Traitorous Lymphocytes

Drug assaults diseases from leukemia to MS

By KATHY A. FACKELMANN

Seventeen years ago, Dennis Carson had an insight that would ultimately lead to federal approval of a new drug for the treatment of leukemia. In reciting the events that led to his fashioning of that compound, Carson is matter-of-fact. To him, it was no big deal.

His boss, however, remembers Carson's dogged pursuit of the substance as nothing short of "remarkable." With the help of just one laboratory technician, Carson synthesized nearly 25 compounds and tested them one by one to find a promising candidate, says Ernest Beutler, chairman of the department of molecular and experimental medicine at Scripps Clinic and Research Foundation in La Jolla, Calif.

"It was a tremendous amount of work," Carson admits, pointing out that he is a physician, not a chemist, by training.

Carson's hard work paid off in a drug called cladribine, which offers people with hairy-cell leukemia the promise of a longer life. Now he, Beutler, and their colleagues at Scripps are reporting another use for cladribine.

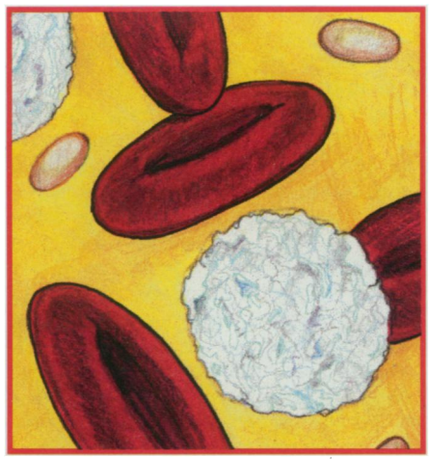
The drug appears to slow the progress of the crippling neuromuscular disease multiple sclerosis (MS). In addition, scientists are exploring cladribine's role as a hedge against a variety of other autoimmune diseases, including the joint disease known as rheumatoid arthritis, the skin disorder psoriasis, and inflammatory bowel disease. In autoimmune diseases, the white blood cells of the immune system mistake the body's own cells for foreign invaders and attack them.

Why would a single compound benefit people suffering from such disparate diseases?

"The common denominator is that these are diseases in which white cells run amok," Beutler says.

Carson's true brilliance, Beutler says, was in homing in on a drug that selectively kills white blood cells. In the end, that mass destruction benefits the patient, who has been suffering from the subversive behavior of those immune cells, called lymphocytes.

It was a long way from the drawing board to the actual development and federal approval of cladribine. No pharmaceutical firm was willing to invest in the project initially. Beutler decided to use discretionary Scripps monies to fund Carson's early tests of the compound.



1. Red blood cells, disk-shaped platelets, and white cells, or lymphocytes, all travel in the human bloodstream.

Carson had the intellectual drive to see his idea transformed into reality, but Beutler had a personal motive: His sister had very severe MS. Convincing evidence of the drug's ability to retard disease came too late for her—she died last year—but for many others with progressive MS or leukemia, cladribine may yet prove beneficial.

The genesis of cladribine can be traced to 1977, when Carson was a junior researcher at Scripps working on a rare genetic disorder called adenosine deaminase (ADA) deficiency. Researchers knew that children with the disease lack the enzyme ADA. They also knew that the disease destroys white cells.

Carson demonstrated the mechanism of that immune breakdown, showing that without ADA, specific chemicals accumulate in the body's lymphocytes. Later, he found that such toxins triggered a process called apoptosis, or programmed cell death, in the white cells.

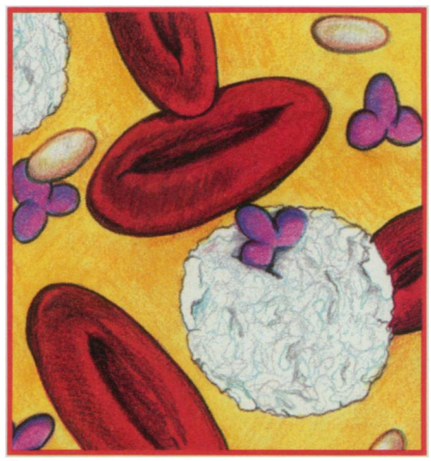
For children deficient in ADA, the loss of lymphocytes leaves them vulnerable to common microbes that a healthy immune system fights off.

People with hairy-cell leukemia have the opposite problem: abnormal proliferation of white cells. Carson used his knowledge of ADA deficiency to search for a compound that would tell the out-of-control white cells to self-destruct.

He turned to 25 chemicals described in the scientific literature as resembling the toxins that cause cell death in ADA deficiency. In theory, at least, those compounds might target the errant lymphocytes causing hairy-cell leukemia. Carson didn't have a pharmaceutical company behind him, so he rolled up his sleeves, made the compounds from scratch, and tested each one using a series of tumor cells growing in culture.

From that pack of candidates, cladribine emerged as a potential star.

Carson recalls the moment: After adding the compound to a test tube filled with human blood, he noticed that the white cells died off while other blood cells remained untouched. This suggested that cladribine homed in on lymphocytes, and it paved the way for testing the drug



2. The drug cladribine (purple) homes in on a white cell.

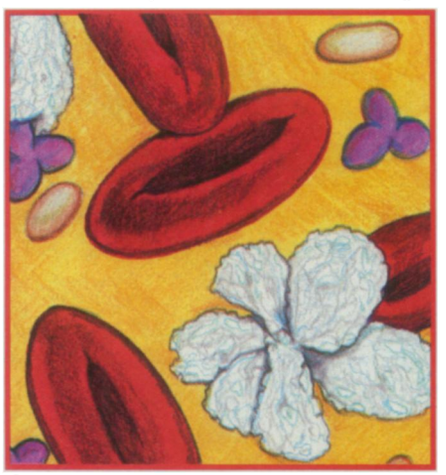
in people with hairy-cell leukemia. Although Scripps paid for the early testing, the federal government provided funding once cladribine reached the clinical trial stage of development.

Since that time, cladribine has demonstrated impressive results against this rare form of leukemia. Of the 278 people treated so far, 236 (85 percent) have experienced a complete remission; that is, no sign of the cancerous white cells can be found. The drug did sometimes cause complications, including severe but rare bacterial and viral infections.

But the "cures" appear durable: Very few of these people have experienced a subsequent bout with leukemia, Beutler said in March at the American Cancer Society's 36th Science Writers' Seminar held in Tucson.

Such reports convinced the Food and Drug Administration last year to approve cladribine for the treatment of hairy-cell leukemia.

Unlike many other anticancer drugs,



3. Once inside the lymphocyte, cladribine tells it to undergo programmed cell death. The lymphocyte begins to break up.

cladribine doesn't cause patients to vomit or lose their hair. That's because most chemotherapeutic agents work by killing all proliferating cells — hair cells, skin cells, and other body cells that are dividing at a normal rate, as well as the rampant malignant cells.

In contrast, cladribine targets only the lymphocytes.

After their early success with hairy-cell leukemia, the researchers turned their attention to MS, another disease in which white cells misbehave. Instead of performing a beneficial role in the body by attacking viruses or other invaders, these white cells turn traitor and attack the fatty myelin sheath that covers the nerve fibers of the central nervous system. As the myelin gets chewed up in the body's misguided immune attack, the patient starts to experience the symptoms of MS: fatigue, impaired vision, loss of balance, and tremors.

To test cladribine's impact on this disease, Beutler and Carson teamed up with Jack C. Sipe, a neurologist also at Scripps.

They enrolled 48 people with chronic MS, the most serious form of the disorder. Such people get progressively worse, often requiring a wheelchair or a cane to help them walk. There's no known drug treatment to stave off chronic MS.

In the Scripps study, the researchers assigned 24 patients at random to a group that received four monthly injections of cladribine. The remaining volunteers got infusions of a placebo, or inactive salt solution. The study was conducted in a double-blind fashion: Neither the patients nor the researchers knew which infusions were given to which patients.

The results were so dramatic that the team ended the study after a year and gave the drug to the 24 patients who had been getting the placebo.

Patients taking cladribine stabilized or improved slightly compared to patients in the placebo group, who continued to deteriorate. In some cases, people who had needed a cane or braces in order to walk could resume walking without such aids, Sipe said. In others, people who couldn't control their shaky gait saw their muscular tremors disappear, he said.

Even more significant, the brain abnormalities that characterize MS appear to be decreasing in the cladribine group.

The researchers also detected signs in the laboratory that the drug had halted the autoimmune attack in patients who received cladribine. Sipe presented his team's results May 5 at the American Academy of Neurology's 46th annual meeting in Washington, D.C.

In general, the researchers reported a reasonable tolerance to the drug. However, a few patients developed shingles, a disorder caused by a herpesvirus that often crops up when the immune system is impaired. Four patients also got a disorder characterized by decreased numbers of platelets, the disk-shaped cells in the bloodstream that aid in clotting.

One patient died of an acute infection from the liver-damaging hepatitis B virus. However, the researchers do not believe this patient's infection was related to treatment with cladribine.

They hope that, much as a diabetic takes insulin to help regulate his or her blood sugar, a person with MS could obtain regular injections of cladribine. Rather than getting worse, Sipe believes, a patient taking the drug might be able to stave off the worst ravages of the disease. But the team has a long way to go before such treatment becomes possible.

The 48-patient study, although encouraging, by no means proves that the drug is efficacious or safe. And the researchers don't know whether this compound will benefit people with less severe forms of

4. Bits of white cell float away in the aftermath of the drug's attack. Nearby cells will soon digest these fragments.

MS, in which the symptoms are very mild or wax and wane with long periods of remission.

"I think it's a very important study," comments Howard L. Weiner, director of the MS center at Brigham and Women's Hospital in Boston. Yet Weiner worries that cladribine may prove too toxic for long-term use. If further studies confirm the drug's benefits, patients might turn to cladribine for a short time to stop the progression of the disease, he adds.

Multiple sclerosis isn't the only disease the Scripps team is targeting with cladribine. Because the drug homes in on white cells, the researchers believe it may prove useful in treating inflammatory bowel disease, psoriasis, rheumatoid arthritis, and other ailments in which lymphocytes veer out of control, Carson points out.

An immunologist as well as a rheumatologist, Carson has already completed a pilot study of cladribine's effects on rheumatoid arthritis, a painful disease in which lymphocytes attack the lining of the joints. Although not designed to test the efficacy of cladribine, the study of 12 arthritis sufferers hinted that this drug might slow the autoimmune blitz on the joints. Therefore, Scripps researchers are organizing a larger, double-blind trial to better gauge the drug's potential.

Studies of such disorders are just beginning. "It's hard to know which autoimmune diseases will respond well to this drug," Beutler says.

In principle, regular doses of cladribine could be administered to dampen the march of these disorders. But even the team's impressive results with chronic MS fall short of a home run. "It's not a cure," warns Carson. "These diseases may not be curable," he adds, noting that once an autoimmune disease takes hold, it has already caused irreversible damage to fragile tissue. □