# Evidence-based medicine

*edited by* M. Matucci-Cerinic

## The addition of adalimumab to methotrexate reduces rheumatoid arthritis activity in patients with longstanding disease

**Author:** A. Weinblatt *et al*.
**Title:** Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADAtrial.
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**Aim**
Methotrexate (MTX) constitutes the gold standard among disease-modifying antirheumatic drugs (DMARDs) for rheumatoid arthritis (RA). However, MTX does not always induce complete remission and sometimes another DMARD must be added. Adalimumab (ADA) (D2E7; Abbott Laboratories, IL) is the only fully human therapeutic monoclonal antibody that blocks TNF-α. To evaluate the efficacy and safety of ADA in patients with active RA despite long-term treatment with MTX, a 24-week, multicentre, randomised, double-blind, placebo-controlled study [Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab in Rheumatoid Arthritis (ARMADA)] was conducted.

**Methods**
336 patients were screened based on the following inclusion criteria: diagnosis of RA [American College of Rheumatology criteria (1)]; active disease (defined as the presence of at least 9/68 tender joints and 6/66 swollen joints); treatment with MTX for a minimum of 6 months and now on a stable weekly dose of 12.5 - 25 mg.
271 patients were enrolled and randomly assigned to 4 groups; 3 received ADA by subcutaneous injection at different dosages (20 mg, 40 mg, 80 mg) and one group received placebo. The primary endpoint was 20% improvement in the ACR criteria (ACR20) (2) at 24 weeks. Secondary endpoints were ACR50 and ACR70 response rates and improvement in the ACR core set of disease activity criteria (tender and swollen joint counts, patient's assessment of pain, patient's and physician's global assessment of disease activity, and health assessment questionnaires (HAQ) (3). SF36 and FACIT (functional assessment of chronic illness therapy) questionnaires were also administered. Serum concentrations of the cartilage destruction markers pro-matrix metalloproteinase 1 (pro-MMP-1) and 3 (pro-MMP-3) were monitored during the study.
After a baseline assessment, checkup visits were conducted weekly in the first month, every other week during the second month, and monthly thereafter. Safety was assessed based on patient reports of side effects and on the results of physical and laboratory examinations. Serum levels of antinuclear (ANA), anti-double-stranded DNA (anti-dsDNA) and anti-adalimumab antibodies were monitored at baseline and at weeks 4, 12 and 24.

**Results**
161/271 patients completed the study. Those receiving ADA + MTX demonstrated significant and rapid improvement in disease activity compared to those on placebo + MTX. More patients in the 3 dosage groups (20 mg, 40 mg, and 80 mg) showed a ACR20 response rate at week 24 (47.8%, 67.2%, and 65.8%, respectively) than those on placebo (14.5%); this difference was statistically significant ($P < 0.001$ for each ADAdosage vs placebo).
At week 24, ACR50 response rates were significantly greater with ADA (31.9%, 55.2%, and 42.5% for the 3 dosage levels, respectively) than with placebo (8.1%) ($P = 0.003$, $P < 0.001$, and $P < 0.001$, respectively). Patients on 40 mg and 80 mg ADAshowed a significantly higher ACR70 response (26.9% and 19.2%, respectively) compared with placebo (4.8%) ($P< 0.001$ and $P = 0.020$).
Response was rapid, with most ADA-treated patients showing an ACR20 response at week 1. Moreover, within each ADA dosage group the percentage of patients achieving an ACR20 response increased from week 1 through week 12 and the response was maintained through week 24. The ACR50 and ACR70 responses also increased through week 24 for all ADA dosage groups.
All 3 ADA + MTX groups showed a statistically significant improvement over baseline in each of the 7 ACR core components at week 24 compared with the placebo + MTX group. The SF36 and FACIT scores were significantly higher in each ADA+ MTX group compared to placebo + MTX. At week 24 pro-MMP-1 and pro-MMP-3 levels were significantly reduced in each ADA + MTX group compared to baseline ($p < 0.05$ for each comparison).
ADA was safe and well tolerated. Comparable numbers of patients from the ADA and placebo groups reported adverse events: the most common were infections (rhinitis, upper respiratory tract infection, flu syndrome) and nausea. Seven patients withdrew due to side effects (4 in the 20 mg group, 1 in the 80 mg group, and 2 in the placebo group).

**Conclusions**
In patients on long-term MTX therapy for active RA, the addition of ADA at a dosage of 20, 40, or 80 mg administered subcutaneously every other week resulted in significant, rapid, and sustained improvement over 24 weeks compared with MTX plus placebo. Moreover, ADAwas safe and well tolerated. ADA + MTX should be considered as a new therapeutic option for patients with longstanding, active RA and an incomplete response to MTX.

## References


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## Comment

*This study by Weinblatt et al. on the fully human monoclonal TNFα antibody adalimumab presents further confirmation that TNFα blockade in rheumatoid arthritis (RA) is efficacious and well tolerated. The improvement was dose-related (i.e. 40 mg every other week seemed to produce better results than 80 mg); however, the best results once again were achieved when treatment was combined with methotrexate (MTX low-dose, average 16 mg/week). The side effects appeared to be less severe with adalimumab than other available monoclonal antibodies; however, further comparisons will be necessary. The study seems to demonstrate that MTX is less effective alone than in combination with adalimumab in long-lasting RA. However, given its complex role as an antiproliferative/antiinflammatory agent, MTX remains the fundamental "gold standard" for RA treatment, although other agents such as leflunomide (LFN) (or even cyclophosphamide) may play a similar role (1).*

*The main question that now arises is: "When is the best time during the course of RA to add the TNFα blockade to the antiproliferative/antiinflammatory agent (and to the frequently associated low-dose prednisolone)?" Various treatment algorithms have recently been proposed (2).*

*Since TNFα is one of the earliest and most active mediators of RA synovitis and since articular damage starts soon in the disease course, it would now appear sensible to consider early intervention with TNFα blockade (3). Of course, both antiproliferative/antiinflammatory agents (MTX or LFN) and prednisone also act as anti-TNFα agents since they start the blockade at the level of inflammatory cell production, but their action may be better sustained by the concomitant directly targeted effect of true TNFα blockers (i.e. adalimumab) (4).*

*The second problem is for how long and with what frequency the RA patient should be treated with the TNFα blocker (apart from such obvious considerations as the well-known differing half-lives of etanercept and infliximab). It is evident that the combination of different drugs such as MTX and prednisolone, plus TNFα blockers, after some time will reduce the body fluid concentrations of TNFα from the levels seen at the beginning of therapy, as well as the activity of the primary TNFα-producing cells (monocytes and macrophages). During this period severe side effects linked to the excessive perturbation of TNFα synthesis might arise and the frequency of the dosage should be reduced. In addition, neither TNFα nor IL-1 blockade will resolve the disease progression in all RA patients and new combination strategies will still be needed (5). Keeping these caveats in mind, adalimumab seems now ready to play a key role in RA treatment.*


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