FALL 2015

biosupply trends

QUARTERLY

Special Focus: **INNOVATION**

CLINICAL TRIALS

THE PERFECT STORM FOR INCREASING PATIENT PARTICIPATION

Redefining Hemophilia Care with New Products

Precision Medicine: Diagnosis to Tailor-Fit Treatment

House Calls in the Modern Age

Treating PANDAS

More Effective Autoimmune Disease Treatment?

Does High-Dose Flu Vaccine Better Protect Seniors?—Page 54

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Twice the factor*

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is now available in a **2000 IU FVIII vial** with a reconstitution volume of only **10 mL**.

*That's **TWICE** the amount of factor of the largest vial available for other FVIII/VWF products,[1-4] so patients may require:

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Alphanate®
Antihemophilic Factor/von Willebrand Factor Complex (Human)

Indications

ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) is 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 (VWD) in whom desmopressin (DDAVP®) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery

Important Safety Information

ALPHANATE is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

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 von Willebrand disease (VWD) patients has 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.

The most frequent adverse events reported with ALPHANATE in >5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain, and fatigue.

Please see brief summary of ALPHANATE full Prescribing Information on adjacent page.

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.

References: 1. ALPHANATE® (antihemophilic factor/von Willebrand factor complex [human]) Prescribing Information. Grifols. **2.** CSL Behring. Humate P Package Insert. August 2013; **3.** Octapharma. Wilate Package Insert. January 2012; **4.** Kedrion. Koate-DVI Package Insert. August 2012.

For more information: **Grifols Biologicals Inc.**
Tel. 888-GRIFOLS (888-474-3657)

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ALPHANATE®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])

Sterile, lyophilized powder for injection.

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.

----------DOSAGE AND ADMINISTRATION ----------

For Intravenous use only.

Alphanate contains the labeled amount of Factor VIII expressed in International Units (IU) FVIII/vial and von Willebrand Factor:Ristocetin Cofactor activity in IU VWF:RCo/vial.

Hemophilia A: Control and prevention of bleeding episodes

- Dose (units) = body weight (kg) x desired FVIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician.

von Willebrand Disease: Surgical and/or invasive procedure in adult and pediatric patients except Type 3 undergoing major surgery

- Adults: Pre-operative dose of 60 IU VWF:RCo/kg body weight; subsequent doses of 40-60 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.
- Pediatric: Pre-operative dose of 75 IU VWF:RCo/kg body weight; subsequent doses of 50-75 IU VWF:RCo/kg body weight at 8-12 hour intervals post-operative as clinically needed.

----------DOSAGE FORMS AND STRENGTHS ----------

- Alphanate is a sterile, lyophilized powder for intravenous injection after reconstitution, available as 250, 500, 1000, 1500 and 2000 IU FVIII in single dose vials.

----------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 has 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.

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

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Pregnancy: No human or animal data. Use only if clearly needed.
- Pediatric Use: Hemophilia A - Clinical trials for safety and effectiveness have not been conducted. VWD - Age had no effect on PK.

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About BioSupply Trends Quarterly
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Advancing Healthcare: From Testing to Treatment

ON AVERAGE, ONLY 25 new experimental drugs were approved by the FDA's Center for Drug Evaluation and Research (CDER) every year during the past decade. Taking more than 10 years to go from testing to treatment, the healing properties of these drugs help countless numbers of patients, sometimes providing life-changing and lifesaving results.

And, it all begins in the lab. After pre-clinical studies, a drug moves into the human clinical testing stage. But, as our article "The Perfect Storm for Patient-Focused Clinical Trials" explains, getting patients to participate in trials has proved challenging, causing them to falter in staggering numbers. Fear, access, cost and awareness are cited as the major barriers to trial participation. What can be done? The federal government is investing in developing a national patient-centered clinical research network to consolidate and share data, and new enacted legislation mandates the inclusion of patients in earlier stages of development, which spurred the pharmaceutical industry to develop its own approaches to encourage participation. In addition, many patient organizations are looking at ways to educate patients, make them feel more empowered and make it easier for them to access clinical trials.

PANDAS, a rare neurological disease, is one example of how research to find new treatments is often limited by small participation numbers. Dr. Rodney Lusk, author of the article "PANDAS Treatment," discusses several case reports that looked at whether tonsillectomy and adenoidectomy might more successfully treat and resolve the symptoms of PANDAS than current treatments. While the results are mixed, more importantly, they reiterate the need for more accurate and thorough studies.

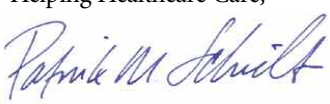
Another challenging area of research centers on autoimmune disorders (ADs), some of which are treated with high doses of human plasma-derived immune globulin (IG). Made from a limited resource, IG is highly expensive to manufacture. Fortunately, as our article "Autoimmune Disease: A More Effective Treatment on the Horizon?" details, a molecular discovery known as sialic acid could pave the way for IG to more effectively treat ADs in smaller doses. Even more exciting is that sialic-switch technology could be used with a laboratory-made molecule to reduce the need for the plasma-derived product.

In fact, research conducted to develop treatments for diseases at the molecular level is a major focus today. In "Precision Medicine: A Seismic Shift in Treatment Strategy," we look at research being conducted to develop treatments targeted to individual patient needs based on genetic, biomarker, phenotypic or psychosocial characteristics. Precision medicine combines information technology with the field of medicine by creating a biobank of patient data research showing which drugs attack diseases at the chemical and genetic level. Physicians can access this biobank to find therapies that might best treat an individual, minimizing the trial-and-error portion of the treatment process.

The value of new treatments can't be overstated. As author and blood expert Keith Berman states in his article "The Future Has Arrived: A Wave of New Products Is Redefining Hemophilia Care," treatment for hemophiliacs has undergone a radical transformation. Berman catalogs the history of coagulation factor products, bringing us up to date on the current extended half-life products that have reduced the number of required infusion sessions and resulted in improved treatment compliance.

As always, 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

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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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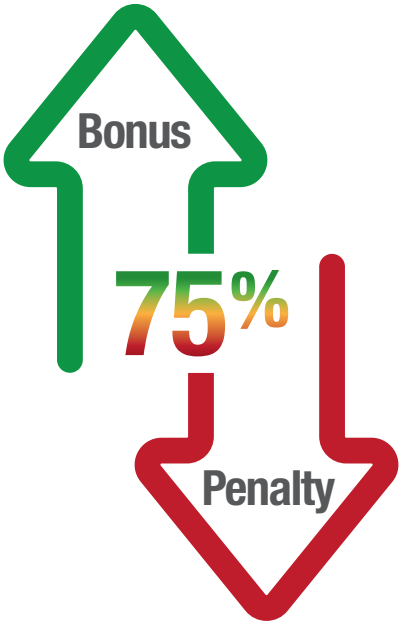
New Law to Prohibit Medigap Plans from Covering Part B Deductible

The Medicare Access and CHIP Reauthorization Act of 2015, which was enacted into law on April 16, will prohibit Medicare supplemental insurance (Medigap) policies from covering the Part B deductible for people who become eligible for Medicare on or after Jan. 1, 2020. The provision is designed to make future Medigap purchasers more price-sensitive when it comes to medical care, which could lead to a reduction in the use of health services and Medicare spending. The Congressional Budget Office estimates that the new law will reduce federal spending by about $400 million between 2020 and 2025.

The plans that currently cover Part B expenses, known as first-dollar coverage, include Medigap policy Plans C and F, Medicare Advantage plans, employer or union-sponsored retiree health plans and Medicaid for individuals with low incomes. The new law will restrict first-dollar coverage for Medigap policies but not other sources of supplemental coverage. However, between 2004 and 2010, the number and share of 65-year-old beneficiaries purchasing a Medigap policy steadily declined from 35 percent to 19 percent. About half of those enrollees had Plan C or F, which cover the Part B deductible. And, as Medigap enrollment declined, Medicare Advantage enrollment increased. If the restriction on first-dollar Part B coverage had been applied to all Medigap policyholders with Plan C or F in 2010, 12 percent of all Medicare beneficiaries would have been affected. Therefore, based on declining Medigap enrollment trends, a smaller share of new Medicare benefits is expected to be affected by the law. ❖

Third Track for Shared Savings ACOs Offers More Flexible Rules

A final rule issued by the Centers for Medicare and Medicaid Services (CMS) is intended to maintain the rigor of the Medicare Shared Savings program (created by the Affordable Care Act), while ensuring providers continue to participate. Under the final rule, a third track will be added for shared savings for accountable care organizations (ACOs). Providers opting into track three will take on more financial risk but could also share in potentially higher savings. According to CMS, the upside and downside risk for the third model will be 75 percent, meaning an ACO's bonus or penalty would be 75 percent of its savings or loss. ACOs in track three are also given a fixed population of beneficiaries to care for.



The first (and safest) track of Shared Savings ACOs originally called for providers to receive rewards for meeting cost and quality targets for three years, after which they would be responsible for both rewards and penalties. However, earlier this year, CMS finalized a proposal that allows ACOs to enter another three-year period in which they can avoid financial penalties. According to Jeffrey Spight, president of Collaborative Health Systems, a division of health insurer Universal American, allowing no risk "is a very strong message from CMS and the administration that they are committed to the long-term viability of the program." In a separate rule later this year, CMS readjusted its methodology for benchmarking and rebasing since several pioneer ACOs have said they faced significant penalties even though they had high-quality scores and saved Medicare money. The new method will account for regional trends and future savings, rather than solely ACOs' own recent spending.

Health and Human Services (HHS) Secretary Sylvia Mathews Burwell set a goal in January to tie 30 percent of all traditional Medicare payments to alternative payment models such as ACOs and bundled payments by the end of 2016. That goal increases to 50 percent by the end of 2018. An independent evaluation report released by HHS showed that the payment model created by ACOs generated more than $384 million in savings to Medicare over its first two years — an average of approximately $300 per participating beneficiary per year — while continuing to deliver high-quality patient care. ❖

Report Provides Stats for 2015 Health Insurance Marketplace Coverage

Nationwide, nearly 11.7 million consumers selected or were automatically re-enrolled in health insurance coverage through the Health Insurance Marketplace as of Feb. 22, according to a report by the U.S. Department of Health and Human Services. Of those, 8.84 million (76 percent) were in states using the HealthCare.gov platform and 2.85 million (24 percent) were in the 14 states (including Washington, D.C.) using their own Marketplace platforms. Nearly 7.7 million individuals with a plan selection in the states using HealthCare.gov qualified for an average tax credit of $263 per month, and more than half (55 percent) paid $100 or less per month after tax credits. The report does not include information on effectuated enrollment. To have coverage effectuated, consumers need to pay their first month's health plan premium. ❖

4.6 million	NUMBER OF PLAN SELECTIONS IN HEALTHCARE.GOV STATES ENROLLED IN BY NEW CONSUMERS WHO DID NOT HAVE MARKETPLACE COVERAGE AS OF NOVEMBER 2014
4.2 million	NUMBER OF CONSUMERS WHO RE-ENROLLED IN MARKETPLACE COVERAGE
2.2 million	NUMBER OF ACTIVE RE-ENROLLEES (THOSE WHO CAME BACK TO THE MARKETPLACE, UPDATED THEIR INFORMATION AND ACTIVELY SELECTED A PLAN)
1.2 million	NUMBER OF ACTIVE RE-ENROLLEES WHO SWITCHED TO A DIFFERENT PLAN FROM WHAT THEY HAD IN 2014

Manufacturers Must Give Six-Month Notice for Stoppages

The U.S. Food and Drug Administration (FDA) has issued a final rule that requires manufacturers to give six months' notice if they plan to discontinue or interrupt production — the same timeline industry has been operating under for the past three years. The rule implements a key provision of the FDA Safety and Innovation Act, which is expected to have an outsized effect on manufacturers of generic injectable drugs. Products listed in the rule don't have to meet the definition of "medically necessary" as used in the Center for Drug Evaluation and Research's Manual of Policies and Procedures and the Center for Biologics Evaluation and Research's Standard Operating Policy and Procedure on shortages of regulated products, which refers to drugs that have no appropriate substitutes.

Under the rule, reportable stoppages include:

• A business decision to permanently discontinue manufacturing a product;

• A delay in acquiring active pharmaceutical ingredients that is likely to lead to a manufacturing disruption;

• Equipment failure or contamination impacting the quality of drugs or biologics;

• Production shutdown for maintenance purposes that extend for longer than anticipated;

• Business mergers or transfer of applications for a covered product to a new firm, if this is likely to cause a disruption in support; and

• An interruption in manufacturing that may not cause a marketwide shortage of the product but will still result in disruption of the drugmaker's product.

Interruptions don't have to be reported if production is expected to resume in a relatively short time frame. In the event of a natural disaster, companies have five business days to file notice.

According to FDA, early notice of production shutdown by manufacturers of life-supporting and life-sustaining drugs and biologics has allowed FDA to avert more than 550 potential drug shortages in the last three years. Since the rule was issued in 2011, early notifications jumped from 10 per month to 60 per month. FDA anticipates it will receive 305 notifications of production shortages from 75 firms annually. ❖

ICD-10, Audits and Authorizations

Healthcare practitioners may feel overwhelmed amid the onslaught of payment reforms brought about by unsustainable increasing healthcare costs. A substantial portion of these changes is related to drugs and biologicals, including immunotherapy agents. The interrelationship between three major issues — ICD-10 conversion, the increasing burden of recovery auditor contractor (RAC) audits and the need to streamline authorizations and meet local coverage determination (LCD) and national coverage determination (NCD) requirements — that all practices and facilities are grappling with presents an interesting opportunity. Rather than being overwhelmed by the perceived complexity of solving three complicated issues, practitioners can learn to be cross-functional by recognizing how solutions to one issue can depend upon and assist with solutions to the other two.

ICD Conversion

Created years ago initially as a mechanism for categorizing death during times of war, the International Classification of Diseases, or ICD (now the responsibility of the World Health Organization), is used to standardize codes for medical conditions and procedures. Standardization allows the world to use a common language to compare and share health information. Even though most countries already use the 10th revision of these codes (ICD-10), the United States is still in the process of adopting it, and it's the last major industrialized nation to do so. ICD-9 codes are now over 35 years old, have a very limited number of new codes that can be created since categories are too full for expansion, and don't accurately represent current detailed specific disease state descriptions and definitions. ICD-9 codes are also inconsistent with current medical practice — so much so that several ICD-9 codes often have to be combined or modified to accurately represent the complexity of the patient. The ICD-10 code set has thousands more codes to choose from to achieve a much greater level of specificity. And, therein lies one of the problems with the transition: It's not just a simple crosswalk; instead, it will require practitioners to completely relearn how disease states are coded.

Healthcare practitioners had to begin using the ICD-10 codes on Oct. 1. Codes are assigned by revenue cycle team coders who review what is in patients' medical records to find disease states and conditions along with procedures and treatments. For the new code set to succeed, the documentation in electronic health records (EHRs) and the modification of order sets in computerized physician order entries (CPOEs) need to be substantially improved in both the inpatient and outpatient settings. If coders cannot find documentation of the complexity of patients' conditions and subsequent treatment plans, they will not be able to code appropriately using the new ICD-10 code set. Although the current procedural terminology and/or healthcare common procedure coding system payment codes do not change either in their descriptions or their rates, the link between these codes and the correct ICD-10 diagnosis codes is essential to ensure payment. The onus definitely is on clinicians to significantly improve their documentation.

Figure 1. Prior Approval vs. NCDs and LCDs

	Prior Approval (Payer)	NCDs and LCDs
Applies to	3rd party carriers (possibly Medicaid)	Medicare (possibly Medicaid)
Need patient's payer status?	yes	yes
Drug tagged in CPOE/PDM?	yes	yes
Link to actual rule needed?	yes	yes
Rule requirements	Ask permission first before drug administration	Understand and follow requirements, document completely and thoroughly. Code correctly and as required
Payment	Only if permission is given first	Determined after the fact and may be denied if not all rules followed

RAC Audits

The increasing burden of RAC audits affects healthcare facilities both administratively and financially. Currently, most RAC audits are for medical necessity issues. This means practitioners must be cognizant of LCD and NCD requirements or prior authorizations for an ever-increasing number of drugs, biologics and immunotherapy agents. It also means that documentation is essential. For instance, when the payer receives a claim for a treatment or drug and the substantiating information that supports that claim has not been sent along with it, that translates to poor documentation. If there is nothing in the medical record for the coders to code, nothing can be sent to the payer.

These audits are designed to ensure that the drug chosen is appropriate for the condition the patient is being treated for. Auditors often rely on published national guidelines (e.g., National Comprehensive Cancer Network guidelines for oncology patients) or on well-documented pathways of treatment. In essence, they link the drug chosen with a diagnosis and the procedures performed. But all those diagnosis codes are about to change. This is why practitioners must be prepared and involved in the process as they transition to ICD-10. They must play a role in planning for possible contingencies related to denied or delayed claims that affect their drug budget.

Streamlining Authorizations

The need to streamline prior authorizations and meet LCD and NCD requirements to ensure payment for drugs is essential. Figure 1 suggests how using existing systems can substantially improve this process.

Following are a couple of suggestions to ensure authorizations are streamlined:

Available Resources

The Centers for Medicare and Medicaid Services (CMS) provides training for conversion to the healthcare community:

1. The CMS website has a lot of information to help practitioners keep up to date on the ICD-10 transition at www.cms.gov/Medicare/Coding/ICD10/index.html?redirect=/ICD10. In addition, Roadto10.org has the latest news and resources to help practitioners prepare.

2. To respond to myths and common misperceptions about ICD-10, CMS has developed a new animated video that features a countdown with 10 facts about the new code set and transition at www.youtube.com/watch?v=PXZ3XOYYyn4&feature=youtu.be

3. The new ICD Quick Start Guide offers five steps to help healthcare professionals prepare for ICD-10 at www.cms.gov/Medicare/Coding/ICD10/Downloads/ICD10QuickStartGuide20150622.pdf

1) Prepare a list of all drugs with LCD and NCD or prior authorization requirements; correct linkage to the new ICD-10 codes will determine payment for them. Pick one or two drugs to use as an example of impact. Although a patient navigator or other individuals may be responsible for actually seeking and fulfilling these requirements, it's the practitioner's budget that will be negatively affected if payment is denied or delayed.

2) Review all medication orders in the CPOE system that are connected to a particular disease state or defined pathway; correct linkage to the new ICD-10 codes is essential. Pick a few order sets to use as an example of impact, and review all clinical trials the practice is involved in because documentation of patient eligibility will be changed with the new codes.

Common Ground

What do these three issues — ICD-10 transition, audits and authorizations — share in common? They use the substantially improved complexities and descriptions in the ICD-10 codes to document why a patient is being treated and for which conditions, along with meeting the requirements posed by prior authorizations, LCDs and NCDs to ensure accurate payment and get rid of RACs! It's all about documentation. What's more is that the new ICD-10 codes compare patients to those with worldwide access to the biosimilar drugs and biologics that will be making inroads in the U.S. ❖

BONNIE KIRSCHENBAUM, *MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.*

Live Life Fully

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

Gammaplex is proven protection

> In 50 patients with PID*, no serious acute bacterial infections were reported during a 12-month trial with Gammaplex[1]

> In 35 patients with ITP† given two days of treatment with Gammaplex, 83% achieved platelet counts ≥50 x 10^9/L by day 9 of the trial[2]

Gammaplex infusion rate can be increased every 15 minutes as tolerated[1,3]

Gammaplex is a pure IVIG product with favorable product characteristics[4]

> Low IgA content
> Low percentage of aggregates
> Viscosity similar to plasma

* PID = primary immunodeficiency
† ITP = immune thrombocytopenic purpura

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

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

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

IMPORTANT SAFETY INFORMATION

Gammaplex® (immune globulin intravenous [human], 5% liquid) is indicated for the replacement therapy in adults with 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.

Gammaplex is also indicated for the treatment in adults with chronic immune thrombocytopenic purpura (ITP).

Thrombosis may occur with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive immune globulin intravenous (IGIV) products, including Gammaplex.

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. Gammaplex does not contain sucrose.

For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Gammaplex is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to human immune globulin; an hereditary intolerance to fructose and in infants and neonates for whom sucrose or fructose tolerance has not been established; and IgA deficient patients with antibodies to IgA and a history of hypersensitivity.

Thrombotic events may occur following treatment with immune globulin products, including Gammaplex. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.

In patients at risk of developing acute renal failure, monitor renal function, including blood urea nitrogen (BUN), serum creatinine and urine output. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

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. Patient risk factors that may be associated with development of hemolysis include high dose (>2 g/kg), non-O blood group, and underlying inflammatory state. 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). If TRALI is suspected, test product and patient's serum for anti-neutrophil antibodies.

Gammaplex is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex.

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

Serious adverse reactions observed in clinical trial subjects with PI were thrombosis and chest pain. Serious ARs observed in clinical trial subjects with ITP were headache, vomiting and dehydration.

Please refer to the Gammaplex Prescribing Information for full prescribing details.

REFERENCES

1. Moy JN, Scharenberg AM, Stein AR, et al. *Clin Exp Immunol.* 2010;162:510-515.
2. Dash CH, et al. *PLoS ONE.* 2014;9(6):e96600.
3. Gammaplex® (Immune Globulin Intravenous [Human], 5% Liquid) Prescribing Information. Raleigh, NC: BPL Limited. 2014.
4. Data on file, BPL: December 2011

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

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Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

BRIEF SUMMARY

CONSULT FULL PRESCRIBING INFORMATION FOR COMPLETE PRODUCT INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION and ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur in predisposed patients who receive immune globulin intravenous (IGIV) products, including Gammaplex. 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. Gammaplex does not contain sucrose. For patients at risk of thrombosis, renal dysfunction or acute renal failure, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

INDICATIONS AND USAGE

Primary Humoral Immunodeficiency (PI) - Gammaplex is an Immune Globulin Intravenous (Human), 5% Liquid indicated for replacement therapy in adults with primary humoral immunodeficiency (PI). Chronic Immune Thrombocytopenic Purpura (ITP) - Gammaplex is indicated for the treatment of adults with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.

CONTRAINDICATIONS

Gammaplex is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. Gammaplex is contraindicated in patients with hereditary intolerance to fructose, also in infants and neonates for whom sucrose or fructose tolerance has not been established. Gammaplex is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity.

WARNINGS AND PRECAUTIONS

Renal Dysfunction / Failure:

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering Gammaplex. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

Thrombotic Events:

Thrombosis may occur following treatment with immune globulin products, including Gammaplex. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. 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 at risk of thrombosis, administer Gammaplex at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

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. Gammaplex contains trace amounts of IgA (<10 µg/mL). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Gammaplex is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction.

Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia:

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because 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 thrombotic events.

Aseptic Meningitis Syndrome (AMS):

AMS may occur 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 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 frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and 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.

Hemolysis:

Gammaplex 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. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration and acute hemolysis, consistent with intravascular hemolysis, has been reported. The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., ≥2 g/kg), given either as a single administration or divided over several days, and non-O blood group. Closely monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching.

Transfusion-related Acute Lung Injury (TRALI):

Noncardiogenic pulmonary edema may occur in patients following IGIV treatment. 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 in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Volume Overload:

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of volume overload.

Transmissible Infectious Agents:

Because Gammaplex is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of Gammaplex. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare providers to **BPL Inc. 1-866-398-0825**. Before prescribing Gammaplex, the physician should discuss the risks and benefits of its use with the patient.

Laboratory Tests:

After infusion of immunoglobulin, 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. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test. Clinically assess patients with known renal dysfunction, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or those receiving nephrotoxic agents, and monitor as appropriate (BUN, serum creatinine, urine output) during therapy with Gammaplex. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with polycythemia, cryoglobulins, fasting chylomicronemia/markedly high triglycerides, or monoclonal gammopathies. Consider measuring hemoglobin or hematocrit at baseline and approximately 36 to 96 hours post infusion in patients at higher risk of hemolysis. If signs and/or symptoms of hemolysis are present after an infusion of Gammaplex, perform appropriate laboratory testing for confirmation. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

ADVERSE REACTIONS

Serious adverse reactions (ARs) observed in clinical trial subjects with primary humoral immunodeficiency (PI) were thrombosis and chest pain. Serious ARs observed in clinical trial subjects with immune thrombocytopenic purpura (ITP) were headache, vomiting and dehydration. The most common ARs observed in the PI clinical trial were headache (18 subjects, 36%), pyrexia (8 subjects, 16%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%), pain (4 subjects, 8%), and vomiting (3 subjects, 6%). The most common ARs observed in the chronic ITP clinical trial were headache (12 subjects, 34%), vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritus (2 subjects, 6%) and arthralgia (2 subjects, 6%).

Clinical Trials Experience:

Because 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 multicenter, open-label, non-randomized clinical trial, 50 subjects with PI received doses of Gammaplex ranging 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. Twenty-four subjects (48%) had an AR at some time during the clinical trial that was considered product-related. The total number of ARs during infusion or within 72 hours of infusion was 237 (a rate of 0.34 ARs per infusion). The percentage of Gammaplex infusions with one or more ARs within 72 hours of infusion was 21%. The upper bound of the 1-sided 97.5% confidence interval for this percentage was 24%, which was below the pre-specified upper limit of 40% for this safety endpoint. The most common ARs observed in this clinical trial were headache (18 subjects, 36%), fatigue (6 subjects, 12%), nausea (6 subjects, 12%), pyrexia (6 subjects, 12%), pain (4 subjects, 8%), hypertension (3 subjects, 6%), chills (3 subjects, 6%), myalgia (3 subjects, 6%) and vomiting (3 subjects, 6%). Two subjects experienced serious ARs (thrombosis and chest pain). Forty-seven of the 50 subjects enrolled in this clinical trial had a negative direct antiglobulin test (DAT) at baseline. Of these 47 subjects, 4 (9%) developed a positive DAT at some time during the clinical trial. However, no subjects showed evidence of hemolytic anemia.

Table 1: Adverse Reactions (ARs*) Occurring in >5% of Subjects with PI

Adverse Reactions	Subjects (%) PI [n=50]	Infusions (%) PI [n=703]
Headache	18 (36%)	53 (7.5%)
Pyrexia	7 (14%)	10 (1.4%)
Sinusitis	8 (16%)	9 (1.3%)
Fatigue	6 (12%)	9 (1.3%)
Nausea	6 (12%)	7 (1.0%)
Nasal Congestion	5 (10%)	3 (0.4%)
Pain	4 (8%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)
Chills	3 (6%)	5 (0.7%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Muscle spasms	3 (6%)	2 (0.3%)
Myalgia	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)

**Adverse Reactions (ARs) are defined as treatment emergent adverse events which met any of the following criteria: (a) adverse events which began during an infusion of Gammaplex or within 72 hours of the end of an infusion, (b) adverse events considered by the investigator or sponsor to have been possibly, probably, or definitely related to administration of Gammaplex, (c) adverse events for which the investigator's causality assessment was either missing or indeterminate.*

Treatment of Chronic Immune Thrombocytopenic Purpura:

In a multicenter, open-label, non-randomized clinical trial, 35 subjects with chronic immune thrombocytopenic purpura were treated with a nominal dose of 1,000 mg/kg on each of two consecutive days (total dose 2,000 mg/kg). Doses of Gammaplex ranged from 482 to 1149 mg/kg on an infusion day. The median total dose per subject was 2035 mg/kg. All 35 subjects received at least one infusion of clinical trial drug, and all but one subject completed the first course of treatment. Twenty-four subjects (69%) reported at least one AR (103 in total); the most commonly reported being headache (12 subjects, 34%), vomiting (8 subjects, 23%), nausea (5 subjects, 14%), pyrexia (5 subjects, 14%), pruritus (2 subjects, 6%), dehydration (2 subjects, 6%) and arthralgia (2 subjects, 6%). Three subjects experienced a total of five serious ARs. Of the five serious ARs, one subject had three concurrently (vomiting, dehydration and headache) and two subjects each had one serious AR (headache). One of these latter two subjects discontinued from the clinical trial because of the severe headache. Table 2 lists the ARs in more than 5% of subjects. Based on a review of clinical and laboratory data, 4/35 subjects (11%) with drops in hemoglobin exceeding 2 g/dL following administration of Gammaplex were considered to have experienced suspected treatment-emergent hemolysis. Milder treatment-emergent hemolysis could not be excluded for an additional 7 subjects, giving a total of 11 of 35 subjects (31%) for whom hemolysis could not be excluded (not including an additional two subjects who lacked follow-up testing for hemolysis, so their hemolysis status was considered unassessable).

Table 2: Adverse Reactions (ARs) Occurring in >5% of Subjects with ITP

Adverse Reactions	Subjects (%) ITP [n=35]	Infusions (%) ITP [n=94]
Headache	12 (34%)	15 (16%)
Vomiting	8 (23%)	9 (9.6%)
Nausea	5 (14%)	5 (5.3%)
Pyrexia	5 (14%)	7 (7.4%)
Pain	2 (6%)	2 (2.1%)
Abdominal pain upper	2 (6%)	2 (2.1%)
Nausea	6 (12%)	7 (1.0%)
Nasal Congestion	5 (10%)	3 (0.4%)
Gastritis	2 (6%)	2 (2.1%)
Contusion	2 (6%)	2 (2.1%)
Arthralgia	2 (6%)	2 (2.1%)
Cough	2 (6%)	2 (2.1%)
Anemia	2 (6%)	1 (1.1%)
Ecchymosis	2 (6%)	3 (3.2%)
Pruritus	2 (6%)	2 (2.1%)
Dehydration	2 (6%)	2 (2.1%)
Hypertension	2 (6%)	1 (1.1%)
Neck pain	2 (6%)	1 (1.1%)

**Adverse Reactions (ARs) are defined as treatment emergent adverse events which met any of the following criteria: (a) adverse events which began during an infusion of Gammaplex or within 72 hours of the end of an infusion, (b) adverse events considered by the investigator or sponsor to have been possibly, probably, or definitely related to administration of Gammaplex, (c) adverse events for which the investigator's causality assessment was either missing or indeterminate.*

In neither of the above trials was there evidence of transmission of HBV, HCV, HIV and parvovirus B19.

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

In addition to the adverse reactions identified in clinical studies, the following adverse reactions have been identified during postmarketing use of Gammaplex: ***Infusion reactions:*** Dizziness, back pain, flushing; ***Respiratory:*** Pulmonary embolism, dyspnea; ***Cardiovascular:*** Myocardial infarction; ***Integumentary:*** Rash, urticarial. The following adverse reactions have been identified during post-marketing use of intravenous immune globulins: ***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

DRUG INTERACTIONS: Transitory rise of the various passively transferred antibodies in the patient's blood after infusion of immunoglobulin may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test. Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella. Inform the immunizing physician of recent therapy with Gammaplex so that appropriate measures may be taken.

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Medicines

Wilate Approved for Perioperative Management of Bleeding in VWD Patients

The U.S. Food and Drug Administration (FDA) has approved revised product labeling for Wilate (von Willebrand factor/coagulation factor VIII complex [human]) to include prevention of excessive bleeding during and after minor and major surgery in adult and pediatric von Willebrand disease (VWD) patients. Formerly, Wilate's product label included only the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe 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.

In a global multi-center Phase III clinical study, the overall efficacy rate of Wilate treatment for surgical procedures was 96.7 percent. The trial observed 28 patients with types 1, 2 and 3 VWD from 24 centers in eight countries who underwent 30 surgeries and 280 infusions. Wilate treatment was successful in 100 percent of minor surgeries and 95.2 percent of major surgeries. The success rate was 100 percent in surgical procedures for type 3 patients, the most serious form of VWD.

"Preventing excessive intra- and postoperative bleeding in pediatric and

adult VWD patients is a continuing challenge," said Octapharma USA President Flemming Nielsen. "We are extremely pleased that Wilate is now available for medical providers managing this important issue." ❖

Manufacturer News

Baxalta Spins Off from Baxter BioScience

On July 1, Baxter International spun off its Baxter BioScience global biopharmaceutical business into Baxalta, which will focus on developing new treatments for people with orphan diseases and underserved conditions. According to Baxter, Baxalta will build on its strengths in hematology and immunology, while seeking to expand its oncology portfolio for patients with limited treatment options.

With its launch, Baxalta has four products under regulatory review. For hematology, Baxalta will add to its roster of existing products, including Advate (antihemophilic factor [recombinant]) and Feiba (anti-inhibitor coagulant complex [human]), with new offerings that include BAX 855, an extended half-life recombinant factor VIII treatment for hemophilia A to be marketed in the U.S. as Adynovate (antihemophilic factor [recombinant], pegylated). It will also advance a Phase I/II open-label clinical trial assessing the safety and optimal dosing level of a factor IX gene therapy treatment for hemophilia B. For immunology, Baxalta hopes to expand its immune globulin portfolio with HYQVIA (immune globulin infusion 10% [human] with recombinant human hyaluronidase) for adults with primary immunodeficiency. And, for oncology, Baxalta has filed for approvals with the U.S. Food and Drug Administration and European regulators to market MM-398 (irinotecan liposome injection), co-developed with Merrimack Pharmaceuticals for metastatic pancreatic cancer. In March, Baxter and partner CTI BioPharma announced positive Phase III PERSIST-1 trial results for the myelofibrosis treatment pacritinib. In addition, Baxalta plans to add the Oncaspar (pegaspargase) product portfolio for acute lymphoblastic leukemia, which Baxter said in May it was buying from Sigma-Tau Finanziaria. That deal is expected to close in the second half of 2015.

Baxalta employs 16,000 people worldwide and is headquartered in Deerfield, Ill., with a global innovation and research and development center set to open later this year in Cambridge, Mass. ❖

Baxalta Spins Off from Baxter. GEN, July 1, 2015. Accessed at www.genengnews.com/gen-news-highlights/baxalta-spins-off-from-baxter/81251456.

Reimbursement

CMS Expands Coverage of HYQVIA for PI Patients to In-Home Use

The Centers for Medicare and Medicaid Services (CMS) has expanded coverage to include in-home use of HYQVIA (immune globulin infusion 10 percent [human] with recombinant human hyaluronidase) to treat primary immunodeficiency patients. Following HYQVIA's U.S. Food and Drug Administration approval in 2014, CMS covered both provider facility and in-office treatment with HYQVIA. The expansion includes durable medical equipment coverage of the infusion pump required to administer the drug. "Today's decision from CMS reinforces the value of HYQVIA and will help expand access to even more people who can benefit from the flexibility of self-administering HYQVIA in their own homes," said Jacopo Leonardi, executive vice president and president, immunology, for Baxalta. "This coverage is a critical step forward in meeting their needs and equipping them to better manage their disease." ❖

Vaccines

AMA Adopts More Stringent Vaccine Requirement Policy

At its annual meeting in June, the American Medical Association (AMA) adopted a new policy to seek more stringent state immunization requirements to allow exemptions only for medical reasons. The policy recommends that states have in place an established decision mechanism that involves qualified public health physicians to determine which vaccines will be mandatory for admission to school and other public venues. That recommendation includes that states grant exemptions to those mandated vaccines only for medical reasons. In addition, the policy states that physicians and other health professionals who have direct patient care responsibilities have an obligation to accept immunization unless there is a recognized medical reason. The AMA will support the dissemination of materials on vaccine efficacy to states as part of its effort to eliminate non-medical exemptions. Currently, immunization requirements vary from state to state, but only two states bar non-medical exemptions based on personal beliefs. ❖

Medicines

Gammaplex Approved for PI Patients 2 Years and Older

In August, the U.S. Food and Drug Administration (FDA) approved Bio Products Laboratory's Gammaplex (immune globulin intravenous [human] 5% liquid) for pediatric patients 2 years of age and older who have primary immunodeficiency disease (PI). The approval was based on study data submitted as part of a post-marketing commitment following the approval of Gammaplex for adults in 2009. In the study, 25 children and adolescents with PI aged 3 years to 16 years were treated with Gammaplex for 12 months. During the study, two serious acute bacterial infections (SABIs) of pneumonia were reported, resulting in an annual SABI event rate of 0.09, well below the maximum SABI event rate of 0.5 per subject required for approval. At some point during the study, 14 children had an adverse reaction that was considered product-related. Of those, two had adverse reactions that were considered definitely related to Gammaplex, including headache, fatigue and myalgia. The most common adverse reactions, occurring in less than 5 percent of children, were dyspnea, otitis media acute and tonsillar disorder (two). Two subjects reported a serious adverse event of lobar pneumonia. Neither serious adverse reaction was considered related to Gammaplex, and neither met FDA-defined SABI criteria. ❖

Research

Influenza Often Overlooked with Bacterial Coinfection

A new study has found that many influenza-positive patients, including those with high-risk conditions, go undiagnosed in favor of a diagnosis of bacterial disease coinfection. In the study, the researchers conducted prospective influenza surveillance of emergency and inpatient settings in three North Carolina hospitals during four consecutive flu seasons from 2009 to 2013. Study enrollment included 4,689 men, women and children within 24 to 48 hours of presentation. More than 70 percent of these patients had cough, nasal congestion and fever, while fatigue/malaise was reported for most adults. Eleven percent were found to have laboratory-confirmed influenza. Of these, 29 percent received a clinical diagnosis of influenza. The number increased to 56 percent for those with laboratory-confirmed influenza and high-risk conditions, which included chronic or pulmonary diseases, diabetes, cancer, HIV and more. Nearly one-third of patients with laboratory-confirmed influenza were diagnosed with bacterial infections and were prescribed antibiotics. Only 18 percent of patients with a bacterial diagnosis who were using antibiotics and with confirmed influenza were diagnosed with influenza.

"We found that the odds of an influenza diagnosis were over threefold lower for all patients with a bacterial diagnosis, including those with high-risk conditions," wrote Katherine A. Poehling, MD, MPH, of the department of pediatrics, Wake Forest School of Medicine, and colleagues. "Thus, during the influenza season, clinicians should consider if persons with symptoms consistent with a bacterial infection could also have influenza and if coinfection with influenza would alter the treatment recommendations." Poehling and colleagues added that other factors for not properly diagnosing influenza include the variable timing and duration of influenza seasons and the limited specificity of rapid influenza diagnostic tests. ❖

Miller MR, Peters TR, Suerkin CK, Snively BM and Poehling KA. Predictors of Influenza Diagnosis Among Patients with Laboratory-Confirmed Influenza. *Journal of Infectious Diseases*, 2015; doi:10. 1993/infdis/jib264.

Medicines

FDA Grants 12-Year Exclusivity to Flublok

The U.S. Food and Drug Administration (FDA) has granted exclusivity to Flublok influenza vaccine for a period of 12 years. The regulatory exclusivity means that no product similar to Flublok can be approved by FDA before Jan. 16, 2025. Flublok is the first vaccine awarded this status. "The FDA's designation prevents a generic product maker from capitalizing on the hard work of our team," said Manon Cox, president and CEO of Protein Sciences Corp. "We are delighted that the FDA recognizes Flublok as a singular innovation in the prevention of an important and often deadly disease caused by the influenza virus." ❖

Manufacturer News

11 Companies Launch Biosimilars Forum

In May, the Biosimilars Forum was launched by 11 of the leading biosimilar developers in the U.S.: Actavis, Amgen, Boehringer Ingelheim, Coherus BioSciences, EMD Serono, Hospira, Merck, Pfizer, Samsung, Sandoz and Teva. According to a press release, "The forum will provide evidence-based information to educate and advocate for public policies and practices that encourage access, awareness and adoption of biosimilars. The officials who will lead the forum include (president) Juliana Reed, vice-president, Global Government Affairs, Hospira; (vice president) Hillel Cohen, PhD, executive director, Scientific Affairs, Sandoz Biopharmaceuticals (a Novartis company); (treasurer) Geoffrey Eich, executive director, External Affairs, Amgen Biosimilars; and (secretary) Stacie Phan, director, State Government Affairs and Public Policy, Boehringer Ingelheim. The forum submitted a public statement to the Centers for Medicare and Medicaid Services Healthcare Common Procedure Coding System to address the need for appropriate coding for biosimilars. ❖

Vaccines

Study Outlines Barriers to and Facilitators of Flu Vaccine Decisions

According to the 2013 National Health Interview Survey, the most recent report used by the Centers for Disease Control and Prevention (CDC), only 29.6 percent of adults ages 18 to 48 receive the flu vaccine, and that number increases to 46.5 percent for adults ages 50 to 64 and 67.9 percent for adults over 68. To understand why more individuals don't get the annual influenza vaccine, researchers at the Oak Ridge Institute for Science and Education analyzed 29 flu vaccine-related communication research reports sponsored by the CDC's National Center for Immunization and Respiratory Diseases between 2000 and 2013. From that, they identified seven reasons that led people to get the annual flu vaccine and six reasons they did not.

The reasons people did get the vaccine were because they believe they are susceptible to getting the flu; they believe the vaccine matters and works; they are older or have a chronic health condition; they have received a recommendation from a doctor; they have experienced a bad flu or flu-like illness; they have been on the receiving end of active vaccination promotion; and they have convenient and easy access to the flu vaccine. The reasons people didn't get a flu shot were that they believe, often as a result of personal experience, that the flu is a "manageable illness"; they don't believe the flu vaccine recommendation applies to them; they don't believe flu vaccines are effective; they have a concern about getting the flu from the vaccine; they believe other measures are more effective; and they have a negative personal experience with the vaccine.

"One of the most important findings was that personal experiences mattered a lot, both for people who got an annual flu shot on a regular basis and for those who didn't," said Glen Nowak, director of the Center for Health and Risk Communication at the Grady College of Journalism and Mass Communication. "I think that is an important reminder that it is really hard to overcome personal experience with persuasive communications. A lot of time communicators think they can just educate someone or just persuade them to take action, but that isn't always the case. It may take a better product or a new and different personal experience."

The 29 studies included participants who were healthcare workers, parents and people with chronic illnesses. One of the biggest surprises involved the perceptions of healthcare workers and their view about the flu vaccine. "Some healthcare workers are aware they can contract the flu, but they didn't acknowledge they can transmit the flu," said Nowak. "They saw patients as the threat and not themselves, which created a barrier for them to get vaccinated."

The study was published in the June 4 issue of *Vaccine*. ❖

Research

Flu Vaccine May Protect Against Guillain-Barré Syndrome

A new simulation study that evaluated the relationship between Guillain-Barré syndrome (GBS) risk and influenza vaccine and illness suggests that the vaccine reduces the risk for GBS. Researchers found that influenza vaccination reduces individual risk for GBS for most patients under typical conditions (vaccine effectiveness >60 percent; influenza incidence rates >5 percent). Results showed a small reduction in absolute risk of GBS with vaccination compared with no vaccination for a hypothetical 45-year-old woman (-0.36/1 million vaccinations; 95% credible interval, -1.22% to 0.28%), as well as for a hypothetical 75-year-old man (-0.42/1 million vaccinations; 95% credible interval, -3.68% to 2.44%). Exceptions to the rule of protection were predicted in conditions of low vaccine effectiveness and/or low influenza incidence. According to the researchers, the efficacy of a vaccine will vary by year and region and is dependent on the antigen match between the circulating virus strains and the vaccine. Previously published studies have separately evaluated the risk that a patient who receives the seasonal influenza vaccine or contracts influenza will be diagnosed with GBS from influenza. The study was published in the Jan. 14 online edition of *Emerging Infectious Diseases*. ❖

BIVIGAM®. Formulated to insPIre.

Enabling More Days to Lead a Normal Life

- Pivotal trial showed that PI patients missed 2.3 days/year of work or school[1]
- BIVIGAM is well tolerated
  - –The rate of adverse reactions per infusion has been calculated at 0.091% with a rate of serious adverse reactions at 0.076%[1]
  - –The most common adverse reactions (≥5%) were headache, fatigue, infusion site reaction, nausea, sinusitis, increased blood pressure, diarrhea, dizziness, and lethargy[2]

A Step Ahead in IVIG*

- First newly approved IVIG* with a validated thrombin generation assay
- All lots of a subset of BIVIGAM lots that have been tested for anti-A and anti-B were found to be ≤1:16[1]
- Sugar-free, 10% liquid preparation, glycine stabilized
- pH of solution: 4.0 – 4.6

Delivering Safety That Matters

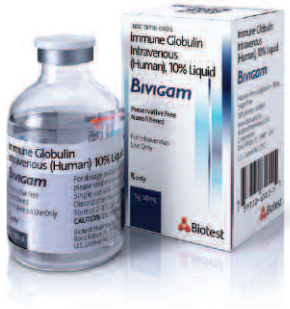
- Tamper-evident seals
- Integrated hanger label
- Latex-free packaging

BIVIGAM® [Immune Globulin Intravenous (Human), 10% Liquid] is indicated for the treatment of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

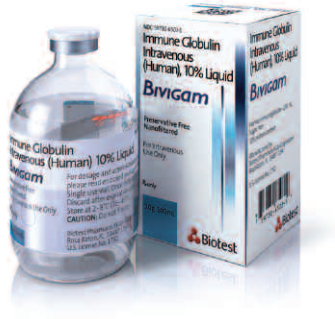
BIVIGAM®
Immune Globulin Intravenous (Human), 10% Liquid
For Uncompromised Living®

BIVIGAM is manufactured in the USA from US plasma for US providers and patients.

Available in Two Vial Sizes



NDC: 59730-6502-1
A carton contains a 50 mL vial
(5 g IgG) and a package insert



NDC: 59730-6503-1
A carton contains a 100 mL vial
(10 g IgG) and a package insert

- May be stored for up to 24 months (until expiration date on vial packaging) at 2°C to 8°C (36°F to 46°F)[2]

Visit bivigam.com to learn more today!

Warning: **Thrombosis may occur with immune globulin intravenous (IGIV) products, including BIVIGAM. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur 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. BIVIGAM does not contain sucrose. For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM at the minimum dose recommended and infusion rate practicable. Ensure adequate hydration in patients before administrations. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for viscosity. *See full Prescribing Information for complete boxed warning.***

Please see BIVIGAM Important Safety Information and Prescribing Information on next page, including black box safety warnings, contraindications, and dosing.

*IVIG is also known as IGIV, Immune Globulin Intravenous (Human).

References: 1. Wasserman RL. A new intravenous immunoglobulin (BIVIGAM®) for primary humoral immunodeficiency. *Expert Rev Clin Immunol.* 2014;10(3): 325–337.
2. BIVIGAM [package insert]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; 2013.

Biotest
From Nature for Life

 06/15 10190-90-IGG-040312_R13

BIVIGAM® [Immune Globulin Intravenous (Human), 10% Liquid] Rx only

Brief summary: Consult the full Prescribing Information for complete product information

WARNING: THROMBOSIS, RENAL DYSFUNCTION, AND ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin (IGIV) products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, 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 receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. BIVIGAM does not contain sucrose. For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Indication and Usage: BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI).

Contraindications: BIVIGAM is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. BIVIGAM is contraindicated in IgA deficiency patients with antibodies to IgA and a history of hypersensitivity.

Warnings and Precautions: Thrombosis: Thrombosis may occur following treatment with IGIV products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. 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 at risk of thrombosis, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity**. Hypersensitivity:** Severe hypersensitivity reactions may occur with IGIV products, including BIVIGAM. In case of hypersensitivity, discontinue BIVIGAM infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions. BIVIGAM contains trace amounts of IgA (≤ 200 micrograms per milliliter). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. BIVIGAM is contraindicated in IgA deficient patients with antibodies against IgA and a history of hypersensitivity reaction. **Acute Renal Dysfunction and Acute Renal Failure**: Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering BIVIGAM. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of >65 years), administer BIVIGAM at the minimum infusion rate practicable. **Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia**: Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy, including BIVIGAM. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because 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 thrombotic events. **Aseptic Meningitis Syndrome (AMS):** AMS may occur infrequently with IGIV treatments including BIVIGAM. 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 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 frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and 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. **Hemolysis:** IGIV products, including BIVIGAM, 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 reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration,[13] and acute hemolysis, consistent with intravascular hemolysis, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If these are present after BIVIGAM 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. **Transfusion-Related Acute Lung Injury (TRALI):** Noncardiogenic pulmonary edema may occur in patients following IGIV treatment including BIVIGAM. 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 in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support. **Transmissible Infectious Agents**: Because BIVIGAM 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. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Biotest Pharmaceuticals Corporation at 1-800-458-4244. Before prescribing BIVIGAM, the physician should discuss the risks and benefits of its use with the patient**. Monitoring Laboratory Tests:** Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. Because of the potentially increased risk of thrombosis with IGIV treatment, 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. If signs and/or symptoms of hemolysis are present after an infusion of BIVIGAM, perform appropriate laboratory testing for confirmation. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum. **Interference with Laboratory Tests**: After infusion of immunoglobulin, 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. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

ADVERSE REACTIONS: Serious adverse reactions observed in clinical trial subjects receiving BIVIGAM were vomiting and dehydration in one subject. The most common adverse reactions to BIVIGAM (reported in ≥5% of clinical study subjects) were headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, and lethargy. **Clinical Trials Experience**: *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.* In a multicenter, open-label, non-randomized clinical trial, 63 subjects with PI, on regular IGIV replacement therapy, received doses of BIVIGAM ranging from 254 to 1029 mg/kg (median dose 462.8 mg/kg) every 3 weeks or 4 weeks for up to 12 months (mean 317.3 days; range 66 – 386 days). The use of pre-medication was discouraged; however, if subjects required pre-medication (antipyretic, antihistamine, or antiemetic agent) for recurrent reactions to immune globulins, they were allowed to continue those medications for this trial. Of the 746 infusions administered, 41 (65%) subjects received premedication prior to 415 (56%) infusions. Fifty-nine subjects (94%) had an adverse reaction at some time during the study. The proportion of subjects who had at least one adverse reaction was the same for both the 3- and 4-week cycles. The most common adverse reactions observed in this clinical trial were headache (32 subjects, 51%), sinusitis (24 subjects, 38%), fatigue (18 subjects, 29%), upper respiratory tract infection (16 subjects, 25%), diarrhea (13 subjects, 21%), cough (14 subjects, 22%), bronchitis (12 subjects, 19%), pyrexia (12 subjects, 19%), and nausea (9 subjects, 14%). Adverse reactions (ARs) are those occurring during or within 72 hours after the end of an infusion. In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of BIVIGAM infusions with one or more temporally associated adverse reactions was 31%. The total number of adverse reactions was 431 (a rate of 0.58 ARs per infusion).

Seven subjects (11.1%) experienced 11 serious ARs. Two of these were related serious ARs (vomiting and dehydration) that occurred in one subject. One subject withdrew from the study due to ARs related to BIVIGAM (lethargy, headache, tachycardia and pruritus). All 63 subjects enrolled in this study had a negative direct antiglobulin (Coombs') test at baseline. During the study, no subjects showed clinical evidence of hemolytic anemia. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. During the clinical trial no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). There was a single positive finding for parvovirus (B19 virus) during the study. This subject came in contact with acute B19 virus from working at a school greeting children where a child was reported to have symptomatic Fifth's disease. There was no cluster (no other cases in other subjects) of B19 virus transmission with the IGIV batch concerned.

Table: Adverse Reactions (ARs) (within 72 hours after the end of a BIVIGAM infusion) in ≥5% of Subjects

ARs	**No. Subjects Reporting ARs (% of Subjects) [n=63]**	**No. Infusions With ARs (% of Infusions) [n=746]**
Headache	27 (43%)	115 (15.4%)
Fatigue	15 (24%)	59 (7.9%)
Infusion Site Reaction	5 (8%)	5 (0.7%)
Nausea	5 (8%)	8 (1.1%)
Sinusitis	5 (8%)	5 (0.7%)
Blood Pressure Increased	4 (6%)	5 (0.7%)
Diarrhea	4 (6%)	4 (0.5%)
Dizziness	4 (6%)	4 (0.5%)
Lethargy	4 (6%)	4 (0.5%)
Back Pain	3 (5%)	3 (0.4%)
Blood Pressure Diastolic Decreased	3 (5%)	5 (0.7%)
Fibromyalgia[a]	3 (5%)	17 (2.3%)
Migraine	3 (5%)	8 (1.1%)
Myalgia	3 (5%)	4 (0.5%)
Pharyngolaryngeal Pain	3 (5%)	3 (0.4%)

[a]**Symptoms occurring under pre-existing fibromyalgia**

DRUG INTERACTIONS Live Virus Vaccines: Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response. The immunizing physician should be informed of recent therapy with BIVIGAM so that appropriate measures may be taken.

Research

Pertussis Vaccine Prevents Infant Mortality

Because American infants are at highest risk of severe pertussis and death, researchers investigated the role of one or more pertussis vaccinations in preventing pertussis-related deaths and risk markers for death among infants aged younger than 42 days. In the study, researchers analyzed characteristics of fatal and nonfatal infant pertussis cases reported nationally during 1991 to 2008. Infants were categorized into two age groups on the basis of eligibility to receive a first pertussis vaccine dose at age 6 weeks. Dose one was considered valid if given at greater than or equal to 14 days before illness onset. They found that pertussis-related deaths occurred among 258 of 45,404 cases. Fatal and nonfatal cases were confirmed by culture and polymerase chain reaction. All deaths occurred before age 34 weeks at illness onset; 64 percent occurred before age 6 weeks. Among infants aged greater than or equal to 42 days, receiving one or more doses of vaccine protected against death. ❖

Research

Studies Find Interventions Increase HPV Vaccine Coverage

Three recent studies have found that interventions increase the rates of human papillomavirus (HPV) vaccination among teens and young women. The HPV vaccine series is recommended for routine use in girls and boys aged 11 to 12 years, in young women up to age 26, in young men up to age 21, and in men up to age 26 who have sex with other men and those with compromised immune systems. However, the HPV vaccine series has the lowest completion rates of any other vaccine.

In one study, researchers reviewed the literature on the effectiveness of practice- and community-based interventions to increase HPV vaccine rates in the U.S. Intervention approaches included reminder and recall, physician-focused interventions (e.g., audit and feedback), school-based programs and social marketing (using multiple approaches). Seven studies used a randomized design, and eight used quasiexperimental approaches (one used both). Thirteen studies included girls, and two studies included boys. The studies were conducted in a variety of populations and geographic locations. Twelve studies reported significant increases in at least one HPV vaccination outcome, one reported a nonsignificant increase, and one reported mixed effects. The researchers concluded that future efforts to increase HPV vaccination rates in the U.S. should focus on programs that can be implemented within healthcare settings such as reminder and recall strategies and physician-focused efforts, as well as the use of alternative community-based locations such as schools.[1]

In another study, researchers found that patients aged 9 years to 18 years were almost three times more likely to start the HPV vaccine series and 10 times more likely to complete it if their health providers received prompts during an appointment alerting them the patient was due for a shot during an appointment. Patients aged 19 years to 26 years were six times more likely to start the vaccine and eight times more likely to complete the series. And, rates were significantly higher for young African-American women.[2]

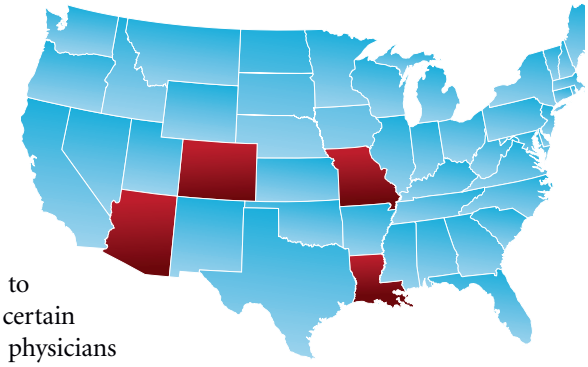
Finally, in a third study, researchers examined how the Affordable Care Act provisions implemented in 2010 that require insurance plans to offer dependent coverage to people aged 19 to 25 years and to provide targeted preventive services with zero cost-sharing affected the use of the HPV vaccine, which is among the most expensive of recommended vaccines, among young women. Using data from 2008 through 2012 from the National Health Interview Survey, they estimated that the 2010 policy implementation increased the likelihood of HPV vaccine initiation and completion by 7.7 percent and 5.8 percent, respectively, for women aged 19 years to 25 years relative to a control group of women aged 18 years to 26 years. The estimates translate to approximately 1.1 million young women initiating and 854,000 young women completing the vaccine series.[3] ❖

1. Niccolai LM and Hansen CE. Practice- and Community-Based Interventions to Increase Human Papillomavirus Vaccine Coverage: A Systematic Review. *JAMA Pediatrics*, May 26, 2015. Accessed at archpedi.jamanetwork.com/article.aspx?articleid=2296146.
2. Ruffin MT, Plegue MA, Rockwell PG, et al. Impact of an Electronic Health Record (EHR) Reminder on Human Papillomavirus (HPV) Vaccine Initiation and Timely Completion. *Journal of the American Board of Family Medicine*, 2015 May-Jun;28(3):324-33. Accessed at www.ncbi.nlm.nih.gov/pubmed/25957365.
3. Lipton BJ and Decker SL. ACA Provisions Associated with Increase in Percentage of Young Adult Women Initiating and Completing the HPV Vaccine. *Health Affairs*, May 2015, vol. 34, No. 5:757-764. Accessed at content.healthaffairs.org/content/34/5/757.abstract.

Editor's note: See the article "HPV Vaccine: A Dose of Untapped Potential" in the Summer 2015 issue of *BioSupply Trends Quarterly*.

Legislation

Four States Introduce Legislation on Right to Try Experimental Drugs

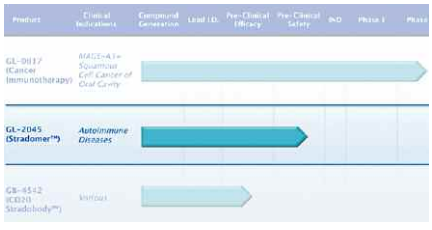


Several states have introduced legislation that would let patients bypass the U.S. Food and Drug Administration's (FDA) Expanded Access program in acquiring investigational therapies. FDA's program allows terminally ill patients to use experimental drugs in certain cases; however, patients and physicians wishing to try experimental drugs as a last-ditch effort to prolong life must first get FDA approval. The four recently introduced bills in Colorado, Louisiana, Arizona and Missouri would grant terminally ill patients access to post-Phase-I experimental drugs without having to go through the agency.

According to Arthur Caplan, director of medical ethics at New York University, "There are people who still do encounter trouble getting through the FDA [with their requests]. Sometimes the paperwork can seem onerous, and sometimes the doctor isn't sure what to do." However, even if patients make it through the application process, "the drug company is under no obligation to release the experimental drug," adds bioethicist Yoram Unguru in the *Johns Hopkins Bioethics Bulletin*. Additionally, even if the state laws are passed, they are superseded by federal laws. ❖

Medicines

Recombinant IVIG Granted Orphan Drug Designation for CIDP



Pfizer (a licensee of Gliknik Inc.) has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA) for its recombinant intravenous immune globulin (IVIG)-mimetic drug GL-2045 to treat chronic inflammatory demyelinating polyneuropathy (CIDP). FDA grants orphan drug designation to novel drugs or biologics that treat a disease or condition affecting fewer than 200,000 patients in the U.S. Several brands of the human blood product IVIG have previously received orphan drug designation for CIDP, but GL-2045 is a recombinant (not blood-derived) drug candidate under development. GL-2045 may eventually provide patients an alternative that is at least as effective as IVIG but potentially more convenient and safer without the risk of bloodborne pathogens. "This orphan drug designation is important in that it provides numerous incentives to develop GL-2045 to address an unmet need in CIDP, a rare neurological disorder," said David Block, CEO of Gliknik. ❖

Research

Shingles Vaccine Reduces Risk of Long-Term Pain in Patients

A new study shows that people who receive a shingles vaccine but still contract shingles have a lower risk of developing post-herpatic neuralgia (PHN), a potentially long-lasting and painful complication of the condition. In the study, researchers reviewed the medical records of 2,400 Kaiser Permanente Southern California patients over 60 years old who developed shingles after Jan. 1, 2007. Of those who received the vaccine, 4.2 percent of vaccinated women experienced PHN compared with 10.4 percent of the unvaccinated women, and 6 percent of vaccinated men experienced PHN compared with 5.8 percent of unvaccinated men. Researchers suggest that the gender-related differences may be due to the differences in how men and women seek care for chronic pain.

PHN is the most common complication of shingles, and treatment for the pain may be necessary for months or even years. As patients get older, the pain associated with PHN is likely to be more severe and may lead to depression, fatigue, insomnia, altered activities of daily living and decreased socialization. "Our study found that the shingles vaccine has an added protective benefit of reducing the risk of PHN for a vaccinated individual who still experiences shingles," said Hung Fu Tseng, PhD, MPH, study lead author, Kaiser Permanente Southern California Department of Research & Evaluation. "This further confirms the importance of shingles vaccination for adults over age 60." ❖

Accessed at www.prnewswire.com/news-releases/shingles-vaccine-associated-with-reduced-risk-of-long-term-pain-among-patients-300092402.html.

Research

Stem Cell Treatment for MS Improves Immune System and Extends Remission

A new report released in December shows that stem cell transplants might soon offer multiple sclerosis (MS) patients an effective way to stave off relapses and improve their overall neurologic condition. The report was a follow up of a study conducted in 2011 of 24 patients who received high-dose immunosuppressive therapy (HDIT) followed by hematopoietic cell transplant (HCT). After three years, progression-free survival had a rate of 90.9 percent, while clinical relapse-free survival was at 86.3 percent. "In the present study, HDIT/HCT induced remission of MS disease activity up to three years in most participants," the authors wrote. "It may

therefore represent a potential therapeutic option for patients with MS in whom conventional immunotherapy fails, as well as for other severe immune-mediated diseases of the central nervous system."

According to National Institute of Allergy and Infectious Diseases Director Anthony Fauci, "These promising results support the need for future studies to further evaluate the benefits and risks of HDIT/HCT and directly compare this treatment strategy to current MS therapies. If the findings from this study are confirmed, HDIT/HCT may become a potential therapeutic option for people with this often-debilitating disease, particularly those who have not been helped by standard treatments."

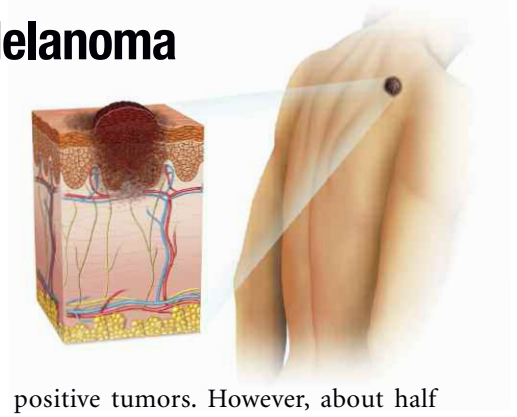
The report was published in the Dec. 29, 2014, issue of *JAMA Neurology*. ❖

Research

Immune Checkpoint Inhibitors Promising in Melanoma

In two recent studies, researchers found that immune checkpoint inhibitors show promise in treating advanced melanoma. In one study of 834 patients with advanced melanoma in 16 countries, patients received one of two types of immune checkpoints inhibitors: Two-thirds received pembrolizumab (Keytruda), and the rest received the current first-line treatment, ipilimumab (Yervoy). Six months after treatment, progression-free survival was 46.4 percent for pembrolizumab and 26.5 percent for ipilimumab. Overall survival rates after one year were 74.1 percent and 68.4 percent for pembrolizumab, depending on the dose patients received, compared with 58.2 percent for ipilimumab. About 33 percent of patients responded to treatment with pembrolizumab, compared with 12 percent with ipilimumab. Only 12 percent of patients taking pembrolizumab suffered from side effects, whereas 20 percent of those who received ipilimumab did.

In another study, patients responded better to a combination of two different types of immune checkpoint inhibitors than to ipilimumab used on its own. The trial involved 142 patients with advanced melanoma, two-thirds of whom received the combination therapy, which included the anti-CTLA drug ipilimumab and the anti-PD1 drug nivolumab (Opdivo). The other third of patients received ipilimumab alone. Among patients with BRAF wild-type tumors, 61 percent responded to the combination treatment, compared with just 11 percent who responded to treatment with ipilimumab alone. Complete responses were reported in 16 patients (22 percent) in the combination group and no patients in the ipilimumab group. Similar results for response rate and progression-free survival were seen in 33 percent with BRAF mutation-positive tumors. However, about half of the patients receiving combination therapy did suffer from moderate to serious side effects, compared with just a quarter of patients treated with ipilimumab alone.



The pembrolizumab trial was funded by Merck, and the combination therapy trial was funded by Bristol-Myers Squibb. The study was published online April 19 and 20 in the *New England Journal of Medicine*. ❖

Immune Checkpoint Inhibitors Promising in Melanoma. MPR, April 21, 2015. Accessed at www.empr.com/immune-checkpoint-inhibitors-promising-in-melanoma/article/410135.

Research

Stroke Drug May Halt Progression of Alzheimer's

Scientists at the University of South Australia and colleagues from Third Military Medical University in Chongqing, China, have found that the drug Edaravone alleviates Alzheimer's disease pathologies at multiple levels and improves learning and memory functions in mice. Edaravone is used to aid neurological recovery following acute brain ischemia and subsequent cerebral infarction, but is currently available only in some Asian countries.

"Edaravone can suppress the toxic functions of amyloid beta to nerve cells; it is a free radical scavenger which suppresses oxidative stress that is a main cause of brain degeneration," said Professor Xin-Fu Zhou, lead researcher and research chair in neurosciences at the University of South Australia. "The drug can suppress the production of amyloid beta by inhibiting the amyloid beta production enzyme. It also inhibits the Tau hyperphosphorylation, which can generate tangles accumulated in the brain cells and disrupt brain functions." According to Professor Zhou, lessons learned from failures of current clinical trials suggest that targeting multiple key pathways of Alzheimer's disease pathogenesis is necessary to halt and delay the disease progression. And, although he doesn't believe Alzheimer's disease could ever be cured, the drug is the best hope of attacking the debilitating disease through multiple signal pathways. ❖

Plouffe J. Drug Discovery Gives Hope to Halting Progression of Alzheimer's Disease. *The Lead*, April 7, 2015. Accessed at www.theleadsouthaustralia.com.au/industries/health/drug-discovery-gives-hope-to-halting-progression-of-alzheimers-disease.

Research

GSK Ebola Shot Is Safe and Provokes an Immune Response

Results from a human trial of GlaxoSmithKline's Ebola vaccine show it is safe and generates an immune response. In the early stage Phase I trial primarily designed to test safety, 60 healthy volunteers were given the vaccine in Britain between Sept. 17 and Nov. 18, 2014. The volunteers received one of three doses: low, medium or high. Data from 28 days after vaccination showed the shot was safe at these doses with only mild side effects. "The safety profile is pretty much as we'd hoped, and the immune responses are OK, but not great," said Adrian Hill, who led the work at Oxford's Jenner Institute. "People typically experienced mild symptoms that lasted for one or maybe two days such as pain or reddening at the injection site, and occasionally people felt feverish." However, the antibody response was weaker than was found in a trial of the same Ebola vaccine in macaque monkeys, in which the animals were also found to be protected. According to Hill, the lower antibody levels, together with a lower response detected in the immune system's T cells, suggest that a booster may be needed. ❖

Medicines

FDA Accepts BLA for CSL's rIX-FP for Hemophilia B Patients

CSL Behring's Biologics License Application for the marketing authorization of its long-acting fusion protein linking recombinant coagulation factor IX with recombinant albumin, rIX-FP, has been accepted for review by the U.S. Food and Drug Administration. When approved, rIX-FP will provide hemophilia B patients with a long-acting treatment option with dosing intervals up to 14 days. CSL engineered rIX-FP to extend the half-life of recombinant factor IX through genetic fusion with recombinant albumin due to its long physiological half-life, as well as its good tolerability profile, low potential for immunogenic reactions and a well-known mechanism of clearance.

CSL's BLA is based on the results from the Phase II/III study in the PROLONG-9FP program, which compared the change in frequency of spontaneous bleeding events between on-demand treatment and a weekly prophylaxis regimen in patients ages 12 to 61 years who develop inhibitors against factor IX. The study evaluated multiple prophylaxis regimens, including seven-day and 14-day intervals. A sub-study evaluated the prevention and control of bleeding in patients with hemophilia B undergoing a surgical procedure. ❖

Influenza

Influenza Detection Test Receives FDA CLIA Waiver

The Alere i influenza A and B test developed and marketed by Alere Inc. has been granted a Clinical Laboratory Improvement Amendments (CLIA) waiver by the U.S. Food and Drug Administration (FDA). Alere i is the only molecular test to detect and differentiate influenza A and B virus in under 15 minutes. It was cleared for marketing by FDA in June 2014 and was made available in September for health facilities and laboratories licensed to conduct tests of moderate complexity under the CLIA program. With the CLIA waiver, the test will be available in a significantly broader range of healthcare settings, including hospitals, physician offices and clinics. "This milestone greatly expands the availability of molecular testing to a wide range of healthcare settings during this influenza season," said Avi Pelossof, global president of infectious diseases at Alere. "By making lab-accurate, actionable results available at the point of care, Alere i empowers healthcare providers to quickly identify and treat people with influenza — improving patients' clinical outcomes, protecting their communities and reducing healthcare costs." ❖

Reimbursement

Octapharma USA Launches Co-Pay Program for Wilate

Octapharma USA has launched the Octapharma Co-Pay Assistance Program available to von Willebrand's disease patients who are currently receiving Wilate (von Willebrand factor/coagulation factor VIII complex [human]) or have a prescription to begin therapy. The new program offers eligible patients a maximum of $6,000 annually for co-pay, co-insurance and deductible expenses associated with their treatment without regard for their ability to pay. Patients must have third-party commercial insurance to participate in the program.

"We realize that patient out-of-pocket expenses associated with healthcare can sometimes be daunting; therefore, Octapharma has committed to support a program specifically designed to supplement these costs," said Octapharma USA President Flemming Nielsen. To enroll in the program, eligible patients should contact the Octapharma Support Center at (800) 554-4440. The program is not available to patients who are covered under Medicaid, Medicare, MediGap, VA, DOD, Tricare or any other state or federal medical or pharmaceutical benefit program or pharmaceutical assistance program. Patients must be residents of the U.S. ❖

Research

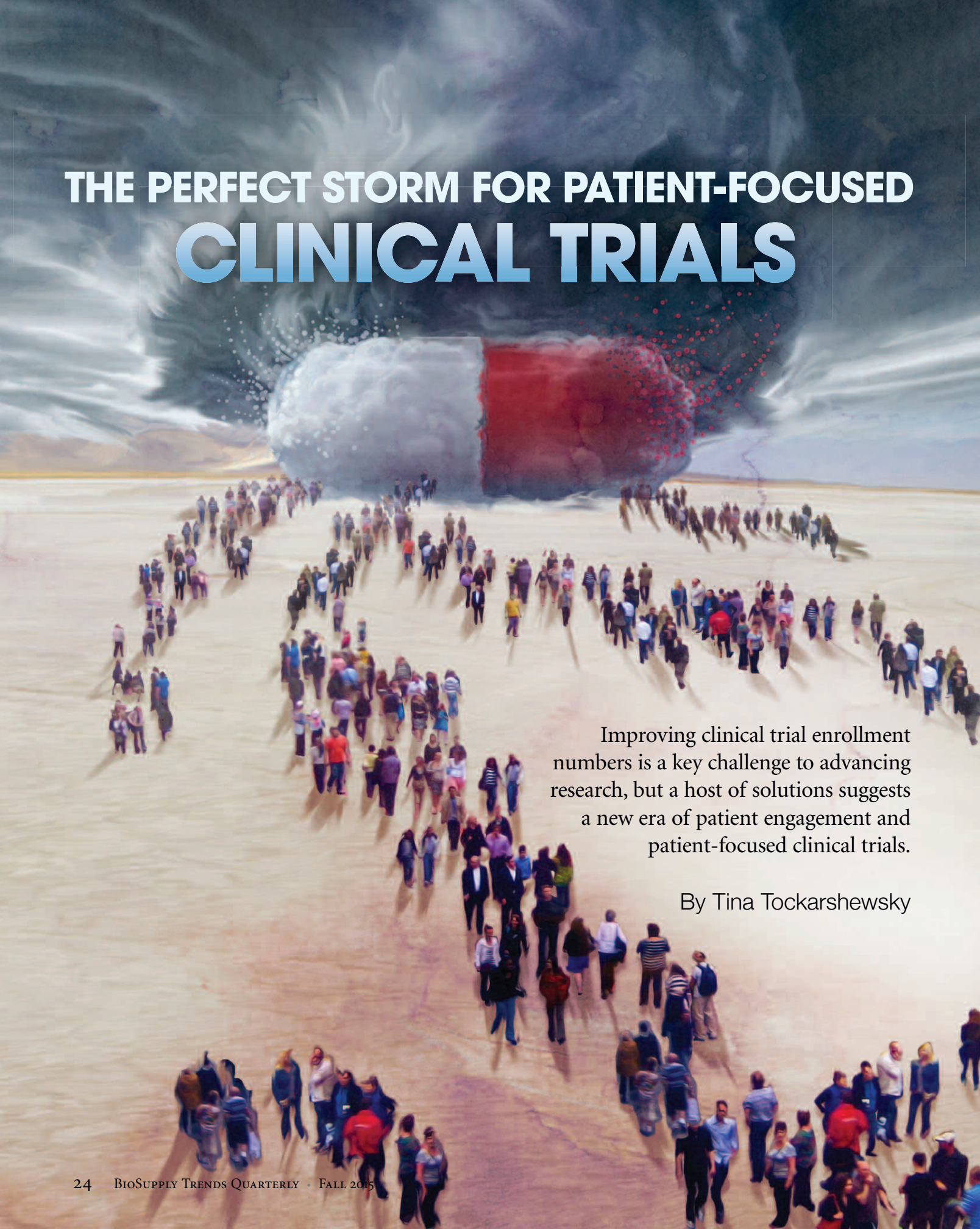
Personal Melanoma Vaccines Evoke Immune Response

In a first-in-people clinical trial, personalized tailor-made melanoma vaccines given to three patients with advanced melanoma appeared to increase the number and diversity of cancer-fighting T cells responding to the tumors. The researchers at Washington University School of Medicine in St. Louis, Mo., developed cancer vaccines by first sequencing the genomes of patients' tumors and samples of the patients' healthy tissues to identify mutated proteins called neoantigens unique to the tumor cells. Then, using computer algorithms and lab tests, they were able to predict and test which of those neoantigens would be most likely to provide a potent immune response and would be useful to include in a vaccine. The patients who received the vaccine had had surgery to remove their tumors, but their cancer cells had spread to the lymph nodes, an indicator the deadly skin cancer is likely to recur. The findings set the stage for a Phase I vaccine trial approved by the U.S. Food and Drug Administration as part of an investigational new drug application. The trial will enroll six patients. If testing in this trial indicates the vaccines are effective, they may one day be given to patients after surgery to stimulate the immune system to attack lingering cancer cells and prevent a recurrence.

"This proof-of-principle study shows that these custom-designed vaccines can elicit a very strong immune response," said senior author Gerald Linette, MD, PhD, a Washington University medical oncologist leading the clinical trial at Siteman Cancer Center and Barnes-Jewish Hospital. "The tumor antigens we inserted into the vaccines provoked a broad response among the immune system's killer T cells responsible for destroying tumors. Our results are preliminary, but we think the vaccines have therapeutic potential based on the breadth and remarkable diversity of the T-cell response." The trial was reported on in the journal *Science*. ❖

Bolz K. Personalized Melanoma Vaccines Marshal Powerful Immune Response. *OncologyNurseAdvisor*, April 28, 2015. Accessed at www.oncologynurseadvisor.com/personalized-melanoma-vaccines-marshal-powerful-immune-response/article/411370.

THE PERFECT STORM FOR PATIENT-FOCUSED CLINICAL TRIALS



Improving clinical trial enrollment numbers is a key challenge to advancing research, but a host of solutions suggests a new era of patient engagement and patient-focused clinical trials.

By Tina Tockarshewsky

"If patient engagement were a drug, it would be the blockbuster drug of the century and malpractice not to use it."[1] Digital health IT strategy consultant Leonard Kish's bold 2012 statement heralds the new era of patient engagement in the medical research and development process. Buzz phrases like "patient-focused," "patient-centric" and "patient-driven" are being bantered about, and while all process stakeholders agree that, theoretically, this patient-facing approach is critical, what those phrases actually mean in practice is still being defined. There is no denying the positive winds of change due to high stakes and a perfect cultural storm fueled by a drug development process that has not been working well.

The common denominator and greatest catalyst for this change is the ultimate end-user: the patient. Patients themselves and patient organizations have always stressed a greater need for patient engagement; however, clinical trial design and development is an inherently data-driven process that often disenfranchises its own end-user. Yet, despite being a numbers-driven process, the numbers are not adding up: Clinical trials are faltering at an alarming rate and with staggering costs.

According to Pharmaceutical Research and Manufacturers of America (PHRMA), in 2013:[2]

• There were 6,199 industry-sponsored clinical trials in the U.S., with 1.1 million participants.

• The U.S. biopharmaceutical industry had nearly $10 billion of direct spending in the conduct of clinical trials at the site level. This does do not include resource investments for clinical trial-related activities occurring outside the individual trial sites.

• Direct and indirect clinical trial investments by industry and clinical trial vendors and contractors generated $25 billion in local community economic activity.

• All 50 states and the District of Columbia had trials, with five states having the highest number of active sites: California (3,111), Texas (2,799), Florida (2,571), New York (2,476) and Pennsylvania (1,972).

Clinical trials are a crucial part of the drug development process, but they are costly, with expenses increasing exponentially as the trial moves through each phase. PHRMA data also show that trial sites tend to be more concentrated in key states having major urban centers (and, by extension, more accessible to those markets). Costs per trial participant can average $36,500 across all phases for each phase, but Phase I through Phase III can have higher per-trial participant costs, ranging from $38,500 to $42,000 per person.[2]

Still, despite this enormous investment, producing market deliverables is difficult. FasterCures, a Milken Institute think-tank center focused on accelerating research and removing barriers to medical progress, cites the following statistics:[3]

• One in three Americans lives with a deadly or debilitating disease that has no cure or few treatment options.

• In 2014, only 41 new drugs were approved despite an annual investment of $100 billion in therapeutic research and development.

• Only one out of every 10,000 scientific discoveries makes it to market.

Clinical trials are faltering at an alarming rate and with staggering costs.

Developing a new medicine takes, on average, 10-plus years and costs $2.6 billion.[4] After adding time for basic science research and regulatory approvals, this nearly two-decades-long, high-cost process now constitutes a high-risk event facing enormous odds of even crossing the finish line. Many of those odds are dictated by patient engagement:[5]

• 80 percent of total trials are delayed at least one month because of unfulfilled enrollment.

• 50 percent of clinical research sites enroll one or no patients in their studies.

• Each day a drug is delayed from market, sponsors lose up to $8 million.

Federal Programs Push Progress

Several U.S. government programs are addressing patient engagement levels in drug development, and these programs are setting into motion new directions taken by industry as well.

Patient-Centered Outcomes Research Institute (PCORI). The Affordable Care Act of 2010 established PCORI, an independent nonprofit, non-governmental organization whose mission is to help "people make informed healthcare decisions, and improve healthcare delivery and outcomes, by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community." PCORI funds comparative clinical effectiveness research (CER), as well as supports methodology improvements for CER studies. Using an approach called Patient-Centered Outcomes Research (PCOR),

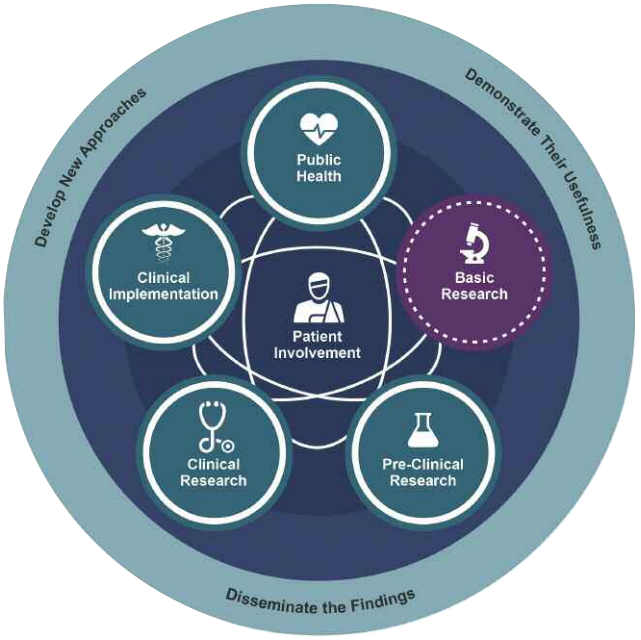
the studies supported by PCORI address the questions and concerns most significant to patients and do so by involving all stakeholders — patients, caregivers, clinicians and other relevant healthcare parties — as well as researchers.[6]

PCORI has invested $250 million to develop PCORnet, a national patient-centered clinical research network, which aims to aggregate national data sourced from a range of healthcare settings (including local hospitals, doctors' offices and community clinics) into a large, highly representative national network for conducting CER. Phase I of a two-phase PCORnet launch process started in 2014 to include Clinical Data Research Networks and Patient-Powered Research Networks, as well as a Coordinating Center led by Harvard Pilgrim Health Care Institute and Duke Clinical Research Institute. Phase II commences late 2015 with the inclusion of rare disease networks, as well as networks and communities with common conditions and/or shared attributes.[7]

Patient-Focused Drug Development (PFDD). First enacted in 1992, the Prescription Drug User Fee Act (PDUFA) aimed to streamline and expedite the U.S. Food and Drug Administration's (FDA) new medicine approval process. The fifth authorization of PDUFA in 2012 mandated the framework for a new FDA initiative, called PFDD, intended to include patients in earlier stages of product development. The legislation called for FDA to enhance patient input in four drug development areas: 1) the benefit-risk framework, 2) patient-reported outcome endpoints (PROs) and other assessment tools used, 3) divisions review and 4) patient involvement in advisory committees, endpoint development and risk communications. While, currently, PFDD is limited to patient insights via 20 disease-specific meetings (the 20 were identified as those with greatest need through a public comment period to shorten a longer FDA-driven list), the patient-centered fashion in which the FDA initiative is designed is seen by many as influencing the pharmaceutical industry to evolve its own patient-centered drug development approaches.[8]

The PCORI and PFDD initiatives contribute to the growing trend to incorporate patients at each and every juncture, from lab bench to bedside.

Figure 1.



The Research Continuum

The PCORI and PFDD initiatives contribute to the growing trend to incorporate patients at each and every juncture, from lab bench to bedside. When it comes to involving patients and patient advocacy groups on the front end of clinical trial design, John Barnes, executive director of the Coalition for Clinical Trial Awareness, urges "that's where the rubber hits the road for including patients, the patient's voice, and patient's family."

In 2012, the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) was established to tackle transforming translation — the process of turning discoveries from the laboratory, clinic and community into actual clinical applications — so new drugs, diagnostics, medical devices and, ultimately, cures could reach patients faster. NCATS does not focus on specific diseases but rather on common denominators among diseases. At the core of all of its translational science programs is the patient.

Petra Kaufmann, MD, MSc, director of the division of clinical

innovation at NCATS, says: "We see research as a cycle, not a linear process. The patient has to be in the center and actively engaged throughout the process." NCATS programs take into consideration all ways in which the patient is engaged with the development of their care (Figure 1). "Observations from patients inform the process," Dr. Kaufmann adds, noting that it is a "continuous learning system" in which the most critical stakeholder is the patient.

From Dr. Kaufmann's perspective, a key challenge across the research continuum is that active engagement of patients is still a new thing. She observes that in many areas there is a lack of awareness by stakeholders of how to incorporate patient engagement and a lack of best practices in terms of the methods and processes this might involve. Specifically, she points out that:

1. *Patients may feel they do not have enough information to be active partners in research.* "To bring more treatments to more patients, we need to engage patients as active partners in research, alongside scientists, industry and government. That requires giving patients and their family the tools and information they need to be empowered as an active participant," Dr. Kaufmann observes.

2. *Raising awareness is needed among investigators to change patient engagement paradigms.* Initiatives like NCATS' Rare Disease Clinical Research Network require that at least one patient group is actively engaged in each of its consortia that work to find answers and treatments for rare diseases. The Clinical and Translational Science Awards (CTSA) program with its national consortium of medical research centers has been looking for innovation and best practices in connecting with all research stakeholders. As Dr. Kaufmann explains, "They all work on engaging communities and patients: We believe patient engagement is a transformative tool and a key part of our CTSA and Rare Disease Network programs."

3. *New understandings of transparency issues are needed.* As stakeholders find new ways to work together, some patient groups may have a learning curve in understanding the need for full disclosure of their network of relationships and funding sources to avoid any unintended potential conflicts of interest.

As another sign of positive change, Dr. Kaufmann points to her previous work with the NeuroNext research network at the National Institute of Neurological Disorders and Stroke. NeuroNext grant recipients are required to incorporate patient protocol monitoring groups and patient advocates during trial design and implementation. "It instills trust in the research process if advocates are on monitoring boards — it offers a two-way street to real change," Dr. Kaufmann explains.

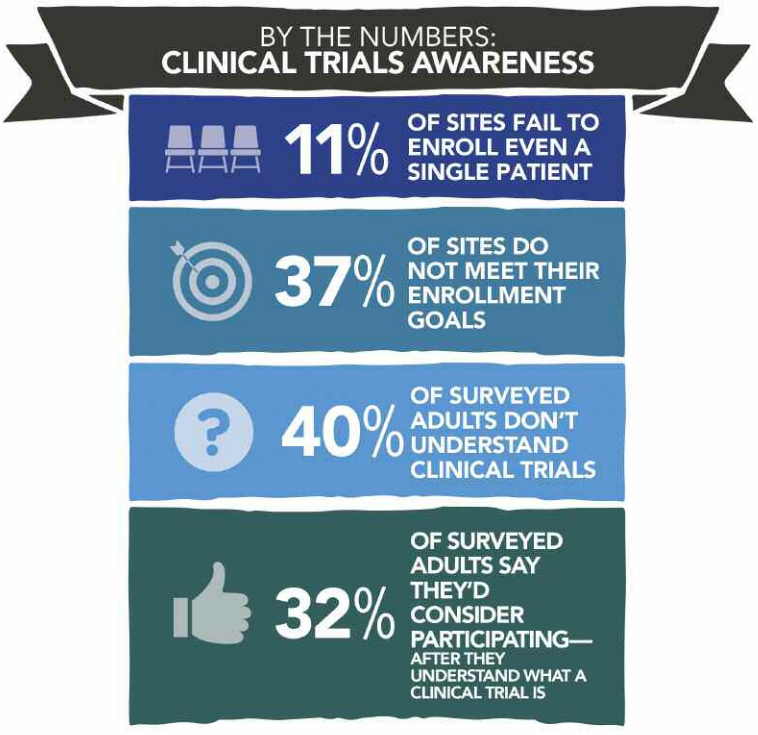
While she is encouraged by cultural shifts like pharma companies designating "chief patient officers," Dr. Kaufmann hopes in the future there will be more sharing between public and private sectors to accelerate the development process.

Maximizing Patient Participation: More Education, Empowerment, Ease of Access

Despite good intentions and cultural changes, if the general public does not have a good foundation in understanding research, they will not get involved. And even those who do engage still face entry barriers that may exclude them.

Patient communities are trying to change this, both by educating their members and by joining together to call for national platforms to accelerate education. The Coalition for Clinical Trial Awareness (CCTA) is advocating for the creation of a federally sponsored public awareness campaign to explain the benefits of clinical trials. John Barnes, a member of CCTA's management team, states the greatest impediment to truly developing patient-focused clinical trials is the lack of awareness of what clinical trials are. But another impediment to trial education and access, he notes, is that "doctors are

Figure 2.



hesitant to talk to patients; they feel they will lose their patients" if enrolled in a clinical trial (Figure 2).

Kim McCleary, managing director and leader for a new FasterCures program to advance the science of patient input and expand patient engagement in FDA's assessment of benefits and risks for medical products, observes: "Patient engagement is still seen as a solution to a problem instead of a guiding philosophy, especially for clinical trial recruitment; by that time, it's too late to address it when recruitment is not going well."

McCleary points out that the timeline for the development process endpoints is extending: "Regulatory approval used to be considered the end of the process — it was the 'Holy Grail.' But now the timeline has shifted to include payers and providers and their impact on access to care. Reimbursement has not been focused on by patient organizations. Now, individuals are sharing more of the cost of healthcare, so they are more concerned about these issues."

McCleary realizes stakeholders are hungry for best practices; however, she feels it is still too early, expressing that she sees stakeholders going through "a spirit of experimentation, a learning period and a shake-out period." She notes the increasing interest in leveraging patient registries, with leading models like PCORI's emphasis on patient-powered registries and the ability to link registries to ask a single research question across different communities as demonstrating the benefit these registries can provide. "PCORI is pushing the conversation at different levels, with patient organizations and with other players," states McCleary. "They are showing leadership for foundational work involving patients, but is this something patients will value?" Ultimately, she acknowledges the perfect storm environment facilitating increased patient engagement: "There will be an inevitable societal and cultural shift of patient empowerment to shed a paternalistic system."

Know Your Customer

While the public's understanding of clinical trials is a major factor impacting enrollment, so too, in reverse, is investigators' understanding of the public they seek to engage. Patient recruitment issues, both for volume and for finding appropriate candidates and avoiding "professional patients" with questionable motives and sketchy medical references, plague the process, frustrating investigators' efforts to move forward. Even the best patient-focused trial design will not succeed if enrollment targets fail.

In a 2013 FDA Workshop on Peripheral Neuropathy Clinical Trials presentation, this author shared enrollment insights resulting from a patient community poll conducted by The Neuropathy Association:

• The key personal drivers for trial participation were access to leading researchers and healthcare providers (35 percent), receiving new therapies before they were publicly available (30 percent) and participating in research to help other patients (25 percent); remuneration motivated only 5 percent of those surveyed.

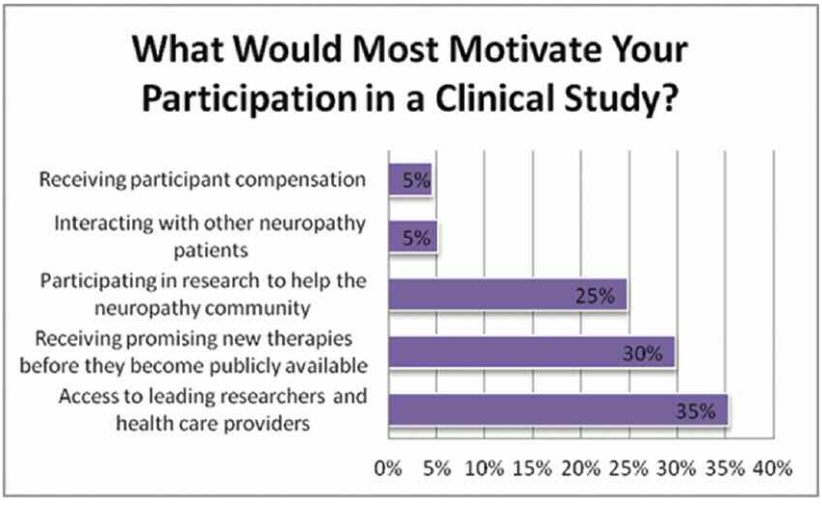
• Main reasons for not participating in clinical trials were lack of awareness of personally-applicable trials (27 percent), inability to travel (18 percent) and lack of access to general trial information (13 percent).

• The patient community likes being proactive partners in their care (i.e., using tools/resources like tracking mechanisms for charting pain and mapping progress) (Figures 3 and 4).

The poll and resulting presentation outlined neuropathy patients' most challenging barriers to trial participation:

Fear. After enduring numerous challenges to get to a diagnosis and a treatment regimen with a certain level of symptom management, neuropathy patients' greatest fear was having to stop or upset their therapeutic balance (even if imperfect). There was also the fear of the unknown — the risks of not tolerating a new therapy or getting worse during a trial.

Figure 3.



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Access and costs. Trial access had another meaning for these patients: Physical, financial and support impediments limited their trial access. Many did not have the physical stamina or mobility to travel to trial sites, often depending on others or challenging public transportation options. With many already on disability or struggling with job absences due to illness, asking them or their family and friends to sacrifice time away from work or time away from their family presented a huge hidden cost burden.

Awareness. Despite proactive outreach to their physicians — whom they viewed as stewards in encouraging trial participation — these patients were disappointed by the lack of engagement or support from their treating physicians, as well as their perception that physicians discounted the disease's impact on their lives.

These points come from a specific disease community, yet contain common themes across illnesses. And the points raised show the value of soliciting patient input about the dynamics within a disease population.

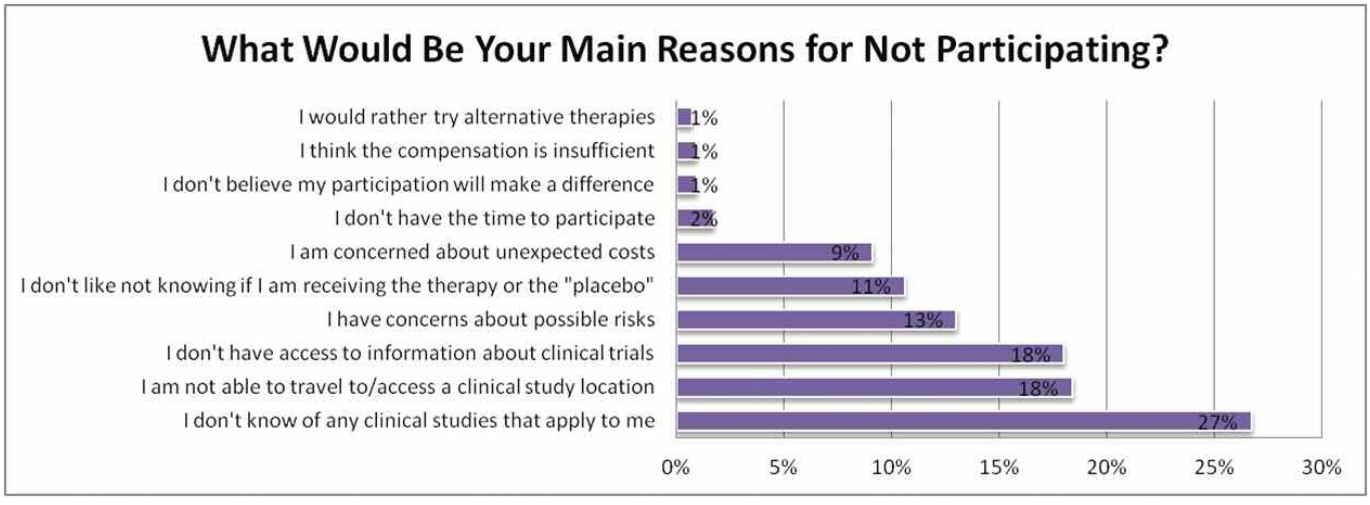
Patient organizations stand ready to help with recruitment efforts to pinpoint targeted patient populations. They are vested in their communities, and they know how to find one another. Today, social media is an enormous aggregator: Patients want to help other patients, peers and those with analogous illnesses, overlapping disease states or shared comorbidities. Trial recruitment efforts have barely scratched the surface in exploring how patient social networks could be leveraged to extend outreach and patient engagement.[9]

Details Driving Data

For those actually designing clinical trials, how to involve patients in design is still a wide playing field open for consideration. Robert Dworkin, PhD, professor in the departments of anesthesiology and neurology and center for human experimental therapeutics at the University of Rochester Medical Center and co-director of the Analgesic, Anesthetic and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) public-private partnership with FDA, says of analgesic trials that one might consider parallel versus crossover, enriched enrollment and randomized withdrawal designs, as well as designs in which patients are offered choices of treatments. He says that there is great interest in options for "phenotyping patients in various ways — identifying specific subgroups of patients who might respond better or tolerate the treatment better than other patients."

If the general public does not have a good foundation in understanding research, they will not get involved.

Figure 4.



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Patient organizations have an opportunity to help researchers and FDA refine this approach. They can provide researchers with what they know about differences in their own patient subpopulations and about varying levels of risk tolerance across their disease's cycles and progressions — from both the patients' and caregivers' perspectives. Researchers can harness these insights to improve their design efforts by asking patients' help with 1) generating hypotheses, 2) developing outcome measures and 3) assessing benefit-risk value propositions. Researchers trained to listen to the voice of the patient and to map patients' symptom articulation and desired outcomes can combine this input with their methodological "know-how" to channel the information into rigorous clinical trial studies.[9]

Patient organizations stand ready to help with recruitment efforts to pinpoint targeted patient populations.

Patient reported outcomes (PROs) are another area of intense focus for process improvements. And, as the process timeline extends out to payers, this is an area where payers could benefit from earlier involvement in a patient-focused drug development process. The biggest challenge for payers making drug coverage and formulary decisions is how to generalize study findings to patients who are different (but perhaps more prevalent) than those enrolled in pre-launch studies. Information from a patient-focused development process can aid payers, helping them better interpret product information, contextualize PRO data and generalize study data to address varied patient populations. Irrespective of the stakeholder, as with other areas, best practices and guidance for PROs are still a work in progress.[9]

Make Way for Disruptors and Innovators

Patient engagement is being bolstered by new technologies. Wearable devices, GPS and tracking technologies, video conferencing, mobile phone apps and other direct-to-consumer devices are being brought into the domain of research for data measurement and collection. Apple's ResearchKit has already expressed its intent to bypass the clinical middleman by offering an open source software framework making app creation for medical studies easier for researchers and developers. The tidal wave of new applications and new uses for technology and data has only just begun, and the opportunities are immeasurable.

Incorporating new technologies and consumer devices to drive patient engagement is still, at best, at a point of experimentation, with best practices still a ways off — but the commitment by stakeholders to try new protocols is there. In 2011, Pfizer announced it was moving forward with a first-ever, fully at-home and completely virtual randomized clinical trial called REMOTE (Research on Electronic Monitoring of OAB Treatment Experience) for their overactive bladder drug Detrol LA (tolterodine tartrate). With a goal to recruit 600 patients from 10 U.S. states, all aspects of the trial were to be "virtual." Recruitment and sign-up were done online, drugs would be mailed to patients' homes, data would be collected via computer or smartphone, and blood samples were to be drawn at local labs and results sent to the clinical trial teams. Candidates would never have to visit a site at all, thus taking away many of the ease-of-access issues often cited as participation barriers. Patients were fully empowered to direct their trial participation, but were they fully engaged in this "clinical trial of the future" format?

By 2012, Pfizer announced that — while no less enthusiastic about incorporating social media and new technologies into the trial process — it was planning to wind the trial down after having disappointing online recruitment numbers. Was it a case of too much too fast? Were patients perhaps so "liberated" from the process that they ended up disengaged in a whole new way? Remember, The Neuropathy Association poll showed that interaction with leading experts was a key driver for trial participation. Was that element lacking? The lessons learned here are still being debated, but the market nonetheless commended the effort, and Pfizer announced it intends to try the virtual approach again very shortly, either here or abroad.[10]

ResearchMatch

Leveraging patient registries is receiving enormous focus as a critical building block for advancing research and improving trial enrollment numbers. One innovator bringing patients and investigators together in new ways by empowering patients and removing access barriers is ResearchMatch.org. Started in 2009, this online platform grew out of a grant to a local Vanderbilt University patient registry for innovating the process of connecting patients and investigators. Developed in partnership with consortia members and fully funded by NCATS,

the platform takes advantage of new novel technologies, including those used by online dating sites like Match.com, to make connections in a secure and convenient environment. It allows patients and researchers to create their own online profiles, respectively, of themselves and of the ideal trial participant sought. This, then, allows the technology to "match" the two together in a blinded, progressive way that aids prequalification to increase match success rates.

Patient profiles do not have to be disease-specific and can include healthy individuals, thus enabling people to express their interest in different types of trials that might not have otherwise found them, like those addressing comorbidities. Researchers using the platform can target patient candidates in a much more directed fashion than available with previous recruitment efforts. Patients can take charge of their own access to trials and no longer have to wait for someone to tell them about a trial or struggle with doing online research. Instead, ResearchMatch helps investigators find them.

Originally only available to NIH-funded researchers, access has now been expanded to any nonprofit investigator in the U.S. and Puerto Rico. After just a few short years, ResearchMatch now hosts:

- Over 84,000 volunteers from 5,890 unique conditions and 832 rare conditions
- 4,169 pediatric volunteers
- 13 condition/disease-specific sub-registries (including six rare conditions)
- 3,000 researchers at 108 institutions
- 532 recruits in active studies

ResearchMatch project manager Catherine Gregor states, "ResearchMatch is challenging itself to constantly evolve to meet the needs of its community." New additions and future plans include:

1. Trial finder, launched in March 2015. Trial finder is a user-friendly interface with www.clinicaltrials.gov to find actively recruiting trials in a more consumer-friendly, searchable format. Patients can filter through trials and generate tabulated results with highlighted locations that can be printed or tabulated for easy sharing with others.

2. Next will be an algorithm program for patients to scan PubMed for clinical trial articles.

3. For investigators, a REDCap (Research Electronic Data Capture) partnership is in the works to enhance pre-screening surveys.

4. And, the future holds an online consumer resource for information about completed trials pertaining to their interests and/or trials that they actively participated in. The application aims to keep volunteers engaged after a trial so they remain invested in the research process. "It's for those interested in knowing 'what did my contribution do?'" says Gregor.

Time Is Ticking

Indeed, this century has truly kicked off with a new era of patient engagement and patient-focused clinical trials. But, like developing the next blockbuster drug, time is of the essence, and the stakes are too high for not getting it right. Talking to all research stakeholders, one can almost hear the clock ticking — ticking off the lives holding out hope (and the lives lost), ticking off the years passing by and ticking off the dollars spent. Whether expressed directly or not, stakeholders' frustration and even exasperation with each other and with the process is palpable. But one also senses the excitement and the optimism that new collaborations could yield extraordinary advances. Patients are claiming their place on the navigation team charting their future, and a journey of untold possibilities now lies ahead. ❖

TINA TOCKARSHEWSKY *is the owner and principal of CeresConsulting. She previously served as president and CEO of The Neuropathy Association, and during her tenure served as a patient advocate for NeuroNext grant award teams and as a presenter to FDA on improving peripheral neuropathy clinical trial patient involvement. She currently serves as an ACTTION Executive Committee member.*

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THE FUTURE HAS ARRIVED:
A Wave of New Products Is Redefining Hemophilia Care

By Keith Berman, MPH, MBA

The major challenges of current [hemophilia] treatment regimens, such as the short half-life of therapeutics with the need for frequent intravenous injections, encourage the current efforts to produce coagulation factors with more prolonged bioavailability.

— Massimo Franchini and Pier Mannucci (2012)

Over the last 50 years, perhaps no serious chronic health disorder has undergone a more radical transformation in its management and long-term prognosis than hemophilia. Prior to the discovery of cryoprecipitate in 1965 and availability of the first factor concentrates a few years thereafter, persons with severe hemophilia spent much of their lives in hospital wards and rehabilitation services; many died in childhood or early adulthood from uncontrollable hemorrhage in the brain or other vital organs. Those who survived endured extremely painful bleeds into the muscles and joints, particularly the ankle, knee and elbow. For children with severe hemophilia A or B, participation in active sports was out of the question. In surviving adults, the sequelae of years of recurrent hemarthroses could be seen on an x-ray or from across a room: joint deformity, degenerative arthritis, flexion contractures and restricted mobility.

Replacement therapy made possible by the introduction of factor VIII and IX concentrates in the late 1960s drastically reduced mortality risk, limited the severity of damage caused by hemorrhages into joints, tissues and vital organs, and freed patients to travel, hold steady jobs and lead near-normal lives. But over the 25 years that followed, the U.S. standard treatment paradigm — reactive "on-demand" self-administration of clotting factor upon awareness of a developing bleed — continued to translate into emergency room visits, hematomas and hemarthroses, major risk of joint damage, and restricted active play and sports participation.

Prophylaxis: The Next Leap Forward

Since 1958, Swedish boys with severe hemophilia have received continuous prophylaxis, beginning in infancy, in an attempt to proactively convert the disease to a milder form and minimize hemophilic arthropathy. In numerous published reports, Swedes and other European treaters showed that primary prophylaxis prevents both crippling joint damage and disabling or fatal brain hemorrhage. Initiating prophylaxis in very young children, before they experience their first joint bleeds, has been shown to be the most effective strategy to reduce later arthropathy risk.

Finally in 1994, the U.S. National Hemophilia Foundation (NHF) issued a new recommendation encouraging physicians to consider routine prophylactic infusions of appropriate clotting factor to prevent bleeding episodes. In 2007, NHF expanded its recommendation to advise that "prophylaxis using the following regimen be considered optimal treatment for any individuals with severe hemophilia A or B: 25-50 factor VIII units/kg three times per week or every other day, and 40-100 factor IX units/kg two to three times weekly."

The emergence of routine prophylactic replacement as the standard of care for children and adolescents with severe hemophilia has also introduced a major new challenge: treatment compliance. Because of the very short intravascular half-life of administered factor concentrates — about 12 hours for factor VIII and 18 hours for factor IX — the product must be administered twice weekly to as often as every other day. It is inconvenient, time-consuming and unpleasant. Compliance can be an issue in particular for teenage boys responsible for performing their own injections, who may become complacent or simply forget in the course of their busy lives. In some children, frequent regular dosing may also necessitate placement and use of central venous access devices, accompanied by risk of significant medical complications that can include infections, sepsis and thrombosis.

The obvious solution was to develop and introduce coagulation factors that persist longer in the circulation, requiring less frequent injections.

Extended Half-Life: The Newest Leap Forward

After years of anticipation, the first of what promises to be a number of bioengineered products featuring extended half-life have finally been approved for marketing, with several others awaiting regulatory approval. These products offer not only the advantage of less-frequent injections and the prospect of improved treatment compliance, but recent evidence suggests the additional benefit of a reduced number of follow-up injections needed to support complete healing following episodic bleeds.

Recognition that the pharmacokinetics of these novel clotting factors can vary widely from one person to the next has added impetus to another important advance in hemophilia treatment: individualized therapy. With individualized therapy, infusion frequency and dosage are guided by 1) trial dosing with the extended half-life product to ascertain the patient's pharmacokinetic profile, 2) the severity of his factor deficiency, 3) his bleeding pattern, 4) the condition of his musculoskeletal system and 5) his level of physical activity.

First to market: Fc fusion proteins. Biogen was first to reach the market last year with ELOCTATE (antihemophilic factor [recombinant], Fc fusion protein) and ALPROLIX (coagulation factor IX [recombinant], Fc fusion protein). The Fc fragment bound to each of these clotting factors exploits the same natural mechanism that protects immunoglobulins from rapid lysosomal degradation following endocytosis by vascular endothelial cells. In essence, recognition of the Fc fragment causes these proteins to be "cycled" instead back into the circulation. The result is circulating half-life that, on average, is increased in relation to conventional factor VIII and IX by 1.8-fold for ELOCTATE and by at least four-fold for ALPROLIX.

In the pivotal clinical trial of ELOCTATE, the treatment interval and dose were individualized to maintain trough levels between 1 percent and 3 percent above baseline or higher, as clinically indicated to prevent bleeding. Among 112 subjects, 111 achieved a dosing interval of three days or longer; ultimately, nearly 30 percent were managed with a dosing interval of five days or longer. With a mean half-life exceeding 80 hours, ALPROLIX can be administered every seven to 10 days — dramatically reduced from the usual standard of two to three times weekly.

PEGylated and glycoPEGylated products. Already proven as a means to extend the half-life of more than a dozen licensed proteins and peptides, PEGylation involves the attachment of long strands of polyethylene glycol (PEG) to selected locations on the therapeutic protein of interest. PEGylation has been applied to a total of four investigational recombinant factor VIII and IX products with the goal of increasing their circulating half-life.

Of the four extended half-life factor VIII products currently in late-stage development, three utilize PEGylation or glycoPEGylation, a variation wherein glycans present on the protein are modified to allow site-specific conjugation of PEG (Table 1). It is thought that the long, constantly moving strands of PEG act to protect the factor VIII protein against immune cells, antibodies, enzymes and other blood constituents that normally attach to it and remove it from the circulation. A glycoPEGylated recombinant factor IX developed by Novo Nordisk (N9-GP) is also in late-stage clinical testing (Table 2). But working with PEGylation technology is not without its own risks, as Novo Nordisk learned when a case of hypersensitivity and a lack of dose-response linearity prompted the company to discontinue development of an investigational glycoPEGylated factor VIIa intended for use in inhibitor patients.

Indications and Usage

Novoeight® (Antihemophilic Factor [Recombinant]) is indicated for use in adults and children with hemophilia A for control and prevention of bleeding, perioperative management, and routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

Novoeight® is not indicated for the treatment of von Willebrand disease.

Important Safety Information

Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components, including hamster proteins.

Anaphylaxis and severe hypersensitivity reactions are possible. Patients may develop hypersensitivity to hamster proteins, which are present in trace amounts in the product. Should symptoms occur, discontinue Novoeight® and administer appropriate treatment.

Development of activity-neutralizing antibodies (inhibitors) may occur. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures factor VIII inhibitor concentration.

The most frequently reported adverse reactions (≥0.5%) were injection site reactions, increased hepatic enzymes, and pyrexia.

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Novoeight®

(Antihemophilic Factor [Recombinant]) — an evolution in treatment for hospital patients with hemophilia A

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1 4 mL pre-filled diluent **SYRINGE**

Facilitates quick reconstitution and consistent preparation of treatment

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Room temperature storage

4-HOUR STORAGE TIME after reconstitution[1]

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Please see Prescribing Information for complete storage instructions.

VALUE

6 **VIAL SIZES**

Multiple dose strengths help infuse patients with fewer vials[1]

Novoeight® — a proven safe and effective treatment for hospital patients with hemophilia A[1]

Indicated for use in adults and children with hemophilia A for:

- Control and prevention of bleeding
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Talk to your authorized distributor to learn more about Novoeight® or visit NovoeightPro.com for answers and resources.

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References: 1. Novoeight® [package insert]. Plainsboro, NJ: Novo Nordisk Inc.; 2014. **2.** ADVATE™ [package insert]. Westlake Village, CA: Baxter Healthcare Corp.; 2014. **3.** ELOCTATE® [package insert]. Cambridge, MA: Biogen Idec Inc.; 2014. **4.** Helixate® FS [package insert]. Whippany, NJ: Bayer HealthCare LLC; 2014. **5.** Kogenate® FS [package insert]. Tarrytown, NY: Bayer HealthCare LLC; 2014. **6.** RECOMBINATE™ [package insert]. Westlake Village, CA: Baxter Healthcare Corp.; 2014. **7.** XYNTHA® [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals Inc., 2014.

Please see Brief Summary of Prescribing Information on the adjacent page.

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

novoeight®
Antihemophilic Factor (Recombinant)

Novoeight®, Antihemophilic Factor (Recombinant)

Rx Only

BRIEF SUMMARY: Please consult package insert for full prescribing information

INDICATIONS AND USAGE: Novoeight®, Antihemophilic Factor (Recombinant), is indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency or classic hemophilia) for: control and prevention of bleeding episodes; Perioperative management; routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Novoeight® is not indicated for the treatment of von Willebrand disease.

CONTRAINDICATIONS: Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Novoeight® or its components (including traces of hamster proteins).

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, are possible with Novoeight®. Novoeight® contains trace amounts of hamster proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins. Early signs of hypersensitivity reactions that can progress to anaphylaxis include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if allergic- or anaphylactic-type reactions occur. **Neutralizing Antibodies:** Formation of neutralizing antibodies (inhibitors) to factor VIII can occur following administration of Novoeight®. Monitor all patients for the development of inhibitors by appropriate clinical observation and laboratory testing. If the expected plasma levels of factor VIII activity are not attained, or if bleeding is not controlled with an appropriate dose, perform testing for factor VIII inhibitors. **Monitoring Laboratory Tests:** Monitor plasma factor VIII activity levels by the one-stage clotting assay or the chromogenic substrate assay to confirm that adequate factor VIII levels have been achieved and maintained, when clinically indicated. Perform assay to determine if factor VIII inhibitor is present if expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with the expected dose of Novoeight®. Determine inhibitor levels in Bethesda Units.

ADVERSE REACTIONS: The most frequently reported adverse reactions (≥ 0.5%) were injection site reactions, increased hepatic enzymes, and pyrexia. **Clinical Trials Experience:** Because 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 clinical trials of another drug and may not reflect the rates observed in clinical practice. During the clinical development of Novoeight®, 214 male previously treated patients (PTPs; exposed to a factor VIII-containing product for ≥150 days) with severe hemophilia A (factor VIII level ≤1%) received at least one dose of Novoeight® as part of either routine prophylaxis, on-demand treatment of bleeding episodes, perioperative management of major and minor surgical, dental, or other invasive procedures, or pharmacokinetic evaluation of Novoeight®. Thirty-one subjects (14%) were <6 years of age, 32 (15%) were 6 to <12 years of age, 16 (7%) were adolescents (12 to <16 years of age), and 135 (63%) were adults (16 years of age and older). The subjects received a total of 33,272 injections with a median of 127 injections of Novoeight® (range 1-442) per subject, and had a total of 32,929 exposure days during prevention and treatment of bleeds. The most frequently reported adverse reactions in previously treated patients was injection site reactions (2.3%), increased hepatic enzymes (1.4%), and pyrexia (0.9%). **Immunogenicity:** Subjects were monitored for neutralizing antibodies to factor VIII and binding antibodies to CHO and murine protein. No subjects developed confirmed neutralizing antibodies to factor VIII. One twenty-two month old child had a positive neutralizing antibody to factor VIII of 1.3 [BU] in the Bethesda assay after 15 exposure days that was not confirmed when checked after 20 exposure days. In vivo recovery was normal for this child and no clinical adverse findings were observed. No patients developed *de novo* anti-murine antibodies. Nineteen subjects were positive for anti-Chinese hamster ovary (CHO) cell protein antibodies. Two of these subjects changed from anti-CHO negative to anti-CHO positive and 6 subjects changed from anti-CHO positive to anti-CHO negative. The remaining 11 subjects were either positive throughout the trials (n=6), negative at baseline and end-of trial but with transient positive samples (n=2), or positive at baseline and end-of trial but with negative samples in between (n=3). No clinical adverse findings were observed in any of these subjects. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

More detailed information is available upon request.

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Antihemophilic Factor (Recombinant)

Table 1. Marketed (blue) and Investigational (green) Factor VIII Concentrates

	Standard Half-Life		Extended Half-Life	Status
	Plasma-Derived	Recombinant		
Baxalta	**Hemofil M** (Antihemophilic Factor [Human], Monoclonal Purified)	**ADVATE Recombinate** (Antihemophilic Factor [Recombinant])	**ADYNOVATE (BAX 855)** (PEGylated Recombinant Factor VIII)	Application filed for approval (December 2014)
Bayer		**Kogenate FS** (Antihemophilic Factor [Recombinant])	**BAY 94-9027** (PEGylated B-Domain-Deleted Recombinant Factor VIII)	Completed Phase III clinical testing
Biogen			**ELOCTATE** (Antihemophilic Factor [Recombinant], Fc Fusion Protein)	
CSL Behring	**Monoclate-P** (Antihemophilic Factor [Human], Monoclonal Purified) **Humate-P** (Antihemophilic Factor/von Willebrand Factor Complex [Human])	**Helixate FS** (Antihemophilic Factor [Recombinant])	**rVIII-SingleChain (CSL627)** (Recombinant Factor VIII Single-Chain)	Completed Phase III clinical testing
Novo Nordisk		**Novoeight** (Antihemophilic Factor [Recombinant])	**N8-GP (NN7088)** (GlycoPEGylated Recombinant Factor VIII)	Completed Phase III clinical testing
Grifols	**Alphanate** (Antihemophilic Factor/von Willebrand Factor Complex [Human])			
Octapharma		**NUWIQ** (Antihemophilic Factor [Recombinant])		
Pfizer/Wyeth		**XYNTHA** (Antihemophilic Factor [Recombinant])		

Single chain factor VIII. CSL Behring is investigating a recombinant factor VIII molecule that exploits the natural stabilizing effect of von Willebrand factor (VWF) to extend half-life. Its single-chain recombinant factor VIII (rFVIII-SingleChain) has a strong affinity for VWF, resulting in enhanced stability and integrity of the protein in circulation. In a prophylaxis study evaluating rFVIII-SingleChain, 32 percent of subjects could be dosed weekly, while another 54 percent were dosed three times per week — again illustrating how individual variability in pharmacokinetics, as well as other risk parameters, can influence bleeding tendency from one patient to the next.

As with other extended half-life factor VIII products that have been evaluated in Phase III studies, there is no evidence of inhibitor antibody development following thousands of infusions of rFVIII-SingleChain.

Albumin fusion proteins. Capitalizing on the long intravascular half-life of human albumin — about 20 days — CSL Behring has designed a novel investigational fusion protein that links it to recombinant factor IX (rIX-FP). Like the Fc portion of IgG1, the albumin bound to factor IX is unlikely to elicit a neutralizing antibody response. Another appeal is that albumin fusion products can be manufactured with fewer post-expression modifications and purification steps than PEGylation, and more efficiently in relation to other fusion protein approaches, including use of the IgG1 Fc fragment.

CSL Behring is evaluating multiple prophylaxis regimens, including seven-day and even 14-day intervals, in a Phase II/III safety, pharmacokinetic and efficacy study of previously treated patients with hemophilia B and baseline factor IX of ≤2 percent. In February, the U.S. Food and Drug Administration (FDA) accepted the company's application for approval of rIX-FP, which is currently under review.

While average 1.5- to 1.7-fold increases in circulating half-life have been reported for ELOCTATE and all of these novel long-acting factor VIII candidates, to about 18 to 20 hours, long-acting factor IX products perform far better. Together with ALPROLIX, four- to five-fold increases in mean half-life have been documented in pharmacokinetic studies of both Novo Nordisk's glycoPEGylated factor IX product (N9-GP) and CSL Behring's factor IX-albumin fusion protein (rIX-FP).

Also in development by CSL Behring is an investigational

Table 2. Marketed (blue) and Investigational (green) Factor IX Concentrates

	Standard Half-Life		Extended Half-Life	Status
	Plasma-Derived	Recombinant		
CSL Behring	**Mononine** (Antihemophilic Factor [Human])		**rIX-FP** (Coagulation Factor IX [Recombinant], Albumin Fushion Protein)	Application filed for approval (December 2014)
Biogen			**ALPROLIX** (Coagulation Factor IX [Recombinant], Fc Fusion Protein)	
Novo Nordisk			**N9-GP (NN79)** (GlycoPEGylated Recombinant Factor IX)	Completed Phase III clinical testing
Baxalta	**Bebulin** (Factor IX Complex)	**RIXUBIS** (Coagulation Factor IX [Recombinant])		
Emergent Biosolutions		**IXINITY** (Antihemophilic Factor [Recombinant])		
Grifols	**AlphaNine S/D** (Coagulation Factor IX [Human]) **Profilnine** (Factor IX Complex)			

anti-inhibitor product based on this same platform: a recombinant fusion protein linking factor VIIa with albumin (rVIIa-FP) for on-demand treatment of patients with congenital hemophilia A or B who have developed inhibitor antibodies to factor VIII or IX replacement therapy. In August of this year, the first patient was enrolled in a Phase II/III study evaluating its pharmacokinetics, efficacy and safety.

Innovations Targeting Other Bleeding Disorders

The current wave of product innovation has produced new treatment options for other important coagulation disorders beyond hemophilia A and B. Below are two products newly licensed and available within just the last two years:

• OBIZUR (antihemophilic factor [recombinant], porcine sequence) (Baxalta) for treatment of acquired hemophilia A; approved October 2014. Baxalta plans to submit additional clinical trial data to support an indication for perioperative management of bleeds in adults with acquired hemophilia A.

• TRETTEN (coagulation factor XIII A-subunit [recombinant]) (Novo Nordisk) for treatment of congenital factor XIII A-subunit deficiency; approved December 2013.*

In addition, an application for marketing approval of the first recombinant von Willebrand factor, Baxalta's VONVENDI (BAX 111) was submitted in late 2014, and is currently under review by FDA. Phase III clinical testing is now in progress to evaluate its efficacy and safety in patients with von Willebrand disease undergoing surgery.

Design Better Products, Patients Come

When allowed to choose between continuing on an extension study with investigational extended half-life products or returning to treatment with their previous standard half-life product, all subjects who have participated in completed Phase III trials have chosen to continue with the long-acting product. This strong preference for a product that reduces the number of factor infusion sessions and needle sticks may translate into improved treatment compliance. Better compliance and more days of protection with each administration should mean fewer days during the year that factor trough levels fall below the target level. And that, in turn, should mean fewer breakthrough bleeding events.

For persons with hemophilia, all evidence suggests that a healthier, safer future has indeed arrived. ❖

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** CSL Behring's Corifact factor XIII concentrate (human), indicated for routine prophylactic treatment and perioperative management of surgical bleeding in adult and pediatric patients with congenital factor XIII deficiency, was approved in February 2011.*

Drawing on the Past and Looking to the Future: The Role of House Calls in the Age of Modern Medicine

As technology advances and more options for healthcare delivery become available, a plethora of service models are emerging. One surprising model, the house call, seems to buck the high-tech trend.

By Dana Henry

Though it may seem like part of a bygone era or an episode of "Little House on the Prairie," the house call is not just an image of American medicine's past; it may also be the way of the future. With patient bases increasing in age and more and more people having mobility issues — transportation and other limitations — house calls are on the rise after a staggering drop in previous decades.

Between 1930 and 1950, the number of physician encounters taking place in homes dropped from 40 percent to 10 percent. By 1980, that figure stood at a mere 1 percent.[1] It seemed the house call was part of a dying breed of medicine, until the trend once again shifted. Between 1999 and 2009, the number of house calls actually increased by 64 percent, from 1.4 million to 2.3 million encounters, according to data from Medicare Part B billings.[2]

A review of several house call practices reveals their benefits for patients, clinicians and practices that want to move to or incorporate home-based care.

Three House Call Models, One Common Goal

Founded in 2002, Doctors Making Housecalls is a medical practice comprising 62 clinicians who make more than 75,000 home visits each year to private residences, retirement communities, apartment buildings and independent and assisted facilities in areas of North Carolina.[3,4] And those numbers are increasing. The practice had 42 clinicians last fall,[4] which means it has grown by more than 47 percent in the past year alone.

Shohreh Taavoni, MD, and Alan Kronhaus, MD, started Doctors Making Housecalls after Dr. Taavoni realized how many patients were too ill or too fragile or lacked the transportation

necessary to make office visits viable. She remembered the medical care she received as a child in Iran, where doctors routinely visited patients in their homes to avoid exposing them to the pathogens present in the office setting.[6] The practice, which began as a small undertaking, now operates from a 15,000-square-foot headquarters and has grown well beyond Drs. Taavoni and Kronhaus.[5]

For seven years, Andrea L. Brand, MD, operated a cash-only house call practice just over a decade ago. She traded in her salaried position, complete with all the tools, services and benefits of a traditional practice, for what she describes as "a cash-only, house call practice that [relied] mostly on a car, a doctor's bag, paper charts, a simple fee structure and cash, which I collect[ed] at the time of service." Brand says she could do about 95 percent of what she did in an office setting. She describes her visits with her patients as comfortable interactions in the living room or at the kitchen table of each patient. "The medical office creates many physical and emotional barriers between doctors and patients; the house call removes them," Dr. Brand explains.[6]

Physicians are also incorporating house calls into their traditional practices. Samantha Pozner, MD, began making house calls in 2002 as part of her practice in New Jersey. Her reason for doing so was that she had patients who could no longer make it in to see her. It started with one patient who was too ill to come into the office. Dr. Pozner would leave for work early, which gave her time to visit the patient at home on the way in. Over the past decade, she has seen about 30 patients in their homes. "Once you have it in your head you can do that, the opportunities present themselves," says Dr. Pozner.[2]

The Benefits and Challenges of the House Call Practice

One benefit of making house calls is that healthcare comes to those who are unable to visit a doctor's office or who would have difficulty doing so. Doctors Making Housecalls states that it can do more tests and procedures in a patient's home or place of business than most primary care physicians perform in the traditional office setting. The practice keeps costs down by contracting with insurance companies and being an in-network provider with nearly every plan.[4] A two-year patient outcome tracking effort as part of a Medicare demonstration project exploring at-home care for complex and elderly patients showed that patients at Doctors Making Housecalls spent less time in hospitals, had fewer emergency room visits and spent less on healthcare overall.

Dr. Taavoni built the practice for patient convenience and has also come to see it as a solid solution to provider burnout and the rising cost of consumer health. She says the practice grew slowly for the first few years. During this period, savings were used to sustain the practice. Now, Doctors Making Housecalls is flourishing, and overhead is lower than in other practices. Dr. Taavoni credits this low overhead for the practice's success, saying the model allows its clinicians to spend more time with patients.[5]

Dr. Brand has a similar story. In an article for *Family Practice Management,* she explains that her overall income was lower with her new house call-based practice, but her hourly income was higher. She says she kept the volume low by design, which allowed her to provide better service to her patients.[6] She was also able to act as her own boss and create her own schedule.[2] In addition, her overhead, while higher at the beginning, declined over time. Using an array of portable medical tools and equipment, as well as drug samples, she says she could provide services that rivaled her level of in-office care with 30 percent of the overhead.[6]

Dr. Pozner says her house calls have kept many of her patients out of the hospital. She also attributes home visits with giving her more insight into her patients' lives — including their environments and their caregivers — as well as developing better relationships with patients and their families.[7] She attributes her success to making home visits work for her. She

The Virtual Home (or Anywhere) Visit: Video Calls via Mobile Devices

Another form of house call takes advantage of technology, namely the widespread availability and increasing sophistication of cell phones. Companies such as American Well, Doctor on Demand and Teladoc offer a virtual office visit with a doctor, psychologist or other provider by way of video visits.[8,9,10] Common ailments are best suited to this type of visit, including colds and flus, sore throats, urinary tract infections, skin issues, sports injuries, diarrhea and vomiting, and eye conditions. Chronic conditions and cancer or other complex conditions don't lend themselves to this type of visit.[11,12] (Read more about virtual office visits and other types of telemedicine in "The Age of Telemedicine," which appeared in the Fall 2014 issue of *BioSupply Trends Quarterly*.)

only visits patients who live in convenient locations such as between her home and office. She also fits her home visits around her office practice rather than setting aside a dedicated time frame for house calls.[2]

Establishing a House Call Practice

Though still relatively low compared with overall office visits, the uptick in house calls is something traditional practices might want to keep on their radar. If a practice wants to incorporate a small number of home visits into an existing practice, little to no marketing is required. The clinicians will know which of their existing patients will be in need of such services. Dr. Pozner says providing house calls has actually been its own form of marketing for the traditional side of her practice. She estimates that she gained 100 new in-office patients as a result of recommendations given by the family of a single house call patient.[7]

Another model that practices can adopt is a concierge approach to home visits. With this model, patients who are able to visit the office but want the convenience of home visits pay out of pocket for the service. For these patients, the fee is necessary because most insurance companies won't reimburse the practice for the added cost of the home visit.[7]

For those who want to create a practice that's dedicated to house calls, the start-up process can pose unique challenges. Though building a house call practice doesn't require the same volume of patients as a traditional practice, finding those patients isn't always straightforward. Referrals from other traditional practices are rare. In addition, many traditional forms of marketing don't work well for this business model. Instead, talking with social workers, home nursing agencies, local aging councils and other individuals and entities who serve the populations that are most likely to be homebound and in need of home-based services might be more effective.[7] Word of mouth has been reported as the main form of marketing for dedicated house call practices.

Having an established patient base and reputation within a community can also facilitate the transition to a house call practice.[6,7] Dr. Brand offers additional advice for capitalizing on one's existing reputation and practice. She recommends sending a letter to patients and colleagues that explains the house call practice and why it's being implemented. She also suggests reaching out to local media outlets. Offering to write an article for the local paper or make an appearance on a local news channel is another way to spread the word about a house call practice.[6]

A Calling for House Calls

If the past few years are any indication, house calls are here to stay and will most likely continue to rise with the country's growing geriatric population. House calls are just one important component in the array of options available to practices and clinicians. Whether large or small, stand-alone or incorporated into an office-based practice, or part of concierge or traditional care, the house call practice is making inroads and changing lives for the better. ❖

If a practice wants to incorporate a small number of home visits into an existing practice, little to no marketing is required.

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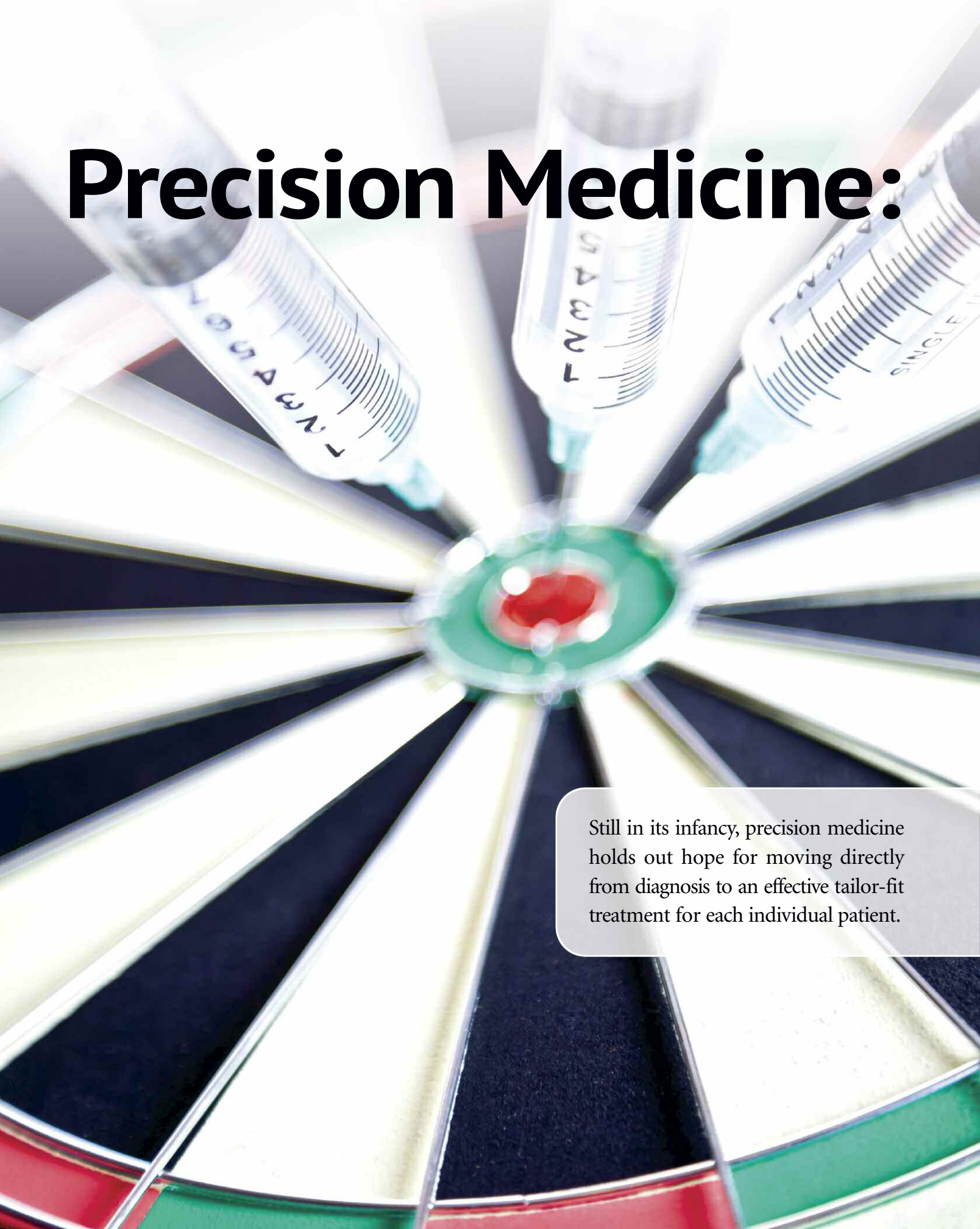
Precision Medicine:



Still in its infancy, precision medicine holds out hope for moving directly from diagnosis to an effective tailor-fit treatment for each individual patient.

A Seismic Shift in Treatment Strategy

By Jim Trageser

President Obama's endorsement of an initiative to promote the study and implementation of precision medicine in his State of the Union address didn't attract much mainstream media attention, but according to many medical researchers, precision medicine offers tremendous promise for improving the treatment efficacy for a host of diseases — from cancer to autoimmune disorders. And, yet, this is no "war on cancer" or a manned mission to the moon. While President Obama promises a revolution in medical care, he proposes doing it for an extremely modest financial investment.

The president's proposal is to build on existing medical treatments and technology but apply them in an exponentially more efficient method using the power of modern databases to maximize effectiveness. This approach of adopting a new treatment philosophy built on present and upcoming technologies applied in novel ways is reflected in the funding the White House has proposed for the Precision Medicine Initiative, which includes no money for new primary research into treatments. Indeed, the president's $215 million pledge toward the Precision Medicine Initiative is less than 1 percent of the National Institutes of Health's (NIH) annual budget of more than $30 billion.[1]

What Is Precision Medicine?

Since it's a fairly recent concept, the term "precision medicine" remains somewhat fluid and amorphous, with nearly as many different definitions as there are people offering them if the search engines are to be believed. But, as invoked by the president, and as increasingly used by the scientific and medical communities involved in the president's initiative, precision medicine signifies the use of advanced genetic and biochemical analysis of a specific patient to implement a treatment plan offering the best chance of success. According to a White House fact sheet on the initiative: "Precision medicine gives clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective."[1]

Writing in the *New England Journal of Medicine*, Dr. J. Larry Jameson of the Perelman School of Medicine at the University of Pennsylvania and Dr. Dan L. Longo of the Dana-Farber Cancer Institute in Boston gave a more technical description. In their article, they wanted to differentiate precision medicine from the existing concepts of "personalized medicine" and "individualized medicine," which many physicians have been employing for decades. They defined precision medicine as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations."[2]

In practice, this means moving away from the historic (and current) one-size-fits-all approach toward treating disease, in which the treatment that has been most successful on the most patients is tried first on all patients, and if it fails, then other treatments or drugs are tried.[3] As the president of the Lupus Foundation of America points out, this generalized approach to treating autoimmune diseases (to offer but one example) costs money and, all too often, lives.[4]

Precision medicine offers the promise of being able to tailor-fit a treatment program offering the best odds of success in an individual patient before treatment even begins, minimizing the trial-and-error portion of the treatment process. For this to occur, physicians — both primary care and specialists — will need access to exponentially greater amounts of data, from genetics to pharmacological trial results.

Precision medicine is nothing less than the application of information technology to the field of medicine. After all, if IT models can allow online retailers to predict consumers' buying habits to the point of having packages ready to ship before they're ordered, it's easy to see why proponents of precision medicine are excited about harnessing that kind of data-driven predictive computational power to the medical field.[5]

How Is the Initiative Being Carried Out?

The president's initiative carved up the $215 million allocation between the NIH, the National Cancer Institute (NCI), the U.S. Food and Drug Administration (FDA) and the Office of the National Coordinator (ONC) for Health Information Technology.

The $130 million NIH component of the initiative will create a one-million-strong volunteer force of study patients,

both healthy and ill, as a "biobank" to establish a baseline of data, including genomes and medical histories, and, perhaps, lifestyle, diet and exercise information. Many of these volunteers will be drawn from those already enrolled in existing studies, extending the reach of the program while controlling costs. NCI will receive $70 million to complete the Cancer Genome Atlas, create a shared database and accelerate clinical trials of promising new treatments.[6] FDA will receive $10 million to create new databases of other genetic mutations that can lead to disease such as those causing cystic fibrosis. And the ONC for Health Information Technology is charged with ensuring that all this new data is treated with respect for privacy.

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NIH Director Dr. Francis S. Collins and former NCI Director Dr. Harold Varmus explain in an opinion piece in the *New England Journal of Medicine* that the primary impetus of the initiative will be on immediate advances in treating cancer, with a parallel goal of achieving increased efficiencies across all disease treatments. Cancer is a particularly promising avenue for applying principles of precision medicine, they wrote, because many of the latest treatments target specific molecules in malignant cells.[7] Conducting lab work to determine the biomolecular makeup of a tumor to determine treatments is already becoming standard practice in oncology.

The expectation of the president's initiative is that this $215 million in federal spending will serve as seed money, spurring much greater spending by the private sector — universities, private researchers, hospitals, pharmaceutical companies and more — to incorporate principles of precision medicine into their ongoing work.[1]

The Promise of Precision Medicine

In their analysis of the promise of precision medicine, Drs. Jameson and Longo point out that it is entirely possible — and perhaps likely — that ongoing technological advances in the medical field will have a disruptive impact similar to what digital cameras had on the photography industry a decade ago.[2] And, a Forbes blog by David Delaney, chief medical officer of German software giant SAP, echoed that argument: "Precision medicine ultimately has the potential to improve both quality and quantity of a patient's life and also have a ripple effect on the economics of the entire healthcare system. With better, faster treatment and less wasted on ineffective therapies, costs will be better controlled. More effective therapies and better prevention and control of chronic illness will result in fewer and shorter hospital stays and a shift from expensive reactive care to prevention."[8]

The fact that software companies now have chief medical officers — that SAP is rolling out database management products to cancer research labs and clinicians — may be more powerful testimony about the changing face of medical care than anything published in the medical community. Still, Drs. Jameson and Longo point out that it is the primary care physician and the specialist who will face the most change and challenge in the shift to precision medicine: "They stand on the front lines of the clinical care delivery system with a mandate to prevent disease, identify early signs of disease, and navigate referral paths that now have many more branches as a result of precision medicine. Increasingly, referral pathways will be needed to help connect selected patients to an expert with increased access to the emerging data and clinical guidelines."[8]

But just as the digital revolution ultimately made photography more affordable and, thus, more popular, precision medicine, they argue, will ultimately provide more effective treatments that increase our quality of life — another point also echoed by Delaney. In fact, Drs. Jameson and Longo are possibly even more effusive in their praise of the promise of precision medicine than are the politicians. From autism to epilepsy, Alzheimer's disease to cystic fibrosis, ongoing research into the chemical and genetic changes that either cause or indicate these diseases offers hope for cures formerly undreamed of. But those cures, which attack disease at the molecular level, will increasingly be targeted at smaller and smaller groups of patients, requiring physicians to navigate an increasingly complex pool of data in designing effective treatment regimens.

Applying Precision Medicine

A few specific examples of how precision medicine is foreseen by its proponents may provide the clearest illustration of both the promise and the challenges.

The Rutgers Cancer Institute of New Jersey describes one model for delivering precision medicine. In this model, a cancer clinic holds weekly team meetings, bringing together representatives from radiology, surgery, pathology, systems biology and the IT department. At these meetings, any new biomarkers discovered through sequencing would be discussed to see if any member of the team sees new treatment options suggested by these discoveries — whether an already approved therapy, or enrollment in a clinical trial.[3]

With genome analysis now taking a month or even less, a tumor can be classified down to the molecular level in a timely enough manner to incorporate into a patient's treatment in real time.[3] Again, though, knowing which drugs may interfere with that newly discovered molecule's normal function requires access to vast amounts of data — all the molecular data for every drug ever submitted to FDA.

This proposed process came to fruition this summer in an unrelated study when researchers discovered that the drug ibrutinib (Imbruvica) is effective against a specific type of diffuse large B-cell lymphoma. The drug locks up an enzyme called Bruton's tyrosine kinase (BTK) in the cancerous cells, preventing their survival. Testing to determine if a lymphoma patient's malignant cells have BTK will now allow oncologists to immediately move to treatment with ibrutinib, or cross it off the list and move on to the next possible treatment.[9]

In Great Britain, women diagnosed with breast cancer now routinely have a genetic test performed on the malignancy to see if it contains the HER2 gene. If multiple copies of the gene are discovered, oncologists can immediately begin treatment with trastuzumab (Herclon, Herceptin), which is known to be effective against these tumors. Beyond cancer, precision medicine is now being used to treat other genetically carried diseases as well. Cystic fibrosis patients who carry the so-called "Celtic gene" are now being treated with ivacaftor (Kalydeco).[10] While only about 5 percent of all cystic fibrosis patients have that gene, it is an important illustration of how precision medicine can eliminate the individual trial-and-error process of treating each patient by moving directly from diagnosis to effective treatment.

What's Next?

As with the analogy to digital photography above, making hard and fast predictions is foolhardy. When NASA developed the first digital camera for use on the Mariner 4 space probe in the early 1960s, few would have thought that 40 years later film cameras would be the domain of hobbyists or that our cell phones would take better photos than a 35mm camera of a generation earlier.

Precision medicine is in its infancy, but when it works, the combination of efficacy and cost-effectiveness makes it difficult to top. The era of the generic "miracle drug" that can cure dangerous diseases in the population at large may not be over, but it does seem highly likely that it is going to at least share the stage (and funding) with narrowly tailored (i.e., precise) drugs that are very effective for a relatively small number of patients.

While precision medicine has already found its early successes — from the HER2 gene in breast cancer to the Celtic gene in cystic fibrosis — millions of other patients await a cure or successful treatment. From lupus to diabetes, epilepsy to rheumatoid arthritis, there are hundreds of diseases with a genetic component that can potentially be cured through the processes of precision medicine described above. Even chronic infectious diseases like HIV or hepatitis that currently have no cure may yet be successfully attacked someday with drugs that operate at the molecular level. But once those treatments are developed, tested and approved, it will then take the infrastructure of precision medicine to get that information out to the physicians on the front lines so that all patients benefit from these advances. ❖

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Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. As with intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling, lethargy, hives, or manifestation of allergic reactions.

During post-approval use of PROFILNINE, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis of disseminated intravascular coagulation (DIC) have been reported.

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DESCRIPTION

Factor IX Complex, Profilnine®, is a solvent detergent treated, nanofiltered, sterile, lyophilized concentrate of coagulation factors IX, II, and X and low levels of factor VII. The factor II content is not more than (NMT) 150 units* per 100 factor IX units, the factor X content is NMT 100 units per 100 factor IX units, and the factor VII content is NMT 35 units per 100 factor IX units. Profilnine is intended for intravenous administration only. Each vial is a single dose container and is labeled with the factor IX potency expressed in international units. Profilnine does not contain heparin and contains no preservatives. Profilnine contains few, if any, activated factors based on results from the non-activated partial thromboplastin time (NAPTT) test.

Profilnine is prepared from pooled human plasma and purified by diethylaminoethyl (DEAE) cellulose adsorption. The risk of transmission of infective agents by Profilnine has been substantially reduced by donor selection procedures and virus screening of individual donations and plasma pools by serological and nucleic acid testing. In addition, specific, effective virus elimination steps such as nanofiltration and solvent/detergent (tri-n-butyl phosphate/TNBP) treatment have been incorporated into the Profilnine manufacturing process. Additional removal of some viruses occurs during the DEAE cellulose product purification step. The ability of the manufacturing process to eliminate virus from Profilnine was evaluated in the laboratory by intentionally adding virus to product just prior to the elimination step and monitoring virus removal. Table 1 shows the amounts of virus that can be removed by solvent detergent treatment, nanofiltration and purification by DEAE chromatography when vesicular stomatitis virus (VSV), human immunodeficiency virus-1 and 2 (HIV-1, HIV-2), parvovirus, West Nile virus (WNV), bovine viral diarrhea virus (BVDV), hepatitis A virus (HAV) and pseudorabies virus (PRV) were evaluated in these virus spiking studies. The results indicate that the solvent detergent treatment step effectively inactivates enveloped viruses and the nanofiltration step effectively removes both enveloped and non-enveloped viruses.

Table 1

			Virus Reduction (log_{10}) Process Step		
Virus	**Virus Type**	**Model For:**	1st DEAE Chromatography	Solvent-Detergent	Nanofiltration
Sindbis	Env	Hepatitis C	1.4	≥ 5.3	NT
VSV	Env	Robust enveloped viruses	NT	≥ 4.9	NT
HIV-1	Env	HIV-1	NT	≥ 12.2	≥ 6.2
HIV-2	Env	HIV-2	NT	≥ 6.0	NT
WNV	Env	WNV	NT	NT	≥ 6.6
BVDV	Env	Hepatitis C	NT	NT	≥ 4.9
Parvo[a]	Non-Env	Parvovirus B19	NT	NT	≥ 6.1
HAV	Non-Env	HAV	NT	NT	≥ 5.8
PRV	Non-Env	Hepatitis B	NT	NT	≥ 5.3

[a] Porcine, NT=Not tested, Env=enveloped

CLINICAL PHARMACOLOGY

Profilnine is a mixture of the vitamin K-dependent clotting factors IX, II, X and low levels of VII. The administration of Profilnine temporarily increases the plasma levels of factor IX, thus enabling a temporary correction of the factor deficiency.

A clinical study that evaluated twelve subjects with hemophilia B indicated that, following administration of Profilnine, the factor IX *in vivo* half-life was 24.68 ± 8.29 hours and recovery was 1.15 ± 0.16 units/dL per unit infused per kg body weight.

Administration of factor IX complex can result in higher than normal levels of factor II due to its significantly longer half-life.

INDICATIONS AND USAGE

Profilnine is indicated for the prevention and control of bleeding in patients with factor IX deficiency (hemophilia B).

Profilnine contains non-therapeutic levels of factor VII, and is not indicated for use in the treatment of factor VII deficiency.

CONTRAINDICATIONS

None known.

WARNINGS

Because Profilnine is made from pooled human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Stringent procedures designed to reduce the risk of adventitious agent transmission have been employed in the manufacture of this product, from the screening of plasma donors and the collection and testing of plasma to the application of viral elimination/reduction steps such as DEAE chromatography, solvent detergent treatment and nanofiltration in the manufacturing process. Despite these measures, such products can potentially transmit disease: therefore the risk of infectious agents cannot be totally eliminated. The physician must weigh the risks and benefits of using this product and discuss these issues with the patient. Appropriate vaccination (hepatitis A and B) for patients in receipt of plasma derived factor IX complex concentrates is recommended.

The use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications and the use of such products may be potentially hazardous in patients undergoing surgery, in patients post surgery, in patients with known liver disease, and in patients with signs of fibrinolysis, thrombosis or disseminated intravascular coagulation (DIC). For these patients, clinical surveillance for early signs of consumptive coagulopathy should be initiated with appropriate biological testing when administering this product. Profilnine should only be administered to patients when the beneficial effects of use outweigh the serious risk of potential hypercoagulation.

PRECAUTIONS

General

Exercise caution when handling Profilnine due to the limited risk of exposure to viral infection. Discard any unused Profilnine vial contents. Discard administration equipment after single use. Do not resterilize components. Do not reuse components.

Information for Patients

After repeated treatment with Profilnine, patients should be monitored for the development of neutralizing antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

Hypersensitivity and allergic type hypersensitivity reactions, including anaphylaxis, have been reported for all factor IX complex concentrate products. Patients must be informed of the early symptoms and signs of hypersensitivity reaction, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia and anaphylaxis. Patients must be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care if these symptoms occur.

Pregnancy Category C

Animal reproduction studies have not been conducted with Profilnine. It is also not known whether Profilnine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Profilnine should be given to a pregnant woman only if clearly indicated.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 16 have not been established. However, across a well controlled half-life and recovery clinical trial in patients previously treated with factor IX concentrates for Hemophilia B, the two pediatric patients receiving Profilnine responded similarly when compared with the adult patients.

ADVERSE REACTIONS

As with other intravenous administration of other plasma-derived products, the following reactions may be observed following administration: headache, fever, chills, flushing, nausea, vomiting, tingling lethargy, hives, or manifestation of allergic reactions.

In addition, during post-approval use of Profilnine, cases of allergic/hypersensitivity reactions (including urticaria, shortness of breath, hypotension, and pruritus) and adverse reactions characterized by either thrombosis or disseminated intravascular coagulation (DIC) have been reported. 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 drug exposure.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

* Unit refers to International Unit in the labeling of Profilnine.

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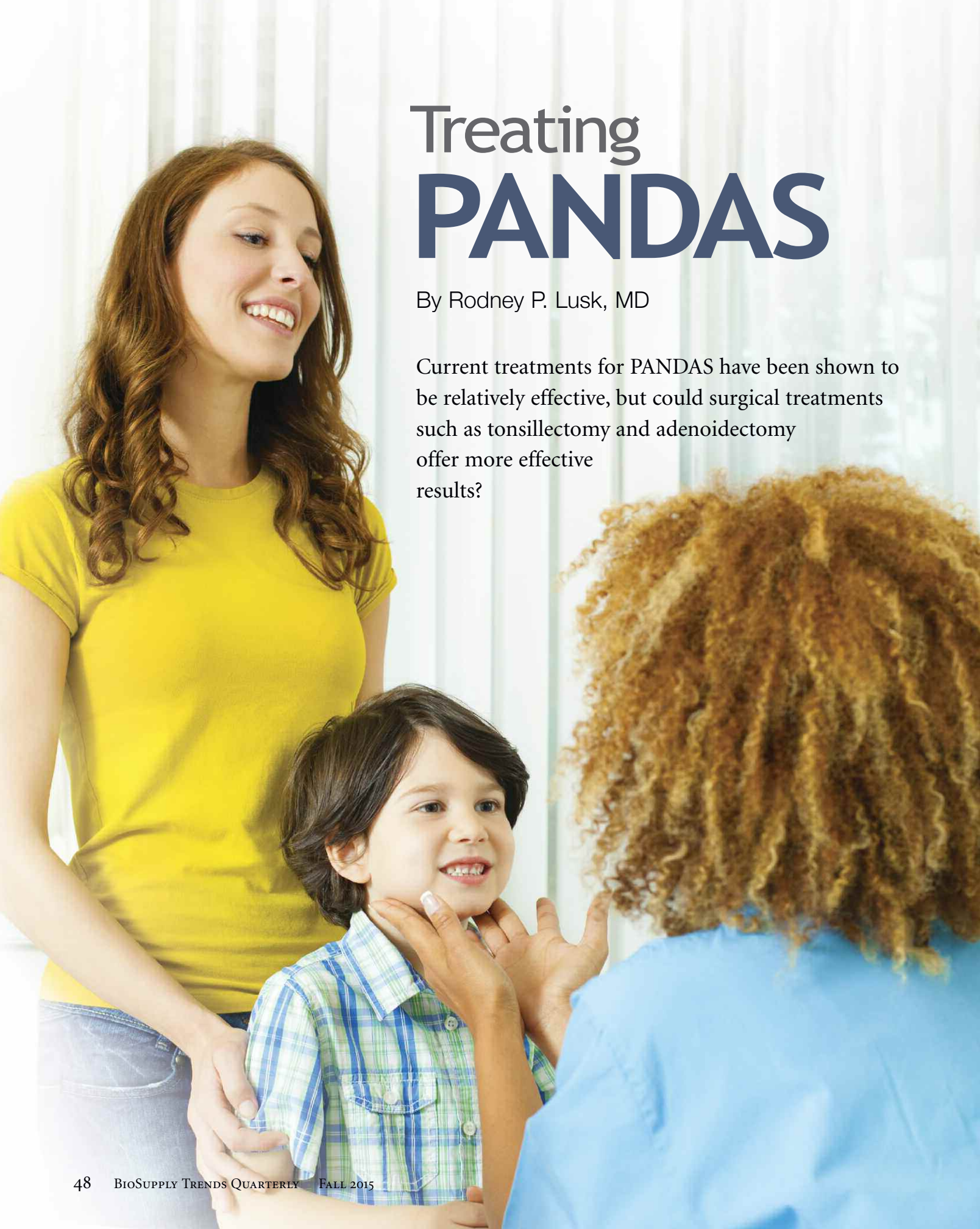
Treating PANDAS

By Rodney P. Lusk, MD

Current treatments for PANDAS have been shown to be relatively effective, but could surgical treatments such as tonsillectomy and adenoidectomy offer more effective results?



Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a relatively new diagnosis thought to be associated with one in 2,000 children with strep infections. It was originally based on 50 cases reported in 1998 in which 77 percent of children had a preceding group A streptococcal (GAS) infection.[1] In this initial report, PANDAS is characterized with the acute onset of obsessive compulsive disorder (OCD)-type symptoms that include aggressive behavior, compulsive handwashing, compulsive cleaning and frequent checking of locks on doors or windows. Muscular tics are also characteristic, with audible tics noted in some children. Other symptoms that are variably expressed include urinary urgency, hyperactivity, impulsivity, deterioration in handwriting, separation anxiety and decline in school performance. Handwriting deterioration appears to be an early hallmark of the disorder. Anorexia is another psychiatric illness that can be comorbid in PANDAS and has less to do with body image and more with the sensation of texture, taste of food or fear of choking.

A closely related disorder is Sydenham chorea, which is associated with rheumatic fever. PANDAS, however, is not associated with any symptoms of rheumatic fever — specifically fever, arthritis or carditis. And, PANDAS is not considered a "milder form" of Sydenham chorea. Recently, the term pediatric acute-onset neuropsychiatric syndrome (PANS) has been used to describe the acute onset of neuropsychiatric conditions similar to PANDAS but with a broader range of potential etiologies. A key diagnostic feature of PANS is the acute dramatic onset of an obsessive compulsive disorder or severely restricted food intake. Sensory issues are thought to be more common in PANS and can manifest themselves as sensitivity to light, food texture (anorexia), olfactory hallucinations, tactile issues with clothing, shoes and socks, and frequent urge to urinate but without the physiological need. Another classification of similar disorder is called childhood acute neuropsychiatric symptoms (CANS). Each classification has its advocates, and there is certainly significant overlap in symptoms. This article will not focus further on this debate other than to say that there is significant overlap in the symptoms and underlying etiology. Current treatment protocols are similar for all three.

Pathophysiology of PANDAS

It is interesting to note that GAS is not the only infectious agent thought to result in a neurological disease. Mycoplasma pneumonia is implicated in Tourette syndrome,[2] with 59 percent of Tourette syndrome patients having elevated antibody titers. Lyme disease is also thought to be a trigger for PANS, with OCD symptoms being prominent. And, there is a large body of knowledge indicating that Toxoplasma gondii, from infected cat feces, may be associated with schizophrenia.[3] The mechanisms of these infectious processes with the neurological system is likely varied, but as we learn more, a common immunological pathway may be implicated.

The underlying pathophysiology of PANDAS is important when considering possible treatment modalities. The pathophysiology of PANDAS is thought to be based on molecular mimicry of GAS antibodies that target brain proteins leading to the clinical manifestations of PANDAS. GAS antibodies may directly stimulate or block receptors of the basal ganglia (a region of the base of the brain that is responsible for involuntary movements), or affect immune complexes that lead to inflammation of the basal ganglia. PANDAS children have also been found to have significantly higher levels of antibodies that trigger calcium-calmodulin–dependent protein kinase II (CaM kinase II) production. These cross-reactive antibodies may interfere with neuronal signals by increasing CaM kinase II production in the basal ganglia, eventually leading to dopamine dysregulation. This dysregulation may subsequently lead to the clinical presentation characteristic of PANDAS. Animal models are being developed to further define the underlying pathophysiology of this disorder.[4]

The underlying pathophysiology of PANDAS is important when considering possible treatment modalities.

PANDAS Diagnosis

Definitive laboratory tests for the diagnosis of PANDAS are lacking; however, certain tests are useful. Identifying strep through cultures is important. As many as 85 percent of patients are positive with one serology test, and 95 percent are positive when multiple tests such as ASO and anti-DNase B titers are used. These two tests are clinically useful and routinely obtained.

Antibodies to human brain enolase (AE), neural tissue and anti-streptococcal antibodies have been shown to be significantly

elevated in patients with the early onset of psychiatric disorders. The use of neuroimaging (MRI) has been used, but it is nonspecific. An MRI most commonly shows inflammation and enlargement of the basal ganglion. With progressive decrease in antineuronal antibody titers, the inflammation in the basal ganglion has been shown to progressively decrease.

Since streptococcal infections are associated with PANDAS, prompt antibiotic intervention remains the primary course of medical management, especially in the acute phase.

Current PANDAS Treatment

Since streptococcal infections are associated with PANDAS, prompt antibiotic intervention remains the primary course of medical management, especially in the acute phase. The primary antibiotics include penicillins (amoxicillin or amoxicillin plus clavulanic acid) or cephalosporins. Other forms of medical management include sporadic reports of successful management with steroids and nonsteroidal anti-inflammatory drugs, which are thought to reduce inflammation of neurological tissue, especially in the basal ganglion. The effects of these mostly appear in case reports, and no general conclusions regarding their effectiveness can be provided.

Two other forms of management, immunotherapy and therapeutic plasma exchange (TPE), have been shown to be somewhat encouraging in small case series. Immunotherapy is based on providing a large number of intravenous immune globulin (IVIG) antibodies pooled from adult blood donors. It is thought that providing a large number of antibodies against bacteria and viruses will result in a greater ability to fight the infection. However, this treatment is not without significant side effects, which include chills, low-grade fever and headache, and rare serious side effects such as difficulty breathing, chest pain, seizures and severe anaphylactic reactions.

TPE is a process by which whole blood is removed from the patient, the plasma is removed from the blood, and then the red blood cells are returned to the patient. TPE is thought to exert benefits by removing autoantibodies and antigen-antibody complexes, which potentially reduces the inflammation. The method seems to be the direct opposite of immunotherapy. The treatment is often provided in an inpatient setting, and requires either a central or femoral catheter. It is also associated with adverse effects that are frequent and can be serious.

While both immunotherapy and TPE have been shown to be effective, they are expensive and require hospitalization. Therefore, it would be advantageous if less expensive therapies with fewer possible adverse effects could be found.

Treating PANDAS with Tonsillectomy and Adenoidectomy

Because of the presumed infectiousness of strep, it would seem logical to remove tissue that is a likely source of strep infections, namely the tonsils and adenoids, as a possible PANDAS treatment. However, reports in the literature have been mixed. Early case reports were encouraging, showing improvement and, in some cases, resolution of symptoms. These were all case or small series reports, so it is difficult to know the true role of tonsillectomy and adenoidectomy.

Recently, a study of 114 patients with PANDAS[5] was conducted to determine whether tonsillectomy and/or adenoidectomy might improve a child's neuropsychiatric course. Patients were divided into two groups: those who had surgery and those who didn't. The researchers found that, because ASO titers (a blood test to measure antibodies against streptolysin O) were not different between the two groups, tonsillectomy and/or adenoidectomy does not prevent PANDAS. They also found that surgery did not result in reduced OCD or tic severity compared with the non-surgery group. In addition, the researchers noted that the symptoms of PANDAS were not different between the two groups. There are, however, problems with this study. First, it had only 20 patients who had previous surgery and subsequently developed PANDAS. Second, tonsillectomy and adenoidectomy were lumped together. This is a problem because both tissues need to be surgically addressed. The researchers acknowledge shortcomings in their study. The patients who had tonsillectomies and/or adenoidectomies had the procedure prior to onset of their neuropsychiatric disorders. None of the patients had their procedure during or shortly after the acute onset of their symptoms. Further, the researchers acknowledged that: "All of our subjects had existing OCD and/or tics at study entry. If a subset of youth did have OCD/tic remission after the surgical procedure, our study

would not have detected those." Therefore, the question remains: Does tonsillectomy and/or adenoidectomy have a role in the treatment of PANDAS during the first few months or years of the onset of neuropsychiatric symptoms?

Similarly, a multi-institutional study in Italy[6] showed that tonsillectomy had no effect on the symptomatology, progression, streptococcal and neuronal antibody titers, or the clinical severity of neuropsychiatric symptoms in children with PANDAS. The researchers concluded that the clinical progression, antibody production and neuropsychiatric symptom severity did not differ with surgical intervention.

Contrary to these results is unpublished data (with a manuscript in review) that shows tonsillectomy and adenoidectomy in children with symptoms of PANDAS. We[8] examined 12 children with PANDAS/PANS who underwent tonsillectomy and adenoidectomy (one out of the 12 had adenoidectomy alone) during a relatively acute phase of their disease. The majority of parents kept a daily symptoms diary before and after surgical intervention. There was significant improvement in symptoms (tics, OCD, anxiety, regressive behavior) in nine of the 12 children who had surgery. Of the nine who were improved, three reported excellent results, were symptom-free and off all medications. The remaining six were markedly improved but still required intermittent antibiotics during upper respiratory tract infections. The three who did not improve were treated with IVIG. One markedly improved and is symptom-free, another is improved but has relapses and the third continues with symptoms and has ongoing IVIG treatments with ongoing symptoms.

We[8] concluded that tonsillectomy and adenoidectomy appear to have remarkable improvement (resolution) in some children, improvement with intermittent relapses in others and no significant improvement in about a quarter of the patients. The cause of the variable responses is unclear, but it could be secondary to genetic predisposition or duration of symptoms. Admittedly, these numbers are very small. But as a pilot study, the results indicate that tonsillectomy and adenoidectomy in the relatively acute phase of disease warrant further study. At this time, however, we would not recommend routine tonsillectomy and adenoidectomy in children with PANDAS/PANS.

These results are supported by other reports in the literature. One multi-institutional study[7] compared nine patients who were treated with tonsillectomy with 10 patients treated with antibiotics. Four of the nine patients had complete resolution of their symptoms after tonsillectomy. The researchers concluded that PANDAS patients who did not respond to antibiotics may have significant benefit from tonsillectomy. There are several other case reports showing resolution of symptoms after tonsillectomy.[9]

If antibody complexes indeed cause inflammation of neural tissue, it would seem that the greater intensity and duration of inflammation, the greater the damage to the neural tissue. This, in turn, may be associated with less responsiveness to any therapeutic intervention. As such, it's possible that tonsillectomy and adenoidectomy are less effective in children with longer duration of symptoms.

Better Studies Are Needed

Investigations to date of successfully treating and resolving PANDAS are woefully inadequate of good prospective data that take into account accurate diagnosis and duration of symptoms. This important data can be gathered only through routine, even daily, assessment of patient symptoms prior to and after any intervention, either medical or surgical. And, adequate numbers for investigation can only be accomplished through a multi-institutional study with data acquired through a central database repository. It is hoped that continued and more accurate and thorough research will find better treatments for this puzzling disorder. ❖

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Autoimmune Disease: A More Effective Treatment on the Horizon?

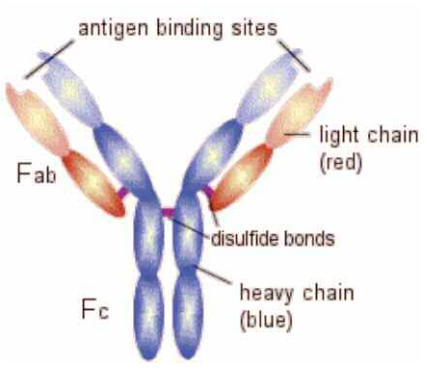
By Elissa Ritt, MAS

INTRAVENOUS IMMUNE GLOBULIN (IVIG) is a life-changing and, in many cases, life-saving treatment. IVIG is used to treat a multitude of disease states from the more familiar primary immunodeficiencies and autoimmune neuropathies to the more esoteric pemphigus vulgaris and even recurrent miscarriages. Treatment dosages for autoimmune diseases that range from 500 milligrams to 2 grams per kilogram of patient body weight (usually given monthly) result in a massive amount of IVIG being used by the healthcare system. Not only is IVIG a very expensive treatment, but because it is made from a limited resource, shortages have occurred.[1] Therefore, researchers are driven to find ways to make IG therapy more effective at smaller doses.

Sialic Switch Technology

- Some IgG antibodies carry a sugar called sialic acid on the Fc portions of the molecule.
- Sialic acid is at the root of anti-inflammatory activity.
- A small fraction of IgG antibodies found in IVIG solution carry sialic acid.
- Enriching IVIG with IgG antibodies with sialic acid increases its anti-inflammatory activity by a factor of 10.
- Soon, it may be possible to create a recombinant form of IgG with a sialic acid molecule.
- Using sialic switch technology, researchers could make a form of IVIG or a recombinant drug to treat autoimmune diseases that is more anti-inflammatory.

Figure 1. Antibody Structure



Source: University of Washington (n.d.). Structure of Antibodies and T Cell Receptors. Accessed at courses.washington.edu/conj/immune/antibody.htm.

The Sialic Acid Discovery

In 2008, Dr. Jeffrey Ravetch and his team at The Rockefeller University made a molecular discovery that could potentially be used to improve the anti-inflammatory effects of IVIG. Dr. Ravetch noted that a small number of the antibodies found in IVIG are different from the others; they exhibit a greater affinity to receptor sites that, when activated, blunt the immune response. This small, distinct subset of antibodies has a molecular entity called a sialic acid group attached to one end.[2]

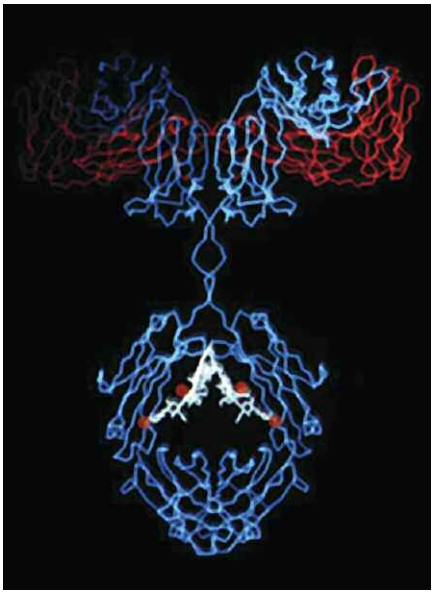
As shown in Figure 1, antibodies are Y-shaped molecules. The stem of the Y is referred to as the Fc region, or heavy chain, which activates the Fc receptors involved in immune response. These Fc receptors appear to have a far greater affinity for the antibodies that have a sialic acid group attached to the Fc region, and when these sialylated anti-

bodies activate the Fc receptors, the inflammatory response ceases (see Figure 2).[2] Prior to this discovery, Dr. Ravetch and his team discovered that antibodies without a sialic acid group might be pathogenic because they actually promote autoimmune disease in mice.[3]

Dr. Ravetch and his team are now faced with how to turn this knowledge into more effective treatments for autoimmune disease. It has previously been demonstrated that enriching IVIG with sialic acid-linked antibodies results in a greater anti-inflammatory response.[4] Even more exciting is that Dr. Ravetch and his team are able to create recombinant (laboratory made) sialylated Fc antibody regions that show a similar enhanced anti-inflammatory response.[5] This means that autoimmune diseases could be treated more effectively at smaller doses using "sialic-switch" technology — either sialic acid-enriched IVIG or a drug that makes use of recombinant sialylated Fc antibody regions.[5] Additionally, the use of a laboratory made molecule instead of a plasma-derived antibody could reduce dependence on plasma supply and even result in less frequent drug shortages.

Sialic switch technology has been licensed to Momenta Pharmaceuticals in hopes of it commercializing an enhanced autoimmune disease treatment.

Figure 2. The Sialic Acid Sweet Spot



Red dots indicate sialic acid on the Fc region of an antibody.

Source: Scientists ID a Sugar that Allows Antibodies to Fight Inflammation. *Science*, 313: 670-673 (Aug. 4, 2006). Accessed at newswire.rockefeller.edu/ 2006/08/03/ scientists-id-a-single-sugar-that-allows-antibodies-to-fight-inflammation.

Commercial Development

Sialic switch technology has been licensed to Momenta Pharmaceuticals in hopes of it commercializing an enhanced autoimmune disease treatment. While Momenta intends to continue to study the potential benefits of sialic acid-enhanced IVIG, it is looking to add recombinant products using the technology to their product pipeline in the near future.[6]

There's no denying that IVIG has enhanced and even saved the lives of many autoimmune disease patients. But, the cost of therapy, large dose size and limited raw materials are serious limitations to an otherwise efficacious, well-tolerated therapy. If Momenta succeeds in exploiting the sialic switch technology, those with autoimmune disease could benefit from improved therapies within just a few years. ❖

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More Is Better: High-Dose Flu Vaccine Helps Protect Seniors

BY KEITH BERMAN, MPH, MBA

AS SURELY AS the sun comes up every morning, every year we can count on the winter-spring epidemic of seasonal influenza, with a heavy toll in flu-related illness and deaths. As the inevitable result of immunosenescence — declining natural immunity over time — persons aged 65 years and older are at the greatest risk, accounting for an estimated 50 percent to 70 percent of all flu-related hospitalizations and 80 percent to 90 percent of flu-related deaths each year in the U.S.[1,2]

Unfortunately, this declining immune responsiveness to flu virus exposure also severely limits the protective benefit of conventional seasonal influenza vaccines in the older age demographic that most needs it. Even as successful public health campaigns have more than doubled the flu vaccination rate for seniors since 1990, overall hospital admission and death rates in that age cohort did not decline over the ensuing two decades, even after accounting for shifting age demographics and year-to-year variation in vaccine effectiveness against each season's dominant new flu strain.[3]

Approved in December 2009, Sanofi Pasteur's Fluzone High-Dose (HD) represents the first seasonal flu vaccine specifically designed to be more immunogenic and, in theory, more effective in preventing influenza-like illness (ILI) and its serious complications. In the same 0.5 mL dose for intramuscular injection, Fluzone HD packs 60 mcg of each of the three hemagglutinin viral surface antigens — four times the 15 mcg present in standard-dose (SD) flu vaccines. Immunogenicity studies have shown that HD vaccine elicits substantially higher hemagglutinin inhibition (HI) titers than SD vaccine. In the largest of these studies, the mean post-vaccination antibody titers elicited by HD vaccine against the A/H1N1, A/H3N2 and B flu strains were 70 percent, 80 percent and 30 percent higher, respectively, than the mean titer elicited by the SD vaccine.[4,5]

But does the increased immunogenicity of HD vaccine translate into reduced rates of influenza or its serious complications in this particular age cohort? Results of two recent large-scale clinical studies have affirmed that, in fact, it does.

High-Dose Vaccine Cuts Flu and Related Hospitalization Risk

The New England Journal of Medicine study. Sponsored by Sanofi Pasteur, a two-year prospective trial involving 126 research centers in the U.S. and Canada randomized nearly 32,000 participants to receive SD (Fluzone) and HD (Fluzone HD) vaccine during the 2011-2012 and 2012-2013 influenza seasons.[6] Consistent with earlier studies, HI titers were again significantly higher for all three strains — A/H1NI, A/H3N2 and B — in the group vaccinated with the HD product. For both A strains across both seasons, geometric mean titers favored HD vaccine by a ratio of between 1.8 and 2.0; for the B strain, that ratio averaged 1.5, but was still highly significant. There was also a significant difference in the seroprotection rate, again favoring the HD vaccine.

A total of 529 participants met the primary endpoint, defined as laboratory-confirmed ILI: 228 in the HD group and 301 in the SD group; the HD vaccine was 24.2 percent more effective (95% confidence interval [CI], 9.7% to 36.5%). In other words, about one-quarter of all breakthrough influenza illnesses could be prevented if HD vaccine were used instead of SD vaccine. While the confidence intervals were wide, study participants with ILI who received HD flu vaccine had a lower relative risk (RR) of pneumonia (RR, 0.66; 95% CI, 0.51-0.81*) and hospitalizations (RR, 0.70; 95% CI, 0.54-0.91*) compared with those in the SD group who contracted ILI.

Assuming an absolute efficacy of 50 percent for the SD vaccine suggested by previous studies, the absolute efficacy of HD vaccine would be estimated at 62 percent — a level of protection similar to that seen with SD vaccines in younger adults.[7] For flu seasons where there is a relatively good match between flu strains selected for the vaccine and those that later become epidemic, the HD vaccine is likely to be even more protective: compared with SD vaccine used in this study, the HD vaccine was 51.1 percent more effective in preventing modified CDC-defined, culture-confirmed influenza disease caused by strains antigenically similar to the strains contained in the vaccine.

Also reassuring was the finding that the HD flu vaccine was efficacious in preventing ILI both in the 2011-2012 season, marked by low influenza activity and a moderate-to-good match between the vaccine and circulating strains, and in the 2012-2013 season, marked by high influenza activity and a relatively poor match between predominant circulating strains and the egg-propagated vaccines used in this study.

The 2012-2013 Medicare cohort study. While the U.S.-Canadian prospective randomized trial enrolling 32,000 participants represents the gold standard for evaluating safety and efficacy in reducing ILI, that study was not powered to characterize efficacy against serious outcomes, importantly including influenza-related hospital admissions. Aware of this limitation, the U.S. Centers for Disease Control and Prevention (CDC) and U.S. Food and Drug Administration (FDA) collaborated to answer this question by exploiting the massive Medicare insurance claims database, analyzing data from more than 2.5 million Medicare beneficiaries who received either the SD or HD flu vaccines between Aug. 1, 2012, and Jan. 31, 2013.

Of the 12.5 million Medicare beneficiaries aged 65 years and older who were vaccinated during the 2012-2013 flu season, a cohort of 2,545,275 were identified who received their vaccine at 24,501 pharmacies that offered both SD and HD flu vaccine options. Overall, 929,730 and 1,615,545 beneficiaries received the HD and SD vaccines, respectively. The two groups were similar in age and underlying comorbidity patterns. Probable influenza infection was defined by the use of a rapid flu diagnostic test followed by treatment with the antiviral agent oseltamivir (Tamiflu).

About one-quarter of all breakthrough influenza illnesses could be prevented if high-dose vaccine were used instead of standard-dose vaccine.

The HD vaccine was 22 percent more effective than the SD vaccine both for prevention of probable influenza infections and for prevention of influenza-related hospital inpatient admissions or emergency department visits. The HD vaccine was more effective in all age cohorts: 65-74 years, 75-84 years and 85 years and older. The benefit in reduction of probable flu infection risk — 36 percent — was even more pronounced in persons aged 85 years and older, whose natural immune responsiveness to influenza virus and other invasive pathogens is most seriously compromised.

High-Dose Flu Vaccine: Well Worth the Cost

No other medical intervention is quite analogous to influenza vaccination: a universally recommended preventive treatment

* In participants with protocol-defined influenza-like illness, regardless of laboratory confirmation.

that confers protective immunity for some, fails to protect others from developing the illness and its complications, and whose protective benefit fluctuates from one year to the next based on the degree of match with circulating strains and the virulence of those circulating strains. But even with its limitations, influenza vaccination represents one of the most cost-effective treatment modalities available to the older adult population.[8]

Even with its limitations, influenza vaccination represents one of the most cost-effective treatment modalities available to the older adult population.

Which brings the next logical question to mind: What is the incremental health benefit of HD flu vaccine on a population basis? At about $20 more per dose than standard trivalent flu vaccine, is this product cost-effective? Researchers at the University of Pittsburgh, University of Toronto and Sanofi Pasteur developed a model to answer these questions, applying U.S. influenza health outcome data from the 32,000-subject prospective randomized referenced earlier, together with the average of U.S. influenza epidemiological experience during the 10 flu seasons from 1999-2000 through 2008-2009.

Their findings are striking. Administered entirely in place of SD vaccine, the HD flu vaccine would be expected to avert 195,958 cases of influenza, 22,567 influenza-related hospitalizations and 5,423 influenza-related deaths in U.S. seniors. The HD vaccine generates 29,023 more quality-adjusted life years (QALYs), at an incremental cost effectiveness ratio (ICER) of just $5,299 per QALY.** This compares very favorably to the ICERs for other Medicare-covered senior immunization programs, such as herpes zoster vaccine ($27,000 to $112,000/QALY) and pneumococcal conjugate vaccine ($62,000/QALY).

Proven Effectiveness, More Demand

Sanofi Pasteur reports that utilization of its Fluzone HD vaccine continues to increase year over year. During the 2014-2015 season, more than one in three immunized persons 65 years of age and older received Fluzone HD, up from just one in five over the first three flu seasons it was available. For this 2015-2016 flu season, propelled by findings from *The New England Journal of Medicine* and CDC-FDA studies, the company projects that it will be the vaccine of choice for over 50 percent of immunized seniors.

While Fluzone HD is currently the most effective available seasonal flu vaccine for U.S. adults aged 65 years and older, it will soon have new competition. A license application for Novartis' Fluad, an adjuvanted influenza vaccine in wide use outside the U.S. for adults aged 65 years and older, has been submitted to FDA for review. If approved, the first doses of Fluad could be distributed in the U.S. before the end of the 2015-2016 flu season.

Assuming Fluad becomes available, a new Medicare claims-based study may ultimately shed light on its efficacy compared with Fluzone HD. Meanwhile, the vaccines industry never rests on its laurels. There remains a very serious unaddressed risk of contracting influenza and its complications in older adults. We can expect still better flu vaccines designed to further drive down those risks in the not-too-distant future. ❖

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** Restricting the analysis to a third-party payer perspective (to only include costs to the healthcare system), the ICER increases to $10,350 per QALY.

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Infusing Hope: Living with Hemophilia

BY TRUDIE MITSCHANG

Advances in treatment of this long-misunderstood disease allow patients like Daniel Kraus to lead normal, active lives.

At age 33, Daniel is now a husband, father of three and a patient advocate, helping others diagnosed with hemophilia.

IT WAS A DAY of celebration. Just one week old, Daniel Kraus was undergoing the traditional circumcision characteristic of his family's Jewish faith. As congratulatory shouts of "mazel tov!" filled the air, another sound gradually competed for attention as doctors and nurses whispered in concerned tones about a routine procedure gone suddenly wrong. As the minutes ticked on, the bleeding from Daniel's circumcision showed no sign of letting up. "At eight days old, I lost half of my blood and had to have a massive blood transfusion. It took three days to come back with my diagnosis of hemophilia A," says Daniel. "This is in Melbourne, Australia, 1981. There's no family history. We have no patient support groups and no Internet. My parents had to educate themselves about a disease they had never heard of, and fortunately for me, they learned quickly."

Hemophilia A, also known as factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by a missing or defective FVIII clotting protein. Typically passed from parents to children, about one-third of cases, like Daniel's, are caused by a spontaneous gene mutation. According to the Centers for Disease Control and Prevention, hemophilia occurs in approximately one in 5,000 live births.

An Evolving Treatment Plan

Growing up as the middle of three siblings, Daniel says his parents tried to make sure he had as normal of an upbringing as possible. In the early days of his treatment, any injury resulting in a bleed had to be handled in the local emergency room. He recalls long hours spent waiting for an ER doctor to confirm his need for blood, followed by more waiting for blood-derived FVIII to arrive from a local blood bank so that he could get his needed infusion. At some point during his years of treatment, young Daniel contracted hepatitis C from the tainted blood supply that was in wide circulation during the mid-1980s. He considers himself fortunate; a majority of patients exposed to the same bad blood batch contracted HIV/AIDS and died.

Over the years, Daniel's treatment plan evolved as new options became available. In early adolescence, he began prophylaxis with regularly scheduled infusions of clotting factor concentrates to prevent dangerous spontaneous bleeding. By 14, Daniel was doing his own infusions, a move he says revolutionized his life. "I was finally managing my own care, and it allowed me to attend camp, youth group and other activities," he explains. "The biggest lifestyle change for me occurred in my early 20s, when recombinant treatments became available. The fact that they came in small vials that did not require refrigeration was a game-changer."

Recombinant activated FVIII was first licensed for use in hemophilia in 1997. The process for making these factors involves inserting a small piece of human DNA into a cell from another animal, and growing these cells in large numbers. Over time, the manufacturing process for recombinant factors has evolved to require no human or animal-derived proteins, and in clinical trials, they have been shown to be as effective as the plasma-derived versions.

Answering the Call to Advocacy

Eleven years ago, Daniel left his life down under and moved to New York to pursue the two major loves of his life: Rachael, the woman who would become

his wife, and a call to rabbinical studies. Today, Daniel is a busy ordained rabbi, husband, father of three, and a patient advocate, donating many hours a month in his role as board member of the New York Hemophilia Chapter. Although he carries signs of the bleeds he suffered as a child in the form of chronic joint pain and arthritis in his left ankle, at 33, Daniel Krause is passionate about helping others overcome the stigma of chronic illness. "My dad was my inspiration because he did a tremendous amount of work for the hemophilia foundation both on a state and national level when I was growing up," Daniel says. "He modeled for me what it meant to give back."

Daniel has traveled around the country as a speaker for Baxter International, a manufacturer of clotting factor products, sharing his experience as a lifelong patient. But he adamantly rejects the title "hemophiliac." "I tell people: 'Your illness is something that can either prevent you from doing things in life, or it can motivate you to do more. Hemophilia is just a piece of who you are, but it doesn't define you,'" he explains. "I'm not a hemophiliac; I'm Daniel, and I have hemophilia." ❖

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

Hemophilia Treatment Through the Years

Early 1900s

• With no method available to store blood, people with hemophilia typically received fresh whole blood transfusions from family members. Life expectancy was 13 years old.[1]

1930s-1940s

• With improved treatment, people living with hemophilia now have a median life expectancy of 27 years. Treatment is still limited to whole blood transfusions and icing joints.[2]

• The National Hemophilia Foundation was founded in 1948.

1950s-Early 1960s

• The World Federation of Hemophilia was established in 1963.

• Fresh frozen plasma (FFP) was the mainstay of treatment for hemophilia A and hemophilia B during this decade.

• FFP contained only miniscule amounts of factor VIII (FVIII) and factor IX (FIX), thus large volumes of intravenously administered FFP were needed to stop bleeding episodes.

• Cryoprecipitate was developed in 1964 by Dr. Judith Graham Poo, and treatment evolved to include intravenous administration of FVIII in smaller volumes allowing for outpatient treatment for bleeds and even elective surgery in persons with hemophilia A.[3]

Late 1960s-Early 1970s

• Scientists and manufacturers develop methods for separating FVIII and FIX from pooled plasma, resulting in neatly packaged bottles of freeze-dried (lyophilized) FVIII or FIX concentrates, allowing more accurate dosing.

• By the early 1970s, the availability of these concentrates led to home treatment, greatly improving quality of life for people with hemophilia.

1980s-1990s

• After thousands of plasma donations were combined as starting material for one batch of plasma-derived FVIII or FIX concentrate, they were found to be tainted by deadly bloodborne viruses, including hepatitis C and HIV. Many patients infected with HIV later died, raising great concern about the safety of plasma-derived products for years to come.

• The successful cloning of the FVIII gene in 1984 was a major breakthrough, allowing production of recombinant human FVIII. Clinical trials in humans began three years later.

• By 1985, a blood test for HIV antibodies was instituted in blood and plasma collection facilities.

• In 1989, the hepatitis C virus (HCV) was isolated, allowing HCV antibody testing of donors to begin in 1990.

• By 1992, two pharmaceutical companies had licensed FVIII products for use in hemophilia A.

2000s

• In 2007, Dr. Marilyn Manco-Johnson, MD, et al., published in *The New England Journal of Medicine* a multi-year study showing a prophylactic treatment prevents joint damage in pediatric patients with hemophilia.

• By the mid-late 2000s, increased attention was being paid to women with bleeding disorders, as well as the development and prevention of inhibitors in hemophilia.[4] Today, the market is seeing an influx of new hemophilia drugs. Some, with slightly longer periods needed between treatments, have already arrived. Other, even longer-lasting clotting factors are also on their way.

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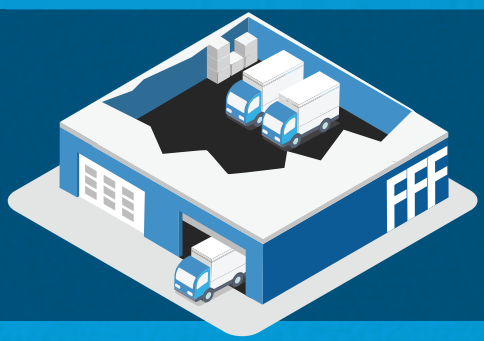

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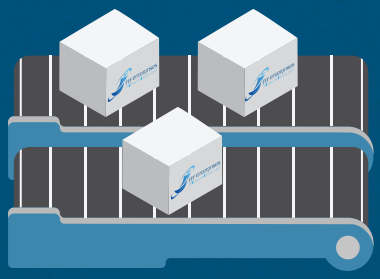
We use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

Interactive Allocation

Assures responsible, demand-based distribution of critical-care products in challenging market conditions. Reduces potential for gray-market purchasing to accommodate critical demand issues.



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Since 1988

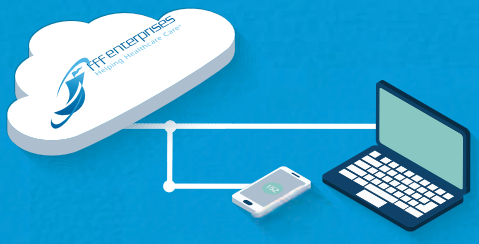
To Guaranteed Channel Integrity™

Delivery

We deliver only to facilities with a state-issued license, and only to the address on the license. We make no exceptions. It is our commitment to do everything in our power to prevent products from entering a secondary distribution channel.

Methods of Delivery

Monitoring and adjusting for extreme weather conditions allows time-sensitive delivery to ensure product integrity.



Verification

FFF's Verified Electronic Pedigree™ (VEP) system allows customers to easily verify online the pedigree of pharmaceuticals purchased through FFF Enterprises.

Tracking

Lot-Track™ electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

FFF enterprises
Helping Healthcare Care®

BioResearch

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

Pegylated Recombinant Factor VIII Appears Safe and Efficacious as Prophylactic and On-Demand Hemophilia A Therapy

Baxalta's BAX 855, a pegylated full-length recombinant factor VIII (rFVIII) based on the licensed rFVIII product Advate, was designed to increase half-life and potentially reduce the frequency of prophylactic infusions while maintaining hemostatic efficacy. This pivotal study assessed pharmacokinetic (PK) parameters of BAX 855, the annualized bleeding rate (ABR) with prophylaxis and on-demand treatment, and efficacy.

PK data from this pivotal study in previously treated patients with severe hemophilia A confirmed that the mean half-life and mean residence time of BAX 855 compared with Advate were 1.4- to 1.5-fold higher. Subjects in the twice-weekly prophylaxis arm experienced a 95 percent reduction in median ABR versus those assigned to the on-demand arm (1.9 versus 41.5, respectively). BAX 855 was efficacious for the treatment of bleeding episodes, with 95.9 percent of bleeding episodes controlled with one or two infusions, and 95.9 percent treatments having "excellent" or "good" efficacy ratings.

No FVIII inhibitory antibodies or safety signals were identified. The authors concluded that BAX 855 was safe and efficacious for on-demand treatment and prophylaxis administered twice weekly in patients with hemophilia A.

Konkle BA, Stasyshyn O, Chowdary P, et al. Pegylated, full-length, recombinant factor VIII for prophylactic and on-demand treatment of severe hemophilia A. Blood *2015 Jul 8 [Epub ahead of print].*

Plasma Exchange Effective in a Subset of Patients with Complex Regional Pain Syndrome

Usually developing following trauma, complex regional pain syndrome (CRPS) has been postulated to be associated with distal degeneration of small-diameter peripheral axons. Based on a recent hypothesis proposing an autoimmune etiology for CRPS and reported efficacy of intravenous immune globulin (IVIG) therapy in some patients, investigators at Drexel University College of Medicine in Philadelphia have recently offered plasma exchange (PE) to CRPS patients with a clinical presentation suggestive of a small fiber neuropathy. A retrospective case series study evaluated 33 CRPS patients who received between five and 11 (mean 7.2) PE treatments over a two- to three-week period.

Thirty of the 33 patients demonstrated significant median pain reduction of 64 percent ($P < 0.01$) following the initial series of PE treatments. Three patients demonstrated no improvement. Twenty-four patients are receiving maintenance therapy, with pain reduction following the initial PE series maintained with either weekly PE (n = 15), oral immune modulating agents (n = 8) or IVIG (n = 1). The remaining six patients did not receive maintenance therapy, and their pain has returned to pre-treatment levels.

Analysis of the study findings suggests that patients with the greatest loss of small fibers and greatest temperature sensory deficits are most likely to benefit from PE therapy. The investigators suggest that large, randomized, placebo-controlled studies may be required to confirm and expand their results.

Aradillas E, Schwartzman RJ, Grothusen JR, et al. Plasma exchange therapy in patients with complex regional pain syndrome. Pain Physician *2015;18:383-94.*

Intravenous Immune Globulin Safe and Effective in Inflammatory Bowel Disease: Retrospective Study

Noting the challenge of managing patients with inflammatory bowel disease (IBD) who are refractory, become intolerant or have contraindications to standard therapies, investigators at Vanderbilt University Medical Center retrospectively extracted data from medical records of IBD patients treated with intravenous immune globulin (IVIG) used to treat these difficult cases.

Twenty-four patients with IBD, 17 of whom had failed standard treatment, received IVIG between February 2011 and June 2013. Six patients received IVIG during active infection. Patients were treated with 0.4 g/kg/day for three consecutive days and then 0.4 g/kg once monthly. The dose was increased to 0.4 g/kg biweekly for loss of response or partial response. Sixteen patients (67 percent) had a response, and three (12.5 percent) obtained remission with IVIG therapy. C-reactive protein decreased significantly after treatment (from 19 mg/dL [0.1-77] to 7.5 [0.2-20], $P < 0.05$). Harvey-Bradshaw Index scores improved (8 [0-19] to 6 [0-17], P = not significant). Notably, 62.5 percent of patients had endoscopic improvement after treatment.

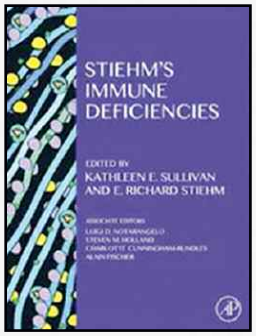
The investigators concluded that IVIG is safe and effective in the short-term management of patients with IBD when standard therapies are contraindicated.

Merkley SA, Beaulieu DB, Horst S, et al. Use of intravenous immunoglobulin for patients with inflammatory bowel disease with contraindications or who are unresponsive to conventional treatments. Inflamm Bowel Dis *2015 Aug;21(8):1854-9.*

KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers.*

BioResources

Recently released resources for the biopharmaceuticals marketplace.

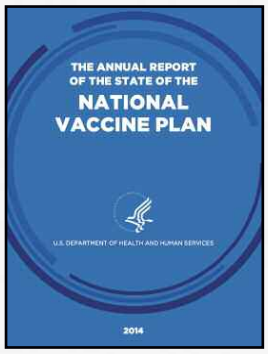


Stiehm's Immune Deficiencies

Authors: Kathleen E. Sullivan, MD, PhD, and E. Richard Stiehm, MD

Stiehm's Immune Deficiencies focuses on immunodeficiencies in children and adults. The book covers the many advances in the study of immunodeficiency with 62 chapters covering topics such as newly described syndromes, genetic diagnosis, molecular abnormalities, newborn screening and current therapies. In addition, it provides practical guidance to practitioners dealing with the day-to-day issues of diagnosis and management of immune deficient patients.

www.elsevier.com/books/stiehms-immune-deficiencies/sullivan/978-0-12-405546-9



The Annual Report of the State of the National Vaccine Plan 2014

Author: National Vaccine Program Office

This report highlights the work done by the Health and Human Services agencies and its partners toward attaining the five goals of the 2010 National Vaccine Plan:

- Goal 1: Details about the discovery and creation of new vaccines
- Goal 2: Information about advancing vaccine safety
- Goal 3: Insight on communications efforts enhancing informed decision-making
- Goal 4: Examples of work expanding access to vaccines
- Goal 5: Summaries of global immunization activities

In addition, the report features accomplishments across the vaccination system and reflects new opportunities and challenges presented by the 21st century immunization landscape.

content.govdelivery.com/accounts/USHHSV/bulletins/110469c

Clinical Trials Adverse Event Reporting Reference Guide: Third Edition

Author: U.S. Food and Drug Administration

Written for clinical trial operators, this is the most up-to-date, comprehensive collection of rules, regulations and guidances available on clinical trials adverse events. It contains more than 200 pages of rules, regulations, interpretations and guidances. The guide provides information on:

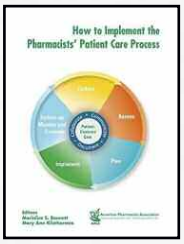
- How to determine if an adverse event needs to be reported
- When an expected adverse event becomes an unanticipated adverse event
- How adverse events differ from unanticipated problems
- How to assess if an event is unexpected
- How to assess whether an event is related to research
- What needs to be included in adverse event reports

New for 2015 are:

- Guidance on reporting incidents to OHRP
- Safety reporting requirements for INDs and BA/BE studies
- Guidance on IRB continuing review of research
- Updates to the FDA Regulatory Procedures Manual

Also featured is an analysis of relevant warning letters, illustrating ways adverse event reporting requirements often are misconstrued or overlooked.

www.fdanews.com/products/category/101/product/50061-clinical-trials-adverse-event-reporting-reference-guide-third-edition



How to Implement the Pharmacists' Patient Care Process

Author: Marialice S. Bennett

This publication introduces the Pharmacists' Patient Care Process, which was adopted in May 2014 by the Joint Commission of Pharmacy Practitioners. The goal is to help pharmacists understand the components of the standard patient care process and apply the process to patients in all pharmacy practice settings. Six sample case studies set in different patient care settings enable the reader to practice applying the process.

ebusiness.pharmacist.com/PersonifyEbusiness/ShopAPhA/ProductDetails.aspx?productId=17920006

Medicare IVIG/SCIG Reimbursement Rates

Rates are effective October 1, 2015 through December 31, 2015.

Product	Manufacturer	HCPCS	ASP+6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM IVIG	Biotest Pharmaceuticals	J1556	$76.98	$75.75
CARIMUNE IVIG	CSL Behring	J1566	$66.21	$65.15
FLEBOGAMMA IVIG	Grifols	J1572	$71.31	$70.17
GAMMAGARD SD IVIG	Baxalta	J1566	$66.21	$65.15
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	$74.56	$73.37
OCTAGAM IVIG	Octapharma	J1568	$85.60	$84.23
PRIVIGEN IVIG	CSL Behring	J1459	$76.10	$74.88
HIZENTRA SCIG	CSL Behring	J1559	$84.69	$83.33
HYQVIA SCIG	Baxalta	J3490/J3590	**	**
GAMMAGARD LIQUID IVIG/SCIG	Baxalta	J1569	$77.13	$75.89
GAMMAKED IVIG/SCIG	Kedrion	J1561	$80.59	$79.30
GAMUNEX-C IVIG/SCIG	Grifols	J1561	$80.59	$79.30

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.
** HYQVIA does not yet have ASP pricing.

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Biotest Pharmaceuticals	IVIG: PI	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PI, ITP	6 g, 12 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PI	2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Baxalta	IVIG: PI, MMN SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Baxalta	IVIG: PI, ITP, CLL, KD	5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Lab	IVIG: PI, ITP	5 g, 10 g, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PI	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Baxalta	SCIG: PI	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PI	1 g, 2.5 g, 5 g, 10 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PI, ITP	5 g, 10 g, 20 g, 40 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease

2015-2016 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
bioCSL	AFLURIA (IIV3)	5 ML multi-dose vial	5 years and older*	90658/Q2035
		0.5 ML prefilled syringes, 10-BX		90656
GlaxoSmithKline	FLULAVAL QUADRIVALENT (IIV4)	5 ML multi-dose vial	3 years and older	90688
	FLUARIX QUADRIVALENT (IIV4)	0.5 ML prefilled syringes, 10-BX		90686
MedImmune	FLUMIST QUADRIVALENT (LAIV4)	0.2 ML live virus intranasal spray	2–49 years	90672
Novartis Vaccines	FLUCELVAX (ccIIV3)	0.5 ML prefilled syringes, 10-BX	18 years and older	90661
	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 years and older	90658/Q2037
		0.5 ML prefilled syringes, 10-BX		90656
Protein Sciences	FLUBLOK (RIV3)	0.5 ML single-dose vials, 10-BX	18 years and older	90673
Sanofi Pasteur	FLUZONE (IIV3)	5 ML multi-dose vial	3 years and older	90658/Q2038
		5 ML multi-dose vial	6-35 months	90657
	FLUZONE QUADRIVALENT (IIV4)	5 ML multi-dose vial	3 years and older	90688
		5 ML multi-dose vial	6-35 months	90687
		0.25 ML prefilled syringes, 10-BX	6-35 months	90685
		0.5 ML prefilled syringes, 10-BX	36 months and older	90686
		0.5 ML single-dose vials, 10-BX		90686
	FLUZONE INTRADERMAL QUADRIVALENT (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 years	90630
	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringes, 10-BX	65 years and older	90662

IIV3 Egg-based trivalent inactivated injectable
ccIIV3 Cell culture-based trivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine. Afluria may be used in persons aged ≥9 years.

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