Drugs 2005; 65 (7): 1002-1003
0012-6667/05/0007-1002/$39.95/0

© 2005 Adis Data Information BV. All rights reserved.

Tacrolimus in Patients with Rheumatoid Arthritis

A Viewpoint by Daniel E. Furst

Division of Rheumatology, University of California at Los Angeles, Los Angeles, California, USA

The treatment of rheumatoid arthritis (RA) has always been difficult, requiring a fine balance between moderate efficacy and significant toxicity. In the last 10–15 years, there has been an increase in understanding of the pathogenesis of rheumatoid arthritis, and, serendipitously, this has coincided with an increased ability to develop specifically targeted agents which might affect that pathogenetic pathway. Prior to approximately 1997, most therapies were relatively broadly based and affected numerous pathways in the inflammatory cascade. However, with the advent of tumour necrosis factor (TNF)-antagonists, both physician and patient expectations have increased.

The combination of methotrexate and TNF-antagonists often result in an American College of Rheumatology (ACR20) response (a combined measure of response, well validated in clinical trials of RA, denoting an overall 20% improvement from baseline) in 50–70% of the patients. More robust responses, such as ACR 50 or 70 responses (denoting a 50% or 70% improvement from baseline) occur in 30–40% and 10–20% of RA patients, respectively. For the first time, the remission of disease is beginning to occur after these treatments. Impressively, 70–80% of patients who continue to use these drugs long term maintain their response for 1–3 years, and the use of these drugs is accompanied by a marked decrease in the rate of radiological damage associated with RA.

No drug is without its side effects, and TNF-antagonists (particularly in combination with drugs such as methotrexate) are associated with an increased incidence of macrophage-dependent infections such as tuberculosis, other infections, congestive heart failure and, potentially, some increase in the incidence of lymphomas. All of these side effects are extremely uncommon, but practitioners must nevertheless be cognisant of them. Minor side effects, such as rashes, occur more commonly in about 4–8% of the patients.

Despite these very positive effects, biologic therapy is very expensive, costing approximately $US10 000–20 000 per year. This allows less expensive drugs such as ciclosporin (cyclosporine), methotrexate, and tacrolimus, I assume, to be used in the treatment of rheumatoid arthritis, if their efficacy and toxicity justify it.

A cousin of tacrolimus, ciclosporin has been used, and is approved by the US FDA, for the treatment of RA, but it is significantly less effective than biologics. Ciclosporin has been relegated to an adjunctive role in most cases, as its ACR20 responses are often in the 40–50% range when used as monotherapy and about 50–70% of patients withdraw from trials with a duration from 6 months to 1 year. In addition, the toxicity of ciclosporin includes hypertension and renal dysfunction, as well as a number of less significant adverse effects.

The efficacy and tolerability of tacrolimus are closer to those of ciclosporin than those of biologics. ACR20 responses are 30–50% and approximately 50% of patients have withdrawn from 6-month studies with this drug. At dosages that are anticipated to be used in RA (3mg once daily), it appears that the renal toxicity of tacrolimus is less than that of ciclosporin. Further, as a once-daily medication, it has a small advantage in terms of convenience and compliance compared with ciclosporin. Importantly, it appears to be associated with better outcomes and less toxicity over the long term in organ transplant patients.

Until there is a direct head-to-head study comparing ciclosporin and tacrolimus, it will not be possible to definitively decide which of these drugs should be the first to be used. Tacrolimus appears to have a place to play in the treatment of rheumatoid

arthritis, but its niche may well be small and, in my view, its place is likely to be as adjunctive therapy. ▲

© 2005 Adis Data Information BV. All rights reserved.