THE PROMISE OF IMMUNOTHERAPY

Finding new ways to use the body's own defense system to treat disease

By Eleanor Mayfield

For decades researchers have sought to better understand the immune system—the elaborate network of cells and organs that protects the body from infection—and find ways of using the body's innate disease-fighting capability to treat serious illnesses such as cancer and autoimmune and inflammatory bowel diseases.

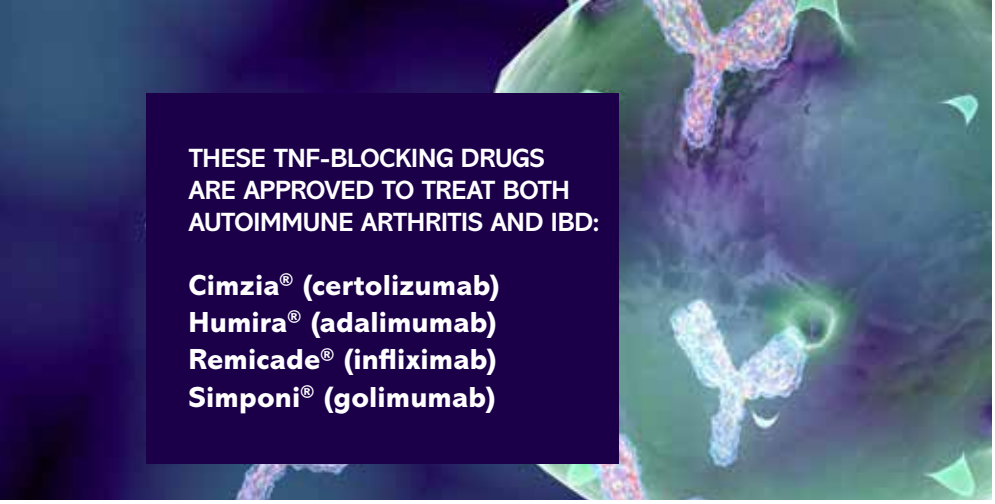
These efforts are now starting to pay off as novel *immunotherapies*—treatments that stimulate, boost, or, by contrast, restrain the immune system—reach the market, offering promising new approaches for treating these conditions. Immunotherapies are also known as *biologics* or *biologic response modifiers*.

THE IMMUNE SYSTEM AND IMMUNOTHERAPY: A PRIMER

When Bob Lahita, MD, PhD, talks to his patients about the immune system, he compares it to a metropolitan police department. Within the immune system, he says, the "criminals" are viruses, bacteria, and other foreign substances that can cause disease. Antibodies are the uniformed cops on the beat, patrolling the body and looking for these invaders. T-cells, a type of white blood cell, are the detectives whose job is to arrest the invaders. Other cells and proteins give orders, provide backup, and serve as dispatchers, sending cops or detectives to where they are needed most.

Sometimes, however, the immune system makes a mistake and attacks healthy cells as if they were foreign invaders. This is *autoimmunity*, explains Dr. Lahita, an autoimmune disease specialist and chair of medicine at Newark Beth Israel Medical Center in New Jersey. As he puts it, "Autoimmunity is when the police department can't tell the criminals from the innocent bystanders."

Lupus, multiple sclerosis, and rheumatoid arthritis (RA) are all examples of autoimmune diseases. Crohn's disease and ulcerative colitis (collectively called inflammatory bowel disease, or IBD), while technically not autoimmune diseases, result from a hyperactive immune system that attacks the gastrointestinal system. In both



THESE TNF-BLOCKING DRUGS ARE APPROVED TO TREAT BOTH AUTOIMMUNE ARTHRITIS AND IBD:

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autoimmune diseases and IBD, the immune system's attack leads to inflammation of the affected body system—for example, the joints in RA and the intestines in IBD—causing pain, swelling, and other symptoms. Immunotherapies for autoimmune diseases and IBD aim to suppress the excessive, inappropriate immune response that is causing the inflammation.

With cancer, by contrast, the problem isn't a hyperactive immune system but an ineffective one. The immune system recognizes cancer cells as foreign and up to a point can get rid of them or keep them in check. But "cancer is a wily foe," says Len Lichtenfeld, MD, deputy chief medical officer for the American Cancer Society in Atlanta, Georgia. Cancer cells are very good at finding ways to hide from, suppress, or wear out the immune system. Immunotherapies for cancer stimulate or boost the immune system so that it can more effectively attack tumors.

BLOCKING INFLAMMATION

Tumor necrosis factor (TNF) is an important player in the immune system, performing multiple jobs, such as helping immune cells communicate and helping wounds heal. A healthy immune system makes just enough TNF for its needs. But when the immune system starts attacking healthy cells, levels of TNF can get too high, causing the inflammation that underlies autoimmune diseases and IBD.

The first drugs to treat Crohn's disease (Remicade® [infliximab]) and RA (Enbrel® [etanercept]) by blocking TNF were approved in 1998. Since then several other drugs targeting TNF have come on the market. They are given by injection, either into a vein (intravenous) or under the skin (subcutaneous).

All TNF-blocking drugs suppress the immune system, so one side effect they have in common is an increased risk of infections. Some people using TNF-blocking drugs have developed a rare, fast-growing type of lymphoma (a cancer of white blood cells). One recent study in people with IBD, however, found no increased cancer risk for those treated with TNF blockers compared with those who were not.[1]

Newer immunotherapies for RA use other strategies to block inflammation. For example, Orencia® (abatacept), available since 2005, stops inflammatory cells from communicating with one another. Actemra® (tocilizumab), available since 2011, blocks interleukin-6, another substance in the immune system that helps cells communicate and is also implicated in causing inflammation.

A new immunotherapy for IBD, Entyvio® (vedolizumab), received US Food and Drug Administration (FDA) approval in May 2014. Instead of blocking TNF, Entyvio reduces inflammation by preventing inflammatory cells circulating in patients' blood from traveling to the intestines.

"Entyvio is an exciting new treatment option for IBD because the drug has a selective impact on the gut without altering systemic immune function and increasing risk for infections," says Jean-

RESOURCES

AUTOIMMUNE DISEASES/ RHEUMATOID ARTHRITIS

- American Autoimmune Related Diseases Association, aarda.org
- American College of Rheumatology, rheumatology.org/Practice/Clinical/Patients/Information_for_Patients
- *Women and Autoimmune Disease: The Mysterious Ways Your Body Betrays Itself*, by Robert G. Lahita, MD, PhD (William Morrow Paperbacks, 2005)

CANCER

- Biological Therapies for Cancer, cancer.gov/cancertopics/factsheet/Therapy/biological
- Cancer Immunotherapy, cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/immunotherapy-types
- TheAnswerToCancer.org a resource on cancer immunotherapy for patients and caregivers supported by the Cancer Research Institute, cancerresearch.org)

INFLAMMATORY BOWEL DISEASES

- Crohn's & Colitis Foundation of America, ccfa.org
- IBDWatch.com (latest IBD news and research)
- Medications: Biologic Therapy, ccfa.org/assets/pdfs/biologic102011.pdf

Frédéric Colombel, MD, co-director of the Leona M. and Harry B. Helmsley Charitable Trust Inflammatory Bowel Disease Center and professor of medicine at the Icahn School of Medicine at Mount Sinai Hospital in New York.

Stelara® (ustekinumab), an immunotherapy drug that blocks the activity of some types of interleukin (another substance that helps immune cells communicate), is being tested as a treatment for Crohn's disease in late-stage clinical trials.

Blocking inflammation may also be an effective strategy in cancer treatment. For example, in patients with advanced pancreatic cancer who had elevated levels of a biomarker for inflammation, those treated with the experimental anti-inflammatory drug Jakafi® (ruxolitinib) in addition to the chemotherapy drug Xeloda® (capecitabine) lived longer than those treated with capecitabine plus a placebo.[2]

TAKING THE BRAKES OFF THE IMMUNE SYSTEM

Using the immune system to treat cancer is not a new idea. Immunotherapies such as interferon and interleukin-2 have been used in cancer treatment for years, although with limited success. A major breakthrough occurred when scientists discovered how to disable a "brake" on the immune system, foiling a key strategy used by cancer cells to avoid detection. The first new drug to emerge from this discovery, Yervoy® (ipilimumab), received FDA approval in 2011 to treat advanced melanoma, the most serious form of skin cancer.

New drugs that disable a different immune system brake have shown promise in early studies. In patients with advanced melanoma treated with one of these drugs, Keytruda® (pembrolizumab), 69 percent were still alive after one year.[3] Keytruda received FDA approval in September 2014.

In a study of another drug, nivolumab, median survival (the point at which half of all patients in the study remained alive) was nearly 17 months. By contrast, among similar patients treated with Yervoy in other studies, median survival ranged from six to 11 months.[4] Nivolumab is awaiting FDA approval.

"We're seeing that these new drugs also benefit patients with kidney cancer, pancreatic cancer, lung cancer, and others that many people had not thought would respond to immunotherapy," says Dr. Lichtenfeld.

Studies also show that tumors may respond differently to immunotherapy than to other types of cancer treatment. For example, tumors may first

PATIENT STORY: ADVANCED MELANOMA

RIGHT AROUND CHRISTMAS 2011, Thèrése Bocklage noticed a lump on her right leg. It wasn't sore or bruised, but when it was still there a month later, she asked a colleague in the pathology lab where she works to take a look at it.

The news was devastating: melanoma, the most serious form of skin cancer, had already spread to her lungs and to lymph nodes in her abdomen and was inoperable. It was a rare recurrence of a very early-stage melanoma that had been surgically removed 20 years before.

As a pathologist, Thèrése understood all too well that her outlook was dire. She immediately began researching clinical trials of experimental treatments for advanced melanoma. Because she has a sister living in Los Angeles, she decided to look into trials at the UCLA Jonsson Comprehensive Cancer Center.

One trial stood out—that of a novel immunotherapy drug known at the time as MK-3475 (now called Keytruda [pembrolizumab]). It targets a protein on T-cells (the "detectives" of the immune system) that acts as a brake on the body's immune response. Inactivating that brake enables the immune system to unleash millions of T-cells to attack the melanoma.

By February 2012, Thèrése had enrolled in the MK-3475 trial. She stayed with her sister for three months. After that she flew to Los Angeles from her home in Albuquerque, New Mexico, every other week to receive a 30-minute infusion of the drug. She found that chronic fatigue was the drug's primary side effect.

The plan for the trial was that patients should be treated for up to two years. In July, five months after she began treatment, a CT (computed tomography) scan found no trace of tumors in Thèrése's body. On a biopsy, "you could see swarms of activated T-cells," she says. She continued receiving treatment until December 2013.

Now 54, Thèrése says she feels "really healthy." Chronic fatigue gone, she works "60 to 80 hours a week" as a professor of pathology and the director of a tumor specimen bank at the University of New Mexico Health Sciences Center. In her free time, she enjoys hiking in the Sandia Mountains near Albuquerque.

"I feel I've been given extra time. It feels miraculous," she says, although she knows that many years of research went into developing the drug. She is also acutely aware that "what worked for me doesn't work for everyone."

For others facing a similar diagnosis, Thèrése has this advice: "Don't give up hope. Ask about other treatment options, including clinical trials. If at all possible, get a consultation at a major cancer center."

PATIENT STORY: RHEUMATOID ARTHRITIS

AUTOIMMUNE DISEASES run in Abby Bernstein's family: Both her parents had rheumatoid arthritis, and her mother also had lupus. A niece was diagnosed with autoimmune hepatitis (in which the immune system attacks the liver) at age eight.

By the time Abby learned at age 39 that she too had RA, she had already been diagnosed with three other autoimmune diseases. As a child she had psoriasis (now recognized as an autoimmune disease, although at the time it was not). In her early thirties, she learned that she had Raynaud's disease (numbness in the fingers and toes in response to cold or stress). At 35, after six years of on-again, off-again symptoms and baffled doctors, she was diagnosed with autoimmune hepatitis.

"Because of my autoimmune hepatitis, my treatment options for RA were limited," she recalls. "Most of the available drugs were broken down in the liver and so might trigger a bout of hepatitis."

Her doctor finally suggested she try the immunotherapy drug Enbrel, approved in 1998 as one of the first drugs to target tumor necrosis factor, a chemical produced by the immune system that causes inflammation in the body.

Enbrel must be injected under the skin. Abby says she resisted at first, hating the idea of injecting herself. Once she decided to try it, though, she felt better in a week. "I got my life back," she says.

Abby started having headaches, a drug side effect, but by reducing the frequency of injections, she found she could keep the headaches at bay and still get adequate symptom relief. Once an avid tennis player, she soon felt well enough to play the occasional game again.

Abby is now 56 and has been taking Enbrel for 13 years. She credits the drug with enabling her to remain employed (she works for a labor organization in Washington, DC) and lead a normal life. Because the drug suppresses her immune system, she stops taking it if she has a cold or other infection and before having a medical procedure like a colonoscopy. She is careful to avoid infections, washing her hands frequently and steering clear of anyone who is coughing or sneezing.

"Even my liver seems to be happy on Enbrel," she says. "From the day I started taking it, I haven't had a bout of autoimmune hepatitis."

seem to get larger and what look like new tumors may appear. With chemotherapy these would be signs that treatment is not working. But with immunotherapy "we may see more of a delayed response," says Lynn Schuchter, MD, chief of hematology-oncology at the University of Pennsylvania's Abramson Cancer Center in Philadelphia.

Tumors may look larger not because they're growing, Dr. Schuchter explains, but because they're being "surrounded" by millions of activated immune cells. Recognizing that the standard way of assessing a cancer treatment's effectiveness is ill suited to immunotherapy drugs, doctors have developed unique "immune-related response criteria" for measuring how well these drugs work.[5]

CANCER VACCINES

Vaccines are another approach to cancer immunotherapy. Unlike conventional vaccines that are used to prevent disease, cancer vaccines are often used in treatment.

In 2010 Provenge® (sipuleucel-T), a treatment for advanced prostate cancer, became the first (and so far only) cancer vaccine to win FDA approval. Treatment with Provenge is customized for each patient by first extracting white blood cells, exposing them to the vaccine in a lab, and reinjecting them into the patient to stimulate an immune response. Numerous other cancer vaccines are being tested in clinical trials.

PROMISE IN THE PIPELINE

As new insights into the mechanisms of the immune system are translated into innovative therapies that take advantage of the body's inherent ability to protect itself, patients with cancer, autoimmune or gastrointestinal diseases, and other serious illnesses have reason to hope that immunotherapy lives up to its promise. ✿

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