BeSt practice: the success of early-targeted treatment in rheumatoid arthritis

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ABSTRACT

Objective. *Targeted treatment is effective in the short term in achieving low disease activity or even remission in patients with rheumatoid arthritis (RA). The benefits of long-term targeted treatment are discussed based on the BeSt study results.*
Methods. *The BeSt study has incorporated 7 years of targeted treatment, aiming at low disease activity (DAS =<2.4), and including both treatment intensification when DAS is high and treatment tapering and discontinuation if DAS is persistently low. Functional ability over time, (drug free) remission percentages, treatment adjustments and radiological outcomes over 7 years are discussed.*
Results. *Targeted treatment resulted in stabilisation of functional ability after initial improvement, minimal radiological damage progression after the first year, and tapering of medication. Drug free remission was achieved in 15% of completers in year 7. Patients who lost drug free remission (46% up to year 5) restarted treatment and mostly regained remission without radiological deterioration. Patients treated with initial combination therapy responded earlier and had less damage progression that remained evident up to five years follow-up.*
Conclusion. *Early and maintained targeted treatment has functional and radiological benefits over the first 7 years of the BeSt study and can include drug tapering and (partial, temporary or permanent) discontinuation.*

Introduction

Over the last few decades, improvements in the treatment of rheumatoid arthritis (RA) have resulted in considerable improvement of outcomes for patients. This has been the effect of new therapies being developed and used in daily practice combined with strategies to frequently adjust the treatment as long as disease activity is insufficiently suppressed. An important advance has involved introduction and use of quantitative measures rather than Gestalt impressions in making clinical decisions. This relies on composite indices since a single gold standard measure (comparable to a blood pressure or a serum glucose) cannot characterise disease activity status in all individual patients. The composite indices make it possible to compare clinical efficacy of various treatments in patient groups, but can also be used to evaluate the effect of therapy in individual patients. They provide the additional bonus of offering a target at which treatment can be aimed, triggering adjustments as long as the target is not reached.

This concept of targeted treatment is closely related to the notion of tight control, which is the practice to measure disease activity at regular intervals of weeks or months, making sure that the target is still met, or adjusting the treatment so that it will be met the next time.

Treatment aiming at low disease activity using the disease activity score (DAS) was first proven to be more effective than interview based treatment decisions in the TICORA trial (1). It remained to be determined whether DAS-steered treatment can be continued over time and could also incorporate drug tapering and discontinuation.

Study design

The BeSt study is a multicentre randomised single blind trial that integrated targeted treatment and tight control with a comparison of 4 treatment strategies in recent onset RA. Patients (n=508) were included between 2000 and 2002 and had to have active disease (at least 6 inflamed joints and either a high ESR or high disease activity as estimated by the patient), a symptom duration of less than 2 years and RA according to the 1987 ACR criteria. They were randomised to initial

monotherapy with methotrexate (group 1: sequential monotherapy and group 2: step-up combination therapy), to combination therapy with methotrexate, sulfasalazine and high dose tapered prednisone (group 3) or combination therapy with methotrexate and infliximab (group 4). Infliximab was left as a secondary treatment option in the other strategies, if patients had failed on at least 3 synthetic disease modifying antirheumatic drugs (DMARDs) and, in arm 2 and 3, prednisone. Every three months, patients were evaluated for treatment efficacy and toxicity. The treatment target was a DAS =<2.4 (2). If the DAS was >2.4, treatment was changed or intensified, according to the allocated treatment strategy. If the DAS was ≤2.4 for at least 6 months, therapy was tapered, first combination therapy to monotherapy, then monotherapy to maintenance dose if appropriate.

Originally designed to be a 2-year follow-up study, the protocol was amended to extend the study to a 10-years follow-up, all the time using three-monthly DAS calculations to steer treatment, and adjusting medication according to the strategy protocols. From year 3, patients who had been in remission (DAS<1.6) (3)) for at least 6 months on maintenance dose, had to taper and stop their last disease modifying anti-rheumatic drug (DMARD). More details on the study protocol were published previously (4).

Primary study outcomes were functional ability, as measured every three months by the Health Assessment Questionnaire (HAQ) (5), and yearly radiological joint damage as measured by the Sharp-van der Heijde score (SHS) (6). Radiographs of the hands and feet were scored by 2 trained readers, blinded for patient identity and time order, using the Sharp/van der Heijde Score. The average score of the two readers was used to assess yearly radiological damage progression.

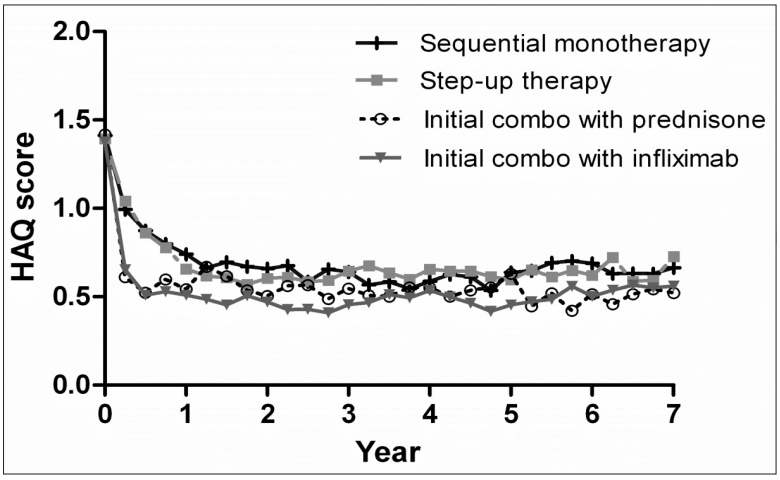

Fig. 1. Health assessment questionnaire score over 7 years per treatment group.

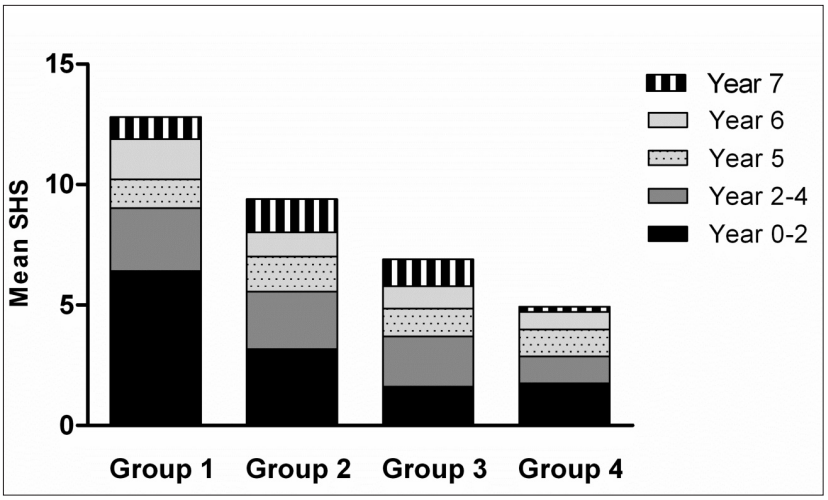

Fig. 2. Joint damage progression (change in Sharp/van der Heijde score) over 7 years per treatment group

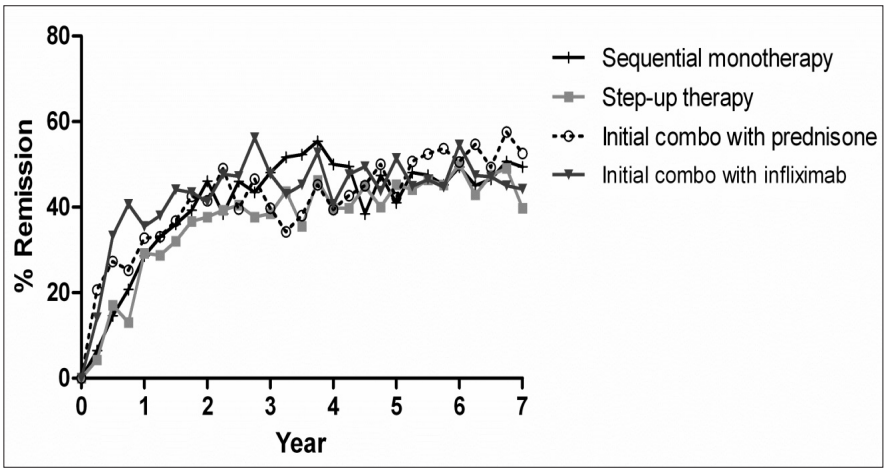

Fig. 3. Remission percentages over 7 years per treatment group.

Study results

The majority of patients were female (67%) and the mean age was 54 years. At baseline disease activity was high, with a mean DAS of 4.4 and a mean Health Assessment Questionnaire-score (HAQ) of 1.4. As in most RA cohorts, rheumatoid factor positivity and anti-citrullinated peptide antibody (ACPA) positivity were found in 2/3 of patients. At baseline, 72% had erosions, but the mean number of erosion was low. No significant differences in demographic and clinical characteristics between the randomisation groups were found at baseline (4).

Primary outcomes

It became clear that patients who were allocated to the initial combination therapy arms, responded earlier to treatment than patients who started with monotherapy. The first evaluation after three months showed 55% and 47% of patients in groups 3 and 4 already achieving the treatment target of DAS ≤2.4 compared to 17% and 19% of patients in groups 1 and 2, respectively, and 21% and 14% of patients in groups 3 and 4 in clinical remission, compared to 4% and 7% in groups 1 and 2 (4). At the end of the first study year, treatment adjustments had been necessary in 61% and 63% of patients in groups 1 and 2, compared to 26% and 19% in groups 3 and 4. As a result, there was no statistically significant difference in functional ability between the 4 treatment groups after 1 year (Fig. 1).

In 36% and 53% of patients in groups 3 and 4, combination therapy had been tapered to monotherapy at the end of year 2 because of persistent low DAS. The BeSt study included the first large group of patients who had successfully tapered and discontinued treatment with infliximab, first in group 4. Later evaluations included patients who had already failed on at least 3 synthetical DMARDs before starting infliximab in groups 1-3, and we found that in these patients permanent discontinuation of infliximab occurred less often than in the unselected patients in group 4 (7). DAS based retreatment with infliximab was mostly successful, although some infusion reactions lead to treatment discontinuation. The frequency of infusion reactions in restarters was similar to that in initially treated patients in group 4 (8).

In subsequent years, targeted treatment resulted in comparable functional ability in all groups (9). We demonstrated that irrespective of the time passed since initiation of treatment, a further DAS reduction resulted in a HAQ improvement (10). That there has been no gradual deterioration, as in earlier RA cohorts, is probably due to the fact that damage progression has been low in the BeSt patients (Fig. 2). Annual radiological progression was 1.5, 1.1, 1.5 and 1.6 in years 2-5. However, up to the end of the 5th year of the study, there remained a statistically significant difference in radiological damage progression between groups 1 and 2 on the one hand and groups 3 and 4 on the other (11). It appears that the initial differences in rapidity of clinical response, lasting less than a year, resonate in differences in joint damage for many years.

As a "side effect" of treatment steered at low disease activity, clinical remission was achieved by up to 50% of patients over time (Fig. 3). The BeSt study is one of the first studies that incorporated a strategy for discontinuation of all medication in the study protocol. During the first 5 years of the study, 115/508 (23%) of patients at some time achieved drug-free remission. Three-monthly DAS calculations continued and by protocol, 53 patients (46%) restarted treatment when the DAS increased to =>1.6 after a median duration of 5 months. Thirty-six (74%) again achieved remission within 3–6 months. The presence of ACPA, having a high DAS before remission was achieved, lower baseline HAQ and sulfasalazine as last DMARD, compared to methotrexate, were independent predictors of having to restart medication. After restarting medication, 39/53 patients again achieved remission (39/53), 11/53 regained low disease activity without treatment adjustments, 2 were lost to follow up, and 1 required further treatment adjustments before low disease activity was regained. Radiological damage progression was rare after drug discontinuation, and on average nil, but progression more than 5 points SHS occurred in one patient in sustained drug-free remission (in the year after discontinuation) and in one patient who had to restart medication (in the year of DAS increase). Fifty-nine patients (51%) did not need retreatment, they remained in drug-free remission for a median duration of 23 months. Three patients in drug free remission (3%) were lost to follow-up. At the end of the 7th year, 13%, 16%, 16% and 14% of patients still participating in groups 1–4, respectively, were in drug free remission.

Choice of initial therapy

Initial combination therapy resulted in earlier improvement of disease activity and functional ability and less radiological damage progression in the first 2 years of treatment on a group level. For individual patients however, starting with this intensive treatment might not be necessary and the benefits may not outweigh the possible increased risk of adverse events and, in the case of biological therapy, the costs. A matrix model that could aid rheumatologists in their initial treatment decision was developed based on the BeSt data (12). This model gives a predicted risk of rapid radiological progression (progression ≥5 points SHS in year 1) for each treatment group: initial monotherapy, initial combination therapy with prednisone or initial combination therapy with infliximab. Predictors for rapid radiological progression are baseline CRP (<10, 10–35, ≥35), the presence of rheumatoid factor and/or ACPA (with a higher progression risk in double positive patients when compared to single positive patients) and baseline erosion score (0, 1–4, ≥4).

Discussion

DAS steered treatment adjustments were the common factor in the four treatment strategies of the BeSt study, setting a clear treatment target for all patients, and providing a series of treatment steps to be taken as long as the target was not reached. Setting a target and purposely working towards it generally results in the target being reached. When we omit either or both, when treating RA, we leave the outcome for our patients to non-quantitative, "Gestalt" impressions, which have been shown to be less adequate than quantitative monitoring in a treat-to-target approach.

The introduction of the DAS, and other composite scores, to measure disease activity in rheumatoid arthritis has made it possible to compare treatments between patients groups, as well as within individual patients. The BeSt study has shown that, using modern DMARDs and combinations while steering treatment by a predefined target, suppression of rheumatoid activity can be achieved at a much lower level than long thought possible: clinical remission is a realistic option, even after

discontinuation of drugs. Nonetheless, studies show that in daily practice rheumatologists do not set, or work towards achieving, disease activity targets (13). Treatment aimed at reducing the DAS results in symptom relief and better functioning, and the earlier, the better. Rapid suppression of disease activity also ensures earlier suppression of radiological damage progression, as demonstrated by the statistically significant difference in radiological damage progression in the first years of the BeSt study between the initial monotherapy groups and the initial combination therapy groups. In subsequent years, with DAS steered treatment, continued suppression of disease activity has reduced yearly progression rates in all groups to close to nil, without significant differences between the treatment groups. However, the initial treatment choice is still important.

We developed a risk model to help determine which patients are most at risk for rapid radiological progression, incorporating the effect of initial treatment. For many patients the current follow up data from the BeSt study merely represent the first part of what will be truly long term outcomes. How slight differences in initial response and early damage progression influence their life in advanced age has yet to be determined.

In conclusion, early targeted therapy ensures suppression of disease activity with significant clinical and radiologic benefits for patients with rheumatoid arthritis. Continued targeted therapy prevents deterioration and allows medication to be tapered and stopped, and increased or restarted if disease activity increases again. Patients with RA have a right to be treated with the aim and method to achieve low disease activity or remission, and rheumatologists, other health professionals, and the medical system have a responsibility to implement this approach to patient care.

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