

Initial combination therapy with prednisone or infliximab improved outcomes in early rheumatoid arthritis more than DMARDs alone

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. *Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt Study)*. *Arthritis Rheum*. 2005;52:3381-90.

Clinical impact ratings: Rheumatology ★★★★★☆

QUESTION

In patients with early rheumatoid arthritis (RA), which treatment regimen is most effective for prevention of joint damage and functional decline?

METHODS

Design: Randomized controlled trial.

Allocation: Concealed.*

Blinding: Blinded (outcome assessors).*

Follow-up period: 1 year.

Setting: 20 hospitals in western Netherlands.

Patients: 508 patients \geq 18 years of age (mean age 54 y, 68% women) with active RA for \leq 2 years and no previous treatment with a disease-modifying antirheumatic drug (DMARD).

Intervention: Group 1 ($n = 126$): sequential monotherapy with methotrexate (MTX) 15 mg/wk, followed stepwise, if Disease Activity Score in 44 joints (DAS44) > 2.4 , by MTX 25 to 30 mg/wk, then monotherapy with sulfasalazine (SSZ) 2000 to 3000 mg/d, and then leflunomide 20 mg/d. Group 2 ($n = 121$): step-up combination therapy starting with MTX as above, then, if DAS44 still > 2.4 , addition of SSZ, then hydroxychloroquine 400 mg/d, and then prednisone 7.5 mg/d. Group 3 ($n = 133$): combined therapy with prednisone 60 mg/d (tapered in 7 wk to 7.5 mg/d), MTX 7.5 mg/wk (increased to 25 to 30 mg/wk if DAS44 > 2.4), and SSZ 2000 mg/d. Group 4 ($n = 128$): combined therapy with infliximab 3 mg/kg at week 0, 2, and 6, then every 8 weeks (dose was increased stepwise if DAS44 > 2.4 , up to 10

mg/kg) and MTX 25 to 30 mg/wk. Treatment adjustments were guided by DAS44, which was measured every 3 months. For responding patients, drugs were tapered to monotherapy at a maintenance dose; treatment could be reintroduced if disease activity flared.

Outcomes: Change in joint damage in the hands and feet assessed by radiography (erosion score [0 to 280], joint space narrowing score [0 to 168], and total of the 2 scores), functional disability (assessed by the Health Assessment Questionnaire [0 to 3]), clinical remission (DAS44 < 1.6), and adverse events. **Patient follow-up:** 92% to 97% (intention-to-treat analysis).

MAIN RESULTS

Groups 3 and 4 showed more rapid response to treatment and improvement in function than groups 1 and 2. At 1 year, groups 3 and 4 had less increase in joint damage scores than groups 1 and 2 (Table). Functional dis-

ability was lower in groups 3 and 4 than in group 1 (Table). Clinical remission was achieved by 32% of patients; each group had similar remission rates and mean DAS44 scores. Groups did not differ for adverse events.

CONCLUSION

In patients with early rheumatoid arthritis, initial treatment with prednisone or infliximab in combination with disease-modifying antirheumatic drugs (DMARDs) resulted in less joint damage and better functional outcome than sequential monotherapy or step-up combination therapy with DMARDs alone.

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*See Glossary.

4 treatment regimens for early rheumatoid arthritis at 1 year†

Outcomes	Group 1	Group 2	Group 3	Group 4
Erosion score	3.5 \pm 8.2	2.6 \pm 4.7	0.9 \pm 1.9‡§	0.7 \pm 2.1‡§
Joint space narrowing score	3.6 \pm 8.4	1.6 \pm 2.9	1.0 \pm 2.4‡	0.6 \pm 2.6‡§
Total joint damage score	7.1 \pm 15.4	4.3 \pm 6.5	2.0 \pm 3.6‡§	1.3 \pm 4.0‡§
Mean score at 1 year (\pm SD)				
Functional disability	0.7 \pm 0.7	0.7 \pm 0.6	0.5 \pm 0.5‡	0.5 \pm 0.5‡

†Treatment groups described in text. SD = standard deviation.

‡ $P < 0.05$ vs group 1.

§ $P < 0.05$ vs group 2.

COMMENTARY

Aggressive treatment of early RA has been shown to limit functional disability and radiographic progression. However, amid the increasing array of therapeutic options, the most effective treatment algorithm has yet to be determined. Currently, many rheumatologists begin therapy of early RA with either sequential substitution monotherapy (as in group 1 of the BeSt trial by Goekoop-Ruiterman and colleagues) or with step-up, add-on therapy (as in group 2). The BeSt trial encourages us to push beyond these options. It corroborates such previous trials as TICORA (1) and COBRA (2), showing that early, aggressive combination therapy, including either prednisone or infliximab, results in earlier functional improvement and diminishes radiographic progression of erosions at 1 year.

Although the radiographic progression differences at 1 year were statistically significant, their clinical effect remains uncertain. More than 40% of participants in groups 1 and 2 sustained adequate suppression of disease with MTX monotherapy, suggesting that not all patients need aggressive combination therapy. Identification of patient sub-

groups with good or poor response to different therapeutic options is vital if we are to optimize our use of these expensive, potentially toxic interventions. The duration of follow-up in the BeSt trial was comparatively short, and the long-term morbidity associated with high-dose steroids and anti-tumor necrosis factor use still needs to be evaluated.

The study by Goekoop-Ruiterman and colleagues provides provocative evidence that early, effective suppression of disease activity can lessen joint damage and, by extension, potentially induce long-term remission for many patients with RA.

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References

- Grigor C, Capell H, Stirling A, et al. *Lancet*. 2004;364:263-9.
- Landewé RB, Boers M, Verhoeven AC, et al. *Arthritis Rheum*. 2002;46:347-56.