RHEUMATOID ARTHRITIS

Time to give up on chemokine receptor antagonism for RA therapy?

A novel, orally active, small-molecule-specific inhibitor of CC-chemokine receptor (CCR) 1, known as MLN3897, is no better than methotrexate for treating the signs and symptoms of rheumatoid arthritis (RA). This agent is the latest in a line of CCR inhibitors to have failed in clinical trials of RA therapy, potentially signifying the end of CCR blockade as a therapeutic target in studies of RA.

Elevated expression of chemokine ligands and their receptors is thought to have an important role in inflammatory disease. “In RA, there is abundant CCR1 expression in the inflamed synovium, and its ligands are also markedly upregulated in the synovial compartment,” explains Paul Peter Tak, principal investigator of the MLN3897 study. “Preclinical studies and a small proof-of-principle study in RA with a CCR1 antagonist have supported the notion that synovial inflammation may be reduced after CCR1 blockade.”

To further test this idea, Tak and colleagues conducted a phase IIa double-blind trial of MLN3897 in 189 patients with active RA who were already taking methotrexate. Patients were randomized to receive 10 mg per day MLN3897 ($n=94$) or placebo ($n=95$) combined with once-weekly methotrexate therapy for 12 weeks. The study agent was safe and well tolerated, with no reports of opportunistic infections or serious adverse events in the treatment group. Analysis of

pharmacokinetic and pharmacodynamic data revealed no drug–drug interactions between MLN3897 and methotrexate, and a high degree of CCR1 occupancy ($\geq 90\%$ in 82% of patients) throughout the study period, as measured by a macrophage inflammatory protein 1 α internalization assay. Unfortunately, the primary outcome measure (percentage of patients achieving American College of Rheumatology criteria for 20% improvement) was similar in the treatment and control groups, both in the intent-to-treat population (35% and 33%, respectively) and in the per-protocol population (data not reported).

Other CCR antagonists that have recently been tested in RA include the CCR1 antagonist CP-481,715 and an anti-CCR2 monoclonal antibody, both of which failed to show efficacy in phase II trials. One reason for these failures could be redundancy of the chemokine system. “It is almost impossible to achieve full blockade of these molecular systems,” says Timothy Radstake, from the Radboud University Nijmegen Medical Center in the Netherlands. “Probably, only a few receptors that are still signaling are enough to leave the disease ongoing. This substantiates the need of combination therapies focused on the partial inhibition of various downstream inflammatory pathways.”

Despite the latest disheartening results, Radstake believes we shouldn't give up on

chemokine receptor inhibition just yet. “I believe it would be warranted to perform a dosing study to investigate whether a further increase of receptor occupancy leads to clinical efficacy before we throw these potential novel treatments down the drain. Next, it might be nice to add this drug on to other patients groups, for example, patients who fail on tumor necrosis factor neutralizing agents.”

The aim of providing more efficacious, better tolerated therapies for patients with RA could still be in reach.

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Original article Vergunst, C. E. *et al.* MLN3897 plus methotrexate in patients with rheumatoid arthritis: safety, efficacy, pharmacokinetics, and pharmacodynamics of an oral CCR1 antagonist in a phase IIa, double-blind, placebo-controlled, randomized, proof-of-concept study. *Arthritis Rheum.* 60, 3572–3581 (2009)