Treatment strategies in recent-onset rheumatoid arthritis : the best study

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Chapter 9

Summary and discussion

Over the last decades the outlook of patients with rheumatoid arthritis has improved considerably. The progression made in understanding underlying mechanisms of the inflammatory response has led to the development of new drugs directed against important mediators of inflammation. Furthermore, refinement in monitoring tools has enabled rheumatologists to optimize the results of treatment. Despite the results of several trials demonstrating superior efficacy of one drug or a combination of drugs over another, it remains difficult how to position the available drugs over time in this chronic, relapsing-remitting disease. This need for a more practice based study comparing treatment strategies rather than drugs, has led to the design of the BeSt study. In this study, four common strategies are compared (Figure 2, page 18-19):

1. Sequential monotherapy, starting with methotrexate, thereafter switching to other single drugs;
2. Step-up combination therapy, starting with methotrexate, thereafter adding other drugs;
3. Initial combination therapy with methotrexate, sulphasalazine and high dose tapered prednisone;
4. Initial combination therapy with methotrexate and infliximab.

Between April 2000 and August 2002, 508 patients with recent onset active rheumatoid arthritis were included and followed for 2 years. The intention was to achieve good clinical response (DAS ≤2.4) in all patients as soon as possible. To resemble the dynamics of daily practice, patients moved through the treatment protocol and proceeded to the next step (increasing dose, switching to another drug, or adding another drug) in case of an insufficient response (DAS >2.4) or started to taper drugs to one drug in maintenance dose in case of a continued good response (DAS ≤2.4 for at least 6 months). Measurements of disease activity were performed every 3 months by a research nurse who was blinded for the allocated treatment strategy. Rheumatologists used the results of these DAS calculations for the adjustment of therapy.

The primary clinical outcome was physical function as measured by the Health Assessment Questionnaire (HAQ) every 3 months. The primary radiographic outcome was change in Sharp-van der Heijde Score for radiographic joint damage. Radiographs of the hands, wrists and feet were obtained at baseline and yearly thereafter and scored paired, independently by 2 trained assessors who were masked for the patient's identity, treatment group and sequence of the films.

CLINICAL OUTCOMES

The patients who started with a combination of drugs had a more rapid relief of clinical signs and symptoms than the patients who started with a single drug, but after the first year of follow-up patients in all groups were performing equally well (chapter 3 and 4). More patients in the sequential monotherapy and the step-up combination group than in the

initial combination groups required treatment adjustments to attain the preset goal of good clinical response (DAS ≤2.4). After 2 years, 38% to 46% of patients in all groups were in clinical remission (DAS <1.6). This remarkable result is probably due to the systematic monitoring of disease activity and adjustments of therapy in case of an insufficient response.

To test the hypothesis that tight disease control is better, clinical and radiographic results of DAS-driven therapy (data from groups 1 and 2 in the BeSt study) and routine care (data from the Early Arthritis Clinic databases from Leiden and Amsterdam) were compared (chapter 5). Although the patients in the routine care group had milder disease at baseline, they had less clinical improvement than the patients treated with DAS driven therapy in groups 1 and 2 of the BeSt study. This observation is in line with other studies demonstrating the efficacy of tight monitoring and disease control (1;2). The rate of joint damage progression was lower in the routine care group than in the DAS-driven group. However, patients in the DAS-driven group had worse baseline characteristics and a higher predicted rate of progression and nevertheless, the predicted joint damage progression could be suppressed adequately.

An additional argument that supports the efficacy of tight disease control is the remarkably low progression rate of radiographic joint damage in all groups of the BeSt study (median progression score over 2 years of 1.5), especially when taking into account the high disease activity and poor prognostic factors at baseline, with an average DAS of 4.4, a positive rheumatoid factor in 65% of patients and joint erosions in 72% of patients.

RADIOGRAPHIC OUTCOMES

During the 2 years of follow-up, patients treated with sequential monotherapy or with step-up combination therapy showed more joint damage progression (median progression score 2.0) than patients treated with initial combination therapy with either prednisone or infliximab (median progression score 1.0). In addition, more patients in the sequential monotherapy and step-up combination therapy group had high progression scores. These differences can be attributed to earlier effective suppression of disease activity in the initial combination therapy groups (3), but could also be the result of specific drug effects of prednisone and infliximab. For several TNF-antagonists, evidence exists that regardless of the level of disease activity, treatment with these agents results in suppression of joint damage progression (4-6). Jeska de Vries-Bouwstra demonstrated in a subanalysis of the BeSt study, that patients in clinical remission from 6 to 24 months on initial MTX monotherapy had more joint damage progression than patient in clinical remission from 6 to 24 months after initial combination therapy (abstract).

The differences in median progression scores are statistically significant, but in the 2 years follow up period can hardly be called clinically relevant. However, rheumatoid arthritis is a chronic disease and small differences in the progression of joint damage during the first years of the disease could have a clinically significant impact on daily functioning over time.

Furthermore, radiographic progression has demonstrated to be longitudinally associated with reduced physical function, independent of disease activity (7).

TOXICITY

During the two year follow-up of the BeSt study, there were no statistically significant differences in toxicity between the groups. The slightly higher number of serious adverse events in the initial combination therapy group with prednisone can be ascribed to a small number of patients in this group who were hospitalized several times for events unrelated to rheumatoid arthritis or the therapy. Continued close monitoring of toxicity, especially of serious infections, malignancies and cardiovascular events, remains important. Given the observation that, after 2 years, the percentage of patients receiving monotherapy or combinationtherapy including prednisone and infliximab within each treatment group still changed, the risk for treatment related toxicity may also change during longer follow-up.

PATIENT PERSPECTIVE

Most outcome measurements of clinical trials focus on clinical and radiographic efficacy and do not take the patient's perspective into account. For the successful implementation of the results of trials such as the BeSt study, not only the outcomes of the study, but also the patients' willingness to accept the new insights based on personal experiences are relevant. With this in mind, a questionnaire to evaluate the patients' opinion on the effects of treatment was sent while the study was still being conducted. The results are reported in chapter 6. The majority of the patients reported to have improved (much or very much) on the treatment they had received and found the state of their health, including the drugs they had to take for it, acceptable for the next year. Interestingly, patients who had received initial combination therapy including prednisone in general were less satisfied with the effect of the therapy than patients who had received initial combination therapy with infliximab, despite virtually equal study outcomes at 2 years (chapter 4). Almost half of the patients expressed no preference or aversion for a particular treatment group, 33% had hoped for assignment to the combination with infliximab group and 38% had hoped against assignment to the combination with prednisone group. This negative perception was much less prominent in patients actually treated with initial combination therapy with prednisone. Nevertheless, half of the patients who had received treatment with prednisone reported to 'dislike having to take' the drug, even when they had shown a good clinical response and had already stopped taking it, while only 8% of patients disliked going to the hospital for intravenous therapy. The majority of patients would prefer 'a combination with a new intravenous antirheumatic drug', implying treatment with infliximab, should they be diagnosed with rheumatoid arthritis now.

PHYSICIAN'S PREFERENCE

Due to rapidly changing insights, physicians have had to adjust their therapeutic strategy for the treatment of patients with recent onset rheumatoid arthritis many times over the last decades. Only 2 decades ago, therapy rested on the use of non-steroidal anti-inflammatory agents. Since then, a gradual increase in the prescription of disease modifying antirheumatic drugs has been observed (8) and nowadays the concept of early treatment seems to have been accepted by the rheumatologic community (9). In 1997, the COBRA trial (10) demonstrated that initial combination therapy with methotrexate, sulphasalazine and prednisone was more effective than sulphasalazine monotherapy. However, this combination has never gathered a large following, and is now subject of a separate implementation study in the Netherlands. In recent years, several trials have demonstrated superior efficacy of TNF-antagonists (with methotrexate) over methotrexate monotherapy in patients with recent onset rheumatoid arthritis (11-13), but high costs and uncertainty about long-term safety has prevented the introduction of TNF-antagonists as initial treatment for rheumatoid arthritis in many countries. Because preferences of rheumatologists for the treatment of patients with recent onset rheumatoid arthritis may influence the implementation of the results of the BeSt study, we introduced a questionnaire on treatment preferences at the time of enrolment of a new patient in the BeSt study. The results given in chapter 7 demonstrate that rheumatologists were conservative at the time the BeSt study started. There was a strong preference for methotrexate monotherapy as initial treatment, and initial combination therapy was favoured only in rheumatoid factor positive patients with higher inflammatory marks. The BeSt study demonstrates that initial combination therapy results in earlier clinical and better radiographic response than initial monotherapy with methotrexate, thus the results of the questionnaire indicate that rheumatologists will have to adjust their preferences in clinical practice again.

COST-UTILITY

Infliximab, as well as the other TNF-antagonists, are very expensive drugs compared to traditional antirheumatic drugs and prednisone. To investigate whether the higher costs of these drugs can be acceptable for the society, a cost-utility analysis was performed (chapter 8). Quality of life, evaluated with different utility measurements, improved most in patients who received initial combination therapy with infliximab compared to patients in the other treatment groups. As expected, the direct costs were dominated by the costs of infliximab. The indirect societal costs were mostly dependent on the patients' ability to retain work. Productivity costs can be valued by different methods. The friction cost method takes the perspective of the employer and considers only those hours as loss that fall in the period, set at 6 months, the employer needs to adjust to the new situation. The human capital method takes the perspective of the patients and takes each hour not worked as loss. Depending on the method used, savings on productivity

could largely or could not compensate for the extra costs of infliximab therapy. The results of future analyses will be influenced by shifts in the number of patients receiving infliximab in each treatment group.

FUTURE PERSPECTIVES

After 2 years of follow-up of the patients in the BeSt study, initial combination therapy with either high dose tapered prednisone or infliximab appears to be the preferred strategy for patients with recent onset rheumatoid arthritis. These initial combination therapies result in a more rapid relief of signs and symptoms than sequential monotherapy or step-up combination therapy, although, in the setting of tight disease control, the latter two therapies catch up towards the end of one year of follow-up. In contrast to the clinical outcomes, the difference in joint damage progression remains statistically significant during the two years of follow-up. Despite the small differences in median progression scores, it is evident that fewer patients in the initial combination therapy groups have severe progression. Furthermore, in patients who started with a combination of drugs, therapy had to be adjusted less often and drugs could be tapered to a single drug in a considerable number of patients. Long-term follow-up will have to demonstrate whether this initial more rapid clinical response will result in sustained suppression of joint damage progression. Furthermore, it will be interesting to study whether there are differences in the number of patients in whom remission can be sustained when drugs are tapered and even stopped, i.e.drug-free remission.

During the first two years of follow-up no statistically significant differences in toxicity were found between the groups. Nevertheless, the long-term safety of the different treatment strategies needs to be established. The group with the highest risk for adverse events could change over time, given the dynamics of the treatment protocol with intensifying and tapering of medication in all groups.

The shift in the number of patients receiving infliximab also has major impacts on the results of future cost-effectiveness analyses. The trends that patients in the initial infliximab group could taper and discontinue infliximab, and that more patients in the other treatment groups started treatment with infliximab therapy had not stabilized after 2 years of follow-up. Longer follow up of the health economical aspects of treatment of RA will give more definite results as to the costs and compensations of the most effective treatment strategies.

Patients have a strong preference to receive treatment with the newest drug with promising results. The dislike of prednisone seems to be strong and widespread. For the implementation of the results of the BeSt study and previous trials, there is a need for better patient education about the efficacy and toxicity of both corticosteroids and TNF antagonists. This may be complicated by the observation that, at the time of the initiation of the BeSt study, rheumatologists were conservative and preferred initial monotherapy in the majority of patients. Given the results of the BeSt study, rheumatologists will have to reconsider their preferences for treatment.

Probably the most important observation of the BeSt study is that comparable clinical improvement can be achieved with different treatment strategies when the goal is set high. By aiming at a DAS ≤2.4, patients in all treatment arms were managed more aggressively than in daily routine practice. As a consequence, more patients than expected actually achieved low disease activity and even clinical remission, and showed little or no joint damage progression. Our attempt to retrospectively compare the results of the BeSt study with the results of routine care in similar patients did indicate that, despite having a worse prognosis at baseline, the DAS-driven group had more clinical improvement than the routine care group, and had adequate suppression of joint damage progression. A randomized controlled trial to compare routine care with DAS-driven therapy using the most effective treatment strategy would be preferable, but, given the results of the TICORA (2) and the BeSt study, it is questionable whether such a study can be ethically sound.

In the BeSt study the goal was to achieve low disease activity (DAS ≤2.4) by 3 monthly treatment adjustments depending on the disease activity score. At the time the BeSt study started, this was regarded as an ambitious goal. With today's knowledge one could argue that remission should be the goal. If DAS-driven therapy is to become standard of care, this will have major implications for the organisation of the outpatient clinic. Regular monitoring of disease activity will require a different approach at the outpatient clinic. Nurse practitioners could assist by assessing disease activity in all patients at regular intervals, giving rheumatologist more time to focus on patients with uncontrolled disease, extra-articular manifestations and/or toxicity.

After 2 years of follow-up of the patients in the BeSt study it can be concluded that initial combination therapies give earlier relief of symptoms, less joint damage progression and require less treatment adjustments than sequential monotherapy and step-up combination therapy. Long-term toxicity will have to be monitored closely, patients will have to be educated properly about the benefits and the risks of the different drugs, and cost-effectiveness analyses will have to be repeated after longer follow-up. Most important, goals to achieve suppression of disease activity should be set high, and disease activity should be monitored closely with vigorous treatment adjustments as long as the disease activity is not yet under control.

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