Autoimmune Disease: Exploring Treatment Options

With the rising rates of autoimmune disease, the quest is on to research and develop new medicines to treat patients who often present with multiple disorders.

By Ronale Tucker Rhodes, MS

A decade ago, no one talked much about autoimmune disease; it simply wasn't well-known, and many believed that some of the autoimmune diseases recognized today were "all in one's head." That's no longer the case. Autoimmune disease is now discussed in all circles of life because it afflicts some 23 million Americans. Even so, fewer than 13 percent of people can actually name an autoimmune disease.[1] It's an evolving area of medicine that has scientists puzzled — not just about what causes it but how to prevent it,

because once it starts, autoimmune activity can be especially difficult to stop. The good news is that scientists are persevering, and many new discoveries are being made, resulting in some promising new treatments.

The Autoimmune Disease Puzzle

An autoimmune disease is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissues. This occurs when the body can no longer tell the difference between healthy body tissues and antigens.[2] Recently, doctors have begun to differentiate between autoimmune diseases and autoinflammatory disorders. Both of them attack the body itself and cause inflammation, but autoimmune diseases target antigens in specific cells and tissues (such as the joints in arthritis) while autoinflammatory disorders launch a less-specific attack against the body (such as in familial Mediterranean fever and type 2 diabetes).[1] For the purposes of this article, the term autoimmune disease is used to refer to both types.

Autoimmune diseases can be broken down into two groups: organ-specific and non-organ-specific. Examples of organ-specific disorders are Addison's disease, celiac disease, Crohn's disease (see the Patient Profile on page 58), multiple sclerosis and type 1 diabetes. Examples of non-organ-specific disorders are juvenile dermatomyositis, lupus and scleroderma.[1]

More than 80 different types of autoimmune diseases have been identified, yet their cause is unknown. It is theorized that they are caused by either genetics, triggers, hormonal factors or a combination of the three. It's possible that susceptibility to the disease, rather than the disease itself, is inherited. And in those who are susceptible, a trigger may cause the disease to develop. Triggers can include a substance in the body that is normally confined to a specific area that is released into the bloodstream (such as a blow to the eye that releases fluid from the eyeball into the bloodstream); a normal body substance that is altered by a virus, drug, sunlight or radiation; a foreign substance that resembles a natural body substance that enters the body; or cells that control antibody production such as B lymphocytes. And, because autoimmune diseases occur more often in women, it is suspected that hormones may be a factor.[3]

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Some of the more common autoimmune diseases and what they attack include autoimmune hemolytic anemia (red blood cells), bullous pemphigoid (skin), Goodpasture's syndrome (lungs and kidneys), Graves' disease (thyroid gland), Hashimoto's thyroiditis (thyroid gland), multiple sclerosis (brain and spinal cord), myasthenia gravis (neuromuscular junction), pemphigus (skin), pernicious anemia (cells in the stomach lining), rheumatoid arthritis (joints or other tissues), systemic lupus erythematosus (joints, kidneys, skin, lungs, heart, brain and blood cells), type 1 diabetes mellitus (beta cells of the pancreas) and vasculitis (blood vessels).[3]

Who is at greatest risk of developing an autoimmune disease depends upon which disease it is. However, researchers have found that females are almost three times as likely as males to have an autoimmune disease, with adolescent girls and young women being at greatest risk. Most autoimmune diseases affect younger and middle-aged people, and a family history of

autoimmune disease puts an individual at higher risk. Some reports show that people of different races are more prone to having certain autoimmune diseases. For example, African-Americans are more likely than Caucasians to develop lupus and scleroderma, but the opposite is true for type 1 diabetes and multiple sclerosis (MS). In addition, it is common for individuals who have one autoimmune disease to develop others.[1]

Treatment Options

Because there is yet no proven cure for autoimmune disease, the only hope is treatment. Treatment options have one of three goals: to relieve symptoms, preserve organ function or target disease mechanisms. Relieving symptoms may involve medication or surgery. When organs are threatened, drugs can be used to prevent damage such as drugs to control an inflamed kidney in people with lupus or insulin injections to regulate blood sugar in people with diabetes.[4]

Drugs can target how the disease works, thereby suppressing the immune systems, which reduces inflammation. WebMD.com lists 46 common drugs to treat autoimmune disease. Steroids have been the cornerstone of drug treatment. However, steroids act nonselectively, resulting in increased susceptibility to infections and decreased cancer immunosurveillance. There also are side effects such as hypertension, dyslipidemia, hyperglycemia, peptic ulcers, lipodystrophy, moon face, and liver and kidney injury. And, they can interact with other medicines and affect their metabolism and action.[5]

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Intravenous immune globulin (IVIG) has been found to be useful in treating several autoimmune diseases, especially autoimmune neuropathies such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and IgM paraproteinemic neuropathy. IVIG is currently approved by the U.S. Food and Drug Administration (FDA) to treat CIDP and MMN. Its anti-inflammatory effect is believed to modulate production of pro-inflammatory cytokines that attract and stimulate cytotoxic T cells, macrophages and other toxic inflammatory mediators, while upregulating anti-inflammatory cytokines. In addition, by interfering with inappropriate complement activation and scavenging active complement components, IVIG acts to prevent formation of the membrane attack complex (MAC) that directly causes tissue damage.[6]

In 2011, the FDA approved the first new treatment for lupus in five decades. Benlysta (belimumab) is used to treat patients with active, autoantibody-positive lupus (systemic lupus erythematosus) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives and nonsteroidal anti-inflammatory drugs. It is delivered directly into a vein (intravenous infusion) in a physician's office or hospital setting, and it is the first inhibitor designed to target the B-lymphocyte stimulator (BLyS) protein, which may reduce the number of abnormal B cells thought to be a problem in lupus. However, clinical trials show that the drug does not appear to work in African-Americans.[7]

Research for Treatment

Scientists from across the globe are working hard to find new ways to better treat autoimmune diseases. In Australia, researchers have discovered that an injection can help regulate the body's natural immune response. This is unlike how current treatments work. Rather than focusing on preventing "bad" cells, this injection increases good regulating cells in the body. The researchers injected cloned interleukin-5 (II-5 cytokine) into rats with Guillain-Barré syndrome and found that the rodents recovered considerably faster; the rats also did not become ill if treated with the injection as a precaution.[8]

Another vaccine, developed by Israeli scientists from the Weizmann Institute of Science, tricks the immune system into attacking one of the players in the autoimmune process, an enzyme known as MMP9. When working properly, this enzyme plays an important role in mobilizing cells and healing wounds; when it dysfunctions, it can aid and abet autoimmune disease, as well as cancer metastasis. The vaccine uses a smart synthetic molecule, which artificially mimics the functional metal zinc-histidine complex at the heart of the MMP enzyme, and tricks the immune system into creating antibodies, named metallobodies, that block the enzyme at the active site. When mice were treated with metallobodies, various symptoms associated with autoimmune disease, including diarrhea, weight loss and tissue destruction, were significantly prevented. And, it was effective in both preventive and therapeutic mode of application. "Our antibodies will mimic the natural protective process in vivo," says Professor Irit Sagi at the Weizmann Institute. "In this respect, the new drug may be more efficient than other therapeutics such as steroids."[9]

Researchers at the La Jolla Institute for Allergy & Immunology say their findings may bolster the possibility of developing a vaccine that blocks the inflammatory response that causes heart disease, which they believe is an autoimmune

disease. They found a specific cell that is responsible for the attack on the artery wall using the deadly combination of inflammation and plaque. These CD4 T cells attack the wall when they sense a buildup of plaque. This discovery, say the researchers, brings them steps closer to developing a vaccine that could stop that reaction by making antigen-presenting cells unrecognizable, which would then stop the inflammation response that might lead to a heart attack.[10]

A 2,000-year-old Chinese herbal remedy known as chang shan, a root extract of a specific type of Himalayan hydrangea plant known as hortensia, also may be effective in treating autoimmune diseases, according to results of a new investigation by researchers from Massachusetts General Hospital, the Harvard School of Dental Medicine and elsewhere. The researchers evaluated the active components of chang shan and found that one component, halofuginone (HF), blocks the development of T helper 17 (Th17) cells, highly inflammatory cells that appear to play a primary role in the development of autoimmune diseases such as multiple sclerosis, psoriasis, juvenile diabetes, rheumatoid arthritis and Crohn's disease. Building upon previous research that identified how HF activates the body's amino acid response (AAR) pathway, the researchers identified that HF specifically targets and blocks the tRNA synthetase EPRS enzyme, which is responsible for incorporating proline, an amino acid, into cells. The blockage tells the AAR not to activate the inflammatory immune responses associated with autoimmune diseases.[11]

There are many other promising new treatments for autoimmune disorders. One is the development of a new compound called Bz-423, which interferes with the ability of diseased white blood cells known as T cells to feed themselves. Developed by Lycera, Bz-423 slows down the cell's ability to manufacture adenosine triphosphate, the molecule responsible for transporting energy between cells, by binding itself to the enzyme underlying the molecule. Lycera is setting its sights on creating orally delivered drugs based on Bz-423. Another is a small-molecule oral pill that interacts with novel protein targets called chemokines and chemokine receptors. Developed by ChemoCentryx, the pill limits the activity of the chemokine system to disrupt a vital process that leads to autoimmunity, without shutting down essential immune defense functions.[12]

Understanding the role of cells in autoimmune disease is where research is focused. At the National Institutes of Health (NIH), researchers have found evidence that a unique type of immune cell contributes to MS, which helps to define the effects of one of the newest drugs under investigation for treating MS — daclizumab — and could lead to a new class of drugs for treating MS and other autoimmune diseases. Their study shows that one effect of daclizumab is to thin the ranks for lymphoid tissue inducer (LTi) cells. In the study of MS patients participating in clinical trials of daclizumab, the number of LTi cells was elevated in patients not receiving daclizumab compared with those on the drug. Patients receiving daclizumab also had reduced signs of inflammation in the cerebrospinal fluid that surrounds the brain. In addition, daclizumab appears to steer the body away from producing LTi cells in favor of another type of cell that counteracts autoimmunity.[13]

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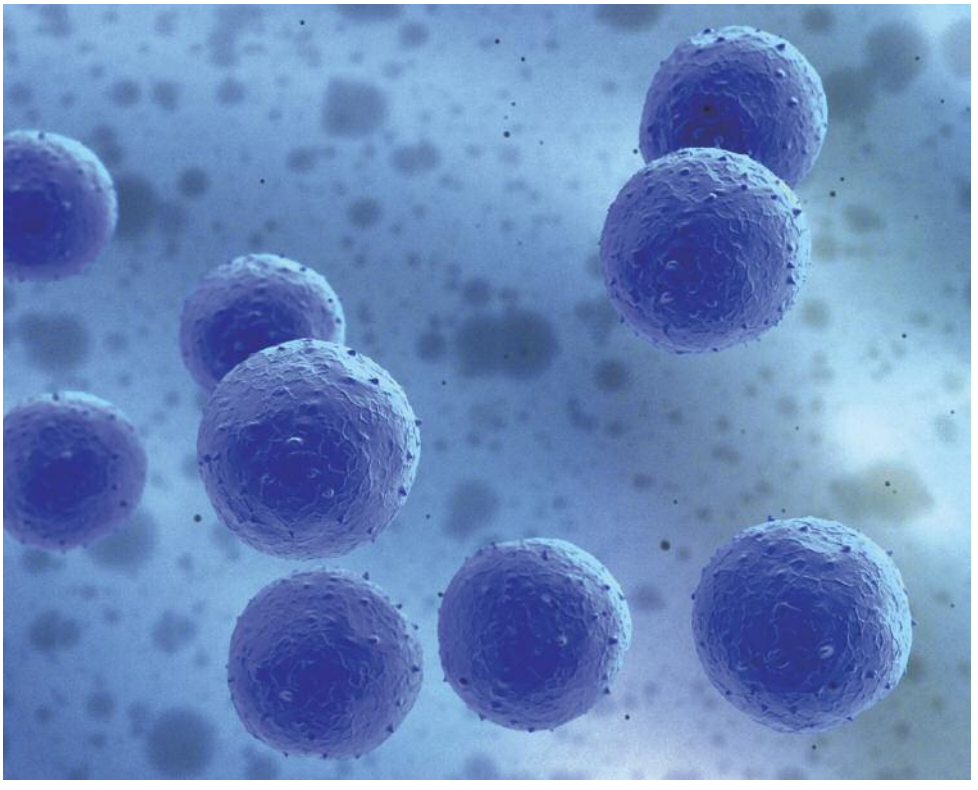
Another cell discovery has been made by researchers at the Department of Pathology and Molecular Medicine at McMaster University in Ontario, Canada. They found a molecule normally used by the body to prevent unnecessary immune reactions could be the key to create an entirely new set of treatments for autoimmune disease. The molecule, alphavbeta6, normally keeps the immune system from overreacting when food passes through the body. The researchers noticed that mice's intestines secreted alphavbeta6 when absorbing food, which induced their bodies to produce immune-tolerant cells to ensure that the food did not cause an excessive immune reaction. The researchers then generated alphavbeta6 using cultured intestinal cells and found that both could be used to generate the immune-tolerant cells needed to reduce or eliminate out-of-control immune reactions. "Our findings have the potential to repair the compromised immune-tolerant system so as to lead the body's immune system to 'correct' the ongoing pathological conditions by itself," said Ping-Chang Yang, a researcher involved in the study.[14]

One emerging field of study that is focusing on autoimmune disease is bioenergetics, the science of manipulating the way cells create, store and consume energy. The University of Colorado at Colorado Springs recently established an Institute of Bioenergetics and Immunology.[12]

Research for a Cure

Could there be hope for a cure rather than just treatment? Some studies suggest a cure may be possible.

While there is a lot of debate, as well as risk, surrounding worm therapy, there are anecdotal reports of it successfully curing autoimmune diseases, as well as one study that showed short-term success. Worm therapy, or helminthic therapy, involves being infected with microscopic hookworm larvae.



The therapy is consistent with the hygiene hypothesis, the theory that the organisms we consider harmful today were protecting our immune systems before modern medicine. In fact, prior to the 20th century, autoimmune diseases like Crohn's, MS and lupus, as well as asthma and allergies, were virtually nonexistent.

Jasper Lawrence, owner of Autoimmune Therapies and moderator of the Yahoo group of helminthic therapy, infected himself with Necator Americanus hookworms after suffering for years with allergies and asthma. Lawrence claims the therapy cured him. Others have had similar success in being cured of other diseases, including Crohn's disease. While the therapy is controversial, Dr. Joel Weinstock, professor and director of gastroenterology at Tufts Medical Center in Boston, has found that parasitic worms have a calming effect on their hosts' immune systems. Applying what he learned to the hygiene hypothesis, he and his colleagues began testing helminths in mice with asthma, type 1 diabetes, MS and inflammatory bowel disease, and they got better. Thereafter, they began a round of human trials in which they used Trichuris suis, or pig parasite, which can stay alive only for a few weeks. The results were published, and 23 out of 29 patients with Crohn's went into remission. Weinstock believes that a worm-based pill may one day be available. Indeed, similar studies are being conducted all over the world.[15]

One such study, being prepared by Coronado Biosciences, is a trial of 220 people with Crohn's disease that will test the drug trichuris suis ova (TSO), which is a pill that consists of the parasite eggs from the excrement of pigs suspended in a tablespoon of saline solution. Participants will receive a dose of 7,500 eggs or a placebo every two weeks for 12 weeks. While the pill does come with a few side effects such as gastrointestinal discomfort, researchers say that the side effects normally go away after the first two doses. The company's European partner, Dr. Falk Pharma GmbH, a German company, is currently in the midst of a mid-stage trial of TSO.

In a more conventional study of a handful of patients, researchers used a tuberculosis vaccine invented a century ago as an experimental cure for type 1 diabetes. While this was an early-stage trial, if the findings hold up, they would mean the generic bacillus Calmette-Guerin (BCG) vaccine in use since 1921 can regenerate insulin-secreting cells in the pancreas that, when lost, cause the disease. In type 1 diabetes, the body's immune system destroys insulin-producing "islet" cells in the pancreas. "We think we're seeing early evidence of effectiveness," says immunology researcher Denise Faustman of Massachusetts General Hospital, who led the trial. "We found that even low doses of the vaccine could transiently reverse type 1 diabetes, and this was in patients who have had the disease for 15 years." The effect, however, lasted for only approximately one week. And, other diabetes experts have expressed doubts about the effectiveness of the vaccine.[16]

Perhaps one of the more promising studies was conducted by researchers at Johns Hopkins University who have developed a technique that reboots the immune system by using a new approach to using stem cells. In the past, researchers focused on ways to destroy the disease-causing lymphocytes that cause autoimmunity and replace them with normal ones. To do this, stem cells were harvested before giving the patients high doses of cyclophosphamide, a chemotherapeutic drug, and then the stem cells were returned after chemotherapy. But, patients who go into remission after this procedure usually

relapse. "Stem cells contain an enzyme, called aldehyde dehydrogenase, which detoxifies cyclophosphamide," says Robert A. Brodsky, MD, assistant professor of oncology and medicine at Johns Hopkins University School of Medicine. "Like most blood cells, lymphocytes have very low levels of this enzyme, so cyclophosphamide destroys them but not the stem cells. That means it is not necessary to do a transplant to preserve the stem cells. Studies have shown that after chemotherapy — as the stem cells turn into the specialized blood cells that have been destroyed — those that become lymphocytes are normal and do not attack the body. The immune system has been repaired."

The researchers first tried this procedure with aplastic anemia patients. Seven out of the first 10 patients treated have remained disease-free for 10 years, and in some cases, more than 20 years. The system was later tried with 27 other patients with autoimmune disease, the majority of whom were lupus patients. "Most are still in remission, and some are off medications two and three years later," says Dr. Brodsky. "All of the patients we've studied have, at the very worst, remained stable. Virtually all have had major reductions in their immunosuppression medications." However, Brodsky cautions that before this procedure can be called a cure for autoimmune diseases, the patients must remain disease-free for 10 or more years.[17]

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An Uncertain Future

Much more research is being conducted about autoimmune disease treatments and cures than what is discussed in this article. Many institutes, including the NIH, are dedicated to supporting research and promoting progress toward conquering autoimmune diseases. As former director of the NIH Elias A. Zerhouni, MD, states in the organization's 2005 report titled *Progress in Autoimmune Diseases Research*,[18] "without a cure, patients face a lifetime of illness and treatment." And, without effective treatment or a cure, "they often endure debilitating symptoms, loss of organ function, reduced productivity at work and high medical expenses." Clearly, he says, "more needs to be learned about the genetic and environmental factors contributing to these diseases to be able to develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body."

In August, U.S. Rep. Marie Buerkle of New York introduced legislation to increase awareness and education about autoimmune diseases. H.R. 6218, The Mary Colella Autoimmune Disease Awareness Act of 2012, will require an assessment of national progress on autoimmune disease research and an update of the national strategic plan and recommendations that can be used to develop a national curriculum on autoimmune diseases. ❖

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