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RHEUMATOID ARTHRITIS

Optimizing treatment strategies in early RA

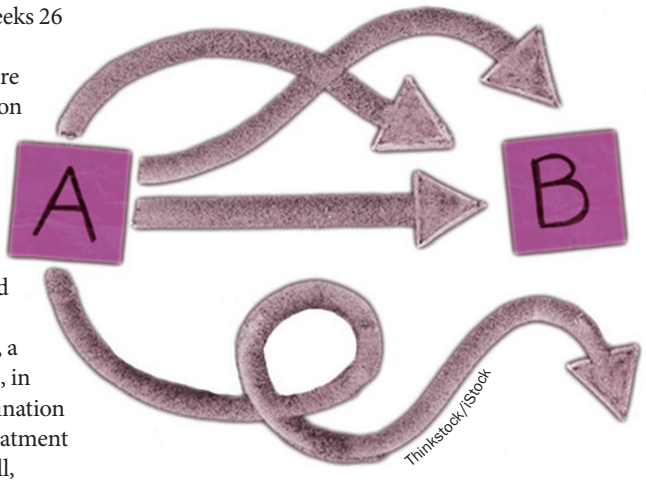
Anti-TNF biologic agents are already a mainstay of therapy for patients with rheumatoid arthritis (RA) who fail to respond to methotrexate. But would the use of such therapies from the outset provide better outcomes? And, once disease activity is suitably controlled, can this state be maintained following the withdrawal of such agents? A study published in *The Lancet* has now addressed these questions, and provides crucial data to help us hone our therapeutic strategies for RA.

Adult patients at multiple centres who had active RA of <1 year duration and were naive to anti-TNF agents and methotrexate were recruited in this 78-week double-blind randomized controlled trial, referred to as OPTIMA (Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab). In the first study period, of 26 weeks, 1,032 patients were assigned to either adalimumab (40 mg fortnightly) plus methotrexate or placebo plus methotrexate. Subsequently, on the basis of disease activity assessments, participants were reassigned for the second study period. Those in the adalimumab group who achieved stable low disease activity (44%), defined as 28-joint disease activity score (DAS28) <3.2 at weeks 22 and 26, were randomized to either continue or withdraw adalimumab. Patients with DAS28 <3.2 in the methotrexate group (24%) continued with this agent alone. Finally, all participants, across both groups, who failed to reach this target received combined therapy for the remainder of the trial.

The primary end point of the trial was low disease activity together with radiographic nonprogression from baseline at week 78. Of the patients who had stable low disease activity at 26 weeks, 70% of those who received adalimumab for the entire study period met the primary end point, a significantly higher proportion than in the group who received methotrexate only for 78 weeks (54%; $P = 0.0225$). However, in both of these groups, the proportions of patients achieving other cutoffs in various disease activity measures mostly remained stable between weeks 26 and 78. Moreover, only small non-statistically significant increases were observed in radiographic progression in the methotrexate group compared with the adalimumab group during this period. "Once patients had achieved the target on methotrexate, they fared similarly well as those who achieved the target on the combination therapy," summarizes Josef Smolen, a lead investigator on the trial. "Thus, in responders, the advantage of combination therapy was only due to the first treatment period and therefore relatively small, especially in radiographic terms."

So, how did the outcomes following adalimumab withdrawal compare? Although adalimumab withdrawal was associated with a significantly reduced proportion of patients achieving DAS28 <3.2 at week 78 compared with adalimumab continuation (91% versus 81%, $P = 0.0361$, in a post-hoc analysis), the degree of response was maintained in most patients. Thus, in contrast to earlier studies showing disease flare following withdrawal of biologic agents in patients with long-established RA, OPTIMA suggests that "induction therapy might be a viable way of treating early RA, which, once confirmed, could change treatment paradigms," claims Smolen.

Finally, adalimumab rescue in patients who failed to respond sufficiently to methotrexate was compared in post-hoc analyses with initial combination therapy. Over 26 weeks, similar proportions of patients in the two groups reached a low disease activity state (51% for initial adalimumab versus 54% for adalimumab rescue), and other response measures were also comparable. Although marked radiographic progression occurred during period 1 in the methotrexate nonresponders (mean TSS change 1.2), average progression was arrested following adalimumab initiation. "Addition of adalimumab in patients who did not achieve stable low disease activity conveyed a very similar overall response as combination therapy from the start with just a very small difference in radiographic progression due to the initial treatment period," sums up Smolen. "Thus, this part of the study validated the treat-to-target and EULAR RA management recommendations," he asserts.



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So, the data from OPTIMA indicate that a strategy of initial methotrexate for 6 months, followed by addition of an anti-TNF agent in methotrexate nonresponders, can achieve good outcomes in early RA. However, whether subsequent withdrawal of the biologic therapy would be possible in such patients, who initially failed to respond to methotrexate, remains an open question. Nonetheless, "some items of the 2013 update of the EULAR RA management recommendations have already been influenced from these results," notes Smolen, highlighting the implications of this study for current clinical practice.

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Original article Smolen, J. S. *et al.* Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet* doi:10.1016/S0140-6736(13)61751-1