A new view of drugs used to treat rheumatoid arthritis

January 21 2008

Powerful drugs used to treat patients with rheumatoid arthritis have a profound, previously unrecognized effect on the immune system, breaking up molecular “training camps” for rogue cells that play an increasingly recognized role in autoimmune diseases like rheumatoid arthritis and lupus.

A team of physicians and scientists at the University of Rochester Medical Center reports that drugs known as anti-TNF compounds – which include drugs such as Enbrel, Humira and Remicade – affect our B cells, which play a role in many autoimmune diseases.

In a study published in the “cutting-edge” section of the Jan. 15 issue of the *Journal of Immunology*, the team found that anti-TNF compounds help eliminate abnormal B cell activity in patients, raising the possibility that the drugs improve the health of patients in a way no one has realized before.

“The most important considerations for any drug are: Is it safe, and does it work?” said Ignacio Sanz, M.D., professor of Medicine, Microbiology and Immunology, and one of two rheumatologists leading the research. “The answer is certainly ‘yes’ to both questions for these anti-TNF compounds. The drugs have revolutionized the treatment of patients with rheumatoid arthritis. But it also turns out that, even though millions of patients have been treated with these medications, we really haven’t understood to a significant degree how they actually work.”

Sanz teamed with Jennifer Anolik, M.D., assistant professor of medicine, and their two laboratories together studied the immune system in a way not often done in people. They worked with ear, nose and throat doctors who took a small snip from a patient's tonsils, giving the scientists a window directly into the structures of the lymph system, rather than basing their analysis on cells afloat in the bloodstream.

Anolik and Sanz found that anti-TNF drugs disrupt the architecture of structures in our lymph system called germinal centers, which are a type of training ground for immune cells. Normally, the structures appear when we're sick, popping up suddenly as a sort of boot camp for immune cells like B cells and T cells that mix and swap information about invaders like bacteria and viruses. The structures swiftly churn out lots of B cells, which the body uses to tag invaders for destruction.

In healthy people, once an infection is beaten off, the germinal centers fade away. But in people with a chronic autoimmune disease like rheumatoid arthritis or lupus, germinal centers stick around too long, training an army of immune cells that wreak havoc throughout the body by mistakenly attacking our own tissues.

"This is a critical piece of the immune response," said Anolik. "Germinal centers are where crucial education of the B cell takes place – where they learn which cells to attack and which ones not to. Dysregulation in germinal center reactions may play a role in many autoimmune diseases."

The team found that anti-TNF compounds inhibit the function and organization of cells known as follicular dendritic cells, which help form the germinal centers. Follicular dendritic cells have long tentacles that lock onto B cells and hold them in place during their "education," playing a role not unlike that of a parent forcing a child to sit still and learn a lesson about friends and foe.

The study included 45 patients with rheumatoid arthritis and 22 healthy adults. Some of the patients with arthritis received etanercept (Enbrel); others received an older medication, methotrexate; and others received both.

In their study, the team found that the anti-TNF medication dropped the percentage of memory B cells in the lymph tissue by about 40 percent in patients. They also found that arthritis patients who received anti-TNF therapy had about one-quarter the number of germinal centers as other arthritis patients. The germinal centers that did exist in patients were smaller and less organized.

“Follicular dendritic cells are like the fabric that keeps together the germinal centers,” said Sanz. “If we can disrupt the formation of that network of cells, as anti-TNF compounds do, that should decrease the number of faulty B cells. And that’s exactly what we found.”

Previous work by the Rochester team and others indicated that B cells play a key role in rheumatoid arthritis. Theirs is one of the first studies to explore how anti-TNF compounds affect B cells in patients with rheumatoid arthritis.

Scientists know that TNF, a chemical messenger that riles up the immune system, is an important player in diseases like rheumatoid arthritis, and it was about 10 years ago that the first drugs to inhibit TNF were approved. More recently, a drug known as rituximab that targets B cells was approved in 2006 to treat rheumatoid arthritis. The effectiveness of that drug against rheumatoid arthritis came largely as a surprise to many doctors, said Sanz, since scientists had long considered other immune cells to be more central in bringing about the disease. The Rochester team’s work shows how both types of drugs may work similarly.

“There is a lot of excitement about the role of B cells in autoimmune disease,” said Anolik. “The connection between TNF-targeted therapy and B cells in rheumatoid arthritis really hasn’t been appreciated.”

Anolik is about to begin a study, funded by the National Institutes of Health, to compare in people how two different anti-TNF compounds affect B cells in patients with rheumatoid arthritis. The results could help explain why some patients respond well to some medications and not others, and could help doctors predict which patients would benefit most from which medications.

Source: University of Rochester