Evidence-based Rheumatology

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In early RA, combination therapy with prednisone or inflixinab leads to earlier functional improvement and minor radiographic progression than other treatment strategies

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Title: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study). A randomized, controlled trial
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Background and aim

In the last decades, many different disease-modifying antirheumatic drugs (DMARDs) and biologic agents have been able to prevent long-term structural damage and functional impairment in Rheumatoid Arthritis (RA). Although many treatment strategies have led to RA improvement, the optimal therapeutic strategy for preventing long-term joint damage and functional decline is unclear.

The BeSt (Dutch acronym for Behandel-Strategieën, "treatment strategies") study, a multi-center, randomized clinical trial, was undertaken to compare clinical and radiographic outcomes of 4 different treatment strategies [sequential monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with the TNF–α antagonist infliximab (group 4)].

The aim, common for all strategies, was the rapid and persistent reduction of disease activity by tight monitoring and immediate adjustment of therapy in the case of an insufficient response. Here, the results at the first year of treatment are presented.

Patients and methods

Five hundred and eight patients with early active RA were enrolled and randomized, to 1 of 4 treatment strategies: sequential DMARD monotherapy (group 1: 126 patients), step-up combination therapy (group 2: 121 patients), initial combination therapy with tapered high-dose prednisone (group 3: 133 patients), and initial combination therapy with the tumor necrosis factor–α antagonist infliximab (group 4: 128 patients).

The protocol described a number of subsequent treatment steps for patients whose medication failed. Treatment adjustments were made every 3 months in an effort to obtain low disease activity [a Disease Activity Score in 44 joints (DAS 44) ≤ 2.4].

If the patient did not reach a DAS $44 \leq 2.4$, the therapy was adjusted by proceeding to the next step in the allocated treatment group. If the clinical response was consistently adequate (DAS44 ≤ 2.4 for at least 6 months), medication was gradually tapered until 1 drug remained at a maintenance dose. The patients of group 1 (sequential monotherapy) started with 15 mg/week methotrexate (MTX), increased to 25–30 mg/week for a DAS 44 > 2.4. If response was insufficient, the subsequent steps were: sulfasalazine (SSZ) monotherapy, leflunomide monotherapy, MTX with infliximab, gold with methylprednisolone, and, finally, MTX with cyclosporin A (CSA) and prednisone.

The patients of group 2 (step-up combination therapy) started with 15 mg/week MTX, increased to 25-30 mg/week for a DAS 44 > 2.4. For a still insufficient response, SSZ was added, followed by the addition of hydroxychloroquine (HCQ) and then by prednisone. Patients who did not respond to the combination of these 4 drugs were switched to MTX with infliximab, MTX with CSA and prednisone, and, finally, to leflunomide.

The patients of group 3 (initial combination therapy with prednisone) started with the combination of 7.5 mg/week MTX, 2,000 mg/day SSZ, and 60 mg/day prednisone (tapered in 7 weeks to 7.5 mg/day). If DAS 44 was > 2.4, MTX was increased to 25–30 mg/week, and if the response was still insufficient, the combination was replaced subsequently by the combination of MTX with CSA and prednisone, followed by MTX with infliximab, leflunomide monotherapy, gold with methylprednisolone, and, finally, by azathioprine (AZA) with prednisone. If DAS 44 was persistently > 2.4, first prednisone was tapered to zero after 28 weeks, and then MTX was tapered to zero after 40 weeks.

The patients of group 4 (initial combination with infliximab) started with 25–30 mg/week MTX with 3 mg/kg infliximab at weeks 0, 2, and 6 and, then, every 8 weeks. After 3 months, the dose of infliximab was increased to 6 mg/kg/every 8 weeks if the DAS 44 was > 2.4. Extra DAS 44 calculations for dose adjustments were performed every 8 weeks within 1 week before the next infusion of infliximab. For a DAS 44 > 2.4, the dose of the next infusion was increased to 7.5 mg/kg/every 8 weeks and finally to 10 mg/kg/ every 8 weeks. If patients still had a DAS 44 of >2.4 while assuming MTX with 10 mg/kg infliximab, medication was firstly switched to SSZ, then to leflunomide, then to the combination of MTX, CSA, and prednisone, then to gold with methylprednisolone, and, finally, to AZA with prednisone. If a persistent good response (DAS 44 $\leq$ 2.4 for at least 6 months) was present, the dose of infliximab was reduced (from 10 to 7.5, 6, and then 3 mg/kg) every next infusion until stopped.

Assessments were performed every 3 months. Primary end points were functional ability, measured by the Dutch version of the Health Assessment Questionnaire (D-HAQ) (1), and radiographic joint damage according to the modified Sharp/Van der Heijde score (SHS), with a range of 0–448 (2), assessed on radiographs of the hands and feet obtained at baseline and after 1 year of follow-up. All radiographs were read by blinded assessors.

Secondary end points were 20%, 50%, and 70% improvement according to the ACR response criteria.

At each control visit, routine laboratory tests were performed. The treating physician recorded all adverse events (AEs) and serious AEs and, if necessary, made treatment adjustments in accordance with the protocol.

All outcomes were calculated in an intention-to-treat (ITT) analysis using all available data.

Results

Seventeen patients out of the 508 enrolled patients dropped out (4, 6, 5, and 2 patients in groups 1–4, respectively). Twenty four patients (5%) discontinued because of non compliance (5, 8, 8, and 3 patients in groups 1–4, respectively), but they were not lost to follow-up, and all available data were included in the ITT analysis.

After 1 year, a DAS 44 $\leq$ 2.4, was reached and maintained by 63 of 118 patients (53%), 72 of 112 patients (64%), 87 of 122 patients (71%), and 89 of 121 patients (74%) in groups 1 4, respectively ($P < 0.05$ for group 1 versus group 3 and group 4).

More patients in groups 3 and 4 than in groups 1 and 2 remained at the initial stage of treatment because of a sustained DAS 44 <2.4 (48 (39%), 43 (37%), 94 (73%), and 102 (81%) of the patients in groups 1–4, respectively).

Patients treated with initial combination therapy including either prednisone (group 3) or infliximab (group 4) had earlier functional improvement than patients treated with sequential monotherapy (group 1) and step-up combination therapy (group 2), with mean scores at 3 months on the D-HAQ of 1.0 in groups 1 and 2 and 0.6 in groups 3 and 4 ($P < 0.001$). After 1 year, the difference in D-HAQ scores were smaller, with mean D-HAQ scores of 0.7 in groups 1 and 2 and 0.5 in groups 3 and 4 ($P = 0.009$).

Thirty-two percent of all patients had clinical remission of their disease (DAS 44 <1.6) after the first year of follow-up. Clinical improvement, as defined by the ACR response criteria, was reached earlier and by more patients in groups 3 and 4 than in groups 1 and 2.

At baseline, 499 radiographs were assessed (123, 118, 131, and 127 in groups 1–4, respectively), but radiographs obtained at baseline and at 1 year of follow-up were available for 467 patients.

The median increases in total Sharp/Van der Heijde radiographic joint score were 2.0, 2.5, 1.0, and 0.5 in groups 1–4, respectively, significantly higher in groups 1 and 2 versus groups 3 and 4 ($P < 0.05$ for the comparisons of group 1 and 2 versus groups 3 and 4).

The number of patients without progression of radiographic joint damage was higher in groups 3 and 4 than in groups 1 and 2. No progression of the total SHS was observed in 76 of 114 patients (67%), 82 of 112 patients (73%), 104 of 120 patients (87%), and 113 of 121 patients (93%) in groups 1–4, respectively ($P < 0.05$ for group 1 and 2 versus groups 3 and 4).

A total of 41% of all patients experienced $\geq$ 1 AEs: 54 (43%), 57 (47%), 49 (37%), and 50 (39%) of the patients in groups 1–4, respectively, with no significant differences between the groups. Gastrointestinal symptoms were the most frequently reported AE, followed by skin rash or other mild dermal or mucosal events, upper respiratory tract infections, and cardiovascular events. In group 4, 10 patients had a mild-to-moderate infusion reaction during treatment with infliximab, that was discontinued, 9 patients had latent tubercolosis and received concomitant isoniazid prior to the initiation of infliximab therapy. No cases of tubercolosis or opportunistic infections were reported. There were 8, 9, 17, and 6 serious AEs in groups 1–4, respectively, with no significant differences either in their number or in withdrawals between the groups.

Conclusions

Patients with early RA, treated with the most frequently used strategies and tightly controlled in their disease activity, initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less progression of radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy.

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Comment

Although controlled clinical trials will remain the mandatory gold standard for the evaluation of novel therapeutic strategies, so called "Real-World Trials" reflecting and investigating the actual everyday situation in a rheumatologic outpatient practice under "controlled conditions" contribute also significantly to the determination of the actual value of a given therapeutic regimen. In the BeSt study, led by the Leiden team, the investigators specifically addressed the question, whether an early combination therapy including a TNF inhibitor results in a superior outcome with regard to DAS and joint destruction when compared to the "usual" initial treatment regimen such as sequential DMARD use, step-up therapies and combination with high-dose steroids. The reason, why the BeSt study is one of the most attractive trials performed in the past years, is the resulting image of this "real-world situation" mentioned above: First, when seen and treated by experienced rheumatologists, only a few (< 5%) of the patients dropped out of the study; second, low disease activity as defined by DAS44 < 2.4 and remission as defined by DAS44 < 1.6 could be achieved in at least 50 % and one third of the patients, respectively, regardless of their treatment underlining the key impact of an early arthritis clinic and immediate treatment; and third, initial combination therapy of MTX either with prednisolone or TNF inhibitor results in superior effects on disease activity with about 3 out 4 patients reaching DAS44 < 2.4 and on inhibition of joint destruction in about 9 out of 10 patients without progression of radiographic joint score. Most notably in the light of the ongoing discussion around severe side effects (1), when applying the adequate precautions as in this study, their occurrence can be minimized. However, specifically with regard to the recent steroid trials (2), it will be most interesting to see the data of the follow-ups in the next years as after one year no statistical difference between the MTX-TNF-inhibitor and MTX-SSZ-steroid combination group could be observed.

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