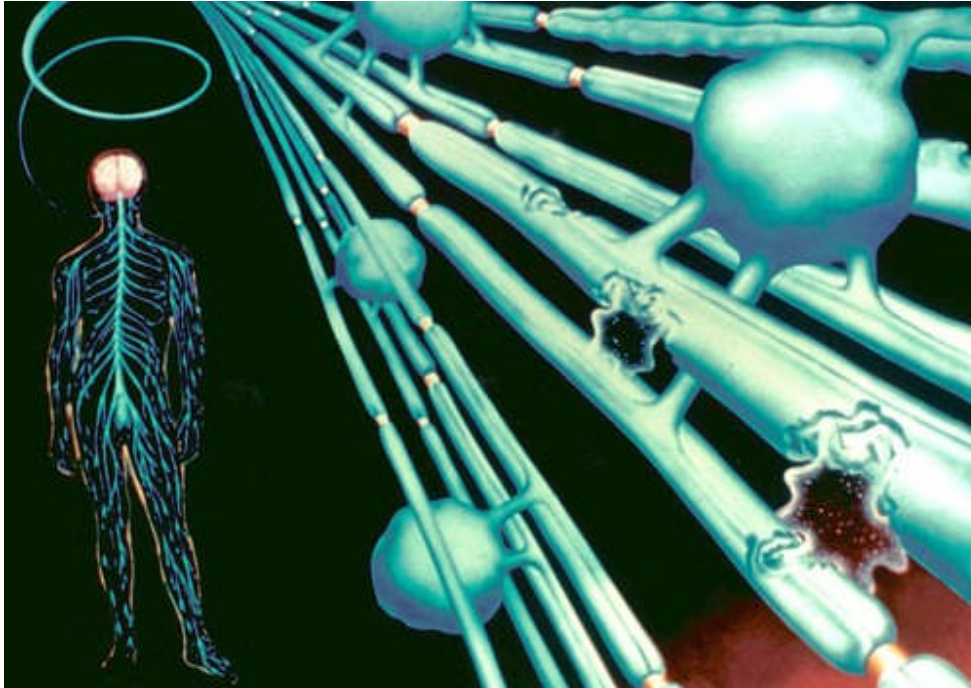


New drugs to battle multiple sclerosis



National Multiple Sclerosis Society

MS is an auto immune disease, meaning that the body's immune system attacks some of its own tissues.

Several new drugs that treat inflammation caused by the disease are showing promise, although serious side effects are still an issue.

By Brendan Borrell
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Multiple sclerosis remains a cruel medical mystery. It strikes in the prime of life and runs an unpredictable course that can end in total disability. Scientists are a long way from halting the disease entirely, but several promising drugs are in late-phase clinical trials and experts anticipate better lives for patients in the near future.

"We will see many new drugs on the market and many new options for patients," says Dr. Diego Centonze, a neurologist at Tor Vergata University in Rome, who is running clinical trials for three new experimental compounds, including one called fingolimod that is the first oral MS drug to move to Phase 3 clinical trials.

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In the early 1990s, there were no Food and Drug Administration-approved therapies for MS on the market. Today, there are at least half a dozen, and Centonze expects as many as eight or nine by 2010.

But there are still many challenges, says Dr. Ari Green, assistant director of the multiple sclerosis center at UC San Francisco, which also is running drug company-sponsored trials. None of the approved drugs is ideal, and each of the new experimental drugs has significant adverse side effects.

MS is an autoimmune disease: The body's immune system attacks some of its own tissues. The common form, known as relapsing-remitting, begins when disease-fighting lymphocytes launch an attack on the brain and spinal cord. These relapses cause short-term inflammation and symptoms such as numbness, but eventually lead to a progressive decline of the nervous system.

The less common form of MS -- primary progressive -- doesn't manifest itself with acute attacks, although patients still exhibit neurodegeneration, leading to fatigue, pain, problems with walking and balance, dizziness and bladder and bowel dysfunction.

Currently approved drugs primarily work by reducing the activity of lymphocytes or reducing their ability to travel from the blood into the nervous system. Some of the new ones do that too -- while others function in different ways.

The first drugs to gain approval in the mid-1990s were interferon beta-1b (Betaseron), interferon beta-1a (Avonex or Rebif) and glatiramer acetate (Copaxone). Because they have minimal side effects (such as flu-like symptoms) they are used as a first line of defense. But they are only moderately effective, says Dr. Rhonda Voskuhl, director of the UCLA multiple sclerosis program. Patients "fail them, and then move on" to more powerful drugs such as natalizumab (Tysabri) and mitoxantrone.

Mitoxantrone, approved in 2000, is a chemotherapeutic drug that suppresses the immune system and can lead to leukemia or heart

damage.

Natalizumab (Tysabri), which received accelerated FDA approval in 2004 and is considered the most effective drug available today, was taken off the market in February 2005 after three patients in clinical trials developed progressive multifocal leukoencephalopathy, a fatal viral disease. After an FDA review, it has been available under a special program in which patients are closely monitored for opportunistic infections.

On the horizon

There's clearly a lot of room for improvement, which is one reason why doctors are excited about options on the horizon.

Fingolimod, originally developed to prevent organ rejection in transplant patients, blocks a signal that allows T-cell lymphocytes to cross into the brain. At the American Academy of Neurology meeting this year, researchers reported that 173 patients with a relapsing form of MS showed a decline in the relapse rate over 36 months from 0.31 relapses per year to 0.20, a 30% decrease in their relapse rate when they took fingolimod. In just six months, the number of patients with brain lesions decreased from an average of 2.2 per patient when taking the placebo down to 1.29. In addition, after 36 months, brain scans revealed that 89% of patients had no evidence of inflammation.

Fingolimod is promising not only for effectiveness but because it comes in pill form, Centonze says. "For patients that must receive injections every other day or every single day, the quality of life is really affected. Taking pills can change this."

Another compound on the horizon is alemtuzumab (Campath), a monoclonal antibody designed and FDA-approved for fighting leukemia. In a trial of 334 patients published in October in the *New England Journal of Medicine*, researchers reported that the drug could reduce the relapse rate in early-stage MS patients by two-thirds relative to the standard MS drug interferon beta-1a.

UCSF's Green says the findings are impressive because this is the first MS trial to compare a new drug to an approved compound rather than a placebo and yet "it still had a remarkable effect on reducing disease activity."

Rituximab, an antibody that was designed for treating rheumatoid arthritis, is also being studied, in a clinical trial headquartered at UCSF. Rituximab is directed at the immune system's B cells, rather than T cells that have been targeted by MS researchers since the 1970s.

Biology of MS

In February, a team led by Dr. Stephen Hauser of UCSF reported in the *New England Journal of Medicine* that in a 48-week trial of 104 patients, rituximab halved the number of patients experiencing relapses relative to a placebo. "It's led to a whole new understanding of the biology of MS," Green says. "There are now a ton of potential therapies that are going to be B-cell directed."

But the downside of taking powerful modulators of the immune system are their serious side effects, including making patients more susceptible to infections and other chronic diseases. Two patients died after taking fingolimod, one with a brain infection and the other with shingles.

And in the alemtuzumab trial published in October, researchers reported that one-quarter of the patients developed an autoimmune disease attacking the thyroid and three developed an autoimmune disease of the blood platelets.

"Drugs like this are toxic," Voskuhl says. "It's a hard sell to people who are very young to expose them to drugs that have dramatic side effects."

A larger problem with the current slate of therapeutics is that they address only the inflammation side of the disease. "But we now know for sure that neurodegeneration is not just caused by inflammation," Centonze says.

As excited as he is about the burgeoning treatment options, he says, "Before judging the real quality of these drugs, you must treat many, many patients for several years."

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