

W Biological treatment in rheumatoid arthritis: when to stop?

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Randomised controlled trials of the effect of stopping treatment are rare, but in *The Lancet* Josef Smolen and colleagues¹ report results showing that it is possible to stop a risky and expensive treatment for many patients with rheumatoid arthritis once an initial response has been obtained. Newly diagnosed adult patients were treated first with either methotrexate plus placebo (n=517) or methotrexate plus the biological drug adalimumab (n=515), a fully human monoclonal antibody that binds to tumour necrosis factor (TNF), preventing it from activating TNF receptors. More patients in the methotrexate plus adalimumab group (207 of 466 [44%] completers, 40% of patients randomised) attained a predefined low disease activity target (28-joint disease activity score with C-reactive protein [DAS28] <3.2) at weeks 22 and 26 compared with methotrexate alone (112 of 460 [24%] completers, 22% of patients randomised).^{1,2}

Patients with low disease activity in the methotrexate plus adalimumab group were then randomly allocated to continue this treatment, or to switch to methotrexate plus placebo. Patients who achieved the target with methotrexate monotherapy continued that regimen. The primary endpoint was a composite measure of DAS28 of less than 3.2 at week 78 and radiographic non-progression from baseline to week 78, compared between adalimumab-continuation and methotrexate-monotherapy, and was achieved by more patients in

the adalimumab-continuation group (73 of 105 [70%]) than the methotrexate-monotherapy group (61 of 112 [54%]; mean difference 15% [95% CI 2–28]). However, importantly, outcomes for clinical symptoms and radiographic progression were assessed in all groups at week 78—by which time patients who withdrew adalimumab mostly maintained their good responses.

This study—the OPTIMA trial—was very large (more than 1000 patients at 161 sites), and in our opinion excellently done, properly analysed, and appropriately interpreted. And yet we find ourselves interpreting the result in a wider context than the investigators, who comment that withdrawal of the biological agent might be an option for most patients with early rheumatoid arthritis who achieve initial disease control. We think this study raises three other questions: **did the patients need to take biological therapy in the first place? Was there another treatment effect hidden within the trial results? And how should the cost-effectiveness of biological therapy be calculated?**

The initial control group of this study was methotrexate plus placebo, but scientific literature on the treatment of newly diagnosed rheumatoid arthritis, some reported since **OPTIMA was designed, very strongly suggests that methotrexate monotherapy is an inadequate and old fashioned therapy.** Combination therapy, particularly including glucocorticoids (which we advocate in our practice) would be a more appropriate comparator group,^{3–6} and some would argue that a so-called treat-to-target policy of dose escalation would be even more effective (although its cost-effectiveness has not yet been shown).^{6,7} Indeed, these combination therapies have been shown to produce treatment effects very similar to biological therapies. We would no longer offer monotherapy with methotrexate to our patients except in rare circumstances. Trial comparisons should compare new treatments to the best available alternative, but many do not. Showing that a new treatment is better than an old treatment that has been superseded does not add useful knowledge.

Other treatments were used in OPTIMA; in particular, more than 40% of patients were treated with glucocorticoids during the first 26 weeks of the study. As is



common in most trial reports, the random allocation of patients meant that roughly equal proportions of patients were taking glucocorticoids in each group, and hence the trial interpretation often ignores this aspect of treatment. But the evidence shows an additional effect of glucocorticoids added to other disease modifying therapies,³⁻⁶ such as methotrexate. Might it be that the therapeutic benefits are also heightened in those patients taking glucocorticoids at the same time as biological therapies? The data from this and other studies of biological therapies should be analysed from this point of view.

How do we estimate the cost-effectiveness of expensive treatments such as biological therapy? Their cost is an order of magnitude greater than those of combinations of standard treatment plus glucocorticoids. In most countries, biological therapy is only reimbursed when methotrexate and one other traditional antirheumatic drug have failed. In the UK, the National Institute for Health and Care Excellence (NICE) has applied the clinical trial outcomes from biological therapy to a mathematical model of costs and benefits, resulting in a strict reimbursement rule compared with many other European countries.⁸ And even in NICE's analysis cost-effectiveness of biological agents might be exaggerated, because the model compares biological agents with methotrexate monotherapy rather than the more effective combination therapy. In this situation, were health-care providers to change the practice for initial treatment of rheumatoid arthritis on the basis of OPTIMA, all patients with early rheumatoid arthritis would receive biological treatment, and less than half would reach the low disease activity target allowing them to stop after 6 months. Costs would skyrocket. At a time of constraint in health-care budgets, health-care providers should spend their money wisely, and NICE should reset its economic model for rheumatoid arthritis to include the outcomes of modern combination therapy, treatment which it itself recommends.⁹ For many patients, the intelligent

use of combination therapy including glucocorticoids will eliminate the need for early biological therapy. For patients who do need biological therapy and then achieve stable low disease activity, the OPTIMA results suggest it might be reasonable to consider switching back to non-biological treatment.

We congratulate Smolen and colleagues for tackling the problem of treating rheumatoid arthritis from a new standpoint, for showing how a trial of stopping treatment can be so informative, and for providing a very useful opportunity for re-evaluating the best possible role of routine combination therapy in the early stages of this important disease.

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