Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility

M F Bakker, J W G Jacobs, S M M Verstappen, J W J Bijlsma

Objective: To evaluate the available evidence on the efficacy and feasibility of the new concept of tight control in randomised trials in patients with rheumatoid arthritis (RA). Tight control is a treatment strategy tailored to the individual patient with RA, which aims to achieve a predefined level of low disease activity or remission within a certain period of time.

Methods: The literature database PubMed was searched and yielded four trials: the FIN-RACo trial, the TICORA study, the BeSt study and the CAMERA study.

Results: Tight control resulted in greater improvement and a higher percentage of patients meeting the preset aim of low disease activity or remission when compared to the control intervention. In the FIN-RACo trial, aimed at DAS28<2.6, 51% of patients in the tight control group achieved remission versus 16% in the contrast group (p<0.001). In the TICORA study, 65% of patients in the tight control group versus 16% of the contrast group achieved remission, based on DAS<1.6 (p<0.0001). In the CAMERA study, 50% of patients in the tight control group using a computer decision model achieved remission, versus 37% in the contrast group (p=0.029). The BeSt study consisted of only tight control groups aimed at a DAS<1.6; remission was achieved in 38–46% of patients. This is higher than the range of remission in earlier trials of 13–36%.

Conclusion: Tight control aiming for low disease activity or even better still, remission, seems a promising option in treating patients with RA in clinical trials and probably also in daily practice.

METHODS
A PubMed search was performed to look for studies which used a predefined level of disease activity or remission as treatment aim using the following terms: rheumatoid arthritis, randomised trial, treatment strategy, low disease activity, remission and tight control. Abstracts were screened for the tight control principle. The search yielded four studies, in chronological order, the FIN-RACo trial, the TICORA study, the BeSt study, and the CAMERA study.

Different outcome parameters and study designs prohibited pooling of the effects of these studies. Therefore, study characteristics including the aim of the study (low disease activity or remission), time schedule, the method of evaluation of the individual patient, the adaptation of medication, and the results of the studies will be described.

RESULTS
Table 1 gives an overview of the inclusion criteria and the different treatments used in the four studies. Except for the TICORA study, disease duration was less than 2 years, and the patients had to fulfil the American College of Rheumatology criteria for RA.

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SJC, swollen joint score; TJC, tender joint score; VAS, Visual Analogue Scale
(ACR) classification criteria for RA for inclusion. Except for the CAMERA study, the inclusion criteria contained active disease and an age over 18 years.

**FIN-RACo**
The Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) study is a multicentre, randomised open-parallel group treatment trial in which 195 patients were included in the period between 1993 and 1995. The goal of the study was to compare the effects of the combination therapy with DMARDS with those of mono DMARD therapy in patients with early RA. Based on the evaluation of the individual patient, medication was intensified after 3 months in the combination group if there was less than 50% improvement on two out of three variables: swollen joint score (SJC), tender joint score (TJC), and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). In the mono DMARD group medication was intensified if there was less than 25% improvement after 6 months. The aim of the FIN-RACo study was remission, defined both with the ACR remission criteria, and as a Disease Activity Score (DAS28) <2.6.

**BeSt**
The Behandel Strategieën (BeSt) study is a multicentre randomised open clinical trial in which 508 patients with early active RA were included between 2000 and 2002. The goal of the study was to compare four treatment strategies: sequential mono therapy, step-up combination therapy, and initial combination therapy with either high-dose prednisone or infliximab. Medication of individual patients was based on Disease Activity Score (DAS44) <2.6. After 2 years, patients on sequential monotherapy or step-up therapy showed that the mean fall in the disease activity score was higher in the tight control group than in the routine group (−3.5 vs −1.9, p<0.0001). Compared with routine care, patients in the tight control group had a good response (82% vs 44%, p<0.0001) or remission (DAS28<1.6) (65% vs 16%, p<0.0001). As well as disease activity, radiographic disease progression, physical function and quality of life in the tight control group were also more favourable than in the routine care group, at no additional financial costs.

**TICORA**
The Tight Control of Rheumatoid Arthritis (TICORA) study is a single-blind randomised controlled trial in which 111 patients, some with disease duration of up to 5 years, were included between 1999 and 2001. The goal of the study was to compare tight controlled treatment and routine treatment. The evaluation and strategy of medication adaptations and escalations was based on an objective disease activity score in the individual treated, tight control group and evaluated in the routine group by the subjective opinion of the clinician. The outcome of the TICORA study was the mean fall in disease activity score, the number of patients with good response (defined as a DAS28<2.4 after 2 years and a fall in this score from baseline of more than 1.2), and the percentage of patients in remission. The results of TICORA showed that the mean fall in the disease activity score was higher in the tight control group than in the routine group (−3.5 vs −1.9, p<0.0001). Compared with routine care, patients in the tight control group had a good response (82% vs 44%, p<0.0001) or remission (DAS28<1.6) (65% vs 16%, p<0.0001). As well as disease activity, radiographic disease progression, physical function and quality of life in the tight control group were also more favourable than in the routine care group, at no additional financial costs.

### Table 1: Characteristics of the tight control studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions/groups</th>
<th>n</th>
<th>Medication at the start</th>
<th>Frequency of assessment</th>
<th>Inclusion criteria</th>
<th>Disease duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIN-RACo</td>
<td>Combination therapy*</td>
<td>97</td>
<td>SSZ, MTX, HCQ, predn</td>
<td>3 months (variable)</td>
<td>ARA criteria RA, 18–65 yr, symptoms &lt;2 yr, active disease ≥3 SJ and 3 of: ≥28 mm/h ESR or ≥19 mg/l CRP, ≥29 min/ms, ≥5 SJ or &gt;10 TJ</td>
<td>&lt;2 yr</td>
</tr>
<tr>
<td></td>
<td>Mono therapy</td>
<td>98</td>
<td>SSZ ± predn</td>
<td>3/6 months (clinical decision/variable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TICORA</td>
<td>Intensive management*</td>
<td>55</td>
<td>DMARD, i.a. steroid</td>
<td>1 month (DAS)</td>
<td>18–75 yr, disease duration &lt;5 yr, active disease (DAS&gt;2.4).</td>
<td>&lt;5 yr</td>
</tr>
<tr>
<td></td>
<td>Routine management</td>
<td>55</td>
<td>DMARD mono</td>
<td>3 months (clinical decision)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BeSt</td>
<td>Sequential mono therapy*</td>
<td>126</td>
<td>MTX</td>
<td>3 months (DAS44)</td>
<td>ACR criteria RA, ≥18 yr, disease duration &lt;2 yr, active</td>
<td>&lt;2 yr</td>
</tr>
<tr>
<td></td>
<td>Step-up combination therapy*</td>
<td>121</td>
<td>MTX</td>
<td>3 months (DAS44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial combination therapy + h.d.</td>
<td>133</td>
<td>MTX, SSZ, predn</td>
<td>3 months (DAS44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial combination therapy + infliximab</td>
<td>128</td>
<td>MTX, infliximab</td>
<td>3 months (DAS44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAMERA</td>
<td>Intensive strategy group*</td>
<td>151</td>
<td>MTX</td>
<td>1 month (computer decision program)</td>
<td>ACR criteria RA, ≥16 yr, early RA (&lt;1 yr)</td>
<td>&lt;1 yr</td>
</tr>
<tr>
<td></td>
<td>Conventional strategy group</td>
<td>148</td>
<td>MTX</td>
<td>3 months (clinical decision)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Based on tight control treatment. ACR criteria RA, American College of Rheumatism criteria for rheumatoid arthritis; ARA criteria RA, American Rheumatism Association criteria for rheumatoid arthritis; BeSt, Behandel Strategieën; CAMERA, Computer Assisted Management of Early Rheumatoid Arthritis; CRP, C-reactive protein; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; HCQ, hydroxychloroquine; h.d., high-dose; i.a., intra-articular; ms, morning stiffness; MTX, methotrexate; predn, prednisone; SJ, swollen joints; SSZ, sulfasalazine; TICORA, Tight Control of Rheumatoid Arthritis; TJ, tender joints; VAS, visual analogue scale; yr, year(s).
of joint damage progression can be achieved with frequent, objective treatment adjustments.20 22

CAMERA
The Computer Assisted Management for Early Rheumatoid Arthritis (CAMERA) study23 is a randomised prospective multicentre trial in which 299 patients with early RA were allocated between 1999 and 2003. The goal of the study was to compare intensive with conventional treatment, both strategies aiming for remission. This is the only tight control study comparing the same treatment in a tight control scheme and a conventional scheme. In the intensive (tight control) group, decisions on therapy were made more frequently and with the use of an objective computer decision program evaluation in the individual patient. The computer decision model was based on the SJC, TJC, ESR, and the Visual Analogue Scale (VAS) general well-being. Medication was intensified if less than 20% improvement had occurred after each month of assessment, unless remission was reached. Every 3 months in the conventional treatment group a decision on medication was made by the clinician, mirroring common practice, and the medication was also intensified when clinically indicated, as judged by the attending physician. Remission was defined as no swollen joints and two out of three of the following variables: number of tender joints ≤3, ESR ≤20 mm/hr, and VAS general well-being ≤20 mm. After 2 years, 50% of the patients in the intensive treatment group versus 37% in the conventional group (p = 0.029) had been in remission for at least 6 months during the study. These results show that tailoring of treatment to the individual patient by a computerised decision program, aiming for remission, is more beneficial than the strategy mirroring daily practice also aiming for remission. Therefore, this strategy could be a helpful tool in daily clinical practice.

DISCUSSION
In the present report efficacy and feasibility of tight control in randomised trials in patients with early RA is evaluated. It seems that tight control and the aims of low disease activity and remission are feasible and favourable.

Of the four studies, TICORA and CAMERA give the best insight into tight control, since they compared a tight control group with a routine or conventional group. Of these two studies, the CAMERA might offer the best comparison, because in this study the same medication in the same dosage has been used in the tight control group and the conventional groups. In contrast, all intervention groups in the BeSt study make use of the concept of tight control so there is no comparison group. In the FIN-RACo study, the efficacy of a less intensive level of tight control was compared with that of a more intensive level; the latter yielded the best results.

In the evaluated studies different protocols in the tight control groups were used to make therapy choices and changes. In both the TICORA study and the BeSt study therapy changes were based on the DAS score. In the FIN-RACo study as well as the CAMERA study therapy changes were based on the percentage improvement in disease activity of the individual patient. In contrast to FIN-RACo, dose adjustments in the CAMERA study were based on a predefined scheme and were made using a computer decision program which increases objectivity. In the future, the protocol for therapy changes in studies used for tight control should be standardised, enabling comparison and pooling different study outcomes.

The aim in all four studies was the number of patients in remission. The range of remission rates in the tight control groups was significantly better than in the comparison groups (51–65% remission vs 16–39%) or, to make a comparison with historical controls for the groups in the BeSt study (38–46% remission), the percentages of remission in earlier trials were within a range of 13–36%.16 28 29 However, different definitions were used to define remission and tight control as a new paradigm needs the use of uniform criteria of low disease activity or remission. Sustained remission is currently, with the arrival of the combination DMARD therapy and the biologicals, an achievable goal in clinical practice.30 31 Before the main goal of treatment was to achieve remission, the ACR20/50/70 improvement criteria were standard for controlled clinical trials. But they do not give any information about the current status of disease activity. A patient could have large improvement and still have active disease.32 Criteria of low disease activity have the drawback that patients may still have progression of radiographic joint damage.33 Therefore remission rather than low disease activity should be our treatment goal today.34 On the other hand, even when remission should be the best feasible outcome measure, this term is still poorly defined and various remission criteria mirror different degrees of disease activity.35 In three out of four evaluated studies, the DAS28 remission criteria were used to define remission. However, the DAS has not been validated for use in individual patients. It is rather sensitive for changes in ESR in the (nearly) normal range (see fig 1).35 Figure 1 shows that the relative contribution of tender joints to the DAS28 score is much higher than that of swollen joints, which is a more specific feature of RA. The DAS could lead to overestimation of disease activity in individual patients due to the DAS components TJS and VAS general well-being. Another problem for assessment of individual patients with RA is that the DAS28 does not include joints of the feet, which are frequently inflamed in RA. This could lead to underestimation of disease activity. The DAS28 remission criterion at a cut-off level of 2.6 has been found to lack construct validity for use in clinical practice for this reason.37

In our opinion, for the practical use of tight control, a new score should be developed and validated for the assessment in individuals, enabling comparison and pooling of different study strategies. Probably the key criterion should be absence of swollen joints, because this is the key feature for RA. Further points of discussion are the duration of remission and whether or not radiographic progression should be included in remission criteria.

Overall, frequent monitoring on the basis of objective evidence of continued disease activity using a validated outcome measure and a quick, aggressive escalation protocol can improve the effects of RA considerably compared with routine care.7 18 39 Other short-term and long-term advantages of tight control might be the greater improvement in physical function and substantially enhanced quality of life,19 improved functional capacity,31 decline of radiographic progression,20 22 and possible cost reductions for the future.38 The disadvantages of tight control might be the frequency and intensity of the assessments, although the frequency might be high in patients with early RA but lower in established disease, and the fear of patients of overtreatment due to the aggressive escalation protocol. The solution for overtreatment might be reduction of medication in case of sustained response as applied in the BeSt and CAMERA study.

CONCLUSION
Tight control seems to be a promising new paradigm for reaching the aim of low disease activity, or even better remission, in clinical trials and possibly daily practice, due to a predefined decision and measurement system. For further implementation of this concept, development of a valid and easy-to-use criterion for remission is recommended.
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