Fostamatinib proven to be safe but not effective

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In a previous study, rheumatoid arthritis (RA) patients who failed to respond to methotrexate were shown to experience positive results with fostamatinib disodium (R788), an oral spleen tyrosine kinase (Syk) inhibitor that is thought to block immune cell signaling involved with bone and cartilage destruction. In the current study, RA patients who failed to respond to biologic agents were studied. In contrast to the prior study, however, fostamatinib was not effective in this group of patients, although the drug did appear to be safe. Results of this phase II trial are published in the February issue of *Arthritis & Rheumatism*, a journal of the American College of Rheumatology (ACR).

Patients with RA experience inflammation, pain and swelling of their joints that often limits daily activities and can lead to permanent disability. The National Arthritis Data Workgroup estimates that 1.3 million (0.6%) of adults in the U.S. have RA, affecting two to three times as many women as men. While many RA patients are successfully treated with disease-modifying anti-rheumatic drugs (DMARDs), those with moderate to severe RA may find that newer biologically-based therapies that inhibit cytokine activity, block T cell stimulation, or modify B cell biology slow disease progression, especially when combined with methotrexate (MTX). However, there remains a subgroup of the RA patient population who do not respond to DMARDs or current biologic therapies.

The three-month double-blind, placebo-controlled trial of R788, led by Mark Genovese, M.D., from Stanford University, enrolled 219 patients with active RA who failed to respond to one or more biologic therapies (TNF inhibitor, anakinra, abatacept, or rituximab). Patients were randomly assigned in a 2:1 ratio to receive 100 mg of R788 or placebo, respectively. Efficacy and safety were evaluated over three months. Researchers evaluated changes in the disease activity score (DAS); inflammation and joint damage were assessed by MRI.

"Our findings did not find an overall difference in efficacy between the small molecule drug, R788, and placebo," noted Dr. Genovese. "However, the drug was well tolerated and clinical benefit was found in only a subset of RA patients." Results showed that the primary outcome, the ACR 201 response, as well as the ACR 50 and 70 responses, were not significantly different between the group receiving R788 and the placebo group. However, in patients who entered the trial with an elevated C-reactive protein (CRP) level, analysis suggested a meaningful difference in the ACR 20 responses between the R788 (42%) and placebo (26%) groups. Additionally MRI results demonstrated improvement in joint inflammation in those patients with the greatest disease activity.

Researchers found that the 100mg dosage of R788 was well tolerated, with the most common adverse effects being nausea and diarrhea. "We found that 100mg of R788 was a tolerable dose for chronic administration in RA," concluded Dr. Genovese. "Phase III trials of R788 need to replicate our findings and identify subpopulations most likely to respond to this novel therapy."

More information: "An Oral Syk Kinase Inhibitor in the Treatment of Rheumatoid Arthritis: A 3 Month Randomized Placebo Controlled Phase 2 Study in Patients with Active RA who had Failed Biologic Agents." Mark C. Genovese, Arthur Kavanaugh, Michael E. Weinblatt, Charles Peterfy, Julie DiCarlo, Michael L. White, Maryann O-Brien, Elliott B. Grossbard, and Daniel B. Magilavy. Arthritis & Rheumatism; Published Online: October 27, 2010 (DOI:10.1002/art.30114); Print Issue Date: February 2011.

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