

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

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Ann Rheum Dis 2007;**66**(Suppl III):iii56–iii60. doi: 10.1136/ard.2007.078360

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Accepted 29 June 2007

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint pain, progressive joint destruction and functional disability,¹ due to the combined effect of chronic synovitis and progressive joint damage.² Treatment of disease in the first months of synovitis is important to retard radiographic progression.³ This window of opportunity suggests that disease activity in patients with early RA is less severe, is characterised by a smaller load of inflammatory cells, and is more responsive to treatment. So aggressive treatment during this phase is more likely to succeed than is the same treatment applied later in the course of disease,⁴ when autoantigens from damaged joints possibly fuel the disease. Therefore it is important that RA should be treated and controlled as soon as possible after diagnosis and that this control should be maintained for as long as possible, consistent with patient safety.^{5, 6}

In the past, the traditional (pyramid model) treatment therapy started with non-steroidal anti-inflammatory drugs (NSAIDs). If this treatment was insufficiently effective, second-line antirheumatic drugs or disease-modifying antirheumatic drugs (DMARDs) were added. However, an immediate start of DMARDs proved to be more efficacious than a delayed introduction of DMARDs in the disease progress of RA.^{7, 8} More recent therapeutic strategies are based on combinations of DMARDs to control inflammation in the critical early stages of RA.^{9–11} Glucocorticoids, which also can be considered as DMARDs because they are able to reduce the progression of joint damage, have been included in DMARD combination treatments of RA.^{12, 13}

The most current treatment strategies are combination therapies with conventional DMARDs and biologicals.¹⁴ With these therapies, improvement in signs and symptoms and also low disease activity and even remission come within reach. Overall, a paradigm shift is observed in the trials of RA: treatment is more frequently aimed at low disease activity or remission in each individual patient,^{15, 16} instead of randomising

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.

groups into standardised therapies. This new way of treatment is called “tight control”. Tight control may be defined as a treatment strategy tailored to the disease activity of individual patients with RA with the aim of achieving a predefined level of low disease activity or preferably remission within a reasonable period of time.

The aim of this evaluation is to investigate how effective and feasible tight control is.

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,^{17, 18} the TICORA study,¹⁹ the BeSt study,^{20–22} and the CAMERA study.²³ 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

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

Table 1 Characteristics of the tight control studies

Study	Interventions/groups	n	Medication at the start	Frequency of assessment	Inclusion criteria	Disease duration
FIN-RACo	Combination therapy*	97	SSZ, MTX, HCQ, predn	3 months (variable)	ARA criteria RA, 18–65 yr, symptoms <2 yr, active disease \geq 3 SJ and 3 of: \geq 28 mm/h ESR or \geq 19 mg/l CRP, \geq 29 min/ms, $>$ 5 SJ or $>$ 10 TJ	<2 yr
	Mono therapy	98	SSZ \pm predn	3/6 months (clinical decision/variable)		
TICORA	Intensive management*	55	DMARD, i.a. steroid	1 month (DAS)	18–75 yr, disease duration <5 yr, active disease (DAS>2.4)	<5 yr
	Routine management	55	DMARD mono	3 months (clinical decision)		
BeSt	Sequential mono therapy*	126	MTX	3 months (DAS44)	ACR criteria RA, \geq 18 yr, disease duration \leq 2 yr, active disease: \geq 6 of 66 SJ, \geq 6 of 68 TJ, \geq 28 mm/h ESR, \geq 20 mm VAS global health	\leq 2 yr
	Step-up combination therapy*	121	MTX	3 months (DAS44)		
	Initial combination therapy + h.d. predn*	133	MTX, SSZ, predn	3 months (DAS44)		
	Initial combination therapy + infliximab*	128	MTX, infliximab	3 months (DAS44)		
CAMERA	Intensive strategy group*	151	MTX	1 month (computer decision program)	ACR criteria RA, >16 yr, early RA (<1 yr)	<1 yr
	Conventional strategy group	148	MTX	3 months (clinical decision)		

*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).

(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) study¹⁸ 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,²⁴ and as a Disease Activity Score including the 28-joint count (DAS28)²⁵ <2.6, and good treatment response according to criteria of the European League Against Rheumatism (EULAR).²⁶ After 2 years, more patients in the combination group had met the ACR remission criteria (14% vs 3%, $p = 0.013$), the DAS28 remission criterion (51% vs 16%, $p < 0.001$), and the criteria of a good treatment response (67% vs 27%, $p < 0.001$) compared to the mono DMARD group. Combination therapy thus was better and not more hazardous than single treatment in induction of remission in early RA. Combination therapy as a tight control strategy in patients with early RA aiming for remission seems to be more efficacious than monotherapy.¹⁷

TICORA

The Tight Control of Rheumatoid Arthritis (TICORA) study¹⁹ 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.

BeSt

The Behandel Strategieën (BeSt) study²¹ 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. Evaluation of individual patients was based on Disease Activity Score 44-joint counts (DAS44) in all four groups.²⁷ Medication was intensified if DAS44 exceeded 2.4 and was decreased if DAS \leq 2.4 for the period of 6 months. The outcomes of the BeSt study were functional ability, radiographic joint damage, and the percentages of patients meeting the criterion of low disease activity (DAS44 \leq 2.4) or remission (DAS44 <1.6). After 1 year patients of the initial combination therapy including either prednisone or infliximab had earlier functional improvement and less radiographic damage than those on sequential monotherapy or step-up therapy. After 2 years of treatment, these differences seem to disappear and no statistically significant differences were seen between the groups in the percentage of patients in remission (46%, 38%, 41%, 42%, respectively; $p = 0.7$). It seems that in patients with early active RA, remarkable clinical improvement and suppression

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^{1st}, 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.^{31–35} In three out of four evaluated studies, the DAS²⁷ 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).³⁶ 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.^{7–38–39} 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.¹⁹ 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.

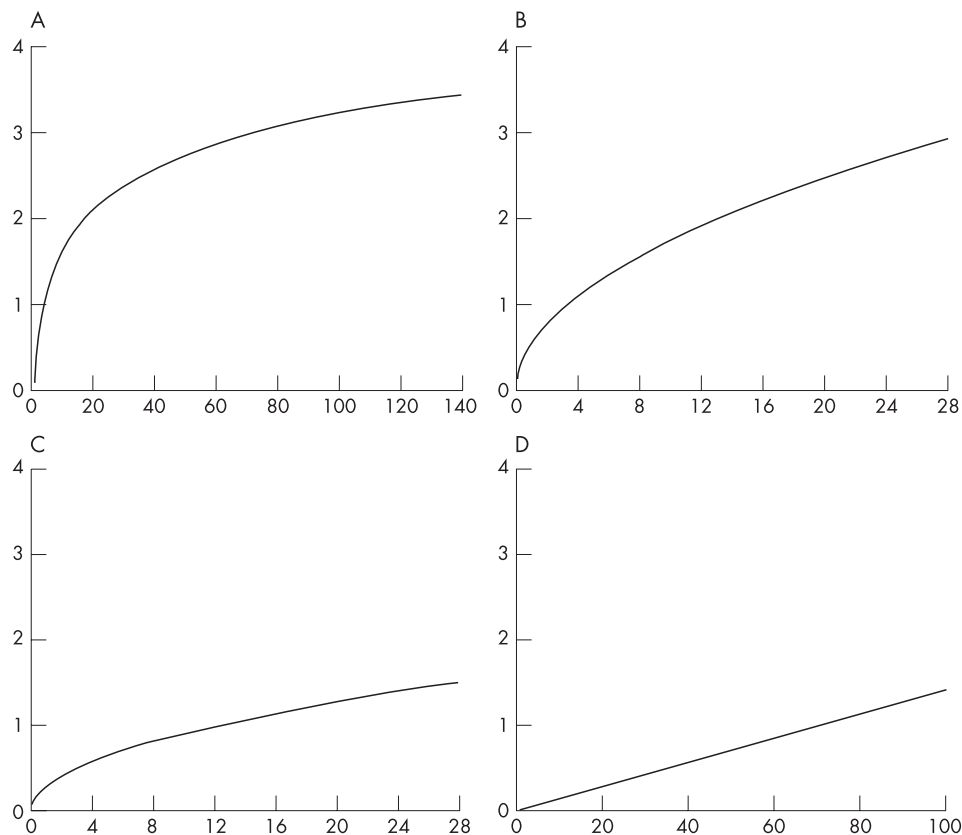


Figure 1 Plots of contribution of individual components of the DAS28 (x-axis) to the total DAS28 score (y-axis). (A) ESR ($0.7 \cdot \ln(x)$). (B) Tender joint count ($0.555 \cdot \sqrt{x}$). (C) Swollen joint count ($0.284 \cdot \sqrt{x}$). (D) Visual analogue scale patient's global assessment ($0.0142 \cdot x$). ESR, erythrocyte sedimentation rate; VAS, visual analogue scale.

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Competing interests: None declared.

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10. **McGuire W**, Hill AV, Allsopp CE, Greenwood BM, Kwiatkowski D. Variation in the TNF-alpha promoter region associated with susceptibility to cerebral malaria. *Nature* 1994;**371**:508–11.

Correction

There was an error in an article published in supplement III last year (Bakker MF, Jacobs JWJ, Verstappen SMM, Bijlsma JWJ. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis* 2007;**66**:iii56–iii60). The reported remission rates of the FIN-RACo trial were of the subset of patients who completed the study and were in sustained remission, which hampers comparison between the studies because the 2 year point remission rates on intention to treat basis were reported for the other three studies. The 2 year intention to treat point remission rates of the FIN-RACo study for ACR remission are 37% in the tight control group and 18% in the contrast group. For DAS-remission (DAS28<2.6), completers' remission rates of the FIN-RACo trial are 68% and 41%, respectively. The amendments to the article are as follows:

Abstract, piii56, line 8 from top should read "In the FIN-RACo trial, analysing the subset of patients completing the study, 68% in the tight control group achieved remission (DAS28<2.6) versus 41% in the contrast group."

Text, piii57, column 1, line 17 from bottom should read "After 2 years, more patients in the combination group compared with the mono DMARD group had met the ACR remission criteria (37% vs 18%, $p = 0.003$)". Analysing the subset of patients completing the study, 68% vs 41% met the DAS28 remission criterion ($p < 0.001$) and 67% vs 27% ($p < 0.001$) the criteria of sustained good treatment response, respectively."

So these reported 2 year remission rates of the FIN-RACo trial are more favourable than those reported erroneously in the paper. The authors believe that this further strengthens their conclusion that tight control aiming for low disease activity and remission is a promising option in treating patients with early RA in daily clinical practice.