope for so many. However, the beneficial effects of IG for many

conditions are under debate in the medical community, and growing demand for IG poses challenges regarding both reimbursement and supply.

On-Label and Accepted Off-Label Uses

Currently, IG is FDA-approved to treat primary immunodeficiency, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, Kawasaki syndrome and chronic inflammatory demyelinating polyneuropathy.

Beyond these approved therapies, IG has become an accepted treatment for some other diseases in which preliminary studies and medical literature have shown the drug's effectiveness as a second-line treatment. According to the FDA (as noted in a 1982 policy guidance): "Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such 'unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature."

Of course, some of these diseases have more extensive medical literature to back the use of IG as an accepted treatment. These include, but are not limited to, Guillain-Barré syndrome, multifocal motor neuropathy and inflammatory myopathies. And, because IG is considered an accepted treatment for these diseases, it is often easier for a patient to be approved for reimbursement, although that is certainly not always the case.

Guillain Barré syndrome (GBS). GBS is an acute inflammatory demyelinating polyneuropathy characterized by progressive symmetric ascending muscle weakness, paralysis and hyporeflexia with or without sensory or autonomic symptoms; however, variants involving the cranial nerves or pure motor involvement are not uncommon. Both plasma exchange (PE) and intravenous IG (IVIG) have proved effective for GBS because they may decrease autoantibody production and increase solubilization and removal of immune complexes, and both have been shown to shorten recovery time by as much as 50 percent.

Randomized trials in severe disease show that IVIG started within four weeks from onset hastens recovery as much as PE. However, combining PE and IVIG neither improved outcomes nor shortened illness duration. IVIG also has been found safe and effective in the treatment of pediatric GBS, and it is the preferential treatment in hemodynamically unstable patients and in those unable to ambulate independently.[1]

Multifocal motor neuropathy (MMN). MMN is a rare autoimmune disorder characterized by progressive weakness in the limbs, leading to significant difficulty with simple manual tasks. If left untreated, MMN often progresses to more severe weakness, including muscle atrophy or involuntary twitching.

It is caused by malfunctions in the conduction pathway of motor nerves, limiting transmission of electrical impulses. Of the one in 100,000 people it affects, 80 percent are between 20 and 65 years of age at the onset of disease, with men more frequently affected than women.

In June 2011, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) gave Baxter International marketing authorization for KIOVIG, the first centrally licensed indication for an immunoglobulin preparation for MMN. The authorization was based on two studies, both of which showed maintenance of muscle strength and improved functionality. Adverse events were reversible and consistent with those seen in other KIOVIG indications, with no serious adverse events. In 2008, Baxter initiated a Phase III clinical trial in the U.S. and Canada for Gammagard Liquid (marketed as KIOVIG outside the U.S.) for the treatment of MMN, and is currently seeking FDA approval.[2]

Inflammatory myopathies. Inflammatory myopathies include polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). Patients with PM and DM typically experience weakness in muscles involved in lifting the arms above the head, getting up from a chair or walking up stairs. In DM, there is skin involvement characterized by a rash either on the eyelids, hands or trunk of the body. Because DM can sometimes be associated with malignancies, screening is conducted for this as well. IBM can affect some of the same muscles as PM and DM, but also often affects the hand muscles

and the quadriceps muscles. IBM usually affects people who are over 50 who do not respond well to medication.[3]

IVIG's immunomodulatory effect can be used to treat DM and PM where other treatments have not proved effective. In a double-blind placebo-controlled crossover trial in patients with DM resistant to other treatments, IVIG produced a significant increase of muscle strength, as well as a marked improvement in immunopathological parameters in repeated muscle biopsies (before and after IVIG). No randomized trials have been undertaken with IVIG for PM. For IBM, three controlled trials showed some muscle strength improvement, although the changes did not reach statistical significance. However, improvement in swallowing was repeatedly observed, suggesting that some patients with severe dysphagia may derive a modest benefit from IVIG therapy.[4]

Despite lack of FDA approval, IG has become an accepted treatment for some other diseases in which preliminary studies and medical literature have shown the drug's effectiveness as a second-line treatment.

Other Diseases Treated with IG

According to the Advocacy for Patients with Chronic Illness website: "Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations." But, even when this occurs, that doesn't mean the drug will ever be FDA-approved to treat a disease. Therefore, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

Right now, many different diseases are being treated with IG other than those that are FDA-approved or accepted usage. These fall under such medical categories as hematology, infectious diseases, neurology, obstetrics, pulmonology and rheumatology, as well as a host of other miscellaneous conditions. Some of the specific diseases being treated with IG include pure red cell aplasia, hemolytic disease of the newborn, epilepsy, multiple sclerosis, Sjögren's syndrome, recurrent pregnancy loss, asthma, systemic lupus erythematosus, narcolepsy and Alzheimer's.

Pure red cell aplasia (PRCA). PRCA is a condition in which red blood cell precursors in bone marrow are nearly absent, while megakaryocytes and white blood cell precursors are usually present at normal levels. PRCA exists in several forms, the most common of which is an acute self-limited condition. It is often chronic and is associated with underlying disorders such as thymomas (tumors originating in the thymus) and autoimmune diseases. There is sufficient evidence that IVIG, which regulates immune function, is effective. In fact, a recent guideline recommends IVIG for red cell aplasia. Most studies show a response to high-dose IVIG, followed by low doses initially to monitor for anaphylaxis and other complications (doses mentioned in the package insert are followed later).[5]

In 2007, specific recommendations were made for routine use of IVIG for seven conditions: acquired red cell aplasia, acquired hypogammaglobulinemia (secondary to malignancy), fetal-neonatal alloimmune thrombocytopenia, hemolytic disease of the newborn, HIV-associated thrombocytopenia, idiopathic thrombocytopenic purpura (an FDA-approved indication) and post-transfusion purpura — all of which are hematologic conditions.[6]

Epilepsy. Epilepsy is characterized by recurrent, unprovoked, spontaneous seizure activities and affects 0.5 percent to 1.5 percent of the world's population. Over the years, it has been suggested that inflammation plays a role in epilepsy, evoked by pro-inflammatory modulators that are meant to

protect from and heal injuries to the body. Because inflammation is known to cause several neurological disorders such as Parkinson's disease, meningitis and encephalitis, it has recently been acknowledged and is the subject of discussion, abstracts and publications at professional epilepsy meetings worldwide.

Since 1977, IVIG has been implicated for treatment of epilepsy, although it has been reported that IVIG responds differently in different forms of epilepsy. Improvement has been seen in children with severe epilepsy being treated for respiratory infections with IVIG, and there are good response rates in patients with West syndrome and Lennox-Gastaut syndrome. How IVIG decreases seizure frequency and severity is not yet fully understood. And, there have not been many large or double-blind, placebo-controlled studies regarding the efficacy of IVIG to treat epilepsy.[7]

Relapsing-remitting multiple sclerosis (RRMS). One of four internationally recognized forms of MS, RRMS is characterized by relapses (also known as exacerbations) during which time new symptoms can appear and old ones resurface or worsen. The relapses, which can last for days, weeks or months, are followed by periods of remission, when the person fully or partially recovers from the deficits acquired during the relapse. During relapses, myelin, a protective insulating sheath around the nerve fibers (neurons) in the white matter regions of the central nervous system (CNS), is damaged in an inflammatory response by the body's own immune system. This causes a wide variety of neurological symptoms that vary considerably depending on which areas of the CNS are damaged.[8]

Treatment of RRMS with IVIG has had mixed results. The American Academy of Neurology Report of the Therapeutics and Technology Assessment Subcommittee from 2001 refers to three studies conducted in the 1990s. According to the report, the first study showed treatment with IVIG reduced the clinical attack rate, the second reduced the total number of enhancing lesions and new lesions when treated with IVIG, and the third showed significant reductions in clinical attack rate. However, the report also states that those studies "have generally involved small numbers of patients, have lacked complete data on clinical and MRI outcomes, or have used methods that have been questioned."[9]

Yet, a recently published paper summarizing four double-blind IVIG studies of RRMS cites two more recent studies with positive results. In one study, published in the October 2004 issue of *Neurology*, 91 patients were studied after their first neurological event suggestive of demyelinative disease. That study showed that IVIG treatment for the first year of these patients significantly lowered the incidence of a second attack and reduced disease activity as measured by brain MRI. Another study published in June 2006 in *Review of Neurology* found that IVIG is "thought to exert a twofold effect: an immunomodulating action and a positive action on remyelization."[9]

Sjögren's syndrome. Sjögren's syndrome is a chronic autoimmune disease in which people's white blood cells attack their moisture-producing glands. It is one of the most prevalent autoimmune diseases, affecting as many as four million Americans, nine out of 10 of whom are women. Symptoms are dry eyes, dry mouth, extreme fatigue and joint pain. And, Sjögren's also may cause dysfunction of other organs such as the kidneys, gastrointestinal system, blood vessels, lungs, liver, pancreas and the central nervous system.[10]

Since 1977, IVIG has been implicated for treatment of epilepsy, although it has been reported that IVIG responds differently in different forms of epilepsy.

A 2011 study evaluated 19 patients with Sjögren's syndrome-related presumed non-necrotizing vasculitic neuropathy who had been treated with one or more doses of IVIG. The patients' mean age was 60 years old and 58 percent were women. They had a variety of neuropathies classified as sensorimotor, ataxic, nonataxic sensory polyneuropathy and conduction block neuropathy. IVIG was administered in monthly infusions of 2 g/kg over either two or five days, and the median duration of IVIG treatment was seven months with follow-up ranging from three to 84 months. A variety of other immunosuppressive agents were used either prior to or along with the IVIG.

Results were measured using the patient-completed Modified Rankin Score (MRS). In eight patients, the MRS improved; in 10 patients, the MRS was stable; and in one patient, the MRS worsened. All patients with sensorimotor, nonataxic sensory neuropathy and conduction block improved; however, of the nine patients with ataxic neuropathy, only two improved, four worsened and three remained stable. Ten of 13 patients treated with steroids were able to lower their doses, presumably as a result of the effects of IVIG. The researchers concluded that IVIG may be useful in the treatment of some neuropathic manifestations of Sjögren's syndrome, but because of the small sample, conclusions are limited.[11]

Recurrent pregnancy loss. Recurrent pregnancy loss, also known as recurrent spontaneous abortion (RSA), is a disease distinct from infertility, defined by two or more failed pregnancies. Any of these pregnancy losses, though unexplained, have an immunologic basis.

A number of studies have looked at the effects of IVIG to prevent RSA, with many of the most recent studies having positive results. In one clinical trial of 47 women with a history of RSA, IVIG was given at a dose of 0.2 g/kg within two weeks of attempted conception. Once conception was achieved, IVIG was given once every four weeks at the same dose through 26 to 30 weeks of gestation. Thirty-six women received IVIG and 11 women refused IVIG. Of the 36 women who received IVIG, 24 became pregnant and 20 of those received IVIG through 26 to 30 weeks of gestation. Nineteen of these patients had a term pregnancy and one miscarried at eight weeks. Four women stopped IVIG therapy at 10 to 12 weeks gestation, and three of these women had term pregnancies. The fourth miscarried at 15 weeks gestation. Seven of the 11 women who refused IVIG became pregnant and all had first trimester miscarriages. The conclusion: The difference in successful pregnancies was significantly higher in the women treated with IVIG. Other studies have not found statistically significant differences between groups of women who were treated with IVIG versus a placebo.[12]

A number of studies have looked at the effects of IVIG to prevent recurrent spontaneous abortion, with many of the most recent studies having positive results.

Steroid-dependent asthma. Individuals with difficult-to-control asthma typically have daily or nearly daily asthmatic symptoms, functional limitations due to asthma that interrupt work, school or recreational schedules, and a requirement for daily or every-other-day corticosteroids. While the mechanism of action is unknown, IVIG is one of the newer types of experimental treatments for severe steroid-dependent asthma. And, because permanent side effects are rare, some specialists view IVIG as a reasonable alternative to continuing treatment with high-dose, daily oral corticosteroids with their associated risks of significant side effects.[13]

In one study, seven patients with severe steroid-dependent asthma were given IVIG at a dose of 1 g/kg each month for six months. Baseline pulmonary function tests and immunoglobulin levels were obtained, and at the end of six months, lung function and the degree of reduction in the dose of oral steroids were observed. The number of hospital admissions during the 12 months following commencement of IVIG also was compared with the preceding 12 months. Results showed a significant reduction in daily prednisolone dose and a decrease in the number of hospital admissions. No significant improvement occurred in lung function. From this, the researchers concluded that IVIG provides a potentially important adjunctive therapy in severe steroid-dependent asthma, reducing steroid requirement and decreasing hospital admissions, but not improving lung function.[14]

Systemic lupus erythematosus (SLE). SLE is a multisystemic autoimmune disease with clinical manifestations ranging from mild to life-threatening, and the course of the disease is unpredictable, with periods of illness (called flares) alternating with remissions. SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys and nervous system. The disease occurs nine times more often in women than in men, especially in women in child-bearing years ages 15 to 35, and is also more common in those of non-European descent. Most deaths due to SLE are caused by kidney failure.

Several studies have demonstrated a significant effect of IVIG on overall disease activity. While the first study on the beneficial effect of IVIG advocated it for acute exacerbation only, several later studies showed significant improvement in chronic refractory SLE. The general efficacy in several small case series involving three to 12 patients ranged between 33 percent and 100 percent. In the largest study reported recently, which included 20 SLE patients with an 85 percent response rate, the authors advocate using IVIG as a useful steroid-sparing agent in SLE patients requiring high doses of steroids. However, that study's authors recommended confirming the recommendation in a double-blind placebo-controlled study. Unfortunately, because of the small number of patients and the conflicting results presented in the literature, it is not possible to ascertain which signs or symptoms will usually respond to IVIG.[15]

Narcolepsy with cataplexy (NC). NC affects 0.02 percent of adults worldwide. It is a disabling sleep disorder characterized by severe, irresistible daytime sleepiness and sudden loss of muscle tone (cataplexy), and can be associated with sleep-onset or sleep-offset paralysis and hallucinations, frequent movement and awakening during sleep, and weight gain. The onset of NC is usually during teenage and young adulthood and persists throughout the lifetime. Pathophysiological studies

have shown that the disease is caused by the early loss of neurons in the hypothalamus that produce hypocretin, a wakefulness-associated neurotransmitter present in cerebrospinal fluid. The cause of neural loss could be autoimmune since most patients have the HLA DQB1*0602 allele that predisposes individuals to the disorder.[16]

The two biggest challenges with using IVIG treatment for off-label indications include reimbursement and supply.

In one study that tested IVIG treatment in early onset NC, two NC children received 1 g/kg/day of IVIG two days per month, five times, at three and six months disease duration, respectively. Cataplexy improved in both children, but only temporarily in one patient. Subjective sleepiness temporarily improved, sleep paralysis emerged and hypnagogic hallucinations and REM sleep behavior disorder worsened in one child. The researchers concluded that IVIG treatment initiated before nine months disease duration has some clinical efficacy. However, they recomended that the final IVIG effect be investigated in a placebo-controlled study.[17]

In another study, IVIG treatment was tested in four children with NC with an early diagnosis and extreme disease severity. One of four patients showed an objective and persistent improvement in clinical features during and after IVIG treatment. The researchers concluded that their data partially support the recent report of the efficacy of IVIG treatment in early diagnosed NC and support the need for a controlled multicenter clinical trial on IVIG in narcolepsy.[18]

Alzheimer's. Alzheimer's is a type of dementia that causes problems with memory, thinking and behavior. It is caused by a buildup of proteins in the brain. The buildup manifests in two ways: plaques (deposits of the protein beta-amyloid that accumulate in the spaces between nerve cells) and tangles (deposits of the protein tau that accumulate inside nerve cells). Alzheimer's symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals lose the ability to carry on a conversation and respond to their environment. Alzheimer's is the sixth-leading cause of death in the U.S. Those with the disease live an average of eight years after their symptoms become noticeable to others, but survival can range from four to 20 years, depending on age and other health conditions.[19,20]

Since the late 1990s, there has been increasing evidence that immunotherapy targeting the amyloid beta peptide can be used to treat Alzheimer's disease. Because IVIG contains anti-amyloid antibodies, many studies have been conducted to determine its treatment efficacy. In a Phase I safety and preliminary efficacy study, eight Alzheimer's patients were treated with IVIG (Gammagard S/D Immune Globulin Intravenous Human). Seven patients completed the study and were evaluated by cognitive testing after six months of therapy. Cognitive function stopped declining in all seven patients and improved in six of the seven patients. Results from a Phase II clinical trial testing of Gammagard showed that IVIG slowed clinical decline, as well as reduced brain atrophy to the rate of age-matched normal control subjects.[21]

Currently, a Phase III double-blind placebo-controlled study, called the GAP (Gammaglobulin Alzheimer's Partnership) Study, is examining whether IVIG treatment will slow the rate or prevent the decline of dementia symptoms in individuals with mild to moderate Alzheimer's patients. The study includes 360 patients and will last 82 weeks. Two-thirds of the participants will receive IVIG, while one-third will get a placebo every two weeks for 18 months.[22]

Challenges of Off-Label Use

The two biggest challenges with using IVIG treatment for off-label indications include reimbursement and supply. Just because the use of a drug is not indicated and, therefore, off label does not mean it is not covered. Nonetheless, reimbursement for off-label uses can be more cumbersome and require more documentation to prove it is medically necessary. The more expensive the therapy is, the more attention a payer is likely to give it. Documentation must be provided to prove a patient's symptoms fit the diagnosis. If a patient's medical profile fits the diagnostic criteria, many payers still require the patient to first fail other forms of treatment; this is known as step therapy or a fail-first policy. Payers also may limit the quantity and/or interval that a drug is given.

With the growing number of indications being researched for IVIG treatment, should some of them gain FDA approval, there is concern that the demand for IG could outweigh the supply. Manufacturing IG differs significantly from traditional pharmaceutical manufacturing processes. IG is a plasma product that relies solely on the proteins present in human blood rather than on chemical processes that can be developed and/or improved for traditional pharmaceuticals. Manufacturing plasma is a lengthy and expensive process; manufacturing costs are about 65 percent of the price of IG, compared with 20 percent to 25 percent for traditional pharmaceutical processes.

A Promising Future?

The next frontier for IG looks extremely promising as this lifesaving therapy proves successful in treating more and more diseases. However, while much attention is being given to researching new indications for IG, an equal amount of attention will need to be devoted to the issues of supply and demand. ❖

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References:

1. Miller, A, et al. Emergent Management of Guillain-Barré Syndrome. Medscape Reference. Accessed at emedicine.medscape.com/article/792008-overview#a1.
2. Baxter Receives Positive Opinion for IVIG Therapy in Europe for Treatment of Multifocal Motor Neuropathy. Baxter, 2011 press release. Accessed at www.baxter.com/press_room/press_releases/2011/06_24_11_ivig_mmn.html.
3. Illa, I. IVIg in Myasthenia Gravis, Lambert Eaton Myasthenic Syndrome and Inflammatory Myopathies: Current Status. *Journal of Neurology*, 2005 May;252 Suppl 1:I14-8.
4. Shetty, T. Inflammatory Myopathies: A Neurological Perspective on Myositis. Summary of a presentation to the Myositis Education and Support Program at HHS on Nov. 12, 2008. Accessed at www.hss.edu/conditions_inflammatory-myopathies-neurological-perspective-myositis.asp.
5. Zimmer, J, Regele, D, and dela Salle, H. Pure Red-Cell Aplasia. *New England Journal of Medicine*, June 24, 1999;340(25):2004-5.
6. Anderson, D, Ali, K, Blanchette, V, Brouwers, M, Couban, S, Radmoor, P, Huebsch, L, Hume, H, McLeod, A, Meyer, R, Moltzan, C, Nahirniak, S, Nantel, S, Pineo, G, and Rock, G. Guidelines on the Use of Intravenous Immune Globulin for Hematologic Conditions. *Transfusion Medicine Review*, 2007, April;21 (2 Suppl 1):S9-56.
7. Siv, M. Role of Inflammation in Epilepsy and Treatment with IVIG. Intractable Childhood Epilepsy Alliance, May 17, 2010. Accessed at www.ice-epilepsy.org/role-of-inflammation-in-epilepsy-and-treatment-with-ivig.html.
8. Relapsing/Remitting Multiple Sclerosis. All About Multiple Sclerosis. Accessed at www.mult-sclerosis.org/relapsingremittingmultiplesclerosis.html.
9. IVIG for RRMS. Advocacy for Patients with Chronic Illness. Accessed at www.advocacyforpatients.org/pdf/ms/ms_ivig_summary.pdf.
10. About Sjögren's Syndrome. Sjögren's Syndrome Foundation. Accessed at www.sjogrens.org/home/about-sjogrens-syndrome.
11. Deane, K. IVIG for Sjögren's Neuropathy: Worth the Price? Medscape Today. Accessed at www.medscape.com/viewarticle/751384?src=smo_neuro.
12. Immunotherapy for Recurrent Pregnancy Loss. United Healthcare Policy # Maternity 018 15 T3. Accessed at www.oxhp.com/secure/policy/immunotherapy_for_recurrent_pregnancy_loss_111.html.
13. Intravenous Immunoglobulin (IVIG). The Asthma Center. Accessed at www.theasthmacenter.org/index.php/disease_information/sinusitis/medical_treatment_of_sinusitis/ivig_treatment/.
14. Haque, S, Boyce, N, Thien, FC, O'Hehir, RE, Douglass, J. Role of Intravenous Immunoglobulin in Severe Steroid-Dependent Asthma. *Internal Medicine Journal*, 2003 Aug;33(8):341-4.
15. Rauova, L, Rovensky, J, and Shoenfeld, Y. High Dose Intravenous Immunoglobulins: A New Step in the Treatment of Systemic Lupus Erythematosus. *Israel Medical Association Journal*, 2000;2:388-293.
16. Dauvilliers, Y, Arnulf, I, and Mignot, E. Narcolepsy with Cataplexy. *Lancet*, 2007 Feb 10;369(9560):499-511.
17. Knudsen, S, Mikkelsen, JD, Bang, B, Gammeltoft, S, and Jennum PJ. Intravenous Immunoglobulin Treatment and Screening for Hypocretin Neuron-Specific Autoantibodies in Recent Onset Childhood Narcolepsy with Cataplexy. *Neuropediatrics*, 2010 Oct;41(5):217-22. Epub 2011 Jan 5.
18. Plazzi, G, Poli, F, Franceschini, C, Parmeggiani, A, Pirazzoli, P, Bernardi, F, Mignot, E, Cicognani, A, and Montagna, P. Intravenous High-Dose Immunoglobulin Treatment in Recent Onset Childhood Narcolepsy with Cataplexy. *Journal of Neurology*, 2008 Oct;255(10):1549-54. Epub 2008 Sep 3.
19. Alzheimer's Association. What Is Alzheimer's. Accessed at www.alz.org/alzheimers_disease_what_is_alzheimers.asp.
20. Hill, C. What Causes Alzheimer's Disease? About.com. Accessed at alzheimers.about.com/od/whatisalzheimer1/a/causes.htm.Alz.
21. Alzheimer's Research Forum. Drugs in Clinical Trials: Intravenous Immunoglobulin. Accessed at www.alzforum.org/dis/tre/drc/detail.asp?id=114.
22. Alzheimer's Disease Cooperative Study. The Gammaglobulin Alzheimer's Partnership Study: Intravenous Immune Globulin (IVIG) Study. Accessed at www.adcs.org/studies/IGIV.aspx.

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Individual IG Dosing

By Ronale Tucker Rhodes, MS, and Kris McFalls

Studies that examine the relationships between therapeutic doses of IG, trough IgG levels and infection rates shed new light on how IG replacement therapy should be prescribed for individuals.

Immune globulin (IG) replacement therapy is the standard treatment for primary immune deficiency disease (PIDD), either via intravenous (IV) or subcutaneous (SC) routes. Yet, even with IVIG and SCIG treatments, patients continue to suffer acute breakthrough and chronic infections. This is because IG treatment is not a standardized treatment. And, because dosing strategies are unique to each patient, there is sometimes confusion about what is the optimal dosing strategy.

Strategies

A History of Dosing Regimens

In the U.S., there is no one national guideline for IG dosing, as there is in the United Kingdom and Australia, for example. However, there are several different published IG dosing guidelines that recommend satisfactory IgG trough levels for patients, yet all of them differ somewhat. And, there is the U.S. Food and Drug Administration's minimal criterion for efficacy, which states that the IG treatment should achieve less than one serious infection per patient per year. Most of the published guidelines regarding IgG trough levels recommend patients achieve a level of around 600 to 800 mg/dL with a dose of 400 mg/kg of IG every three to four weeks. The problem, then, says Dr. Melvin Berger, a specialist in allergy and immunology and pediatric medicine in Cleveland, Ohio, and the senior medical director of clinical research and development at CSL Behring, is that some patients may need a biological trough level of only 600 to achieve less than one serious infection per year, whereas other patients may need a trough level of 900 to attain the same measure of health. Therefore, it has been questioned whether treatment protocols that use IgG trough levels as a determinant of the IG dose patients receive during therapy are most effective for reducing infections.

According to Dr. Berger, there have been about 10 studies over the years that have looked at IG dose and effect, comparing lower and higher doses in PIDD patients. All those studies except one, he says, have found that the higher dose was more effective in lowering the incidence of infection. Additionally, several recent studies have shown that while general dosing guidelines are a great starting place, each patient needs individualized dosing to prevent infections.

Study: Lucas et al. (2010), Oxford University

An extensive study published in the *Journal of Allergy and Clinical Immunology* by a group led by Dr. Helen Chapel at Oxford University in the United Kingdom examined the relationships among therapeutic IG doses, trough serum IgG levels and infection rates over 22 years in a single clinic. Its objective was to provide data to support the hypothesis that each patient requires an individualized IG dose to prevent breakthrough infections, rather than to achieve a serum IgG trough level.

The study followed the practice in Dr. Chapel's clinic to adjust IG doses in real time in accordance with infection episodes, rather than to achieve a particular trough IgG level. Patients without chronic lung disease were started with initial doses of 0.4 g/kg per month of IG, and patients with bronchiectasis were treated with initial doses of 0.6 g/kg per month. Those doses were then adjusted in line with breakthrough infections. If there were no serious breakthrough infections, those patients with a rate of three moderate bacterial infections per year got an increase in IG dosage of around 0.15 g/kg per month, usually given as SCIG or IVIG every two weeks.

Ninety patients with confirmed common variable immune deficiency (CVID) and 15 with X-linked agammaglobulinemia (XLA) were included in the study. (The group of XLA patients was analyzed in this study for comparison.) To participate, CVID patients were selected if they had a serum IgG level <6.0 g/L (600 mg/dl) and either a serum IgA level of <0.8 g/L or a serum IgM level of <0.5 g/L or both; if they were over 4 years

of age at diagnosis; and if there were no other conditions or therapies associated with antibody failure. Patients were excluded if there was less than 12 months of data or noncompliance with therapy or monitoring. The same exclusion criteria were used for XLA patients for comparison purposes.

To collect the data, the Oxford PID Database was created in which demographic and infection data correlating to IG therapy were logged. The specific information logged included data on infections (infection site, pathogen type and treatment details), administration route of IG, IG dose in grams per kilogram per month, and clinical complications. Baseline data were entered from patient notes at the start of IG therapy or on referral to Oxford for patients previously diagnosed.

Additional data on treatment and response were collected over a follow-up period of 22 years, and then validated and analyzed. The entry point for each patient into the analysis was the point at which the serum IgG level was stable (defined as ≤1.5 g/L variation from the mean trough IgG over at least four months). Data were analyzed for IgG, IgA and IgM levels against time for each patient, commencement of replacement therapy and dose changes. In addition, the analysis allowed for seasonal variations in infections. And, confirmation of bacterial infection was made using radiologic/laboratory/microbiological findings and responses to antibiotics.

It has been questioned whether treatment protocols that use IgG trough levels as a determinant of the IG dose patients receive during therapy are most effective for reducing infections.

Results of treatment with therapeutic IG doses adjusted in accordance with infection data rather than to achieve a particular trough IgG level showed that overall bacterial infection frequency was low (2.16 infections per patient-year), and the incidence of serious infection was particularly low. And, in any period, the mean trough IgG level correlated strongly with the replacement dose of IG, but there was a weak relationship between infection score per patient-period and mean trough IgG.

According to the study's authors: "This study provides evidence to support the clinical view that the trough IgG and dose of replacement therapy to maintain minimal infectious burden is unique to the individual." They conclude by stating: "The goal of replacement therapy should be to improve clinical outcome and not to reach a particular IgG trough level."

Meta-Analysis of SCIG: Dr. Berger (2011)

Dr. Berger substantiates the Oxford study's conclusions with his meta-analysis that summarizes seven studies conducted on SCIG. The analysis, which was published as a letter to the editor in the *Journal of Clinical Immunology*, notes that having a consensus targeted trough level is complicated, in part because of the differences in pharmacokinetics of SCIG versus IVIG therapy. Consensus is further complicated by the different regulatory authorities of individual countries and the different practices of different physicians.

The seven studies utilized four different SCIG preparations from three different manufacturers. In total, the reports include data from 322 SCIG patients who were treated in multiple settings and who received treatments on a weekly basis. Trough levels were reported after 12 to 16 weeks of SCIG therapy. All studies defined serious bacterial infections (SBIs) according to published FDA guidance. Non-serious infections other than SBIs such as sinus or upper-respiratory infections with fever were defined by the treating physician. Mean trough levels in the different studies were reported to be between 810 and 1250 mg/dl (8.1 to 12.5 g/l).

A total of seven SBIs were reported in four of the seven studies, all of which were pneumonias. The remaining three studies reported no SBIs. Studies with a higher mean trough level did not demonstrate a lower incidence of SBIs. Therefore, no linear correlation could be made between the annualized incidents of SBI and the mean steady trough levels of the different studies. In contrast, however, the incidence of non-serious infections showed that a decrease in the number of infections correlated significantly with a higher steady-state serum IG level, and there did not appear to be a plateau above which higher IgG levels did not correlate with lower incidence of infection.

Dr. Berger concluded: "For any individual patient, factors other than the IgG dose and resulting serum IgG level unquestionably contribute to the type and the frequency of infections which may occur. Therefore, treatment regimens, doses, and target serum IgG levels should be individualized to optimize treatment effects and costs for individual patients."

Meta-Analysis of IVIG: Dr. Orange (2010)

Although pharmacokinetics of SCIG and IVIG are not similar, the belief that higher serum IgG levels correlate with lower infection rates also was shown to be true in a meta-analysis published in *Clinical Immunology* that evaluated the incidence of pneumonia with varying doses of IVIG.

Conducted by Dr. Jordan S. Orange, a pediatric immunologist at Children's Hospital of Philadelphia and consultant to Baxter Healthcare, Talecris Biotherapeutics (now Grifols) and CSL Behring, and colleagues, this was the first meta-analysis to enumerate the relationship between IgG trough levels and pneumonia in PIDD patients treated with IVIG.

As previously discussed, serum trough IgG levels of PIDD patients historically have been used as a guide to determine appropriate levels of IVIG therapy. However, a sufficient trough level to prevent SBIs has not been established. And, while many immunologists have considered 500 mg/dL a minimum target trough level, the level of benefit gained above 500 has been debated.

Pneumonia was chosen for this meta-analysis because it is one of the most frequent manifestations of PIDD that can result in hospitalization and require the use of intravenous antibiotics. Additionally, it is one of the primary validated SBIs used to determine efficacy of IG therapy.

A total of 17 clinical studies reported from 1982 to 2009 comprising 676 total patients and 2,127 patient-years of follow-up were included in the meta-analysis. Of the total studies conducted in the United States, Canada, Europe, the Middle East and Argentina, 11 were prospective and six were retrospective. All the studies included PIDD patients predominately diagnosed with CVID and XLA. However, no patients with subclass deficiency were enrolled in 14 of the 17 studies. Other PIDD diagnoses such as hyper-IgM, hypogammaglobulinemia and ataxia telangiectasia also were included.

Incidence rates of pneumonia were analyzed at serum trough levels of 500, 600, 700, 800 and 1,000 mg/dL (10 g/l), and at doses of 100, 200, 300, 400, 500 and 600 mg/kg. The median IVIG treatment interval between doses was 24.6 days. Results were highly statistically significant and showed that pneumonia incidence declined by 27 percent with each 100 mg/dL (1 g/l) trough increment.

Dr. Jordan and colleagues concluded that "PIDD patients receiving IVIG therapy and experiencing pneumonia are likely to be helped by increasing the IgG trough levels to at least the mid-normal range of IgG," which they defined as up to at least 1,000 mg/dL. No apparent plateau in efficacy was observed. However, they stated additional research "is needed to determine whether a general threshold trough of optimal protection against pneumonia may exist above 1,000 mg/dL."

Meta-Analysis of Transitioning from IVIG to SCIG: Dr. Berger (2011)

To further evaluate the use of IgG trough levels to determine the rate of IG dosing in patients with PIDDs, Dr. Berger conducted a meta-analysis that looked at optimal dosing adjustments when switching from IVIG to SCIG. Currently,

according to Dr. Berger, "The optimum dosing strategy when switching patients from IVIG to SCIG replacement therapy has not been established. The [FDA] requires that the weekly SCIG dose should result in a total systemic serum IgG exposure (area under the curve of serum IgG level versus time [AUC]) non-inferior to that of previous IVIG treatment." However, he points out: "The use of this PK (pharmacokinetic) endpoint to correlate with clinical outcomes has not been established in practice."

The meta-analysis explored the relationships between IVIG dose, SCIG dose, serum IgG levels and AUCs of two different PK substudies of two different SCIG products prepared using different manufacturing processes. These included studies of a 16% SCIG product (Vivaglobin, CSL Behring) conducted in the U.S. and Europe/Brazil, and a licensing study of a 20% SCIG product (Hizentra, CSL Behring) conducted in the U.S. The two U.S. PK studies assessed the AUC of IgG versus time and the ratio of IgG trough levels of SCIG versus IVIG.

Forty-two subjects participated in the U.S. studies, with 17 completing all the required assessments in the U.S. 16% study and 18 completing them in the U.S. 20% study. For all subjects, the mean IVIG dose was significantly higher in the U.S. 20% study compared with the U.S. 16% study. And, in both studies, each subject's IVIG starting dose was that which was already prescribed by that subject's physician.

Trough IgG levels were initially recorded during three cycles of routine IVIG infusions, which were administered according to each subject's pre-enrollment regimen. A fourth IV infusion was followed by frequent blood sampling to calculate the AUC.

Another routine scheduled IVIG infusion was administered, and within seven to 10 days, SCIG administration was initiated at a weekly dose calculated to provide 120 percent of the previous monthly IVIG dose in the 20% study and 130 percent of the previous IVIG dose in the 20% study. After 12 weeks of SCIG at that dose, blood was sampled every two days for two weeks to calculate the AUC on SCIG as compared with the weekly equivalent previously measured while the subject was on IVIG. The SCIG doses were then individually adjusted to achieve AUCs equal to those on IVIG, and subjects continued to receive this adjusted SCIG dose for another 12 weeks, at which time AUCs were determined again to test for non-inferiority of the AUC on SCIG versus the AUC on IVIG.

Results showed that mean cumulative monthly doses of SCIG corresponding to 137 percent and 153 percent of the previous monthly doses of IVIG resulted in AUCs on SCIG very similar to those achieved with IVIG. Thus, the AUCs achieved in both studies met the FDA's preset criterion for non-inferiority. However, there was considerable variability among the individual dose adjustments and in the resulting ratios of the steady state serum IgG level on SCIG compared with the trough level on IVIG (termed the trough level ratio [TLR]) in subjects. This suggests that achieving the mean TLR doesn't necessarily provide satisfactory assurance that any given patient is receiving an optimal dose of IgG after switching from IVIG to SCIG.

These findings provide evidence-based guidelines from which treatment protocols can be developed that will result in a higher quality of life for a large portion of PIDD patients.

Dr. Berger concludes, then, that "the mean dose adjustment coefficient and the mean TLR should only be used as rough guides, and each patient's optimal IgG level and the dose necessary to maintain that level should be determined individually." Additionally, he suggests that "the ultimate determination of the target IgG level should be determined by the individual patient's clinical response and that pharmacokinetic parameters be used only to assist the clinician in achieving the necessary serum IgG levels."

From Paper to Practice?

What do these research findings mean for PIDD patients being treated with IG? Is it possible that they could result in a national guideline for IG dosing in the U.S. such as those guidelines in effect in Australia and the U.K.? Dr. Berger doesn't see a need for a national guideline. "I don't know what role published guidelines actually play," he says. "There's no obligation for a doctor to follow a published guideline. In general, the idea of a guideline is just a suggestion of where to start. It's not an end unto itself. I think most doctors probably recognize that."

What these findings do provide is evidence-based guidelines from which treatment protocols can be developed that will result in a higher quality of life for a large portion of PIDD patients. For instance, Dr. Berger says, "What is the goal of therapy? To keep the patient barely alive or to produce a normal citizen who can go to school or work?" The goal, he says, is the latter and that can be achieved only by reducing the number of infections. So, since these studies show that higher doses of IG will produce higher IgG levels and lower rates of infection, there are two take-home messages: 1) higher doses lead to lower morbidity due to infection, and 2) there's no threshold value. And, he says, this information needs to be incorporated into the currently available guidelines.

However, change will not happen overnight. A change like this requires a paradigm shift from the way things have been done for decades. Even within the field of immunology, there will be doctors who want to see more evidence. At the end of the day, though, doctors prefer to treat patients, not numbers. And, this type of research encourages them to do just that. ❖

RONALE TUCKER RHODES, MS, *is the editor of* IG Living *magazine, and* **KRIS MCFALLS** *is* IG Living*'s full-time patient advocate.*

Editor's Note: This article is a summary of four published studies: 1) Lucas, M, Lee, M, Lortan, J, Lopez-Granados, E, Misbah, S, Chapel, H. Infection Outcomes in Patients with Common Variable Immunodeficiency Disorders: Relationship to Immunoglobulin Therapy Over 22 Years, Journal of Allergy and Clinical Immunology, *Vol.125, No.6:pp1354-1359. More detailed information about this study can be obtained online at www.jacionline.org/issues. 2) Berger, M. Incidence of Infection Is Inversely Related to Steady-State (Trough) Serum IgG Level in Studies of Subcutaneous IgG in PIDD,* Journal of Clinical Immunology, *June 4, 2011. 3) Orange, JS, Grossman, WJ, Navickis, RJ, Wilkes, MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies,* Clinical Immunology, *2010 Oct;137(1):21-30. Epub 2010 Aug 1. 4) Berger, M, Rojavin, M, Kiessling, P, and Zenker, O. Pharmacokinetics of Subcutaneous Immunoglobulin and Their Use in Dosing of Replacement Therapy in Patients with Primary Immunodeficiencies.* Clinical Immunology, *Jan. 23, 2011.*

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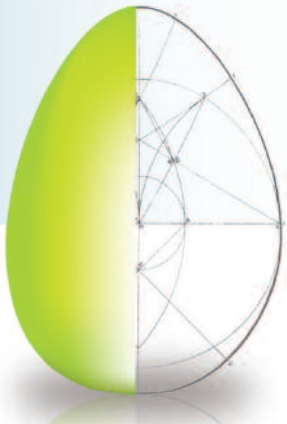

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Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Also monitor patients with risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.

Patients could experience increased serum viscosity, hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion). There have been reports of IVIg-related hemolysis, hemolytic anemia, and pulmonary adverse events, including transfusion-related acute lung injury (TRALI). Avoid high-dose regimen where fluid volume is of concern.

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

In clinical studies of patients being treated with Privigen for chronic ITP, the most serious adverse reactions were AMS (one subject) and hemolysis (eight subjects). Adverse reactions seen in >5% of subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, increases in conjugated and unconjugated bilirubin, hyperbilirubinemia, and increased blood lactate dehydrogenase.

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing.

Please see brief summary of full prescribing information on following pages.

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
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CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

- **Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.[1] Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (*see* *Warnings and Precautions [5.2]*). Privigen does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (*see* *Dosage and Administration [2.3]*, *Warnings and Precautions [5.2]*).**

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (*see Warnings and Precautions [5.1]*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (*see Contraindications [4]*). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA (≤25 mcg/mL) (*see Description [11]*). Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IGIV products, including Privigen. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable (*see Boxed Warning*, *Dosage and Administration [2.3]*).

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.[2]

5.4 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.[3-5] Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and/or known/suspected hyperviscosity.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable (*see Dosage and Administration [2.3]*).

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen (*see Adverse Reactions [6]*) and other human immune globulin products. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae.[6] AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis.[7-9] Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[10]

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (*see Adverse Reactions [6]*). These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after a Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen.[11] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

The high-dose regimen (1 g/kg/day for 2 days) used to treat patients with chronic ITP is not recommended for individuals with expanded fluid volumes or where fluid volume may be of concern (*see Dosage and Administration [2.2]*).

5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen.

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.10 Interference with Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in >5% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

6.1 Clinical Trials Experience

Because different clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen every 3 or 4 weeks for up to 12 months (*see Clinical Studies [14.1]*). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during an infusion or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2: PI Pivotal Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, *Irrespective of Causality*

Adverse Event (Excluding Infections)	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Event [n=1038]
Headache	35 (43.8)	82 (0.079)
Pain	20 (25.0)	44 (0.042)
Fatigue	13 (16.3)	27 (0.026)
Nausea	10 (12.5)	19 (0.018)
Chills	9 (11.3)	15 (0.014)
Vomiting	7 (8.8)	13 (0.013)
Pyrexia	6 (7.5)	10 (0.010)
Cough	5 (6.3)	5 (0.005)
Diarrhea	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privigen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Reaction [n=1038]
Headache	24 (30.0)	62 (0.060)
Pain, all types*	12 (15.0)†	26 (0.025)
Nausea	10 (12.5)	18 (0.017)
Fatigue	9 (11.3)	16 (0.015)
Chills	9 (11.3)	15 (0.014)
Vomiting	6 (7.5)	11 (0.011)

* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain, pain in extremity, and pharyngolaryngeal pain.

† Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative DAT at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (*see Dosing and Administration [2.3]*). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporally associated with one or more AEs occurring during a Privigen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, *irrespective of causality*, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privigen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/L or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle, *Irrespective of Causality (Two consecutive daily infusions)*

Adverse Event	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Event [n=114]
Headache	37 (64.9)	41 (0.360)
Pyrexia/hyperthermia	21 (36.8)	22 (0.193)
Nausea	6 (10.5)	6 (0.053)
Epistaxis	6 (10.5)	6 (0.053)
Vomiting	6 (10.5)	6 (0.053)
Blood unconjugated bilirubin increased	6 (10.5)	6 (0.053)
Blood conjugated bilirubin increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	4 (7.0)	4 (0.035)
Hematocrit decreased	3 (5.3)	3 (0.026)

Table 7: Chronic ITP Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Reaction [n=114]
Headache	37 (64.9)	52 (0.456)
Pyrexia/hyperthermia	19 (33.3)	21 (0.184)
Positive DAT	6 (10.5)	7 (0.061)
Anemia	6 (10.5)	6 (0.053)
Vomiting	5 (8.8)	6 (0.053)
Nausea	5 (8.8)	7 (0.061)
Bilirubin conjugated, increased	5 (8.8)	5 (0.044)
Bilirubin unconjugated, increased	5 (8.8)	5 (0.044)
Hyperbilirubinemia	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)

Of the 149 non-serious AEs related to Privigen, 103 were mild, 37 were moderate, and 9 were severe.

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding that was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.[12]

- **Infusion Reactions:** Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive DAT (Coombs' test)
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

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Immune Globulin Reimbursement

By Kris McFalls and Trudie Mitschang

A high-cost therapy coupled with a complex and evolving reimbursement model has created what some are calling a healthcare crisis for tens of thousands of chronically ill patients.

Immune globulin (IG) is a life-enhancing and life-sustaining product for tens of thousands of chronically ill patients in the U.S. It contains antibodies that protect individuals from a broad spectrum of bacteria and viruses, and it is prescribed primarily to treat three categories of illness: primary immunodeficiencies, autoimmune neuromuscular disorders and certain rheumatological conditions. Although IG is most commonly delivered through a needle placed into the vein,

known as intravenous IG (IVIG), some IG products also can be administered under the skin, known as subcutaneous IG (SCIG).

Because IG is an especially high-cost drug therapy, the issue of reimbursement for IG treatment is always front-of-mind for patients and their prescribing physicians. One of the reasons IG is so costly is that its manufacturing process tends to be both lengthy and complex. Immune globulin is made from pooled plasma taken from literally thousands of donors. Its procurement, testing and fractionation protocols designed to produce a product that is safe and contaminant-free, coupled with current reimbursement models, create the perfect storm in terms of access and cost issues. A closer look reveals that some reimbursement policies, including prior authorizations, fail-first requirements and specialty tiers, can create barriers to care.

Prior Authorizations Are Not Universal

Doctors who prescribe IG for their patients are keenly aware of reimbursement issues that commonly arise. Likewise, payers are attentive to the high cost and growing number of indications, both on and off label, for which IG is used. Over time, most if not all payers have developed medical policies regulating coverage for the use of IG. Frequently, problems and confusion arise because coverage criteria and forms for accessing care are unique to the payer, rather than being standardized for the physicians who must comply with them. Additionally, reasons for denial are often very generic and, in general, do not clearly detail what is needed to access care.

For such an expensive treatment as IG, most payers utilize medical management and require a preauthorization request be submitted before therapy can begin. Payers are happy to provide preauthorization forms to fill out, but those forms are not always accompanied with the medical policies that physicians must follow to attain authorizations, making this process especially confusing and time-consuming for physicians and their office staff. "I have the equivalent of one full-time [employee] just dedicated to IVIG approvals," says Todd Levine, MD, clinical assistant professor, University of Arizona, and co-director of Samaritan Neuropathy Center, Phoenix Neurological Associates. "In addition, the review process tends to be arbitrary. With the same insurance company, there can be very different decisions with no clear reasoning. It takes a lot of my time to educate medical directors to make them understand why I am prescribing IVIG."

Currently, prior authorization requests must be submitted with a letter of justification, office notes and lab reports substantiating the diagnosis and a treatment plan. In addition, reauthorization requests must show office notes detailing the progress made and, if applicable, indicate attempts have been made to reduce the dose or increase the interval between treatments.

Further complicating the paper trail, payer denials tend to be generic statements that do not fully explain the denial. Reasons most commonly given for denial are that the prescribed treatments are investigational, experimental or not medically necessary. These denial terms usually mean one of two things: 1) the reason for treatment in the authorization is not eligible for coverage under the insured's plan, or 2) the payer was not given enough information to substantiate the authorization request.

"The approval process could be streamlined by finding a way to let experts take more control of the field, make decisions more transparent, or by forming better relationships between experts and insurance companies in designing criteria and making decisions," says Jon Katz, MD, director, Neuromuscular Clinic, Forbes Norris Center, San Francisco, Calif.

Whether an authorization request is for an indication that is FDA approved or considered off label but a proven use, it still can be denied as not medically necessary.

Experimental or Investigational

Figuring out upfront what treatments a payer covers used to be mostly guesswork. Thankfully, most payers now clearly list online the diagnoses they will and will not pay for. If the diagnosis is not covered, the reason for denial of authorization will most likely be given as experimental or investigational. Providers confronted with an authorization request deemed experimental or investigational should double-check their request for clerical mistakes. If an incorrect or ambiguous code such as "immune deficiency not otherwise specified" was used on the authorization request, it can be quickly corrected.

On the other hand, if the code is correct and the plan simply does not cover the diagnosis, further research may help reverse the coverage decision. To strengthen an appeal, it is important to include peer-reviewed materials that support the recommended treatment.

Not Medically Necessary

Even if an authorization request is for an indication that is FDA approved, or considered off label but a proven use, it still

can be denied as not medically necessary. Unfortunately, such a generic term does not provide the patient or the physician with the details needed to effectively craft an appeal.

The term "not medically necessary" generally means the information submitted is incomplete, does not meet all the diagnostic criteria listed in the policy, and/or the patient has not yet failed other treatments that are considered the least-costly alternative. While some payers are beginning to give more written detailed information regarding denials, many still do not.[1] "In my opinion, payers should have to explain the reason for denial in medical language," says Katz. "Form letters are not reasonable; the denial should prompt a transparent peer review."

Payers routinely require physicians to provide documentation demonstrating that a particular diagnosis is accurate and/or the treatment requested is medically necessary. Payers also are clear that office notes or letters detailing the condition without supporting test results do not constitute medical necessity. Consider, for example, an authorization for a patient diagnosed with multifocal motor neuropathy (MMN) that includes a doctor's note that reiterates abnormal electrodiagnostic studies and high-titer serum IgM anti-GM1 antibody levels, but does not include copies of the reports for all findings in the authorization request. The result is the payer denies the request as not medically necessary, but fails to inform the doctor that the missing test results were the basis for the denial. The doctor is then left spending more valuable (and unreimbursable) time first trying to figure out why the authorization was denied and then providing the missing documentation in an appeal. Meanwhile, the patient's treatment is delayed, perhaps limiting the chances for a good recovery.

As another example, Medicare recently changed its policy regarding SCIG to only reimburse claims in which the provider has used the Freedom 60 infusion pump. If a provider bills for any other pump, the entire claim will be denied as medically unnecessary because the least-costly infusion pump was not used. Illogically, even though the treatment was medically necessary, the entire claim is rejected as not medically necessary.[2]

Fail-First Policy

Payers also often insist on step therapy or fail-first policies for certain diagnoses before IG will be authorized. This is especially common for off-label indications. As an example, a fail-first policy might come into play with the indication of dermatomyositis. Most payer policies require patients with this disorder to first fail corticosteroid therapy before IG therapy is approved. Failure can be due to a patient being either refractory to corticosteroids or to corticosteroids causing detrimental side effects. In either case, the use of IG becomes a second line of therapy. Disregarding fail-first policies also will result in denials citing reasons of medical necessity.

Payers also often insist on the use of step therapy or fail-first policies for certain diagnoses before IG can be used.

When appealing a denial based on medical necessity, physicians and/or patients should first request a copy of the medical policy detailing what parameters the payer uses to determine diagnostic criteria; if there is a fail-first policy; and what, if any,

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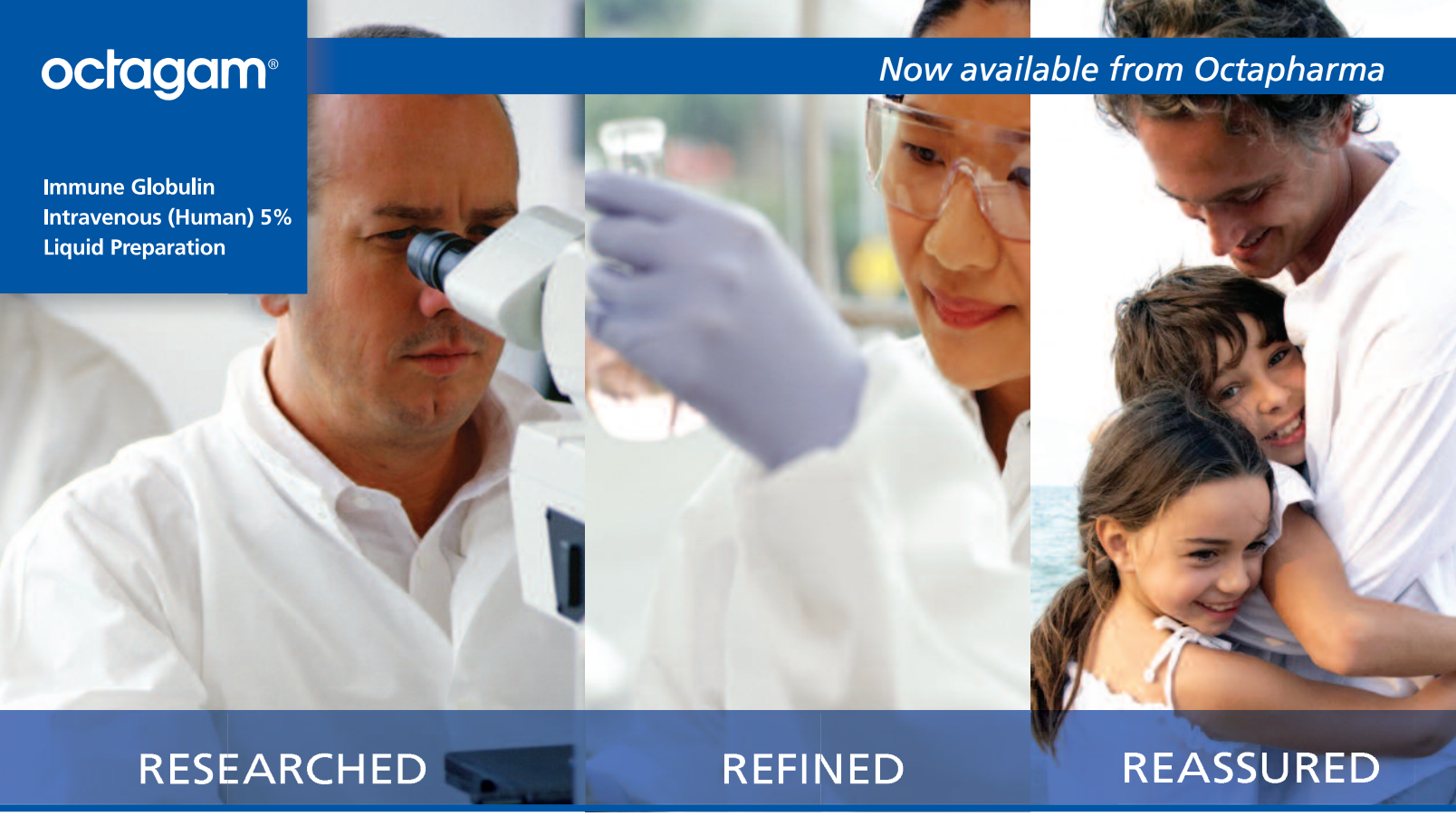

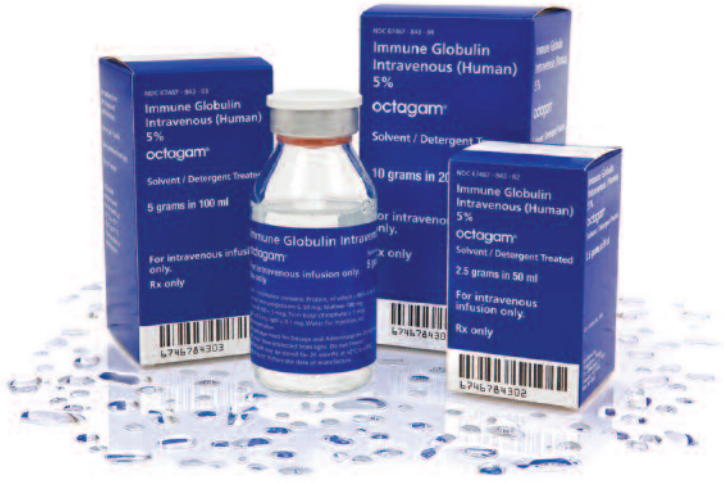

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formulary there is regarding choice of product. Often, the quickest way to get specific information is for the treating physician to speak directly with the payer's medical director. While on the phone, it is likely that the treating physician will be offered a chance to appeal without resubmitting documentation or to submit only the missing documentation. This approach may appear to expedite resolution, but to avoid a second denial, it is advisable to resubmit the entire file with an appeal, while also supplying any missing documentation and any compelling reasons why the appeal should be considered. Keeping detailed notes of conversations with medical directors and others assigned to the claim is also suggested.

Specialty Tiers

The recent introduction of specialty tiers that increase the beneficiary's share of the costs has had detrimental effects on IG patient outcomes. Specialty tiers require the patient pay a certain percentage of the cost of their medication rather than a fixed copayment and often do not have a maximum out-of-pocket limit. The out-of-pocket expenses are becoming prohibitive.

Specialty tiers coupled with lower reimbursement rates and falling profit margins force healthcare providers into a particularly precarious position. Doctors treating immune-mediated diseases with IG have few if any other treatment options. At the same time, healthcare providers simply cannot absorb all of the risk plus the extra costs and still stay in business. For these reasons, some providers support legislation that will mitigate the out-of-pocket liabilities to patients. "The concern [about] specialty tiers is [that] it [is] shifting more of the financial burden onto patients," says Dr. Levine. "I have many patients who cannot get IVIG because of their high deductible. Specialty tiers will only make this worse, and more and more patients won't get the best therapy available simply based on cost."

Dr. Katz agrees: "It seems ridiculous to put this on patients. The drug is so expensive that the insurers and doctors should be the ones who ensure that therapy is rational. The goal is to create appropriate checks and balances. The patients need to understand that the issues here are not black and white, but they should not have to pay large amounts for appropriate ordering."

A Crisis of Care

In 2003, the Medicare Modernization Act altered the formula by which the Centers for Medicare and Medicaid Services (CMS) reimburses physicians and hospitals for administering drugs from an average wholesale price (AWP) model to one based an average sales price (ASP). While this ASP model was originally intended to apply to Medicare reimbursement, it has since expanded to include the physician office setting and the hospital outpatient setting under Medicare Part B. How has this impacted IVIG therapy? A lowered payment rate in all sites of care is preventing many providers from purchasing IVIG since the costs exceed reimbursement payments. This conflict is causing what some are calling an "IVIG crisis," with many patients being denied access to IVIG or receiving a reduction in product or frequency of treatment. Depending on the diagnosis, this crisis could put patients' lives at risk.[3]

A Complex Problem with No Easy Solutions

The diseases treated by IG are rare and often misunderstood. As a complicating factor, the reimbursement issues surrounding this miraculous treatment are often complex and equally misunderstood. What is clear is that a cookie-cutter approach to reimbursement does not serve the interests of the patient or the provider.

How IG is reimbursed under a payer's plan can have a direct effect on patient outcomes.

While there is no quick fix, it seems evident that all stakeholders, including payers, providers and patient advocacy groups, will need to work together to identify solutions that will ultimately prioritize patient health and welfare and put prescribing physicians back in the driver's seat when it comes to treatment recommendations. "The best process would be to have one universally accepted criteria for who will and will not get IG therapy," suggests Dr. Levine. "In a perfect world, there also should be a standard process for reauthorization once a patient has been on IG therapy for three to six months. This would help prescribing physicians maintain continuity of care and avoid putting patients at risk." ❖

KRIS MCFALLS *and* **TRUDIE MITSCHANG** *are staff writers for* BioSupply Trends Quarterly *magazine. Kris also is the patient advocate for* IG Living *magazine.*

References

1. Health Insurance Online. Claim Denials on the Grounds that a Treatment Is Not Medically Necessary. Accessed at www.online-health-insurance.com/health-insurance-resources/part2/page79.php.
2. DME website article template document number: TMP-EDO-0049 Release Date: 07/06/2010 Version: 1.0.
3. The Alliance for BioTherapeutics. Summary of the IVIG Crisis. Accessed at www.bioalliance.org/IVIGCrisis.html.

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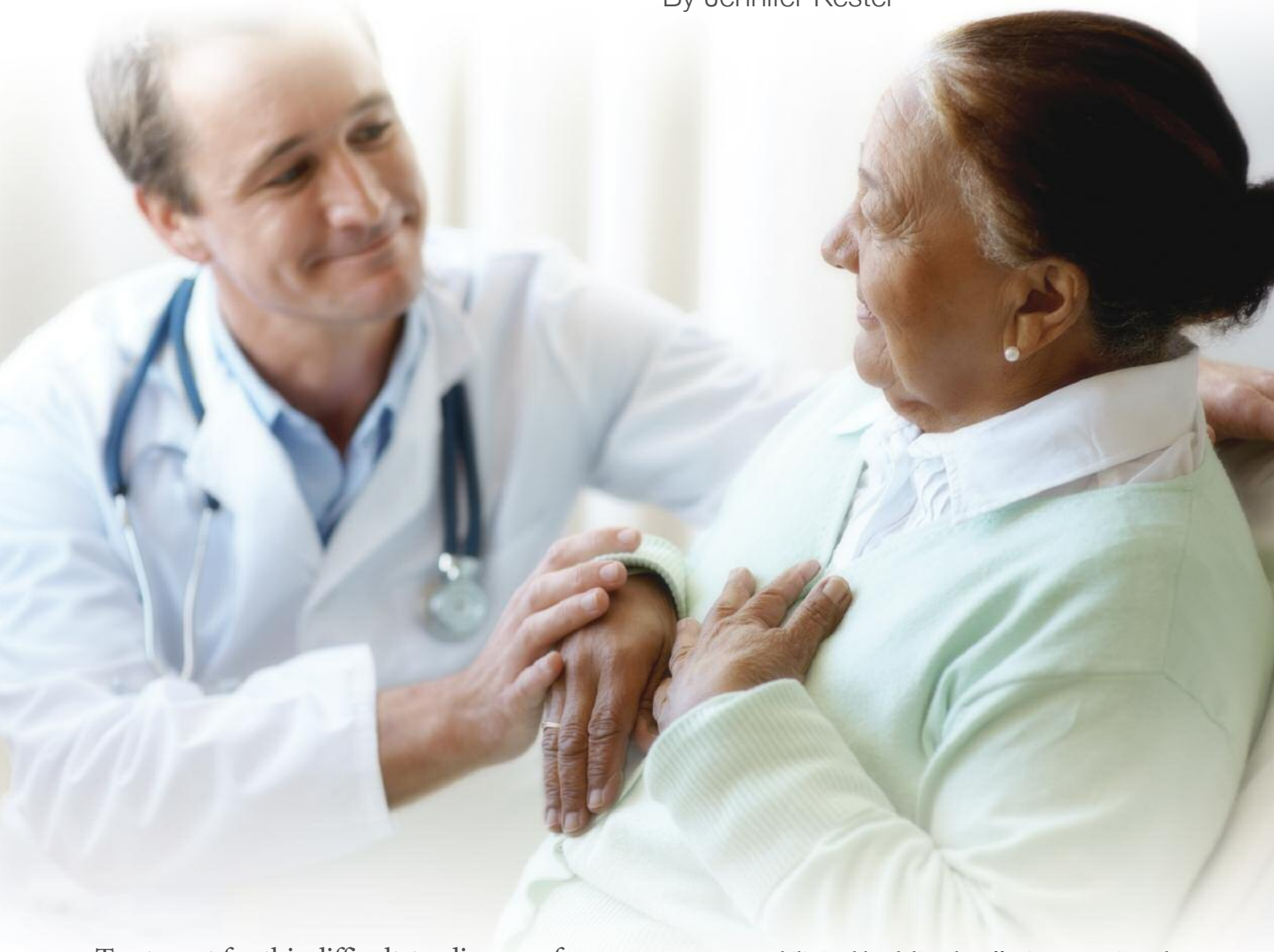
The State of Acquired Hemophilia

By Jennifer Kester



Treatment for this difficult-to-diagnose form of hemophilia has to be individualized for each patient, but the prognosis is often good.

Hemophilia is a blood disorder affecting approximately 20,000 males in the United States, with positive tests for approximately one in every 5,000 births, according to the National Hemophilia Foundation. Hemophilia A, typified by a drop in clotting factor VIII, and its rarer cousin, hemophilia B, marked by a deficiency of clotting factor IX, are relatively straightforward to diagnose. These forms of hemophilia are passed down genetically and often are discovered in the first weeks after birth.

In recent years, however, researchers and clinicians have begun to fill in the gaps of knowledge about acquired hemophilia (AH). This type of hemophilia is both far more rare and far more difficult to diagnose since it presents with a different set of symptoms than hemophilia A and B. It typically affects older patients suffering from other disorders, and it occurs in patients without a family history of immunological syndromes. Given the mortality rate of those affected by AH, which ranges between 7 percent and 21 percent, as well as the importance for clinicians to work quickly to relieve its associated bleeding, it is imperative that medical practitioners be able to diagnose AH when symptoms arise and understand the range of therapies available for its treatment.

What Is AH?

AH is a rare blood disorder marked by sudden bleeding in patients without a previous personal or family history of hemophilia. Incidences of acquired hemophilia are believed to occur in up to one case per million persons per year. However, it's likely that available statistics underestimate the true figure, given that AH can be difficult to diagnose and many cases of AH remain uncounted unless discovered during surgery or testing for other disorders.[1]

Almost all known cases of AH are characterized by autoantibodies that either disrupt the functioning of coagulation factor VIII or that clear this clotting factor from the plasma, which results in unpreventable bleeding in AH patients.[2] Approximately half of AH incidences have been linked to a wide variety of underlying medical conditions, such as collagen, vascular and other autoimmune diseases (different studies put the percentage of cases between 16.7 percent and 18 percent); lymphoproliferative malignancies or solid tumors (between 6.7 percent and 14.7 percent of cases); skin diseases (between 3.3 percent and 4.5 percent of cases); possible drug reactions (between 2.0 percent and 4.5 percent of cases); and pregnancy (between 2.0 percent and 11 percent of cases).[3] Other reported factors for AH include diabetes, respiratory diseases such as asthma, acute hepatitis B infection and acute hepatitis C infection.

A 2007 study cited by Medscape suggests that in up to 63.3 percent of cases reported, the occurrence of AH remains without an identifiable source. However, because the occurrence may be a result of adverse drug reactions in patients taking several such medications, the figure for this reported factor might be artificially low. According to the World Federation of Hemophilia, pharmaceuticals implicated in the acquisition of AH include antibiotics such as a penicillin, sulphonamides and ciprofloxacin; immunological drugs such as interferon and fludarabine; psychotropics such as phenytoin, flupentixol and zuclopenthixol; as well as the antiplatelet agent clopidogrel. And, since this list is not exhaustive, clinicians should look to other recently used medications as the source for AH in patients.

Data shows that there is a peak in incidence rates among patients between the ages of 20 and 30, and an even greater number of incidences occurring between 60 and 80 years old.[4] In the 20 to 30 age group, most patients are female, given AH's link to women going through their first pregnancies[5] and, by and large, they occur in the three months following delivery. However, deaths from AH have been reported more than one year postpartum.[4] There are no known genetic components to the disorder, and AH is reported across all racial groups.[1]

The prognosis for AH patients ranges from life-threatening losses of blood to mild or no-bleeding tendencies, although it should be emphasized that life-threatening bleeding occurs in 80 percent of patients.[6] And, according to a 2007 study in the *Journal of Thrombosis and Haemostasis*, most deaths from AH occur in the first weeks after the appearance of symptoms. Only in recent years have clinicians in the U.S. and Europe attempted to develop recommendations on best practices for responding to AH, and their task has been made difficult since the low numbers of patients involved preclude proper, statistically significant longitudinal studies.

AH is a rare blood disorder marked by sudden bleeding in patients without a previous personal or family history of hemophilia.

Diagnosing AH

Despite the common threat to the functioning of coagulation factor VIII, there are very different symptoms between AH and the hereditary form of hemophilia A.[7] Typical symptoms for hemophilia A include blood in the urine or stool, hemorrhaging in the gastrointestinal or urinary tracts, and swelling in the joints. For reasons still not clear, patients with AH display a different set of symptoms, including bleeding into the skin and musculature, haematemesis, haematuria, as well as longer-than-usual postpartum or postoperative bleeding.[6] Often, the condition is misdiagnosed as other types of acquired bleeding disorders, including disseminated intravascular coagulation.[7]

Commonly, AH patients exhibit an unexplainable and prolonged activated partial thromboplastin time (aPTT), which is an indicator for determining the efficiency of both

the contact activation pathway and common coagulation pathways.[2] For patients with any of the above symptoms, as well as a prolonged aPTT at less than 45 percent mean normal level, clinicians measure the levels of clotting factors VIII, IX, XI and XII, and a low level of clotting factor VIII alone is highly suggestive of the appearance in the blood of an inhibitor related to AH. Other indications of AH are normal prothrombin time assays, template bleeding times, and platelet and leukocyte levels. Tests for the presence of lupus anticoagulant or heparin are often conducted to rule out these factors in a patient's symptoms. The antibodies in acquired hemophilia directed toward clotting factor VIII are typically polyclonal IgG4 antibodies, although more rarely, they are of the IgM or IgA varieties.

The World Federation of Hemophilia suggests repeating tests after a few days if an inhibitor is not at first revealed. The Bethesda assay, used to measure residual clotting factor VIII after incubating the patient plasma with normal plasma for two hours at 37 degrees Celsius, may be used to determine the quantity of the inhibitor in the patient's plasma. Making diagnoses more difficult, clotting factor VIII may form a complex with other antibodies, which may create some residual clotting factor VIII activity and, thus, interfere with ascertaining AH's signature drop in factor VIII. The upshot for clinicians is that AH patients may still exhibit factor VIII baseline levels even as they have high-titer inhibitory antibodies.

A 2007 study cited by Medscape suggests that in up to 63.3 percent of cases reported, the occurrence of AH remains without an identifiable source.

Treatment Options

The first objective for the treatment of AH is to control the affected areas of bleeding, while the long-term objective is to remove the inhibitor causing the disorder in the first place. Due to bleeding complications, the World Federation of Hemophilia recommends patients receive care in specialist hemostasis units that have experience in treating the disorder and the requisite blood products for treatment, which must be specific to the needs of each patient. In the U.S., the federal government supports a network of hemophilia care centers. Experts on staff provide not just direct treatment, but also education and support for specialists and AH patients. The Centers for Disease Control and Prevention provides a list of more than 100 centers on its website.

For many patients, especially those cases appearing postpartum or due to drug-induced inhibitors, the AH inhibitors may disappear on their own, and these patients, therefore, require only initial care with follow-up for maintaining their blood supply after the original hemorrhaging. However, older patients with underlying malignancies and other autoimmune disorders experience cases of AH that do not resolve on their own. For these patients, practitioners need to weigh the use of steroids against a range of health factors. Historically, because human factor VIII is likely to face the same assaults as the patients' own factor VIII, clinicians had widely prescribed the use of porcine factor VIII. It was believed that the similarity to human factor VIII would provide some hemostatic effects, while being different enough to avoid inactivation by the bodies' production of antibodies. However, results proved inconclusive on its uses.

For the last 30 years, according to the National Hemophilia Foundation, the typical treatment for AH bleeding episodes included the use of activated prothrombin complex concentrates, such as Factor VIII Inhibitor Bypassing Activity (FEIBA), which contains activated factors VII, IX and X. According to the World Federation of Hemophilia, doses of 50 to 100 units are to be provided intravenously in the treatment of AH, although doses exceeding 200 units per kilogram within any 24-hour period carry the risk of venous thromboembolism. FEIBA is no longer approved by the FDA to treat AH.

In 2006, the U.S. Food and Drug Administration (FDA) approved another bypassing agent for the treatment of AH, Novo Nordisk's NovoSeven, which also is FDA approved for the treatment of bleeding episodes in patients with congenital

if you spot it, you can stop it

Name: Joseph Miller Age: 62 years

Model is used for illustrative purposes only.

Symptoms[1,2]:

- Arrives at the ER with spontaneous, severe gastrointestinal bleeding
- No prior history of bleeding

Labs[1,3]:

- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests and additional testing ordered by the attending physician

Treatments[1]:

- Did not respond to treatments, including platelets and fresh frozen plasma

Diagnosis: ACQUIRED HEMOPHILIA

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- Do you have a patient with congenital hemophilia?
- Is bleeding under control?
- What diagnostic tests, such as an aPTT or a mixing study, have been performed?
- Was the aPTT prolonged?
- Have you consulted a hematologist?
- Have you considered acquired hemophilia?

Find out more about acquired hemophilia and treatment at **CoagsUncomplicated.com/Joe**.

References: 1. Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94(4):566-575. **2.** Collins PW, Hirsch S, Baglin TP, et al; for UK Haemophilia Centre Doctors' Organisation. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109(5):1870-1877. **3.** Collins PW, Percy CL. Advances in the understanding of acquired haemophilia A: implications for clinical practice. *Br J Haematol*. 2010;148(2):183-194. **4.** Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis*. 2009;20(7):517-523.

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FVII deficiency and in patients with hemophilia A or B with inhibitors to FVIII or FIX. According to Novo Nordisk's website, NovoSeven's intravenous bolus injection, a recombinant activated factor VII, has a half-life of 2.5 hours, which requires more frequent dosing — approximately 90 to 120 micrograms per kilogram given every three hours until the patient's bleeding is under control.

Sabah Sallah, Novo Nordisk's executive director in clinical development in hemostatis, says there are several benefits of NovoSeven for treating AH, including a well-established mode of action and safety profile, its effectiveness as a treatment regardless of the magnitude of inhibitor titer or anamnestic response, and its proven efficacy in life-threatening bleeding episodes in patients with AH. Several analyses have "demonstrated a high efficacy of rFVIIa in a very difficult-to-treat setting like AH and without major safety issues," says Sallah. The World Federation of Hemophilia notes that in a 2006 study of 74 bleeding episodes in 34 patients, 75 percent of the patients demonstrated a good response, with another 17 percent demonstrating at least some partial response. The patients in this study were unable to respond to other blood products, and the World Federation of Hemophilia notes that response rates could be higher in patients who received no prior forms of treatment.

Survival rates for AH are greatest in patients with postpartum inhibitors, those who are younger than 65 years old and those whose symptoms are drug-induced.

There are several possible side effects of NovoSeven, says Sallah, including deep vein thrombosis, pulmonary embolism, thrombotic stroke and ischemic cardiac episodes. And, because AH patients usually are elderly with other potential concomitant chronic illnesses such as diabetes, ischemic heart disease, hypertension, etc., they require close follow-up and monitoring for thrombotic events. However, these events have been reported in less than 1 percent of all bleeds, so NovoSeven for AH patients demonstrates a positive risk/benefit profile.

NovoNordisk is curently in Phase 3 clinical trials for the development of a variant of rFVIIa to treat AH.

Prognosis of AH Patients

Survival rates for AH are greatest in patients with postpartum inhibitors, those who are younger than 65 years old and those whose symptoms are drug-induced. According to Medscape Reference, those patients suffering from underlying malignancies face a worse prognosis, with between 50 percent and 70 percent of patients able to eradicate the inhibitor after the onset of AH, and with about 20 percent of patients suffering a relapse between one week and 14 months after the immunosuppressive therapy is stopped. In those patients who have relapsed, approximately 70 percent are able to realize another remission.

Education Key for Patients and Clinicians

Educating patients with AH is important, since its recurrence can lead to severe bleeding after even slight traumas, and minor activities may trigger bleeding in the body's soft tissues. Patients should report any prolonged or abnormal bleeding and, in the months following treatment, avoid activities that would risk significant trauma to the body. Just as important, frontline clinicians should be made aware of this rare disorder, since part of the reason for its high mortality rate is misdiagnosis for those who contract this rare, yet grave, disease. ❖

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References

1. Acquired Hemophilia Etiology. Medscape Reference. Accessed at emedicine.medscape.com/article/211186-overview#a0156.
2. Huth-Kühne, A, Baudo, F, Collins, P, Ingerslev, J, Kessler, CM, Lévesque, H, Mingot Castellano, ME, Shima, M, and St-Louis, J. International Recommendations on the Diagnosis and Treatment of Patients with Acquired Hemophilia A. *Haematologica*, 2009; 94:566-575, doi:10.3324/haematol.2008.001743. Accessed at www.haematologica.org/cgi/reprint/94/4/566.
3. Acquired Hemophilia Epidemiology. Medscape Reference. Accessed at emedicine.medscape.com/article/211186-overview#aw2aab6b2b3aa.
4. Collins, PW. Treatment of Acquired Hemophilia A. *Journal of Thrombosis and Haemostasis*, 2007, 5: 893–900, doi: 10.1111/j.1538-7836.2007.02433. Accessed at onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2007.02433.x/full.
5. Tagariello, G, Sartori, R, Radossi, P, Risato, R, Roveroni, G, Tassinari, C, Giuffrida, A, Gandini, G, and Franchini, M. Acquired Haemophilia A as a Blood Transfusion Emergency. *Blood Transfusion*, 2008 January; 6(1): 8–11, doi: 10.2450/2008.0030-07. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC2626855.
6. Delgado, J, Jimenez-Yuste, V, Hernandez-Navarro, F, and Villar, A. Acquired Haemophilia: Review and Meta-Analysis Focused on Therapy and Prognostic Factors. *British Journal of Haematology*, 2003, 121: 21–35. doi: 10.1046/j.1365-2141.2003.04162. Accessed at onlinelibrary.wiley.com/doi/10.1046/j.1365-2141.2003.04162.x/full.
7. Acquired Hemophilia Background. Medscape Reference. Accessed at emedicine.medscape.com/article/211186-overview.
8. Giangrande, P. *Acquired Hemophelia*. A publication of the World Federation of Hemophelia. Accessed at www.wfh.org/2/docs/Publications/Diagnosis_and_Treatment/TOH38_Acquired_Hemophilia.pdf.

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ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])
Sterile, lyophilized powder for injection

For Intravenous Use Only

Initial U.S. Approval: 1978

INDICATIONS AND USAGE

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

CONTRAINDICATIONS

- Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

WARNINGS AND PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients have been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

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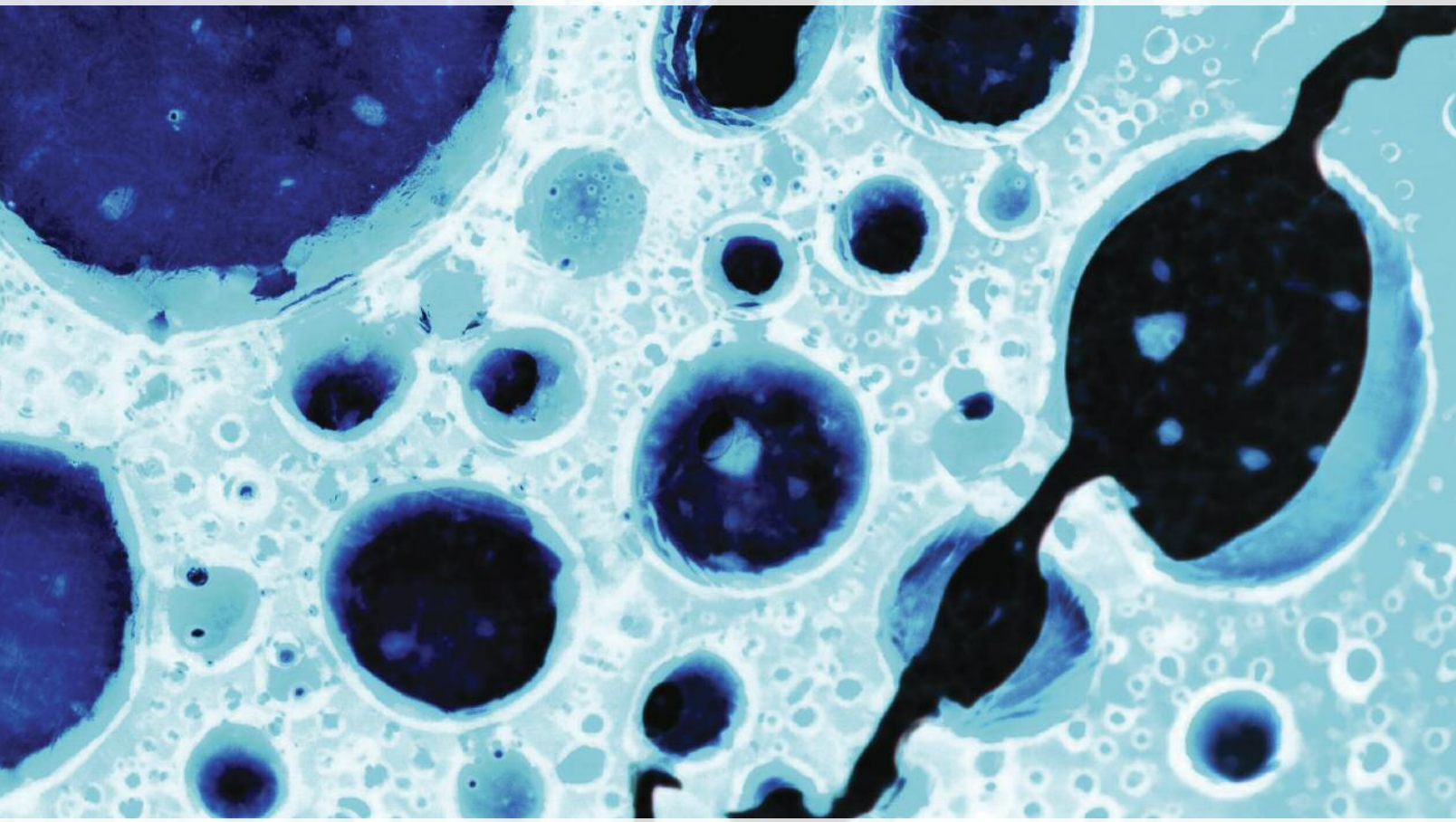
Cancer Treatment and Care: Promising Next Steps



From genetic assessment and prediction modeling to the study of genetics and genomics and the formulation of palliative care and self-management plans, the search for better cancer treatment and care is progressing rapidly.

By Amy Scanlin, MS

There are more than 1,000 diseases lumped into the diagnosis of cancer, where neoplastic cells divide uncontrollably, invade other tissues, damage DNA and continue replicating new mutated cells. It is estimated that half of all men and a third of women will develop cancer at some point in their lives.[1] Epidemiological evidence shows that more than 1.5 million people will be diagnosed with new cancers in 2011 in the U.S. and more than 500,000 of those will die from the disease.[2]

Genetic Assessment of Cancer Risk

In the last two decades, more than 50 highly penetrant cancer susceptibility syndromes have been linked to inherited genetic mutations.[3] In fact, 5 percent to 10 percent of every case of cancer diagnosed is thought to have a hereditary component. So, it is no wonder that science is looking closely at genetics and genomics as not only a method of individualized targeted therapy, but even as a method for risk assessment and prevention.

Evaluating an individual's cancer risk against the totality of their family history can prove challenging. But, other than an earlier-than-expected onset of cancer, family history is the best predictor of determining genetic links that may lead to cancer. Patterns of disease transmission can determine whether further investigation is warranted. And, the National Comprehensive Cancer Network, an alliance of top cancer centers, can provide guidelines to help clinicians determine who might be an appropriate candidate for genetic testing.[3]

Clearly, it is recommended that counseling for a genetics risk assessment be undertaken by one trained in the field. However, while there is no cancer specialty in the field of genetics, most who provide cancer risk assessments are oncologists and geneticists. Other allied health professionals who practice genetic risk assessments are genetic counselors or advanced practical nurses. In some cases, genetic assessments may fall on the primary care practitioner.

Currently, there is a need for more specialists and yet a lack of resources for education and training. Cancer genetic seminars, online courses and the American Society of Clinical Oncology (ASCO) curriculum titled Cancer Genetics and Cancer Predisposition Testing all are available, but registration is limited and the waiting list for such programs can be long. And, even with education and training, it may be impractical if not impossible for one person to effectively counsel a patient in the intricacies of genetics and genomics, as well as a course of treatment.

The success of genetic counseling is evidenced by the increased adherence to surveillance that, in turn, leads to the detection of tumors at an earlier and more treatable stage. As the field of genetics and genomics grows, patients will find a new era of biologists, pathologists and other scientists who are able to deliver a comprehensive picture of overall risk.

Prediction Modeling for Cancer

Predicting cancer's course from screening to end-of-life care can improve with multivariable prediction modeling, which is becoming well-recognized and -utilized in the field. It is even considered to be more useful and accurate than staging in regard to patient survival for numerous types of cancer. Indeed, a study of physicians' estimation of life expectancy for near end-of-life cancer patients improved significantly with prediction modeling over subjective predictions alone.[4] And, insurance companies may be more likely to approve genetic testing if probability models indicate a high risk in the context of overall family history.

It is estimated that half of all men and a third of women will develop cancer at some point in their lives.

There are numerous well-regarded prediction models for a whole host of cancers from the Gail Model for breast cancer prediction (www.cancer.gov/bcrisktool) to the Kattan Nomogram for the risk of reoccurrence of prostate cancer after a radical prostatectomy (www.nomograms.org) to the ACCENT Model for the value of adjuvant therapy for colon cancer patients (www.mayoclinic.com/calcs/colon/index-ccacalc.cfm). However, clinicians need to be aware of which prediction model they are choosing of the many thousands available, as many have not been independently validated.[4]

It should be noted that today's electronic health records (EHRs) are somewhat limited in the ability to pull patient risk assessment and test results into prediction models, as well as incorporating that information into patient care.[4] It is expected that newer generations of EHRs should fare better in this regard.

Genes and Genomes — A Growing Field of Study

Genomics research is progressing rapidly, and the impact on cancer cannot be overstated. While genes and genomes do not need to be fully understood to effectively identify cancer risk, they do need to be understood to develop treatments to

combat the disease. A lack of understanding is a limiting factor in today's ability to produce cancer-preventing drugs.

Cellular metabolism. Drugs targeting metabolic enzymes in the treatment of cancer are proving to be successful. However, finding a therapeutic window between normal and proliferating cancer cell metabolism is a challenge, as the metabolic requirements are the same. All proliferating cancer cells divert nutrients away from normal cells, and most of that diversion is to support biosynthesis. Another challenge is that different types of cancer use differing amounts of nutrients in different manners. Understanding how this nutrient rebalancing works is the key to redirecting and rewiring the pathways away from cancer cells as a means for therapy because there are different needs for each type of cancer, as well as for metabolism and DNA synthesis.

The idea of metabolism affecting cancer cell proliferation is rooted in the knowledge that obesity, hyperglycemia and insulin resistance are associated with increased cancer risks, possibly by activating signaling pathways that promote cell growth. Patients who are on the anti-diabetic drug metformin have shown fewer cancer-related deaths; however, this is not the case with other blood glucose-controlling drugs. This, then, begs the question of whether the drug is targeting the cancer directly or indirectly via lowered blood glucose or insulin-related growth factors. Metformin in high doses is also toxic to cancer stem cells. Preliminary findings suggest women who take the drug while undergoing chemotherapy have a better response, and clinical trials for women with breast cancer are in the planning stages to determine who might best benefit from metformin and whether the drug could be used as a chemoprevention for those at high risk.[5]

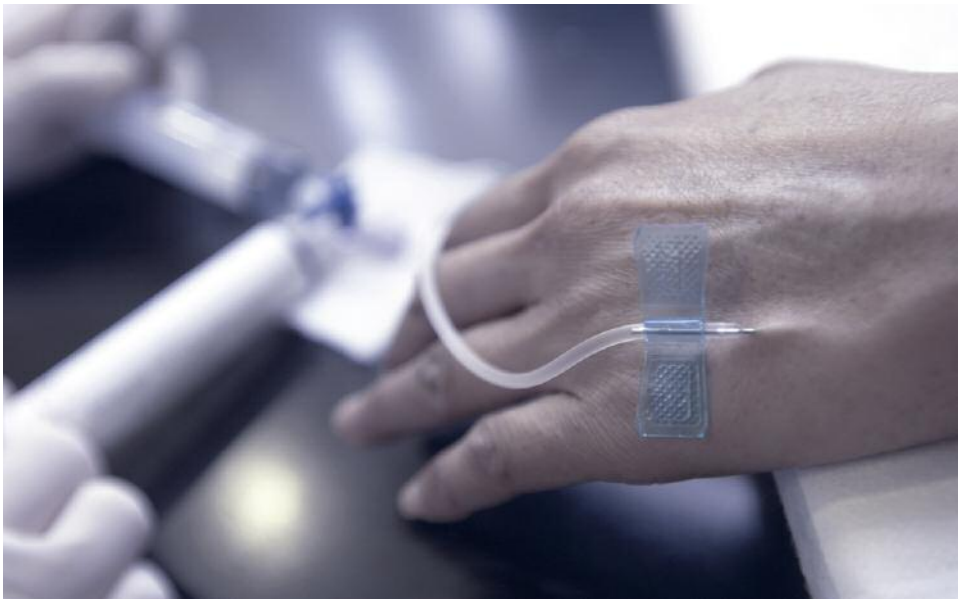
It is likely that drugs targeting metabolic enzymes will enter the clinical trial stage within the next few years because results in preclinical settings are encouraging in two approaches: 1) they limit the macromolecular synthesis needed for cell growth, and 2) they limit the supply of nutrients to the cell to impair cancer growth.

In the last two decades, more than 50 highly penetrant cancer susceptibility syndromes have been linked to inherited genetic mutations.

Biological response modifier therapy. When natural or laboratory manufactured monoclonal therapies are introduced, the hope is the body will use them like natural antibodies to fight tumor target antigens (this process is known as apoptosis). The first monoclonal antibodies were approved in the late 1990s and are proving effective for treating breast and lymphoma cancers. Today, others are being studied.

A small study is showing promise for leukemia patients who received re-engineered versions of their own T-lymphocyte cells to boost the immune system. The patients who had chronic lymphocytic leukemia (CLL) and had been previously treated using other methods had their T cells removed and modified with a virus to enable new genes that target B-lymphocyte cells. After reinjection into the body, the cells began killing CLL tumor cells and, within weeks, the tumor had been "blown away," said one of the study authors. Another small-scale study will begin shortly, and if successful, a large-scale study is anywhere from five to 10 years away.[6] Targeted therapies leading to apoptosis are a growing field.

Thirty years after the discovery of the p53 tumor suppressor protein, encoded in the TP53 gene, scientists are looking at the effectiveness of drugs in targeting the tumor cell and at p53 as a predictive factor in the diagnosis and spread of cancer. TP53 is often mutated with cancer, clustering at a hot spot and leading to one of three alterations of p53 at the DNA binding domain. It appears that all cancers have a defective p53 either by TP53 mutation or altered pathway of p53, and the effects



of a mutated p53 differ depending on which cancer cells are affected. Scientists are working to define p53 molecular profiles in hopes of having more clearly defined disease predictors and treatments.[7]

Two drugs have been shown effective in activating wild-type p53 proteins in tumors: Nutlin-3, which induces accumulation of p53 and Mdm2, and RITA, which binds and stabilizes p53 while suppressing Mdm2. PRIMA-1 is one of several drugs that can restore wild-type p53 activity; however, at present the exact mechanism by which this happens is unknown. These drugs are ready to move into clinical trials, and it is hoped that in 10 years, the aim of personalized medicine will be closer.[7]

The immune system's T cells are a frequent focus of clinical studies in treating cancer, and the dream of reprogramming immune cells to target cancer cells has potential. After a clinical trial was stopped in 2010 due to the death of two study participants, researchers at the University of Pennsylvania Medical Center have successfully engineered a T cell to recognize the CD19 protein on the surface of the cancerous cell, as well as on B cells. This engineered T cell, in combination with an antibody to target the cancer and part of a receptor that increases the T-cell response, has shown a 1,000-fold proliferation, much of which was still present after six months. In their small study, two of the participants were in complete remission and a third was showing marked improvement. Because the study group was so small, the results are preliminary but clearly promising.[8]

A new class of therapy called PARP inhibitors is showing promise in killing cancer cells in those with defective BRAC1 and 2 genes who have cancers of the breast, ovary and prostate. Scientists also are looking at the possibility that this treatment may work in those without the mutation. PARP-1, or poly (adenosine-diposphate-ribose) polymerase, allows cancer cells to repair DNA damage, including damage made by cancer treatment. And, these PARP inhibitors can make cancerous cells more sensitive to treatment, prevent the repair and cause the cell's death.

There are numerous PARP inhibitors under review and two in particular are causing excitement — olaparib (AstraZeneca) and BSI-201 (BiPar Sciences) — because of their "synthetic lethality" in killing cancer cells while not disturbing healthy cells.[9]

A new drug, recently approved by the U.S. Food and Drug Administration, Adcetris (brentuximab vedotin), is an antibody-drug conjugate, much stronger than "naked antibodies," that can directly target CD30 proteins on lymphoma cells and kill them. It is hoped that the direct target will prevent toxicities from methods like chemotherapy from being transported via the bloodstream through the body. A recent study showed 74 percent of the 102 study participants with Hodgkin's lymphoma saw a partial or complete remission, and 94 percent saw their tumors shrink. There are now about 25 additional antibody-drug conjugates in ongoing trials, and it is expected that more variations of this therapy will soon be on the market.[10]

Genomics research is progressing rapidly, and the impact on cancer cannot be overstated.

Stem cell therapy. Cancer stem cells, making up just 1 percent to 3 percent of cells in a tumor, are the driving factor in a tumor's growth. First identified in 2003, cancer stem cells have been isolated in breast cancer, tumors of the neck and head, an aggressive brain cancer called glioblastoma and in the pancreas. Cancer stem cells look just like regular cancer cells, so they are identified by certain proteins that regular cancer cells do not have.

As the ability to better isolate and identify cancer stem

cells improves, physicians will have a better understanding of a patient's risk for developing cancer, as well as new targeted therapies to treat it, potentially killing cancer stem cells in the original tumor before it has an opportunity to spread.[11]

Self-Management and Palliative Care

Providing the best quality of life for a cancer patient, no matter where they are in their diagnosis and treatment continuum, is a priority for both caregivers and patients, and is being offered at more and more hospitals, outpatient clinics and in-home settings.

Thanks to early detection, diagnosis and successful treatments, some can manage cancer like a chronic illness, rather than an acute disease. Family members, patients, oncologists and primary care providers can work together via guidance of the American Cancer Society's Chronic Care Model (CCM) to formulate a self-management plan that ensures the right tools are available for management and comfort long after traditional treatments have ceased. This includes forming relationships with those who can help, improving skills in problem-solving, decision-making and the ability to take decisive action with regard to healthcare, emotional care and comfort care. Numerous studies have shown the validity and usefulness of self-management through all stages of cancer and survivorship and even end of life.

Thanks to early detection, diagnosis and successful treatments, some can manage cancer like a chronic illness, rather than an acute disease.

The CCM includes six steps: self-management support, delivery system design, decision support, clinical information systems, healthcare organizations and the identification and use of community resources.[12] Mutually agreed-upon care plans are the goal, allowing for patients to feel good about their plan and their ability to have some control over the outcome, even if the outcome is based on emotion or comfort. One major limitation that providers need to keep in mind is a common language that is understandable to the patient and family. Another limitation is the patient's willingness to accept their role in self-management and to take charge. Expectations of providers often outweigh the patient's ability or motivation.

Self-management and palliative care interventions are most successful for the patient when incorporated early. The American Society of Clinical Oncology has set a goal of incorporating palliative care into cancer care practices by the year 2020.

Better Treatments Moving Forward

The search for better cancer treatments continue to move forward at a rapid pace as scientists better understand the disease and how therapies target it. Of course, better treatment also encompasses a patient's level of comfort and security of their situation and their ability to impact it in numerous ways. As improvements in the scientific process move forward, as well as improvements in palliative care, the entire experience for the patient will be changed for the better — from identification of risk to early diagnosis, improved and targeted therapies and the informed decision-making continuum for all involved. ❖

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References

1. American Cancer Society. Learn About Cancer. Accessed at www.cancer.org/Cancer/CancerBasics/what-is-cancer.
2. American Cancer Society. Estimated New Cancer Cases and Deaths and Deaths by Sex for All Sites, 2011. Accessed at www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029817.pdf.
3. Weitzel, J, Blazer, K, MacDonald, D, Culver, J, and Offit, K. Genetics, Genomics and Cancer Risk Assessment. *CA, A Cancer Journal for Clinicians*, Volume 61, Sep-Oct 2011. Accessed at www.cacancerjournal.com/details/journalArticle/1325299/Genetics_genomics_and_cancer_risk_ assessment.html.
4. Vickers, AJ. Prediction Models in Cancer Care. *CA, A Cancer Journal for Clinicians*, 61: 315–326. doi: 10.3322/caac.20118. Accessed at www.cacancerjournal.com/details/journalArticle/1325295/Prediction_models_in_cancer_care.html.
5. Vander Heiden, M. Targeting Cancer Metabolism — A Therapeutic Window Opens — Review. *Nature Reviews Drug Discovery*, 10, 671-684, Sep 2011, doi:10.1038/nrd3504. Accessed at www.nature.com/nrd/journal/v10/n9/full/nrd3504.html.
6. Simon, S. Early Results of Gene Therapy Show Promise Against Leukemia. American Cancer Society, Aug 12, 2011. Accessed at www.cancer.org/Cancer/news/News/early-results-of-gene-therapy-show-promise-against-leukemia.
7. Goldstein, I, Marcel, V, Olivier, M, Oren, M, Rotter, V, and Hainaut, P. Understanding Wild-Type and Mutant P53 Activities in Human Cancer: New Landmarks on the Way to Targeted Therapies. *Cancer Gene Therapy*, 2011, 18, Oct 22, 2010.
8. Ledford, H. Cell Therapy Fights Leukemia. *Nature Journal*, Aug 10, 2011. Accessed at www.nature.com/news/2011/110810/full/news.2011.472.html.
9. Mulcahy, N. PARP Inhibitors Represent New Direction in Cancer Treatment. Medscape.com, Jun 25, 2009. Accessed at www.medscape.com/viewarticle/704990.
10. Ledford, H. Toxic Antibodies Blitz Tumors. *Nature.com*, August 2011, doi:10.1038/476380a. Accessed at www.nature.com/news/2011/110822/full/476380a.html.
11. University of Michigan Medical Center. Cancer's Stem Cell Revolution. Accessed at www.med.umich.edu/cancer/research/stemcells.shtml.
12. McCorkle, R, Ercolano, E, Lazenby, M, Schulman-Green, D, Schilling, LS, Lorig, K, and Wagner, EH. Self-Management: Enabling and Empowering Patients Living with Cancer as a Chronic Illness. *CA, A Cancer Journal for Clinicians*, 61: 50–62. doi: 10.3322/caac.20093. Accessed at www.cacancerjournal.com/details/journalArticle/983349/Selfmanagement_Enabling_and_empowering_patients_living_with_cancer_as_a_chronic_.html.

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Myths and Facts: Stroke

Stroke is the third-leading cause of death in the U.S. due simply to ignorance about its symptoms, but that can change by separating the myths about the disease from the facts.

By Ronale Tucker Rhodes, MS

This year, approximately 795,000 individuals in the U.S. will suffer a stroke. While the number of strokes fell 18 percent and the stroke death rate fell 33.5 percent from 1996 to 2006, stroke is still the third-leading cause of death in the U.S., killing about 137,000 people each year and leaving many with serious, long-term disability.[1]

Unfortunately, it is a lack of understanding about stroke that causes death and disability. In a recent study, 40 percent of people were unable to name a single stroke symptom.[2] And, almost 60 percent of stroke patients don't get to a doctor or hospital until 24 hours after the stroke — too late for effective treatment.[3] Doctors say they see misconceptions about stroke and their devastating repercussions all the time. Therefore, it's imperative for people to understand the myths about stroke that lead to mistakes and how to avoid them.

Separating Myth from Fact

Myth: Strokes are rare.

Fact: A stroke occurs every 45 seconds in the U.S., causing thousands of deaths each year.

Myth: Strokes happen to the heart.[4]

Fact: A stroke happens to the brain, and it also is known as a "brain attack."[5] A stroke occurs when a blood vessel in the brain bursts or gets clogged.[6]

Myth: There is only one type of stroke.

Fact: There are two major types of stroke. The most common is called ischemic, which occurs when arteries are blocked by blood clots or by the gradual buildup of plaque and other fatty deposits. About 87 percent of all strokes are ischemic.[1,7] Ischemic strokes include silent strokes and mini strokes (also known as transient ischemic attacks, or TIAs). A silent stroke

is found incidentally on an MRI of the brain, and typically, the individual never remembers experiencing any symptoms. A mini stroke is a brief but discrete and memorable clinical event that causes symptoms of a stroke for a few minutes to a few hours that disappear in less than 24 hours. By age 69, approximately 10 percent to 11 percent of people who consider themselves stroke-free have suffered at least one ischemic stroke.[8] Up to 25 percent of people who suffer a TIA die within one year, and up to 17 percent of all TIAs are followed by a stroke — most of them within 30 days of the TIA occurrence.[2]

The second type of stroke is called hemorrhagic, which occurs when a blood vessel in the brain breaks, leaking blood into the brain. Hemorrhagic strokes account for 13 percent of all strokes, yet they are responsible for more than 30 percent of all stroke deaths.[7] Up to 70 percent of strokes seen in the hospital are ischemic, while the remaining 30 percent are a mixture of TIAs and hemorrhagic strokes.[2]

Myth: Only the elderly suffer strokes.

Fact: A stroke can strike anyone at any age, even infants, regardless of race, sex or age. Nearly 25 percent of all strokes occur in people younger than 65 years of age. After age 35, the risk of having a stroke doubles every 10 years.[4] And, while men's stroke incidence rates are greater than women's at younger ages, this is not true at older ages.[5]

The percentage of adults from each race affected by stroke are: American Indians/Alaska natives, 5.3 percent; African-Americans, 3.2 percent; whites, 2.5 percent; and Asians, 2.4 percent.[2] African-Americans have almost twice the risk of first-ever stroke compared with whites.[1]

Myth: The risks for suffering a stroke do not run in the family.

Fact: The risk of having a stroke increases if a parent, grandparent or sibling has had a stroke.[4]

Myth: It's easy to detect stroke symptoms because they are noticeable and painful.

Fact: Symptoms of a stroke are not painful. Common stroke symptoms include sudden numbness or weakness of the face, arm or leg (especially on one side of the body); sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; and sudden severe headache with no known cause.[1] Oftentimes, strokes can cause even subtler neurological sensations, and some strokes are called silent strokes because they cause no symptoms.[9]

An individual can recognize if they are having a stroke by using the FAST (face, arms, speech, time) test. To employ the test, an individual simply looks in the mirror to determine whether one side of their face droops when smiling or whether one arm drifts downward when raising both arms, and to hear whether their speech sounds slurred or strange when speaking. If any one of these signs is present, it's time to seek treatment.[1]

Myth: It's OK to wait to see if stroke symptoms will subside.

Fact: Two million brain cells die every minute during a stroke, which increases the risk of permanent brain damage, disability or death.[1] Generally, there is an eight-hour window for stroke treatment, but during that time period, treatment becomes less effective. Ideally a stroke victim should be treated within the first three hours of symptoms.[7] Unfortunately, only 20 percent to 25 percent of patients who are admitted to the hospital with a stroke arrive in the emergency department within three hours of the onset of symptoms.[2]

In a recent study, 40 percent of people were unable to name a single stroke symptom.

Myth: It's OK for a family member or friend to drive someone suffering from stroke symptoms to the hospital.

Fact: If someone is having a stroke, 911 should be immediately dialed. Having a family member or friend drive a stroke victim to the hospital wastes time. An ambulance provides the stroke patient with the fastest access to medical care because paramedics and EMTs can evaluate the person and relay information to the doctors while the patient is en route to the hospital, allowing treatment to begin sooner.[7]

Myth: Strokes cannot be prevented.

Fact: While some risk factors for stroke are beyond a person's control, including being over age 55, being a male, being African-American, having diabetes and having a family history of stroke, there are many medical and lifestyle changes that can be made to help prevent stroke. Medical risk factors include a previous stroke, previous episode of TIA, high cholesterol, high blood pressure, heart disease, atrial fibrillation and carotid artery disease — all of which can be controlled and managed. Lifestyle risk factors include smoking, being overweight and drinking too much alcohol. Quitting smoking, maintaining a healthy weight and limiting alcohol consumption can help to control these risks. [1]

Myth: Strokes cannot be treated.

Fact: More people are surviving stroke due to better health education and medical advances. A clot-dissolving drug commonly referred to as t-PA (tissue plasminogen activator) can reduce long-term disability if it is given within the first three hours after an ischemic stroke starts. Unfortunately, t-PA is not used as it could be because many people don't seek medical treatment as quickly as they should.[6] Between three to six hours after onset of symptoms, the clot can be dissolved

with drugs delivered directly to the brain vessel by way of a catheter. And, up to eight hours after onset of symptoms, a clot can be mechanically removed through a catheter. However, noninvasive actions are always the first choice.[7]

Treatment also includes rehabilitation, which needs to begin in the hospital as soon as possible after the stroke. The goal of rehabilitation is to improve function so that the stroke survivor may regain a level of independence. Stroke survivors may be seen in a rehabilitation unit in the hospital, a subacute care unit, a rehabilitation hospital or a long-term care facility providing therapy and skilled nursing care. Home therapy or a combination of home and outpatient therapy also may be options, depending on the stroke survivor's individual needs.[5]

Myth: There are no long-term effects of stroke.

Fact: The effects of a stroke depend on several factors including the location of the obstruction of blood to the brain and how much brain tissue is affected. Each side of the brain controls the opposite side of the body. If a stroke occurs on the right side of the brain, long-term effects can include paralysis on the left side of the body; vision problems; quick, inquisitive behavioral style; and memory loss. If a stroke occurs on the left side of the brain, the effects may include paralysis on the right side of the body; speech/language problems; slow, cautious behavioral style; and memory loss.[6]

Approximately 38 percent of stroke survivors experience severe spasticity — tight or stiff muscles that make movement, especially of the arms and legs, difficult or uncontrollable. Severe spasticity can be very painful and can make simple activities of daily living time-consuming and difficult. When spasticity limits activity for long periods, it can cause additional medical problems such as sleep disturbances, pressure sores and pneumonia.[5]

Two million brain cells die every minute during a stroke, which increases the risk of permanent brain damage, disability or death.

Age, severity of stroke, and success and timing of treatment all determine the recovery rates of stroke survivors. General recovery guidelines show that 10 percent of survivors recover almost completely, 25 percent recover with minor impairments, 40 percent experience moderate to severe impairments requiring special care, 10 percent require care in a nursing home or other long-term care facility, and 15 percent die shortly after suffering a stroke.[5]

Dispelling the Myths Now

Statistics show that four out of five American families are affected by stroke,[5] a devastating illness that affects not only the stroke victims, but also their families who care for them and the public who pays the bill. In 2007, it was estimated that the total cost of stroke was $62.7 billion in the U.S.[2] In the face of its ruinuous impact on health and finances, it is more important than ever to minimize the risks of stroke. Dispelling the myths about this disease can bring about a better understanding of its symptoms, risks and the need to get treatment quickly, thereby reducing the number of stroke victims. ❖

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References

1. Stroke 101. National Stroke Association. Accessed at www.stroke.org/site/DocServer/STROKE_101_Fact_Sheet.pdf?docID=4541.
2. Vega, J. Interesting Facts and Statistics About Stroke. About.com. Accessed at stroke.about.com/od/strokestatistics/a/StrokeStats.htm.
3. Myths and Interesting Facts About Stroke. Health24. Accessed at www.health24.com/medical/Condition_centres/777-792-822-1849,17707.asp.
4. Busting Stroke Myths. The University of Tennessee Medical Center. Accessed at www.utmedicalcenter.org/brain-and-spine-institute/medical-services/stroke-services/busting-stroke-myths.
5. Stroke Facts. National Stroke Association. Accessed at www.stroke.org/site/DocServer/Stroke_Fact_Sheet_with_Graphics_6.26.06.pdf?docID=1944.
6. Stroke Facts. St. John's Hospital. Accessed at www.st-johns.org/services/stroke_center/stroke_facts.aspx.
7. Stroke Myths: Advice from Doctors — What They Wish You Knew. My Family Doctor. Accessed at familydoctormag.com/heart-and-brain/1320-stroke-myths-advice-from-doctors-what-they-wish-you-knew.html.
8. Vega, J. What is the difference between silent stroke and mini stroke? About.com. Accessed at stroke.about.com/od/glossary/f/silenvsmini.htm.
9. Myths & Facts About Stroke. HealthMonitor. Accessed at www.healthmonitor.com/heart-health/ stroke/myth-or-fact-insight-stroke.

Influenza can kill almost as many people a year as AIDS or breast cancer.[1,2]

Order FLUVIRIN® now and help protect your patients for the 2012-2013 flu season.

In 2011, more than 17,000 people are expected to die from AIDS[1] and nearly 40,000 women from breast cancer.[2] Though influenza may not seem like a serious disease, in any given flu season it may cause 3,000 to 49,000 flu-associated deaths.[3]

The ACIP recommendation for annual influenza vaccination now includes all persons aged 6 months and older.[4] FLUVIRIN® is indicated for persons 4 years of age and older.[5]

Novartis Vaccines is committed to providing seasonal flu vaccine doses on time. In fact, in 2011 Novartis Vaccines completed the shipping of over 27 million seasonal flu vaccine doses ahead of schedule, allowing for early and convenient administration.

Make sure you have your supply of vaccine ready for the next flu season.
Contact FFF Enterprises at (800) 843-7477 or visit www.MyFluVaccine.com

Indication

FLUVIRIN® is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza virus disease caused by influenza virus subtypes A and type B contained in the vaccine.[5]

FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.[5]

Please see reverse for Important Safety Information.

NOVARTIS VACCINES

Influenza Virus Vaccine
Fluvirin®

Important Safety Information

FLUVIRIN® should not be administered to anyone with known history of severe allergic reactions (e.g., anaphylaxis) to egg proteins (eggs or egg products), or to any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

Prior to administration of any dose of FLUVIRIN®, the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with FLUVIRIN® and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

Vaccination with FLUVIRIN® may not protect all individuals.

In clinical trials, the most common adverse events in adults were headache, fatigue, injection site reactions (pain, mass, redness, and induration), and malaise.[5]

Please see a Brief Summary of the FLUVIRIN® Prescribing Information on the following pages.

References: 1. United States HIV & AIDS statistics summary. Avert Web site. http://www.avert.org/usa-statistics.htm. Accessed August 12, 2011. **2.** Breast cancer facts and figures 2011-2012. American Cancer Society Web site. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-030975.pdf. Accessed November 21, 2011. **3.** Seasonal influenza. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/flu/about/qa/disease.htm. Accessed August 15, 2011. **4.** Prevention and control of influenza with vaccines recommendations of the advisory committee on immunization practices (ACIP), 2010. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/mmwr/pdf/rr/rr59e0729.pdf. Accessed November 21, 2011. **5.** Fluvirin [Prescribing Information]. Liverpool, UK: Novartis Vaccines and Diagnostics Limited; 2011.

NOVARTIS VACCINES

Novartis Vaccines and Diagnostics, Inc.
Cambridge, MA 02139

Printed in USA November 2011 NVDFLU311 Printed on Recycled Paper

FLUVIRIN® (Influenza Virus Vaccine)

Suspension for Intramuscular Injection
2011-2012 Formula
Initial US Approval: 1988
4 May 2011

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

FLUVIRIN® is an inactivated influenza virus vaccine indicated for immunization of persons 4 years of age and older against influenza virus disease caused by influenza virus subtypes A and type B contained in the vaccine. [see DOSAGE FORMS AND STRENGTHS (3)]

FLUVIRIN® is not indicated for children less than 4 years of age because there is evidence of diminished immune response in this age group.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Do not administer FLUVIRIN® to anyone with known history of severe allergic reactions (e.g., anaphylaxis) to egg proteins (eggs or egg products), or to any component of FLUVIRIN®, or who has had a life-threatening reaction to previous influenza vaccinations.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLUVIRIN® should be based on careful consideration of the potential benefits and risks.

5.2 Altered Immunocompetence

If FLUVIRIN® is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.3 Preventing and Managing Allergic Reactions

Prior to administration of any dose of FLUVIRIN®, the healthcare provider should review the patient's prior immunization history for possible adverse events, to determine the existence of any contraindication to immunization with FLUVIRIN® and to allow an assessment of benefits and risks. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

The tip caps of the FLUVIRIN® prefilled syringes may contain natural rubber latex which may cause allergic reactions in latex sensitive individuals.

5.4 Limitations of Vaccine Effectiveness

Vaccination with FLUVIRIN® may not protect all individuals.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

Serious allergic reactions, including anaphylactic shock, have been observed in individuals receiving FLUVIRIN® during postmarketing surveillance.

6.2 Clinical Trial Experience

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating the rates of these events. However, because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect rates observed in clinical practice.

Adult and Geriatric Subjects

Safety data were collected in a total of 2768 adult and geriatric subjects (18 years of age and older) who have received FLUVIRIN® in 29 clinical studies since 1982.

In 9 clinical studies since 1997, among 1261 recipients of FLUVIRIN®, 745 (59%) were women; 1211 (96%) were White, 23 (2%) Asian, 15 (1%) Black and 12 (1%) other; 370 (29%) of subjects were elderly (≥65 years of age). All studies have been conducted in the UK, apart from a study run in the US in 2005-2006 where FLUVIRIN® was used as a comparator for an unlicensed vaccine.

After vaccination, the subjects were observed for 30 minutes for hypersensitivity or other immediate reactions. Subjects were instructed to complete a diary card for three days following immunization (i.e. Day 1 to 4) to collect local and systemic reactions (see Tables 1 and 2). All local and systemic adverse events were considered to be at least possibly related to the vaccine. Local and systemic reactions mostly began between day 1 and day 2. The overall adverse events reported in clinical trials since 1998 in at least 5% of the subjects are summarized in Table 3.

TABLE 1
Solicited Adverse Events in the First 72-96 Hours After Administration of FLUVIRIN® in Adult (18-64 years of age) and Geriatric (≥65 years of age) Subjects.

	1998-1999*§		1999-2000*§		2000-2001*§	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 66	N = 44	N = 76	N = 34	N = 75	N = 35
Local Adverse Events						
Pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Ecchymosis	4 (6%)	1 (2%)	3 (4%)	1 (3%)	4 (5%)	-
Edema	2 (3%)	1 (2%)	1 (1%)	2 (6%)	3 (4%)	1 (3%)
Reaction	2 (3%)	-	2 (3%)	-	4 (5%)	1 (3%)
Hemorrhage	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	7 (11%)	1 (2%)	17 (22%)	3 (9%)	4 (5%)	-
Fatigue	3 (5%)	2 (5%)	4 (5%)	1 (3%)	3 (4%)	-
Malaise	2 (3%)	1 (2%)	2 (3%)	1 (3%)	1 (1%)	-
Myalgia	1 (2%)	-	2 (3%)	-	-	-
Fever	1 (2%)	-	1 (1%)	-	-	-
Arthralgia	-	1 (2%)	-	1 (3%)	-	-
Sweating	-	-	3 (4%)	-	1 (1%)	1 (3%)

	2001-2002*^		2002-2003*^		2004-2005*^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Local Adverse Events						
Pain	12 (16%)	1 (3%)	14 (13%)	7 (8%)	15 (20%)	9 (15%)
Mass	4 (5%)	1 (3%)	-	-	-	-
Ecchymosis	2 (3%)	-	3 (3%)	3 (3%)	2 (3%)	1 (2%)
Edema	2 (3%)	1 (3%)	6 (6%)	2 (2%)	-	-
Erythema	5 (7%)	-	11 (10%)	5 (6%)	16 (22%)	5 (8%)
Swelling	-	-	-	-	11 (15%)	4 (7%)
Reaction	-	-	2 (2%)	-	-	-
Induration	-	-	14 (13%)	3 (3%)	11 (15%)	1 (2%)
Pruritus	-	-	1 (1%)	-	-	-
Systemic Adverse Events						
Headache	8 (11%)	1 (3%)	12 (11%)	9 (10%)	14 (19%)	3 (5%)
Fatigue	1 (1%)	1 (3%)	-	-	5 (7%)	2 (3%)
Malaise	3 (4%)	-	3 (3%)	4 (5%)	1 (1%)	1 (2%)
Myalgia	3 (4%)	-	5 (5%)	3 (3%)	8 (11%)	1 (2%)
Fever	-	-	-	1 (1%)	-	-
Arthralgia	-	-	2 (2%)	-	1 (1%)	-
Sweating	3 (4%)	1 (3%)	-	2 (2%)	-	-
Shivering	-	-	-	1 (1%)	-	-

Results reported to the nearest whole percent; Fever defined as >38°C
– not reported
* Solicited adverse events in the first 72 hours after administration of FLUVIRIN®
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MEDDRA preferred term

TABLE 2
Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age).

	2005-2006 US Trial FLUVIRIN® N = 304
Local Adverse Events	
Pain	168 (55%)
Erythema	48 (16%)
Ecchymosis	22 (7%)
Induration	19 (6%)
Swelling	16 (5%)

(continued)

TABLE 2
Solicited Adverse Events in the First 72 Hours After Administration of FLUVIRIN® in Adult Subjects (18-49 years of age).

	2005-2006 US Trial FLUVIRIN® N = 304
Systemic Adverse Events	
Headache	91 (30%)
Myalgia	64 (21%)
Malaise	58 (19%)
Fatigue	56 (18%)
Sore throat	23 (8%)
Chills	22 (7%)
Nausea	21 (7%)
Arthralgia	20 (7%)
Sweating	17 (6%)
Cough	18 (6%)
Wheezing	4 (1%)
Chest tightness	4 (1%)
Other difficulties breathing	3 (1%)
Facial edema	-

Results reported to the nearest whole percent
– not reported

TABLE 3
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

	1998-1999§		1999-2000§		2000-2001§	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 66	N = 44	N = 76	N = 34	N = 75	N = 35
Adverse Events						
Fatigue	8 (12%)	2 (5%)	8 (11%)	2 (6%)	5 (7%)	-
Back pain	4 (6%)	3 (7%)	-	-	-	-
Cough increased	2 (3%)	2 (5%)	-	-	-	-
Ecchymosis	4 (6%)	1 (2%)	4 (5%)	1 (3%)	5 (7%)	-
Fever	3 (5%)	-	-	-	-	-
Headache	12 (18%)	5 (11%)	22 (29%)	5 (15%)	14 (19%)	2 (6%)
Infection	3 (5%)	2 (5%)	-	-	-	-
Malaise	4 (6%)	4 (9%)	4 (5%)	1 (3%)	-	-
Migraine	4 (6%)	1 (2%)	-	-	-	-
Myalgia	4 (6%)	1 (2%)	-	-	-	-
Sweating	5 (8%)	1 (2%)	-	-	-	-
Rhinitis	3 (5%)	1 (2%)	-	-	5 (7%)	2 (6%)
Pharingitis	6 (9%)	1 (2%)	10 (13%)	-	6 (8%)	-
Arthralgia	-	-	-	2 (6%)	-	-
Injection site pain	16 (24%)	4 (9%)	16 (21%)	-	9 (12%)	-
Injection site ecchymosis	4 (6%)	1 (2%)	-	-	4 (5%)	-
Injection site mass	7 (11%)	1 (2%)	4 (5%)	-	8 (11%)	1 (3%)
Injection site edema	-	-	1 (1%)	2 (6%)	-	-
Injection site inflammation	5 (8%)	2 (5%)	6 (8%)	-	7 (9%)	1 (3%)
Injection site reaction	-	-	-	-	4 (5%)	1 (3%)

	2001-2002^		2002-2003^		2004-2005^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Adverse Events						
Fatigue	5 (7%)	4 (11%)	11 (10%)	8 (9%)	4 (5%)	2 (3%)
Hypertension	-	-	1 (1%)	4 (5%)	-	-
Rinorrhea	-	-	2 (2%)	5 (6%)	-	-
Headache	20 (27%)	2 (6%)	35 (33%)	18 (20%)	12 (16%)	1 (2%)
Malaise	6 (8%)	1 (3%)	13 (12%)	8 (9%)	-	-
Myalgia	4 (5%)	1 (3%)	10 (9%)	4 (5%)	-	-
Sweating	3 (4%)	3 (9%)	2 (2%)	5 (6%)	-	-
Rhinitis	4 (5%)	-	-	-	-	-
Pharingitis	-	-	-	-	6 (8%)	-

(continued)

TABLE 3
Adverse Events Reported by at least 5% of Subjects in Clinical Trials since 1998

	2001-2002^		2002-2003^		2004-2005^	
	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs	18-64 yrs	≥ 65 yrs
	N = 75	N = 35	N = 107	N = 88	N = 74	N = 61
Adverse Events						
Arthralgia	-	-	5 (5%)	4 (5%)	-	-
Sore throat	4 (5%)	1 (3%)	5 (5%)	4 (5%)	-	-
Injection site pain	13 (17%)	3 (9%)	14 (13%)	7 (8%)	6 (8%)	2 (3%)
Injection site ecchymosis	4 (5%)	1 (3%)	4 (4%)	4 (5%)	-	-
Injection site erythema	5 (7%)	2 (6%)	11 (10%)	5 (6%)	4 (5%)	-
Injection site mass	4 (5%)	1 (3%)	-	-	-	-
Injection site edema	-	-	6 (6%)	2 (2%)	4 (5%)	1 (2%)
Injection site induration	-	-	14 (13%)	3 (3%)	7 (9%)	-

Results reported to the nearest whole percent; Fever defined as >38°C
– not reaching the cut-off of 5%
§ Solicited adverse events reported by COSTART preferred term
^ Solicited adverse events reported by MEDDRA preferred term

Adults (18 to 64 years of age)
In adult subjects, solicited local adverse events occurred with similar frequency in all trials. The most common solicited adverse events occurring in the first 96 hours after administration (Tables 1 and 2) were associated with the injection site (such as pain, erythema, mass, induration and swelling) but were generally mild/moderate and transient. The most common solicited systemic adverse events were headache and myalgia.

The most common overall events in adult subjects (18-64 years of age) were headache, fatigue, injection site reactions (pain, mass, erythema, and induration) and malaise (Table 3).

Geriatric Subjects (65 years of age and older)
In geriatric subjects, solicited local and systemic adverse events occurred less frequently than in adult subjects. The most common solicited local and systemic adverse events were injection site pain, and headache (Tables 1 and 2). All were considered mild/moderate and were transient.

The most common overall events in elderly subjects (≥65 years of age) were headache and fatigue.

Only 11 serious adverse events in adult and geriatric subjects (18 years and older) have been reported to date from all the trials performed. These serious adverse events were a minor stroke experienced by a 67 year old subject 14 days after vaccination (1990), death of an 82 year old subject 35 days after vaccination (1990) in very early studies; death of a 72 year old subject 19 days after vaccination (1998-1999), a hospitalization for hemorrhoidectomy of a 38 year old male subject (1999-2000), a severe respiratory tract infection experienced by a 74 year old subject 12 days after vaccination (2002-2003), a planned transurethral resection of the prostate in a subject with prior history of prostatism (2004-2005), two cases of influenza (2005-2006), a drug overdose (2005-2006), cholelithiasis (2005-2006) and a nasal septal operation (2005-2006). None of these events were considered causally related to vaccination.

Clinical Trial Experience in Pediatric Subjects
In 1987 a clinical study was carried out in 38 'at risk' children aged between 4 and 12 years (17 females and 21 males). To record the safety of FLUVIRIN®, participants recorded their symptoms on a diary card during the three days after vaccination and noted any further symptoms they thought were attributable to the vaccine. The only reactions recorded were tenderness at the site of vaccination in 21% of the participants on day 1, which was still present in 16% on day 2 and 5% on day 3. In one child, the tenderness was also accompanied by redness at the site of injection for two days. The reactions were not age-dependent and there was no bias towards the younger children.

Three clinical studies were carried out between 1995 and 2004 in a total of 520 pediatric subjects (age range 6 - 47 months). Of these, 285 healthy subjects plus 41 'at risk' subjects received FLUVIRN®. No serious adverse events were reported.

FLUVIRIN® should only be used for the immunization of persons aged 4 years and over.

6.3 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use of FLUVIRIN®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure. Adverse events described here are included because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

- *Body as a whole:* Local injection site reactions (including pain, pain limiting limb movement, redness, swelling, warmth, ecchymosis, induration), hot flashes/flushes; chills; fever; malaise; shivering; fatigue; asthenia; facial edema.
- *Immune system disorders:* Hypersensitivity reactions (including throat and/or mouth edema). In rare cases, hypersensitivity reactions have lead to anaphylactic shock and death.
- *Cardiovascular disorders:* Vasculitis (in rare cases with transient renal involvement), syncope shortly after vaccination.
- *Digestive disorders:* Diarrhea; nausea; vomiting; abdominal pain.
- *Blood and lymphatic disorders:* Local lymphadenopathy; transient thrombocytopenia.
- *Metabolic and nutritional disorders:* Loss of appetite.
- *Musculoskeletal:* Arthralgia; myalgia; myasthenia.
- *Nervous system disorders:* Headache; dizziness; neuralgia; paraesthesia; confusion; febrile convulsions; Guillain-Barré Syndrome; myelitis (including encephalomyelitis and transverse myelitis); neuropathy (including neuritis); paralysis (including Bell's Palsy).
- *Respiratory disorders:* Dyspnea; chest pain; cough; pharyngitis; rhinitis.
- *Skin and appendages:* Stevens-Johnson syndrome; sweating; pruritus; urticaria; rash (including non-specific, maculopapular, and vesiculobulbous).

6.4 Other Adverse Reactions Associated with Influenza Vaccination

Anaphylaxis has been reported after administration of FLUVIRIN®. Although FLUVIRIN® contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis [see CONTRAINDICATIONS (4)].

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangiitis (vasculitis) has been reported temporally associated with influenza vaccination.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

There are no data to assess the concomitant administration of FLUVIRIN® with other vaccines. If FLUVIRIN® is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites.

FLUVIRIN® should not be mixed with any other vaccine in the same syringe or vial.

7.2 Concurrent Use with Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLUVIRIN®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with FLUVIRIN®. It is also not known whether FLUVIRIN® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLUVIRIN® should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether FLUVIRIN® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLUVIRIN® is administered to a nursing woman.

8.4 Pediatric Use

The safety and immunogenicity of FLUVIRIN® have not been established in children under 4 years of age.

The safety and immunogenicity of FLUVIRIN® have been established in the age group 4 years to 16 years. The use of FLUVIRIN® in these age groups is supported by evidence from adequate and well controlled studies of FLUVIRIN® in adults that demonstrate the immunogenicity of FLUVIRIN® [see ADVERSE REACTIONS (6) and CLINICAL STUDIES (14)].

8.5 Geriatric Use

Since 1997, of the total number of geriatric subjects (n = 397) in clinical studies of FLUVIRIN®, 29% were 65 years and over, while 2.1% were 75 years and over.

Antibody responses were lower in the geriatric population than in younger subjects. Adverse events occurred less frequently in geriatric subjects (≥65 years) than in younger adults. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. [See ADVERSE REACTION (6) and CLINICAL STUDIES (14)].

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New Against the Flu

An adjuvanted influenza vaccine to protect the young and elderly may be just around the corner in the U.S.

by KEITH BERMAN, MPH, MBA, and LUKE NOLL

Image © Novartis AG

EVERYONE KNOWS that getting the flu can be a miserable, temporarily debilitating annoyance. But for young children, the elderly and people with certain chronic diseases, contracting seasonal influenza can sometimes lead to hospitalization with bacterial pneumonia or other serious complications and death. The reason is starkly simple: Natural protective immunity in young children is still underdeveloped, while in the elderly it is in a long decline.

Ironically, for these two particularly vulnerable ends of the age spectrum, immunization with seasonal influenza vaccine is less effective in preventing the flu than it is for older children and non-elderly adults, who mount a stronger protective immune response to the vaccine antigens and, subsequently, the circulating influenza virus itself. While conventional flu vaccines generally provide protection to 70 percent to 90 percent of healthy young adults, the protection rate is far lower in young children and people in their mid-60s and older.

This obvious need for a more immunogenic flu vaccine for the young and elderly who most need it has driven intensive research efforts for decades. Finally, a vaccine that promises to fill this void may be nearing approval. And in an echo of groundbreaking work by British physician Edward Jenner, who in 1796 reported the first successful vaccination against smallpox by use of cowpox from skin lesions of milkmaids, the origins of this new kind of "adjuvanted" influenza vaccine can be traced to keen observation and experimentation.

Adjuvants Provide a Boost

The journey begins in 1925, when a French veterinarian named Gaston Ramon noticed that horses that developed abscesses at the site of injection of diphtheria toxin vaccine produced higher antitoxin titers than horses without abscesses.[1] Soon thereafter, he discovered that sterile abscesses generated by the injection of various substances — lecithin, tapioca, even bread crumbs — along with the diphtheria toxoid also increased the animals' immune response to the toxoid.[2] Ramon coined the term "adjuvant," from the Latin word *adjuvare,* which means to aid or help, to describe these vaccine potentiators.

Shortly following Ramon's discovery, U.S. scientists reported that diphtheria toxoid precipitated with aluminum salts (alum) induced better antibody responses

than toxoid alone, particularly in young children.[3,4] But while alum salts or gels have an excellent safety record and are used in a number of licensed human vaccines, they are relatively weak adjuvants and rarely induce a cell-mediated immune response to combat certain bacteria, parasites and viruses — including the influenza virus.

Then in 1937, a Hungarian-born immunologist named Jules Freund described what immunologists still refer to as the "gold standard" adjuvant: a mineral oil-in-water emulsion containing killed mycobacteria called Freund's Complete Adjuvant (FCA).[5] While far more potent than alum-based adjuvants, FCA was found to be relatively toxic, frequently inducing keloid formation and abscesses at the site of inoculation. A Freund's Incomplete Adjuvant (FIA), formulated without the killed mycobacteria, proved far less toxic. Clinical trials of mineral oil-based influenza vaccines, first conducted in 1953, demonstrated high and sustained antibody responses and protective immunity compared with standard nonadjuvanted trivalent inactivated influenza vaccine (TIV).[6] Adjuvants similar to FIA were incorporated in some human influenza vaccines, but small numbers of delayed side effects including cystic swelling and persistent muscle induration prompted manufacturers to discontinue their use by the mid-1960s.

This didn't stop experimentation with other oil-based emulsions to find a safe and effective vaccine adjuvant. Vegetable oil, sesame oil and peanut oil, among others, were tried, all with disappointing results.[5] Not knowing the underlying mode of action complicated the search for a good adjuvant to potentiate the immunogenic effect of vaccines for which a boost was needed. Finally, scientists at what today is Novartis Vaccines and Diagnostics focused on squalene, a natural lipid produced in plants and animals, including humans. Squalene is found in abundance in human skin, where it acts as a natural moisturizer, and in tissues throughout the body.

After years of clinical testing, in 1997 Novartis introduced Fluad, a seasonal influenza vaccine containing a squalene-in-water microemulsion dubbed "MF59," in Europe for immunization of persons ages 65 years and older. Earlier this year, Canadian health authorities approved Fluad to target this same age group, which accounts for some 70 percent of influenza-related hospitalizations and 90 percent of deaths.

The obvious need for a more immunogenic flu vaccine for the young and elderly who most need it has driven intensive research efforts for decades.

Fluad: Safety and Immunogenicity in the Elderly

With advancing age, the likelihood of a protective antibody response to conventional TIV steadily diminishes. By age 85, there is a 16-fold higher risk of dying from any flu-related cause, and a 30-fold higher likelihood of dying directly from influenza infection or secondary pneumonia than those between age 65 and 69.[7]

In five pivotal trials involving 1,168 subjects ages 65 and older, those immunized with Fluad experienced consistently higher hemagglutinin-inhibition (HI) antibody titers than subjects who received conventional TIV. Greater percentages also achieved seroconversion or a significant increase in HI titers for homologous virus strains.[8]

The safety profile for Fluad approved in Canada is based on 39 studies in which a total of 12,889 subjects were exposed to at least one dose, 492 of whom received a second consecutive dose one year later, and 150 a third dose the following year. Pooled safety data showed that the most frequently reported local adverse events within four days of vaccination were injection site pain (26 percent in the Fluad group vs. 14 percent in the comparator group) and a "warm" or "hot" temperature at the injection site (18 percent vs. 11 percent). Generally of mild or moderate intensity, these reactions usually resolved within two or three days. Systemic reactions, most notably headache, fatigue, malaise and myalgia, were reported by similar percentages of subjects after the first, second and third vaccinations in both the Fluad and comparator vaccine groups.

Whether the superior immunogenicity of Fluad to TIV translates into reduced influenza-related complications and mortality remains to be answered by future clinical studies.

Fluad Appears Protective in Young Children

Fluad's safety and immunogenicity record in the elderly population has raised hopes that this adjuvanted seasonal flu vaccine can be shown safe and protective in the next-largest at-risk group: children under 6 years of age. Findings from a newly published study involving 4,707 previously unvaccinated German and Finnish children ages 6 to 72 months appear to have justified these hopes.[9]

Over two influenza seasons, children were stratified first by age — 6 months

to less than 36 months and 36 months to less than 72 months — and then randomly assigned in a ratio of 2:2:1 to receive two doses, 28 days apart, of 1) MF59 adjuvant-containing TIV (ATIV; Fluad), 2) conventional TIV with hemagglutinin antigens from the same three viral subtypes, or 3) a non-influenza "control" vaccine.* Key efficacy results are summarized in Table 1.

Table 1. Efficacy of MF59-Adjuvant Trivalent Influenza Vaccine (Fluad), TIV and Control (Noninfluenza) Vaccine Against Confirmed Influenza Over Two Seasons in Children Ages 6 to <72 Months[9]

	Relative Efficacy			
	6 to <72 months	6 to <24 months	6 to <36 months	6 to <72 months
Fluad vs. Control	86 (74 to 93)	77 (37 to 92)	79 (55 to 90)	92 (77 to 97)
Fluad vs. TIV	75 (55 to 87)	73 (29 to 90)	64 (23 to 83)	86 (59 to 95)
TIV vs. Control	43 (15 to 61)	11 (-89 to 58)	40 (-6 to 66)	45 (6 to 68)

Over both influenza seasons, the absolute efficacy of Fluad against all influenza strains was 86 percent (95 percent confidence interval [CI], 74 to 93) and 89 percent against vaccine-matched strains (95 percent CI, 78 to 95). Just 13 confirmed cases of influenza occurred among 1,937 children immunized with Fluad — an attack rate of less than 0.7 percent. By contrast, 47 of 993 control group children (4.7 percent) contracted influenza. Relative to TIV, Fluad was 75 percent effective (95 percent CI, 57 to 87) against all flu strains.

Fluad was effective relative to both control vaccine (77 percent) and TIV (93 percent), albeit with wide confidence intervals due to the low (2.3 percent) overall influenza attack rate.

A subanalysis showed that Fluad was efficacious in both younger and older age groups. Fluad efficacy against all flu strains was 79 percent in children 6 months to less than 36 months and 92 percent in those 36 months to less than 72 months of age. TIV efficacy versus controls was just 40 percent (with 95 percent CI overlapping zero) and 45 percent in the younger and older age cohorts, respectively.

Fluad's safety and immunogenicity record in the elderly population raised hopes that this adjuvanted seasonal flu vaccine can be shown safe and protective in the next-largest at-risk group: children under 6 years of age.

Even more striking was the superior efficacy of Fluad in infants from 6 years to less than 24 months of age — the least immunocompetent and thus the least responsive to conventional flu vaccine. While TIV didn't show significant efficacy in relation to control vaccination (11 precent, 95 percent CI, -89 to 58),

As with previous studies of Novartis' MF59-adjuvanted seasonal and pandemic flu vaccines,[10,11] Fluad induced a significantly greater antibody response than TIV, both against homologous (vaccine) and other flu strains. Remarkably, the response to the first of two Fluad injections in these young children met the standard seroprotection threshold (HI antibody titer ≥40) for both A-subtype viruses.

Vaccine-related adverse events were generally mild to moderate in both age cohorts. Systemic reactions, including mild fever, were slightly more frequent in older children after Fluad, but they were mostly mild and of short duration. Rates of serious adverse events were similar in the TIV and Fluad group, and confirm previous experience with MF59 adjuvant in trials of other vaccines involving some 33,000 children.

Approval Prospects Look Good — with a Caveat

With these excellent supportive data, together with experience from more than 50 million Fluad doses supplied to the elderly population since 1997 and twice that number of doses of MF59-adjuvanted pandemic influenza vaccine administered to all age groups, the prospects appear good that Fluad will eventually become available in the U.S.

A new U.S. Phase III clinical trial is now under way to evaluate Fluad in persons ages 65 years and older. Novartis expects to file for regulatory approval of the product for use in this age group in 2012. Meanwhile, the company filed in

*Meningococcal C conjugate vaccine given in 0.25 mL doses in children 6 to <12 months of age, and tickborne encephalitis vaccine given in 0.5 mL doses to children 12 to <72 months of age.

2010 for approval of Fluad in European Union countries for pediatric use.

But still lingering in some minds are safety questions raised by studies in small animal models describing induction of arthritis-like inflammation and lupus autoantibodies following administration of small quantities of squalene, as well as other endogenous lipids.[12,13] A core concern is whether injection, year after year, of even the minute quantity of squalene (about 10 mg in a 0.5 mL dose) in Fluad could trigger immune cross-reactivity with endogenous squalene found in the joints, nervous system or other parts of the body. This hypothetical concern that injection — rather than ingestion — of an important lipid tissue component could trigger autoimmune disease likely figures into the conservative, "go slow" approach of the U.S. Food and Drug Administration (FDA) with respect to vaccines generally that include oil-in-water emulsions.

There is little question that the MF59 adjuvant in Fluad makes it more immunogenic and more protective against seasonal influenza infection than nonadjuvanted flu vaccines.

There is little question that the MF59 adjuvant in Fluad makes it more immunogenic and more protective against seasonal influenza infection than nonadjuvanted flu vaccines. Not unlike Sanofi Pasteur's recently licensed Fluzone High-Dose, there is good reason to expect that Fluad can reduce the risk of hospitalization for major influenza complications in the elderly compared with standard TIV. Assuming this vaccine performs well again in U.S. trials and clears the FDA's high safety hurdle, Fluad together with Fluzone High-Dose could make a serious dent in the terrible toll of influenza in tens of millions of Americans who are most at risk. ❖

References

1. Ramon, G. Sur L'aumentation Anormale de L'antitoxine Chez Les Chevaux Producteurs de Serum Antidiphterique. *Bulletin de la Société de Médecine Vétérinaire*, 1925; 101:227-34.
2. Ramon, G. Procedures pour Acroitre la Production des Antitoxins. *Annales de l'Institut Pasteur*, 1926; 40:1-10.
3. Glenny, A, Pope, C, Waddington, H, et al. Immunological Notes: XVII-XXIV. *Journal of Pathology and Bacteriology*, 1926;29:31-40.
4. Park, WH, and Schroder, MC. Diphtheria Toxin-Antitoxin and Toxoid: A Comparison. *American Journal of Public Health*, 1932;22:7-16.
5. Freund, J, and Hosmer, E. Sensitization and Antibody Formation After Injection of Tubercle Bacilli and Paraffin Oil. *Proceedings of the Society for Experimental Biology and Medicine*, 1937;37:509-13.
6. Stuart-Harris, CH. Adjuvant Influenza Vaccines. *World Health Organization Bulletin*, 1969;41:617-21.
7. Thompson, WW, Shay, DK, Weinstaub, E, et al. Mortality Associated with Influenza and Respiratory Syncytial Virus in the United States. *Journal of the American Medical Association*, 2003;289:179-86.
8. Prescribing Information, FLUAD (Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1). Novartis Vaccines and Diagnostics, Inc. Approved by Health Canada, June 23, 2011.
9. Vesikari, T, Knuf, M, Wutzler, P, et al. Oil-in-Water Emulsion Adjuvant with Influenza Vaccine in Young Children. *New England Journal of Medicine*, 2011;365(15):1406-16.
10. Atmar, RL, Keitel, WA, Patel, SM, et al. Safety and Immunogenicity of Nonadjuvanted and MF59-Adjuvanted Influenza A/H9N2 Vaccine Preparations. *Clinical Infectious Diseases*, 2006;43:1135-42.
11. Vesikari, T, Pellegrini, M, Karvonen, A, et al. Enhanced Immunogenicity of Seasonal Influenza Vaccines in Young Children Using MF59 Adjuvant. *Pediatric Infectious Diseases*, 2009;28(7):563-71.
12. Carlson, BC, Jansson, AM, Larsson, A, et al. The Endogenous Adjuvant Squalene Can Induce a Chronic T-Cell-Mediated Arthritis in Rats. *American Journal of Pathology*, 2000;156(6):2057-65.
13. Satoh, M, Kuroda, Y, Yoshida, H, et al. Induction of Lupus Autoantibodies by Adjuvants. *Journal of Autoimmunity*, 2003;21(1):1-9.

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LUKE NOLL *is director of vaccine sales and corporate accounts at FFF Enterprises, Inc.*

Leading with Diplomacy

"The attributes of a good leader include the ability to work with diverse groups and lead them forward while channeling them toward the art of compromise." — Abbie Cornett

BY TRUDIE MITSCHANG

WHEN IT COMES to being a leader, Abbie Cornett commands a following in many different public and private arenas. As chair and president of The Alliance for Biotherapeutics, Cornett leads a diverse group of constituents that includes patient groups, physicians, manufacturers and distributors. Additionally, her role as a state senator from Nebraska chairing the influential Revenue Committee puts her front and center with the country's key decision makers. Cornett's other leadership positions include university marketing consultant and serving as vice chair of the Environment Committee for the National Conference of State Legislators. When asked about balancing these various responsibilities, Cornett says setting priorities and avoiding procrastination is what keeps her at the top of her game. "The attributes of a good leader include the ability to work with diverse groups and lead them forward while channeling them toward the art of compromise," Cornett explains. "You have to be organized and strategic while also knowing how to delegate when necessary."

A Patient and an Advocate

The mother of three young children, Cornett stepped into her role as president of the Alliance with a unique perspective: She is a patient with a primary immune deficiency disease (PIDD) who understands firsthand what it's like to struggle with access to care. In 2007, Cornett was one of the founding visionaries of the Alliance, which was originally formed under the name The Alliance for Plasma Therapies, a not-for-profit organization created to address the difficulties patients face in having access to intravenous immune globulin (IVIG) therapy.

As president of the Alliance, Cornett advocates for patients who lack access to lifesaving therapies, have reimbursement restrictions and/or are denied coverage.

As of its founding, The Alliance for Plasma Therapies became the first national group to represent all patients and providers of plasma therapies. In March 2011, the Alliance changed its name to The Alliance for BioTherapeutics to become the leading voice for all who benefit from biotherapeutics therapies. "The mission of the Alliance is to help ensure that all individuals in need receive access to, and adequate reimbursement for, lifesaving and life-enhancing biotherapeutics," Cornett says. "We represent patient groups, not specific diseases — we are working to give all patients affordable access to medications."

Promoting Change at the State Level

As president of the Alliance, Cornett advocates for patients who lack access to lifesaving therapies, have reimbursement restrictions and/or are denied coverage. In her role, she also is passionate about

helping patients who can no longer afford therapies prescribed by their physicians because of new policy restrictions. "Currently, the Alliance is focused on policy issues that work against the availability of lifesaving biotherapeutics," Cornett says. "For example, one of the Alliance's areas of focus is on specialty tiers, legislation that requires the patient to pay a certain percentage of the cost of their medication rather than a fixed copayment. This can make necessary medication unaffordable for many of the patients who need it most."

In the debate over affordable care, Cornett notes that the contentious climate in Washington, D.C., has led to political gridlock that has made it more advantageous to pursue legislative change at the state level. "We realized that D.C. was becoming more and more difficult politically, so we've been looking at legislature at the state level, and the good news is there are several important bills on the table in Nebraska, Pennsylvania and California," she explains. "Because the federal government has been stymied, states are stepping up to pass legislation, and I think the outcry from patient groups is bringing a lot of issues to the forefront."

Because her role with the Alliance puts her in front of so many key constituents, Cornett can act as mediator between differing viewpoints and move everyone closer to agreed-upon solutions.

Bringing Stakeholders to the Table

As medical science expands, biotherapeutics are being used for a wider range of disease states and touching the lives of more and more patient groups. But the high cost of treating these patients has created a stalemate between the various stakeholders. Because her role with the Alliance puts her in front of so many key constituents, Cornett can act as mediator between differing viewpoints and move everyone closer to agreed-upon solutions. "I travel to various states looking at the issues, listening to pharmaceutical companies and representatives for insurance groups," Cornett says. "The truth is, there has to be buy-in from all of the stakeholders in order to reach a solution. Everybody acknowledges there is a problem — the question is how do we solve it?"

Although stalemates exist, Cornett asserts that resolutions are in sight. While some patient groups have accused the Alliance of "being in bed with the industry," Cornett disagrees, stating that bringing all of the stakeholders to the table is an essential part of fixing a very broken healthcare and reimbursement system. "I'm proud of how far the Alliance has come, and our goal is to continue to grow nationally as a patient advocacy group and resource," she says. "I'd like nothing better than to add an insurance representative to our board one day because even if we disagree, putting diplomacy into action is essential as we move toward arriving at agreed-upon solutions." ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

The Heart of the Matter

After being misdiagnosed with indigestion, Carolyn Thomas lived to tell what it's like to be a heart attack survivor. Her mission? To help other women foil this all-too-common killer.

by TRUDIE MITSCHANG

Carolyn Thomas is one of many women who are sent home from the emergency room after experiencing textbook heart attack symptoms, only to find out they have suffered a myocardial infarction.

MANY OF US think we'd recognize the symptoms of a heart attack. Movies and television depict heart attack victims clutching their chests, gasping for air and collapsing. The reality for most women heart attack patients, however, is quite different, with symptoms that are less dramatic and consequently downplayed or misdiagnosed. Just ask heart attack survivor Carolyn Thomas.

In 2008, Carolyn was 58 and at the top of her game as a public relations professional and community volunteer. Active and health conscious, Carolyn was out for her morning walk when she suddenly experienced crushing chest pain, waves of nausea, sweating and radiating pain down her left arm. A trip to the emergency room was inconclusive; her cardiac tests, including EKG, blood work and stress test, all came back "normal." The diagnosis? A bad case of acid reflux and a prescription for antacids. "I went home and continued to experience the same symptoms for a period of two weeks," recalls Carolyn. "I tried to downplay what was happening, even joking that 'I better not be having a heart attack!' but deep down I knew something was seriously wrong."

Carolyn's gut instinct was accurate; her second trip to the emergency room confirmed that she'd had a myocardial infarction, and this time test results uncovered significant heart disease. Carolyn was rushed to the operating room and had a stainless steel stent implanted into one of her arteries, which was 99 percent blocked. "What I've learned since my heart attack is that many women still mistakenly consider heart disease to be a man's problem, and sadly, so do some doctors," says Carolyn. "The first doctor I saw in the ER sized me up quickly and thought I had indigestion. That experience is part of what motivated me to become active as a patient advocate."

Educating and Advocating

Five months after her heart attack, Carolyn attended the annual WomenHeart Science & Leadership Symposium at the Mayo Clinic in Rochester, Minn. There, she met dozens of heart attack survivors whose stories mirrored her own. Many had also been sent home from emergency rooms, despite having textbook heart attack symptoms (one woman was told she needed antidepressants — she eventually underwent double bypass surgery). "I thought my story was dramatic until I met some of these other women. When I returned, I began blogging about my experience and launched a series of community presentations about heart health, eventually speaking to thousands of women," says Carolyn.

Carolyn's gut instinct was accurate; her second trip to the emergency room confirmed that she'd had a myocardial infarction, and this time test results uncovered significant heart disease.

Lifestyle and Heart Health

By now, it should be common knowledge that an inactive lifestyle and fast food diet are red flags for heart disease

Heart Facts: What Women and Their Doctors Should Know

- Heart disease is the third-leading cause of death among women ages 25 to 44 years and the second-leading cause of death among women ages 45 to 64 years.
- Sudden or more gradual onset of unremitting chest pain is the most common symptom of a heart attack.
- Forty-five percent of women having heart attacks do not experience chest pain.
- Because the heart can't "feel" pain, the brain resorts to what's called referred pain. Victims commonly perceive pain as coming from the neck, throat, shoulder, arm or back.
- Symptoms of a heart attack can mimic heartburn. Women are more likely to experience these atypical symptoms.

Sources:

Women's Health (www.womenshealth.gov/publications/our-publications/fact-sheet/heart-disease.cfm)

Centers for Disease Control and Prevention Heart Disease Fact Sheet (www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_ women_heart.htm)

risk. But what about lesser known risk factors? One of the biggest surprises about Carolyn's heart attack was that she already was living what she considered to be a healthy lifestyle. She was a distance runner who watched her weight and diet and considered herself to be in good shape. At 58, her career in public relations was stressful — but no more so than the typical business executive, proving yet again that what you don't know can hurt you. "I didn't know that the preeclampsia I experienced during pregnancy increased heart attack risk," she says. "I learned at Mayo Clinic that women with pregnancy complications are four times more likely to develop heart disease." Although symptoms can appear suddenly, heart disease actually develops slowly over the course of 20 or 30 years, which means that many young women may experience risk factors that can lead to heart disease decades down the road — when they least expect it.

According to the Mayo Clinic, other risk factors include high blood pressure, high cholesterol, chronic stress, inactivity, diabetes and smoking. The good news: Women who make even simple lifestyle changes can profoundly influence their odds of avoiding a heart attack. These lifestyle changes can include getting regular exercise; eating a low-salt, high-fiber diet that is low in trans fats; stopping smoking; practicing relaxation techniques; and managing stress.

Gender Disparity in Research

Even though the statistic that heart disease is the No. 1 killer of women is widely touted, misdiagnosis is still common, in part due to gender disparity when it comes to clinical trials and diagnostic tools. Research reported in the *New England Journal of Medicine*, for example, looked at more than 10,000 patients (48 percent women) who went to their hospital emergency rooms with chest pain or other heart attack symptoms. Investigators found that women younger than 55 were seven times more likely to be misdiagnosed than men of the same age. Part of the problem is that many diagnostic tools widely considered to be accurate in identifying heart disease in men are far less accurate in women, especially when it comes to specific types of cardiac events common to women, including single vessel coronary artery disease; nonobstructive coronary artery disease; and spontaneous coronary artery dissection (SCAD). Up to 80 percent of SCAD cases occur in young healthy women with no cardiac risk factors.

In another study, Toronto cardiologist Dr. Wendy Tsang reviewed landmark cardiac clinical trials published over a 10-year period in the *Journal of the American Medical Association*, *The Lancet*, and the *New England Journal of Medicine*. She found that although women comprise 53 percent of patients with cardiovascular disease, in clinical trials they represented only 34 percent with cardiac arrhythmias, 29 percent with coronary artery disease, and 25 percent with congestive heart failure. "Our study shows the proportion of women enrolled in landmark cardiovascular clinical trials is substantially lower than you would find in the general disease population," says Tsang. "What is even more of a shock is that this underrepresentation has not drastically changed over the past decade."[1]

Many women are not alone in their ignorance. In a 2005 American Heart Association study, physicians were asked if they were aware that cardiovascular disease kills more women than men each year. Only 8 percent of family physicians and 17 percent of cardiologists were aware of this fact.

"Without accurate gender-specific diagnostic tests, how can our physicians even begin to decide on appropriate life-saving treatment, drugs or devices for us?" says Carolyn. "Until these cardiac tests are researched and developed, women heart patients will continue to be sent home from the ER misdiagnosed with everything from indigestion to anxiety or even menopause." ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

Reference

1. Where Have All the Women Gone? Heart & Stroke Foundation of Canada. Accessed at www.heartandstroke.on.ca/site/apps/nlnet/content2.aspx?c=pvl3leNWJwE&b=4718797&ct=6273001&printmode=1.

BioResearch

Summaries of up-to-date clinical research published internationally.

Human Albumin Improves Endothelial Dysfunction and Survival in Experimental Endotoxemia Model

In an experiment to better understand the mechanisms by which human albumin might protect against sepsis-induced organ dysfunction and improve survival, French scientists injected three groups of Swiss mice with lipopolysaccharide (LPS) followed by 10 mL/kg of 4% human albumin, 10 mL/kg of 20% human albumin or 30 mL/kg of normal saline. Separately, human uterine vein endothelial cells were exposed to both LPS and tumor necrosis factor-α (TNF-α) for eight hours in the presence or absence of 4% or 20% albumin.

Endotoxemic mice infused with 4% albumin, but not 20% albumin or normal saline solution, experienced an improved average survival time. The 4% albumin treatment also 1) activated endothelial nitric oxide synthase, 2) restored LPS-impaired flow-dependent endothelial dilation in mesenteric arteries, 3) reduced LPS-induced renal dysfunction and 4) enhanced endothelin-1 production and glutathione plasma levels. In the uterine vein model, 4% albumin but not 20% albumin blunted LPS-TNF-α-induced oxidative and nitrosative stresses in endothelial cells and increased their glutathione levels.

"The present data confirm a protective effect of 4% human serum albumin both on [mouse] survival and endothelial dysfunction by inhibiting inflammatory and oxidative stress pathways induced by endotoxins," the investigators concluded. "Conversely, higher [albumin] concentrations were detrimental, suggesting a dose-dependent effect."

Kremer, H, Baron-Menguy, C, Tesse, A, et al. Human serum albumin improves endothelial dysfunction and survival during experimental endotoxemia: concentration-dependent properties. Critical Care Medicine*, 2011 Jun;39(6):1414-22.*

IVIG Produces Sustained Long-Term Clinical Remission in Patients with Epidermolysis Bullosa Acquisita

Specialists at the Center for Blistering Diseases in Boston report on outcomes of administration of intravenous immunoglobulin (IVIG) in 10 patients with severe and widespread epidermolysis bullosa acquisita (EBA) who were nonresponsive to conventional therapy. The four Caucasian males and six females, whose ages ranged from 37 to 75 years (mean 57.4) were treated according to a protocol published in a Consensus Statement for treatment of autoimmune mucocutaneous blistering diseases. The patients received 16 to 31 cycles (mean 23.1) of 2 g/kg/cycle over a period of 30 to 52 months (mean 38.8). Once IVIG was initiated, earlier drugs (prednisone, dapsone and others) were gradually withdrawn over a five- to nine-month period. Thereafter, IVIG was used as monotherapy.

A satisfactory clinical response was observed in all 10 patients. No serious side effects were observed. The follow-up period after discontinuation of IVIG varied from 29 to 123 months (mean 53.9). During this follow-up period, recurrence of disease was not observed in any patient. These data suggest that IVIG can produce a long-term sustained clinical remission in patients with EBA while permitting concomitant therapy to be discontinued, the co-authors concluded.

Ahmed, AR, and Gürcan, HM. Treatment of epidermolysis bullosa acquisita with intravenous immunoglobulin in patients non-responsive to conventional therapy: clinical outcome and post-treatment long-term follow-up. Journal of the European Academy of Dermatology and Venereology*, 2011 Aug 8 [Epub ahead of print].*

Less Pain and Shorter Convalescence with Fibrin Sealant vs. Tacks in Mesh Fixation After Laparoscopic Hernia Repair

Noting that the use of tacks for mesh fixation may induce pain after laparoscopic ventral hernia repair (LVHR), Danish surgeons designed and conducted a randomized clinical trial to compare conventional mesh fixation using titanium tacks against fibrin sealant. Of 40 patients enrolled, 38 were available for intention-to-treat analysis after one month. Acute pain was the primary outcome, and was measured on a 0 to 100 mm visual analogue scale (VAS).

Patients in the fibrin sealant group reported less pain than those in the tack group on days zero to two after surgery, both at rest (median 19 versus 47 mm; $p = 0.025$) and during activity (38 versus 60; $p = 0.014$). The absolute difference in pain score between groups was 19 mm (95% confidence interval, 3 to 34) and 20 mm (95% CI, 4 to 35) at rest and during activity, respectively. Patients in the fibrin sealant group also resumed normal daily activity earlier (after a median of seven versus 18 days; $p = 0.027$), and reported significantly less discomfort. No hernia recurrences were observed.

The investigators concluded that mesh fixation in LVHR was associated with less acute postoperative pain, discomfort and a shorter convalescence than tack fixation. They suggested long-term follow-up to determine whether the benefits of fibrin sealant use persist in terms of chronic pain and non-recurrence.

Eriksen, JR, Bisgaard, T, Assadzadeh, S, et al. Randomized clinical trial of fibrin sealant versus titanium tacks for mesh fixation in laparoscopic umbilical hernia repair. British Journal of Surgery*, 2011 Nov;98(11):1537-45.*

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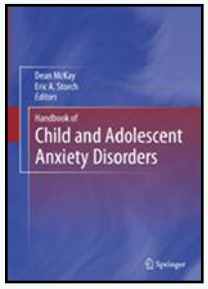
BioResources

Recently released resources for the biopharmaceuticals marketplace.



Handbook of Child and Adolescent Anxiety, 1st ed.

Author: Dean McKay & Eric A. Storch (eds.)

This comprehensive text has the latest information on treatment, assessment, treatment augmentation and basic science. It addresses comorbid and complicating factors in treating children and adolescents with anxiety disorders, as well as discusses cutting-edge controversies in the field of anxiety disorders, such as the placement of obsessive-compulsive disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* and novel augmentation approaches to behavioral therapy. Also included are diagnostic and etiological models of children's anxiety disorders (i.e., genetic, cognitive-behavioral, taxonomic, neuropsychological, dimensional); differential diagnosis guidelines for generalized anxiety disorder, phobic conditions, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) in youth; psychological, pharmacological, and combined treatments for childhood anxiety disorders; special populations and emerging areas of interest, including anxiety disorders in the contexts of chronic health problems and developmental disabilities; and more.
www.springer.com/psychology/child+%26+school+psychology/book/978-1-4419-7782-3

Guide to FDA Drug Safety Regulation

Author: U.S. Food and Drug Administration

This all-in-one desk reference includes the FDA's guidances on postmarketing studies, pre- and postmarketing risk assessment and management, REMs, adverse event reporting, and ICH guidances on clinical safety data management, data elements for transmission of individual case safety reports, and periodic safety update reports for marketed drugs. It also includes manuals of policies and procedures on granting waivers from postmarketing safety reporting and preapproval safety conferences; relevant references from the U.S. Code of Federal Regulations; and text of all the safety-related guidances, including those covering advertising, clinical trials, electronic submissions and risk management.
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State Health Insurance Exchanges and Children's Coverages: Issues for State Design Decisions

Author: National Governors Association Center for Best Practices (NGA Center)

As states consider implementation options under the Affordable Care Act, this brief looks at ways states may pursue several goals with respect to children and exchanges. It was developed based on input during a daylong meeting hosted by the NGA Center. Participants at the meeting included state government officials, general healthcare experts, federal representatives and individuals from nonpartisan health policy institutions.
www.nga.org/cms/home/nga-center-for-best-practices center-publications/page-health-publications/col2-content/main-content-list/state-health-insurance-exchanges.html

Neurology App for the iPad

Author: American Academy of Neurology

Available free of charge at the App Store, the same information that is so critical to neurologists' practices and professions is now available on the iPad. The app optimizes the best in digital technology to enhance a print-like reading experience with article-sharing features, multimedia links and more. Plus, each week, there is a free 20-minute neurology podcast featuring interviews with top experts on the latest issues.
www.aan.com/go/elibrary/journal

NeuroFrontiers

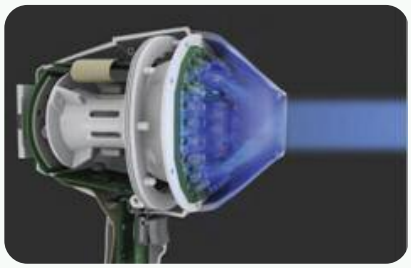
Author: American Academy of Neurology

NeuroFrontiers is a radio show produced in collaboration with the AAN and explores new research, diagnosis and treatment in all areas of neurological disease. This series also addresses the most relevant clinical topics, trends, news and advances pertaining to all areas of the practice of neurology. The show is hosted by AAN member Anthony Alessi, MD, FAAN, and covers a 15-minute topic every week through May. Shows feature interviews with AAN members on a variety of neurology issues, as well as notable news, editorial and clinical discussion, and other hot topics pertaining to neurology and the academy, such as AAN practice parameters and position statements wherever applicable. Shows are available via XM Satellite Radio (Channel 167) and online as a live stream or downloadable podcast (MP3).
www.aan.com/go/elibrary/neuro

BioProducts

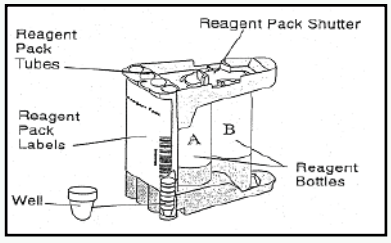
Remote Presence Medicine

Remote Presence is a modality for physician-patient consults that can extend the physician's reach to manage patient care, thereby removing time and distance barriers, wherever access to medical expertise is limited. Through a single interface, physicians can extend their presence across the entire healthcare delivery continuum — from primary and outpatient care, to acute care, rehabilitation and long-term care. Five Remote Presence endpoint devices are available, including the company's flagship RP-7 and RP-7i mobile robotic platforms with the panoramic Virtually There visualization system, which are the first and only FDA-cleared Remote Presence devices that allow direct connection to Class II medical devices; the RP-Lite, which offers full capabilities of pan-tilt-zoom controls to view and speak with patients and medical staff, all through the InTouch Health interface; the RP-Vantage, an FDA-cleared product designed to enable surgical telementoring and remote collaboration in operating and procedure rooms; the RP-Xpress, designed for portability and flexibility, enabling specialist telemedicine consults to take place anywhere across the healthcare continuum; and VisitOR1, which allows expert opinion leaders and consulting surgeons to beam into the operating room environment and observe or confer with the onsite surgeon. A ControlStation allows the remote physician to maneuver the RP-7 Robot through the healthcare facility while interacting with patients, family members and staff. There are three varieties of ControlStations: laptop, desktop or ControlStation Kit (CS Kit), all of which include the Remote Presence software, camera, microphone, speaker and joystick.
InTouch Healthcare, (805) 562-8686, www.intouchhealth.com



Melanoma Detection Tool

MelaFind is a tool for the evaluation of clinically atypical cutaneous pigmented lesions when a dermatologist chooses to gather additional data before making a final decision to biopsy to rule out melanoma. Mela Sciences says that MelaFind is a "non-invasive and objective multi-spectral computer system designed as a tool to aid dermatologists in the detection of early (e.g., non-ulcerated, not bleeding or less than 2.2 cm in diameter) melanoma." It is not a screening device and is not indicated for non-pigmented lesions, lesions that are clinically confirmed as melanomas, or lesions on special anatomical sites, such as acral, mucosal or subungual. The hand-held imager is used to capture lesion images. It is made up of an illuminator that shines light of 10 different specific wavelengths, including near infrared bands; a lens system composed of nine elements that creates images of the light scattered back from the lesions; and a photon (light) sensor. MelaFind received FDA approval in September.
Mela Sciences, (914) 591-3783, www.melasciences.com



Hepatitis B Virus Test

The VITROS Anti-HBe Reagent Pack, Calibrator and Controls is a laboratory test used to detect antibodies produced by the immune system in patients who are chronically infected with hepatitis B virus (HBV). The test is designed for use with the VITROS ECi/ECiQ Immunodiagnostic System, which runs the assay and analyzes the results. It works by mixing a person's blood sample with the test chemicals. If anti-HBe antibodies are present in the blood, a light signal is generated through special chemical reactions. The amount of produced light is measured by the analyzer and the result, reactive or non-reactive for anti-HBe, is printed out. The VITROS Anti-HBe test result is used in combination with other blood tests and clinical information to aid in the laboratory diagnosis and staging of the HBV disease in individuals with hepatitis B infection. It also is used during treatment with antiviral agents to aid in patient management. The test has not been FDA-licensed for screening blood, plasma or tissue donors, and it has not been FDA-approved for testing immunocompromised or immunosuppressed persons or for testing children under the age of 2 years. There are no known contraindications.
Ortho Clinical Diagnostics Inc., (800) 828-6316,
www.orthoclinical.com/en-us/ProductInformation/ClinicalLaboratories/Pages/default.aspx

CALCULATOR

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective January 1, 2012 through March 31, 2012.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+4% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$60.48	$61.64
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$70.15*	$70.15
GAMMAGARD LIQUID	Baxter BioScience	J1569	$74.43	$75.86
GAMMAGARD S/D	Baxter BioScience	J1566	$60.48	$61.64
GAMMAKED	Kedrion	J1561	$73.82	$75.24
GAMMAPLEX	Bio Products Laboratory	J1557	$74.59*	$74.59
GAMUNEX-C	Grifols	J1561	$73.82	$75.24
OCTAGAM	Octapharma	J1568	$111.60†	$ 113.75‡
PRIVIGEN	CSL Behring	J1459	$68.81	$70.13

*ASP + 6% (pass-through drug)
†WAC + 4% (based on Wholesale Acquisition Cost until ASP is re-established)
‡WAC + 6% (based on Wholesale Acquisition Cost until ASP is re-established)

Calculate your reimbursement online at www.FFFenterprises.com.

REFERENCE TABLES

IVIG/SCIG Reference Table

Product	Indications	Size	Manufacturer
CARIMUNE NF Lyophilized	IVIG: PIDD, ITP	3 g, 6 g, 12 g	CSL Behring
FLEBOGAMMA 5% & 10% DIF Liquid	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
GAMMAGARD LIQUID 10%	IVIG/SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g	Baxter BioScience
GAMMAGARD S/D Lyophilized, 5% or 10%	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g	Baxter BioScience
GAMMAKED Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Kedrion
GAMMAPLEX Liquid, 5%	IVIG: PIDD	5 g, 10 g	Bio Products Laboratory
GAMUNEX-C Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
HIZENTRA Liquid, 20%	SCIG: PIDD	5 mL, 10 mL, 20 mL	CSL Behring
OCTAGAM Liquid, 5%	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g	Octapharma
PRIVIGEN Liquid, 10%	IVIG: PIDD, ITP	5 g, 10 g, 20 g	CSL Behring

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
PIDD Primary immune deficiency disease

2012-2013 Influenza Vaccine

Administration Codes: G0008 (Medicare plans) 90471 (non-Medicare plans)
Diagnosis Code: V04.81

Product	Size	When Administered to Indicated Age Group	Code
FLUZONE Intradermal	0.1 mL microinjection	Influenza virus vaccine, split virus, preservative free, for intradermal use	90654
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
FLUARIX	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	0.5 mL single-dose vial		
FLUZONE	0.5 mL prefilled syringe		
FLUZONE	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUMIST	0.2 mL nasal spray	Influenza virus vaccine, live, for intranasal use, when administered to individuals 2-49 years of age	90660
FLUZONE High-Dose	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	90662
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	Q2035
FLULAVAL	5 mL multi-dose vial		Q2036
FLUVIRIN	5 mL multi-dose vial		Q2037
FLUZONE	5 mL multi-dose vial		Q2038

GAMUNEX®-C

Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX-C, [Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified]

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.**

----------INDICATIONS AND USAGE----------

GAMUNEX-C is an immune globulin injection (human) 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

----------CONTRAINDICATIONS----------

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

----------WARNINGS AND PRECAUTIONS----------

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- Passive transfer of antibodies may confound serologic testing.

----------ADVERSE REACTIONS----------

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMUNEX-C were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMUNEX-C were infusion site reactions, headache, fatigue, arthralgia and pyrexia.
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia.

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- The passive transfer of antibodies may transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella. Passive transfer of antibodies may confound serologic testing.

----------USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable.

Talecris BIOTHERAPEUTICS

Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1716

08939771/08939782-BS
Revised: October 2010

The PROOF is everywhere you look

GAMUNEX-C has proven efficacy and patient outcomes in CIDP, PI, and ITP*[1]

Important Safety Information for GAMUNEX-C

Gamunex-C, Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gamunex-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gamunex-C at the minimum concentration available and the minimum infusion rate practicable.

Gamunex-C is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

Gamunex-C is not approved for subcutaneous use in patients with ITP or CIDP. **Due to the potential risk of hematoma formation, Gamunex-C should not be administered subcutaneously in patients with ITP.**

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV.

The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Gamunex-C is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

In clinical studies, the most common adverse reactions with Gamunex-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PI) and infusion site reactions, headache, fatigue, arthralgia and pyrexia with subcutaneous use (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP).

*CIDP=Chronic inflammatory demyelinating polyneuropathy; PI=Primary immunodeficiency; ITP=Idiopathic thrombocytopenic purpura.

Reference: 1. Data on file, Grifols.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see adjacent page for brief summary of GAMUNEX-C full Prescribing Information.

gamunex®-C

immune globulin injection (human), 10% caprylate/chromatography purified

Evidence based. Patient proven.

To get GAMUNEX-C call 1-888-MY GAMUNEX (694-2686)
USA Customer Service: 1-800-243-4153
www.gamunex-c.com

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