

What is the optimal treatment for patients with RA who fail to respond to monotherapy with methotrexate?

Original article van der Kooij SM *et al.* (2007) Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. *Ann Rheum Dis* 66: 1356–1362

SYNOPSIS

KEYWORDS disease activity score, DMARDs, methotrexate, rheumatoid arthritis

BACKGROUND

Maintenance of low disease activity is essential to prevent progression of joint damage in patients with active rheumatoid arthritis (RA); however, some individuals fail to respond to standard treatment with methotrexate.

OBJECTIVE

To determine the efficacy of conventional DMARD therapies in patients with early RA who do not respond to methotrexate monotherapy.

DESIGN AND INTERVENTION

This study was a post-hoc analysis of patients with recent-onset RA who formed two subgroups within the multicenter, randomized, controlled BeSt (Behandelstrategieën voor Reumatoïde Artritis) trial. Patients' disease activity score (DAS; European League Against Rheumatism criteria) was assessed every 3 months for the 2-year study period. Patients were classified as treatment 'successes' if they achieved a DAS ≤ 2.4 and continued on that therapy during the remainder of the 2-year follow-up, or as 'failures' if they did not achieve a DAS ≤ 2.4 . All patients began on monotherapy with methotrexate 7.5 mg/week, which was increased to 15 mg/week after 4 weeks. At 3 months, methotrexate dose was increased to 25 mg/week in patients with a DAS > 2.4 . Patients who continued to have a DAS > 2.4 , or experienced adverse events, proceeded to the next treatment step with sequential DMARD monotherapy (group 1) or DMARD combination therapy (group 2). Sequential monotherapy, with a 1 month overlap period when treatments were switched, involved sulfasalazine 2,000–3,000 mg/day, then leflunomide 20 mg/day

and finally methotrexate 25 mg/week plus 3–10 mg/kg/8 weeks infliximab; combination therapy comprised methotrexate 25 mg/week plus sulfasalazine 2,000–3,000 mg/day, then the addition of hydroxychloroquine 400 mg/day and prednisone 7.5 mg/day, and an eventual switch to methotrexate 25 mg/week and 3–10 mg/kg/8 weeks infliximab.

OUTCOME MEASURES

The main outcome measure of treatment success or failure was DAS, assessed every 3 months. Radiography of hands and feet was assessed at baseline and after 2 years.

RESULTS

A total of 244 patients were included in this analysis (126 in group 1 and 118 in group 2), of whom 107 (44%) were methotrexate successes after 6 months of therapy and 79 (32%) remained methotrexate successes at 2 years. Hand and foot radiographs from 213 patients showed that methotrexate successes had significantly less joint damage than did methotrexate failures ($P=0.007$). During follow-up, 69 methotrexate failures proceeded to sulfasalazine monotherapy (group 1) and 69 added sulfasalazine to methotrexate (group 2); 15 (22%) patients in each group were treatment successes. Ninety-eight patients were sulfasalazine failures and progressed to the next therapy; a significantly greater proportion of these patients achieved treatment success with methotrexate, sulfasalazine and hydroxychloroquine than with leflunomide monotherapy (16 [36%] versus 7 [13%]; $P=0.028$). Methotrexate and infliximab therapy was initiated in 48 patients (38 from group 1 and 10 from group 2) who were failures on ≥ 3 DMARDs, 34 (71%) of whom achieved treatment success.

CONCLUSION

Patients with early RA who do not respond to methotrexate do not benefit from further treatment with conventional DMARDs and should be switched to a tumor necrosis factor blocker.

COMMENTARY

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Methotrexate is the preferred and recommended first-line DMARD for the treatment of RA.¹ Rapid dose escalation (up to 20–25 mg/week) and switching to the subcutaneous route of administration have been suggested in cases of suboptimal response or tolerability issues.²

Several early RA clinical trials have confirmed that monotherapy with methotrexate is effective in achieving the American College of Rheumatology criteria for 20% improvement in RA signs and symptoms (ACR20) in more than 50% of patients, but a substantial clinical response, such as an ACR70 response (70% improvement), is reached by only 25–30% of patients.³ The question is then: “What is the optimal next therapeutic step for the more than 70% of patients who fail to show a substantial clinical response to methotrexate monotherapy?”

This subanalysis of the BeSt trial answers that question in part. The authors provide evidence that switching to, or sequentially adding, traditional DMARDs is efficacious in a small percentage of methotrexate failures, and they question the value of such an approach both in terms of sustainability of the clinical response and suppression of radiographic damage. In conclusion, they recommend that patients who fail methotrexate monotherapy should be treated with an anti-TNF agent without any further delay.

The answer is not that simple, however, as other alternatives have not been completely explored. The strategy of switching to traditional DMARDs (group 1) is markedly less effective than the add-on strategy that was used in group 2. Indeed, the retention rate for triple combination therapy (methotrexate, sulfasalazine and hydroxychloroquine) in group 2 is remarkable, as only 24 patients (20%) required the addition of prednisone after failing the previous three steps; moreover, only 10 patients (8.5%) required eventual anti-TNF therapy. The immediate addition of two DMARDs after methotrexate failure could possibly be a valid alternative to the addition of a biologic agent.

Previous clinical trials have compared the addition of placebo with the addition of another traditional DMARD (e.g. ciclosporin, leflunomide and gold) or a biologic agent to methotrexate. There are, however, no studies that compare two active agents except for the ATTEST trial, which

unfortunately was not sufficiently powered to show a difference in efficacy between infliximab and abatacept.⁴ An interesting alternative approach was used in the ADORE trial, whereby patients with a suboptimal response to methotrexate were randomly allocated to add or switch to etanercept;⁵ at 12 weeks, substantial clinical improvement was achieved and no difference was observed between the 2 groups, although long-term data are not available.

Hence, the question of which is the next optimal therapeutic step for patients who fail to respond to methotrexate remains mostly unanswered. Unfortunately, the BeSt trial was not designed to determine the efficacy of immediately adding an anti-TNF agent to methotrexate, as this combination was administered either as a first step (group 4) or after the failure of multiple DMARDs (groups 1 and 2).

Other strategies also need to be explored, such as the first-line combination therapy of high-dose parenteral methotrexate (20–25 mg) with one or two traditional DMARDs. The benefit of low-dose prednisone also needs to be investigated, especially in terms of its long-term safety. New, well-designed trials—with both clinical and radiographic outcome measures—are needed.

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Competing interests

The author has declared associations with the following companies: Abbott, Amgen, Bristol-Myers Squibb, Roche, Schering and Wyeth. See the article online for full details of the relationships.

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PRACTICE POINT

Although anti-TNF agents might be the best therapy for a subset of patients with early RA who do not respond adequately to methotrexate monotherapy, a significant percentage of patients can be adequately treated with the combination of 2–3 DMARDs