Combination therapy in rheumatoid arthritis

CHAPTER 12

SUMMARY AND GENERAL DISCUSSION

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Summary and general discussion

The systematic review in **chapter 2** summarizes the many developments in the combined drug treatment of rheumatoid arthritis (RA). We concluded that in early RA patients, step-down bridge therapy with oral corticosteroids leads to enhanced efficacy at acceptable or low toxicity (see Chapter 3). In patients with established disease, cyclosporin improves suboptimal clinical response to methotrexate (MTX) [1], and the triple combination of MTX, sulphasalazine (SSZ), and hydroxychloroquine appears to be clinically better than these single components [2]. Other combinations are either untested, tested at low sample size, or show negative interaction. In view of the low volume of evidence, it was stated that most studies needed confirmation by replication. Since then, confirmation for the usefulness of corticosteroids in early and active disease has been provided by the FINRACO study [3,4]. An important issue is the alleged progression of joint damage after corticosteroid therapy has been withdrawn [5]. Hickling *et al* found progression resumed once the low-dose prednisone added to standard disease-modifying anti-rheumatic drug (DMARD) therapy was stopped [5,6]. Other researchers even speak of an rebound effect which might implicate that patients are in the end worse off due to the use of steroids before [7]. Data from the COBRA trial did not confirm such an effect, on the contrary; the protective effects of combined-therapy – presumably the prednisolone component in it – persisted up to 3 years after their withdrawal according to trial protocol [8].

The randomised clinical COBRA trial in **chapter 3** shows the value of intensive combination therapy by comparing the clinical outcomes of combined step-down prednisolone, MTX and SSZ with SSZ alone in patients with early and active RA. Combined therapy immediately suppressed damage progression, whereas SSZ did less effectively and with a lag of 6 to 12 months. Notably, there were fewer withdrawals in the combined-therapy than the SSZ group, and these occurred later. The combined-therapy regimen thus offers additional disease control [9] over and above that of SSZ alone and persists for at least a year after corticosteroids are stopped.

The design of the COBRA trial does not allow separate evaluation of MTX and prednisolone effects, as both drugs were part of a triple therapy compared to single SSZ. However, the timely pattern of reduced disease activity – with convergent effects directly after the withdrawal of prednisolone and no change after withdrawal of MTX – suggests that MTX does not have a large protective – nor harmful – effect on bone in addition to the effect that had already been achieved by 7.5 mg/day prednisolone and 2000 mg/day SSZ. This view is supported by findings of Haagsma et al's trial with no significant difference in clinical or radiological outcomes between treatment groups with SSZ, MTX or their combination [10].

Presently, other studies and long-term follow-up are available to prove the soundness of aggressive treatment of early and active rheumatoid arthritis as well as the persistence of beneficial effects over many years [5,6,8]. Notably, the follow-up of patients in the COBRA trial shows an persisting beneficial effect on progression of joint damage as visible on radiographs; 3 and more years after medication dictated by the study protocol has been stopped there are still significant differences in progression of RA related joint damage (erosions in small joints of hands and feet). Analysis on follow-up data on erosion scores show regression lines per treatment group that diverge, instead of converge as might be expected with shrinking between-group differences in medication after withdrawal of short-term trial medication by protocol [8].

Recently, a new class of biological anti-tumor necrosis factor alfa (anti-TNFα) has come available with drugs named: etanercept and infliximab. These are a recombinant human TNF receptor and a chimeric human-murine monoclonal TNF antibody that bind to and thereby inhibits the biological activity of TNFα. Corticosteroids are presumably 'less precise in their action' as they inflict a series of systemic effects - including adverse like osteoporosis. The first trials with etanercept and infliximab used in combination are published [11,12]. The results are very promising but high costs and concerns about toxicity profiles presently limit their use. Post-marketing surveillance is important as various serious adverse effects of etanercept and infliximab have been reported [13-15]. With others we urge the scientific community to compare the effects and (long-term) toxicity of parental anti-TNFα factors with those of oral corticosteroids in initially high doses [16]. The COBRA medication protocol might serve as a model for this 'aggressive' corticosteroid approach [17].

Chapter 4 demonstrates the cost-effectiveness and cost-utility of early intervention in RA patients, with combined step-down prednisolone, MTX and SSZ, compared to SSZ alone. This conclusion is based on enhanced efficacy at lower or equal direct costs: Clinical, radiographic and functional outcomes significantly favored combined treatment at week 28 (radiography also at week 56 and 80) and utility scores measured by rating scale were significantly better at week 28. Based on, among other factors, fewer days spent in the hospital, direct costs of combined therapy were lower, although the level of significance was not reached. Notably, this is a regular phenomena in – so-called 'piggy-back' – economic evaluations linked to clinical trials; a priori power calculations based on clinical outcomes, and a skewed distribution of costs (caused by a small number of patients with extreme high costs) often have make it hard to reveal more than a 'trend' in lower cost with one of the treatment options under evaluation [18]. Moreover, the narrow timeframe of just over one year made it also difficult to find a between-treatment group differences in costs and QALYs. Nevertheless, our report was the first state-of-the-art cost-effectivity analysis of therapy for rheumatoid arthritis based on prospective data (previous studies were based on models or rates instead of 'real-time' measurements and costprices) [19]. We were nor the first nor the only research group to conclude that in patients with a chronic condition (such as arthritis) utility scores measured with the rating scale technique are more responsive than with standard gamble [20]. Indirect costs were not included in this first publication but the trial design comprised patient dairies and questionnaires to evaluate indirect costs (manuscript submitted; Korthals-de Bos IBC *et al*).

After initially positive experiences with corticosteroids for RA during the fifties, the recognition of important side effects of high doses and lower doses in established disease caused a communis opinio that this should not be done. However, these observations may be biased by the fact that corticosteroids are usually prescribed in patients with established and therapy-resistant disease. These patients are especially vulnerable to all kind of adverse effects that are associated with corticosteroids. Corticosteroids can play an important role in the reduction of disease activity in RA patients with early and active disease as illustrated by the COBRA trial as well as other studies. Therefore they should not be considered as a class of drugs that merely reduce symptoms but as DCARDs; disease-controlling antirheumatic drugs [9]. The systematic review in **chapter 5** showed that bone loss due to corticosteroids in the spine and hips of RA patients is in general more limited than in patients with other diseases. This conclusion was based on data from cohorts in papers published between 1966 and 1995 but is confirmed and accepted by recent publications [21,22]. Non-RA patients on high doses of corticosteroids regularly lose clinically relevant amounts of bone (arbitrarily set at 5% within 1 year), but this is rare in patients with RA. Most bone is lost in early or uncontrolled disease. Disease control with corticosteroids neutralises – at least partially – the corticosteroid induced bone loss. Patients in the combination therapy group of the COBRA trial – to whom 2345 mg prednisolone was subscribed during 28 weeks – 8 of 64 patients lost more than 5% of spinal bone (versus 6 of 62 in the SSZ group). Mean bone loss in the lumbar spine was indeed larger in the combination group ($P = 0.06$) but this stabilized after the withdrawal of prednisolone.

In RA the pathological destruction of collagen in bone and cartilage, causes the crosslink bridges in mature collagen to be resorbed more rapidly than normal. These collagen crosslinks are excreted in urine. Apart from the crosslink resorption at the site of inflamed joints, there might be increased resorption due to general bone loss associated with RA disease activity. Important collagen crosslinks and markers of destruction of bone and cartilage are pyridinoline (PYD) and deoxypyridinoline (DPD). Because of circadian rhythm in bone remodelling excretion in 24-hours collection is the standard. The findings described in **chapter 6** support that in longitudinal studies also urinary spot samples collected during a fixed day time (with concentrations corrected for creatinine) reflect 24-hour excretion levels well. In **chapter 7** we conclude from the available data in the COBRA trial, that prednisolone and DMARD therapy in these patients with early and active RA were both independently associated with decreased levels of urinary excretion of the bone collagen resorption markers PYD and DPD. In early RA the markers of bone formation *and* resorption closely followed changes in disease activity measure such as ESR in *both* treatment groups [23]. Reduced bone resorption together with reduced bone formation – reduction of formation initially at a somewhat faster pace – resulted in less bone turnover and may explain the observed small and partially reversible extra bone loss in the lumbar spine associated with prednisolone.

Chapter 8 confirms that patients with longer disease duration do not respond as well to treatment in RA, and female gender, prior DMARD use, ARA class and disease activity also have effects on the likelihood of patient response to treatment. This has implications for trial interpretation and for clinical expectations of patients. It also supports the view that there is a 'window of opportunity' in the treatment of RA. Aggressive suppression of disease activity in the early phase of active disease (with apparent inflammation of small joints of hands and feet) is mandatory to prevent joint damage. Association of cumulative disease activity with joint erosions and function loss at later stages stresses the importance of disease duration. The opportunity to intervene early with second-line antirheumatic drugs relies heavily on the early diagnosis and rapid referral of patients; health care systems should be specifically organized to facilitate this process [24].

The analysis described in **chapter 9** focussed on the validation of responsiveness and discriminative power of the World Health Organization/ International League of Associations for Rheumatology (WHO/ILAR) core set, together with the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria for improvement/response, and other single and combined measures (indices) in a trial in patients with early RA. It shows that at the moment of maximum between-group difference standardized response means (as sign for responsiveness) for various core set measures differs largely. Performance of patient oriented measures (for example, pain, global assessment) is best when the questions were focused on the disease. The most responsive single measure is the patient's assessment of change in disease activity. Patient utility, a generic health status measure was moderately (rating scale) to poorly responsive (standard gamble). Combined measures (indices) no matter how simple did better than most single measures; the simple count of core set measures improved by 20% was the most responsive. Discrimination performance yielded similar but not identical results: best discrimination between treatment groups was achieved by the EULAR response and ACR improvement criteria (at 20% and other percentage levels), the pooled index, and the disease activity score (DAS), but also by the Health Assessment Questionnaire (HAQ) and grip strength. We concluded that responsiveness and discrimination between levels of response are not identical concepts. As a matter of fact they need separate study. The WHO/ILAR core set comprises responsive measures that discriminate well between different levels of response in early RA. However, the performance of patient oriented measures is highly dependent on their format. The excellent performance of indices such as the ACR improvement and EULAR response criteria confirms they are the preferred primary endpoint in RA clinical trials.

When ACR improvement criteria are applied, measured scores should decrease on improvement. This, not only on the basis of methodological considerations (illustrated by data examples from the COBRA trial in **chapter 10** of this thesis) but also to facilitate comparisons between trials. Where necessary, raw data should be recoded before the ACR criteria are applied. This advice seems to gain importance with thresholds for improvement larger then the classical 20%.

The MACTAR interview evaluated in **chapter 11** (indeed an interview rather than a questionnaire) is a valid and highly responsive instrument to assess change in functional ability of early RA patients with active disease. The items that directly address change were among the most responsive of all. The MACTAR interview provides insight into problems – mainly of physical function – that really matter to patients. The feasibility of the MACTAR in standard clinical trials as well as clinical care, is considered to be limited compared with widely used instruments for physical disability such as the Health Assessment Questionnaire [25].

Patients that are willing to participate in clinical studies are rare and in almost every instance more rare than was expected. Our patients were prepared to be interviewed, touched, squeezed, and punctured. For this they deserve compassion and deepest respect; their participation is an act of philanthropy aimed at the benefit of future fellow-patients. In this context, valid and sensitive measurement, sound methodology, and careful and 'economic' use of eligible patients should be a matter of course. The quest for – the most – valid and responsive measures should never stop. Both disease-specific and generic measures of function and health-related quality of life are capable to detect improvements in RA patients. Using both types of measures for evaluating therapies will identify discernible changes that are important to patients, and will facilitate comparisons across different disease states [26].