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Phase-3 drug trial for refractory rheumatoid arthritis succeeds

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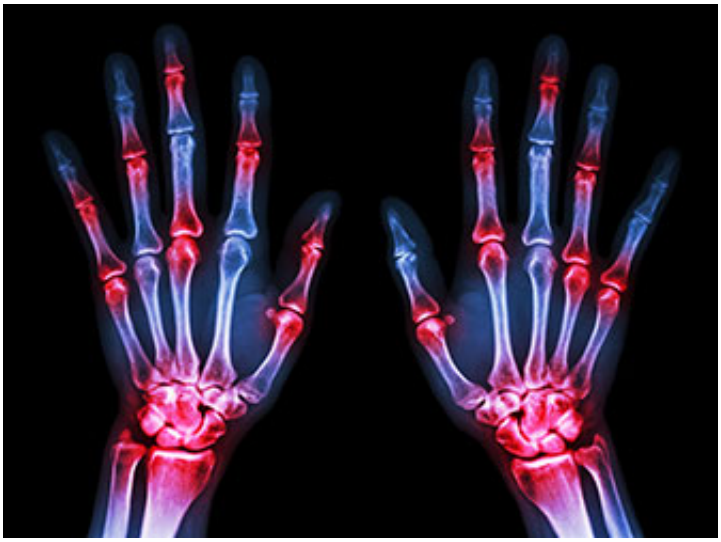

New drug for the treatment of rheumatoid arthritis shows promising success

In a pivotal phase-3 trial led by a Stanford University School of Medicine investigator, a novel drug for rheumatoid arthritis substantially reduced symptoms and improved daily physical functioning in patients for whom other therapies had failed.

A study summarizing the 24-week randomized, double-blind, placebo-controlled trial, which was carried out at 178 centers in 24 countries and involved more than 500 adults who had been living with the painful autoimmune condition for 14 years on average, will be published in the March 31, 2016 issue of *The New England Journal of Medicine*.

"This is the first drug to demonstrate meaningful clinical benefit in patients who've failed virtually every other commercial drug for rheumatoid arthritis," said Mark Genovese, MD, professor of immunology and rheumatology and the study's lead author. The senior author was Josef Smolen, MD, of the Medical University of Vienna, in Austria.

The drug, baricitinib, belongs to a new category of small-molecule drugs, available in pill form, called Janus-kinase inhibitors. They work by interfering with intracellular enzymes whose signaling action is necessary for various inflammatory substances in the body to be effective.

Pain, stiffness and swelling

Rheumatoid arthritis is a progressive, inflammatory autoimmune disease affecting about 1.5 percent of the population of developed countries. It most commonly manifests between the ages of 30 and 60. It causes pain, stiffness, swelling and eventual destruction of multiple joints, typically smaller ones such as in the hands and feet. About three of every four people with the disease are women. The reasons for this gender skew are unknown.

A diagnosis of rheumatoid arthritis once came hand in hand with a bleak prognosis: a greater than 50 percent likelihood of becoming disabled within 20 years. But advances in treating the disorder since the mid-1990s have made for a much-improved outlook, Genovese said. A major innovation, he said, has been the introduction of several kinds of injectable, bioengineered protein drugs, or biologics, beginning in the latter part of that decade.

Three of the eight top-selling drugs in the United States in terms of dollar sales—adalimumab, etanercept and infliximab—are biologics prescribed for rheumatoid arthritis. These three drugs share a common

property: They block the action of a substance called tumor necrosis factor, or TNF, secreted by various immune cells, that potently stimulates the immune response and accompanying inflammation. Other biologics prescribed for rheumatoid arthritis—including abatacept, tocilizumab and rituximab, in whose development Genovese also played a key role—act through different immune-modulatory mechanisms.

Refractory patients

The success of the plethora of drugs now used for treating rheumatoid arthritis carries a downside: Increasing numbers of patients become refractory. The drugs they're taking no longer provide sufficient benefit, or they produce unacceptable side effects, or both. As a result, Genovese estimates, some 15 to 20 percent of rheumatoid arthritis patients find themselves in the position of having exhausted the current inventory of available medications.

"It's an ever-growing population," Genovese said.

It was these refractory patients who were the focus of the new trial. They had moderate to severe cases of rheumatoid arthritis, with at least six joints affected. All of them had failed at least one anti-TNF biologic, and many had failed two or more. In addition, the trial included a number of patients who had failed other classes of biologics targeting different sources of immune activation. All patients were currently on other medications for their rheumatoid arthritis.

The 527 patients who participated in the trial were randomly assigned to one of three study arms, where they received once-daily regimens of, respectively, 4 milligrams of baricitinib, 2 milligrams of baricitinib or a placebo for 24 weeks.

Reduced symptoms

Some 55 percent of the patients assigned to the higher dose experienced a reduction of at least 20 percent in the number of affected joints at week 12, the primary endpoint of the study. For patients on the lower dose, 49 percent experienced a similar reduction. In contrast, only 27 percent of the patients receiving a placebo saw this effect.

Patients on either dose of baricitinib also had improved physical function and reductions in markers of inflammation, both in absolute terms and in comparison with placebo, the study found.

The improvements in all baricitinib-treated groups largely remained at 24 weeks, said Genovese.

Patients' individual medical histories and prior drug regimens didn't much effect their response to baricitinib treatment, Genovese said. "The drug worked well across all patient subgroups, independently of what they'd been taking before or how long they'd had the disease," he said.

Adverse events, most often in the form of mild upper-respiratory infections, as of 24 weeks into the trial were more common among high-dose and low-dose baracitinib recipients—77 percent and 71 percent, respectively—than among those receiving placebo—64 percent. Adverse events deemed serious affected 10 percent of the high-dose group, 4 percent of the low-dose group and 7 percent in the placebo group.

Shingles incidence

At week 12, about 2 percent of patients in the high-dose group, versus 1 percent and 0.5 percent in the low-dose and placebo groups, respectively, had developed herpes zoster, also known as shingles. The disease stems

from a reactivation of the latent chicken-pox virus that triggers painful skin eruptions in people whose immune systems have been weakened by, for example, old age or immunosuppressant drugs. At 24 weeks, the corresponding rates were 4 percent, 1 percent and 1 percent.

Baricitinib also appeared to raise both high-density and low-density lipoprotein levels, with unclear clinical implications, Genovese said.

Three other Lilly-sponsored phase-3 trials of baricitinib for rheumatoid arthritis—one in newly diagnosed patients, another head-to-head versus adalimumab and a third for patients for whom a first-line treatment, methotrexate, proved inadequate—have shown that the drug reduces symptoms and prevents structural damage.

More information: Mark C. Genovese et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis, *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMoa1507247

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