
Overview and analysis of treat-to-target trials in rheumatoid arthritis reporting on remission

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Received and accepted on September 14, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 73): S56-S63.

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EXPERIMENTAL RHEUMATOLOGY 2012.

Key words: rheumatoid arthritis, disease-modifying anti-rheumatic drugs, tight control, treat-to-target, meta-analyses, overview

ABSTRACT

Objective. To present an updated overview of tight control studies with a fixed treatment target (“treat-to-target”), reporting on (sustained) remission in rheumatoid arthritis (RA).

Methods. A search of the electronic databases Medline (PubMed), Embase and Cochrane was performed in July 2012 to identify trials and studies addressing tight control with treat-to-target reporting on (sustained) remission, regardless of definition or duration. Next to a narrative overview of the identified studies, a formal meta-analysis was performed pooling study results of studies comparing the effects of a tight control and treat-to-target strategy arm with those of a usual care strategy.

Results. Thirteen studies were found, 4 comparing effects of tight control to those of usual care, 1 comparing the effects of 2 strategies with the same DMARDs but using different treatment targets, and 8 comparing the effects of tight control strategies with different DMARDs but with the same treatment target. Remission rates differed over a wide range in these studies, but in general were not higher in studies applying a biological DMARD from start compared to studies with initial conventional DMARD strategies. The meta-analysis of the 4 studies comparing tight control versus usual care shows that applying a treat to (any) target strategy appeared to approximately double the remission rates of the participating early RA patients.

Conclusion. The trials comparing tight control arms show in general that the more intensive the strategy, the more strict the treatment aim and the more tight the tight control, the better the remission rates. It does not appear obligatory to start with a biological DMARD to get good results in tight control studies.

Introduction

Rheumatoid arthritis (RA) is a progressively disabling chronic disease, characterised by severe pain and stiffness symptoms and persistent synovitis, systemic inflammation and autoantibodies (1). Many patients experience joint destruction, deformity, a decrease in quality of life, and premature mortality (1, 2), though substantially improved outcomes have been seen in recent decades (3, 4). In industrialised countries RA affects 0.5–1.0% of adults, with 5–50 per 100,000 new cases each year (1).

Over the years, treatment paradigms have changed (5–7). Up till the 80s the paradigm was to first start after diagnosis with a non-steroidal anti-inflammatory drug (NSAID) and if insufficient effective, to add a disease-modifying anti-rheumatic drug (DMARD): the pyramid strategy (5, 8). That changed to a start with a DMARD as soon as possible after diagnosis (9), and combination therapy with DMARDs if needed (10), especially with methotrexate (MTX) as anchor-DMARD (11, 12). Glucocorticoids have been proven to be DMARDs for early RA (13), and several types biological DMARDs have been developed. With all these developments, in early RA low disease activity and remission are achievable goals, which, if occurring within the so called ‘window of opportunity’ may alter the long-term disease course.

To provide guidance for earlier inclusion – and thus treatment – in research studies, new criteria for RA have been developed (14). For optimal effect, tight control strategies are now used (11), which have been shown to be effective (5, 15, 16).

A tight control strategy is a treatment strategy with dose and medication adjustments tailored to the individual RA patient to achieve within a certain limited period of time a predefined level of low disease activity or remission: the

Competing interests: none declared.

target (16), hence the term treat-to-target. The target can be a level of a quantitative index for disease activity, such as the disease activity score assessing 28 joints (DAS28), or a Boolean definition, such as used in the computer-assisted management in early RA (CAMERA) trials (17, 18), or as described in the 2011 remission criteria (19). Remission as treatment goal might be preferred over low disease activity, particularly in early disease, as joint damage may progress significantly in some patients with low disease activity (20). The European League Against Rheumatism (EULAR) has recommended remission as the primary treatment goal for RA (21).

Although reviews have been published concerning tight control strategies (15, 16, 22), in most of them remission has not been addressed specifically as outcome of a systemic review. This report aims to give an updated overview of tight control studies with a fixed treatment target, reporting on (sustained) remission.

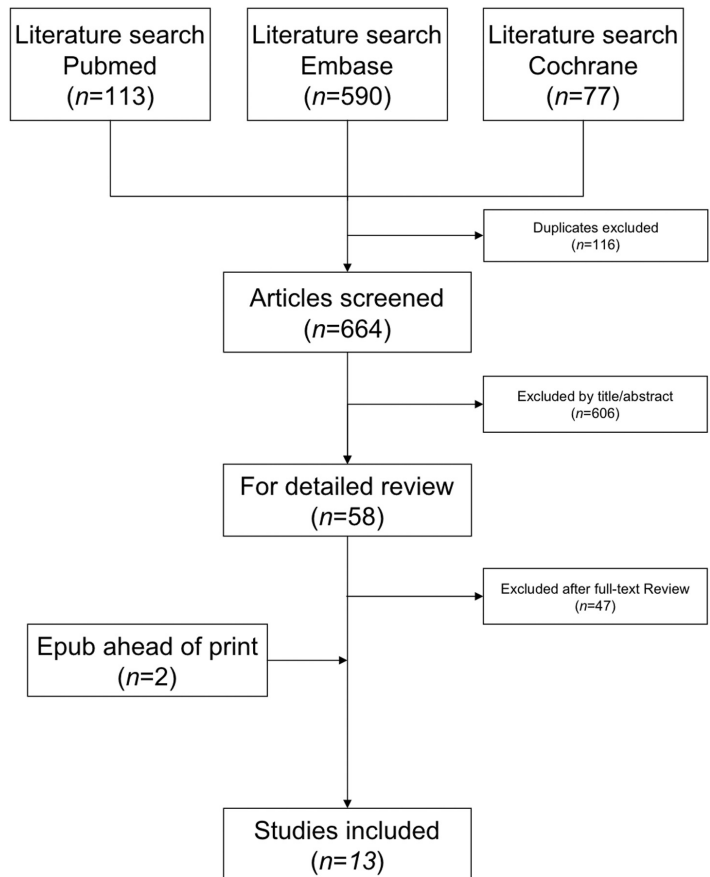
Methods

Literature search

A search of the electronic databases Medline (PubMed), Embase and Cochrane was performed in July 2012 to identify trials and studies addressing tight control with treat-to-target reporting on (sustained) remission, irrespective of definition or duration.

Different synonyms for RA, connected with the Boolean operator [OR] and different synonyms for treat-to-target that were also connected with the Boolean operator [OR], were combined with the Boolean operator [AND]. The keywords were required to be present in title and/or abstract. No restrictions in publication years were made. Systematic reviews and articles were studied to search for additional references. Selection criteria were English language and availability as full paper; reporting remission results on the patient level in numbers, percentages or proportions; and a minimum of two treatment arms, at least one of them a tight control and treat-to-target strategy arm. The treatment target was required to be predefined and unequivocal; patients were

Fig. 1. Flow chart of the performed search strategy



required to have RA according to the American College of Rheumatology (ACR) 1987 or 2010 criteria (14, 23). Study selection was performed by one reviewer (M.S. Jurgens) who screened titles, abstracts and full text. The final selection of studies was based on full consensus of all authors.

Statistical analysis

In addition to a narrative overview of the studies found in this systemic review, a meta-analysis was performed by pooling the results of the studies comparing the effects of a tight control and treat-to-target strategy arm with those of a usual care strategy. This was performed to estimate the net effect of tight control, compared to usual care.

Results

The results of the search are summarised in Figure 1; 13 studies met the criteria for this review, 4 comparing effects of tight control to those of usual care (18, 24-26), 1 comparing the effects of 2 strategies with the same DMARDs but different treatment tar-

gets (27), and 8 comparing the effects of tight control strategies with different DMARD strategies but with the same treatment target (17, 28-34). All the studies applied MTX and most studies allowed use of glucocorticoids.

Tight control vs. usual care

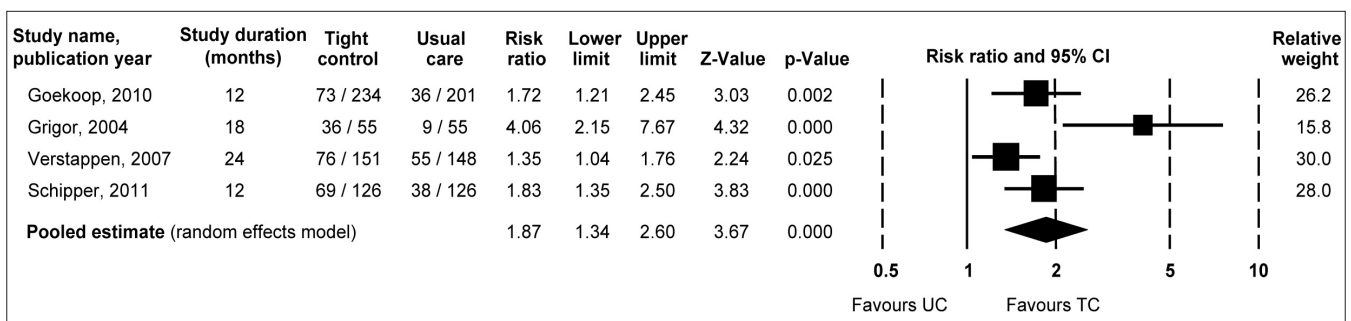
The 4 studies comparing effects of tight control with treat-to-target vs. usual care were pooled to estimate the net effect of tight control, see Table I and Figure 2. There is large heterogeneity between studies, probably based on different study designs and patient populations. The CAMERA trial was the only trial in which a computer model was used to implement the protocol. The definition of remission, report of time when remission was reached, and duration of treatment differed between the trials. The two most recent studies were conducted over 1 year, the TICO-RA (Tight Control for RA) trial over 18 months and the CAMERA trial over 2 years. Nonetheless, each of the 4 individual studies indicated superiority of tight control over usual care in analyses

Table I. Treat-to-target trials reporting on remission. Tight-control *versus* Usual Care & Target *versus* Target.

Study characteristics			Baseline characteristics								
Tight Usual Care	Control vs Study duration‡	Strategy arms	Study target	n	Female(%)	Age (yrs) †	RF+(%)	Disease duration†‡	Disease activity	Erosive damage(%)	Remission reached
Grigor et al, 2004 (TICORA)											
	18	Tight-control	DAS < 2.4	55	71	51 (15)	75	16 (16)	DAS: 4.9 (0.9)	x	36 (65%)
	18	Usual care		55	69	54 (11)	73	20 (16)	DAS: 4.6 (1.0)	x	9 (16%)
Verstappen et al, 2007 (CAMERA)											
	12 and 24	Tight-control	Remission∞	151	69	54 (14)	66	≤ 12	x	x	12: 53 (35%) 24: 75 (50%)
	12 and 24	Usual care		148	66	53 (15)	62	≤ 12	x	x	12: 21 (14%) 24: 55 (37%)
Goekoop-Ruiterman et al, 2010											
	12	Tight-control	DAS ≤ 2.4	234	70	54 (13)	66	6.0 (3.6-12)•	DAS28: 6.1 (1.0)	71	73 (31%)
	12	Usual care		201	73	54 (15)	42	4.8 (3.6-7.2)•	DAS28: 5.7 (1.0)	53	36 (18%)
Schipper et al, 2011											
	12	Tight-control	DAS28 < 2.6	126	62	56 (13)	63	3.4 (1.8-6.0)•	DAS28: 5.0 (1.2)	x	69 (55%)¥
	12	Usual care		126	61	57 (14)	74	4.1 (2.1-8.5)•	DAS28: 4.8 (1.1)	x	38 (30%)¥
Target vs. Target											
van Tuyt et al, 2008											
	9.2	Tight-control-1	DAS28 ≤ 3.2	11	73	52 (14)	73	9 (11)	DAS28: 5.37 (0.98)	56	10 (91%)¥Δ
	9.2	Tight-control-2	CTX-II ≤ 150	10	60	50 (13)	78	13 (7)	DAS28: 5.19 (0.62)	75	9 (90%)¥Δ

‡: Duration given in months, †: mean(sd) unless stated otherwise, x: Not available in this form in article, ∞: a swollen joint count of 0 (range 0-38 joints), and at least 2 of the following factors: tender joint count ≤3 (range 0-38 joints), VAS score ≤20mm and ESR ≤20mm/h, • median (IQR), ¥: n or (%) calculated using available data, Δ: data extracted from figure, DAS(28): Disease Activity Score (in 28 joints), RF+= positive Rheumatoid factor status

TICORA, Tight Control for Rheumatoid Arthritis; CAMERA, Computer Assisted Management in Early Rheumatoid Arthritis

**Fig. 2.** Forest plot of tight control studies reporting on remission.

Cochran Q 10.3, $p=0.016$ and I-squared 71%, indicating large heterogeneity. UC: usual care, TC: tight control.

of the number of patients in (sustained) remission. The likelihood for a patient to obtain (sustained) remission was 1.87 times higher in the tight control arms, compared to the usual care arms.

Target vs. target

One study compared the effects of two arms applying the same DMARDs but with different treatment targets.(27) These were DAS28 ≤3.2 *versus* urinary level of C-terminal cross-linked telopeptides of type II collagen (CTX-II) ≤150 ng/mmol creatinine. The DAS28 is a score of a composite index of number of swollen joints, tender joints,

ESR and Visual Analogue Scale (VAS) general health; DAS28 ≤3.2 corresponds with low disease activity.

The level of CTX-II excretion is hypothesised to reflect the amount of cartilage destruction in active RA (35). This study with a duration 40 weeks and an intensified COBRA (“Combinatie therapie Bij Reumatoïde Arthritis”) scheme showed no significant difference in remission rates between the two arms, 90 and 91 percent, respectively. The intensified COBRA scheme differed from COBRA in that hydroxychloroquine (HCQ) was added to the scheme, that the dose of

MTX could be increased and that additionally infliximab could be started, if needed.

Tight control vs. tight control

Of the 8 studies comparing effects of 2 tight control arms, 4 studies applied initially synthetic DMARDs only and 4 had arms with an initial biological DMARD (Table II).

Synthetic DMARD studies

Of the 4 studies, in 2 the same drugs were applied, but with different schemes (the Finnish Rheumatoid Arthritis Combination Therapy (FIN-

Table II. Treat-to-target trials reporting on remission. Tight-control *versus* Tight control.

Synthetic DMARD	Study characteristics		Treatment arms	Baseline characteristics							Disease activity †	Erosive damage(%)	Remission reached
	Study duration ‡	n		Study target	n	Female(%)	Age (yrs)†	RF+†(%)	Disease duration ‡‡				
Möttönen et al, 1999 (FIN-RACO)													
24		97	Remission*	97	58	47 (range 23-65)◊	70	7.3 (range 2-22)◊	x		48	36 (37%)	
24		98	Remission*	98	66	48 (range 20-65)◊	66	8.6 (range 2-23)◊	x		53	18 (18%)	
Saunders et al, 2008													
12		47	Combination: SSZ+MTX+HCQ+Prednisone	47	79	55 (11)	72	13 (12)	DAS28: 6.9 (0.9)		85	21 (45%)†	
12		49	Single: SSZ or MTX or HCQ ± Prednisone	49	76	55 (15)	69	10 (9)	DAS28: 6.8 (0.9)		84	16 (33%)†	
Bakker et al, 2012 (CAMERA-II)													
24		117	Step-up therapy: SSZ→MTX→HCQ	117	60	54 (14)	55	≤ 12	DAS28: 5.8 (1.3)		17	84 (72%)	
24		119	Tripple therapy: SSZ+MTX+HCQ	119	61	53 (13)	61	≤ 12	DAS28: 5.5 (1.1)		12	73 (61%)	
Montecucco et al, 2012													
12		110	Remission∞	110	65†	57 (45-67)†	x	2.97 (1.93-5.10)†	DAS28: 5.0 (4.2-5.9)†		x	43 (44.8%)	
12		110	Remission∞	110	63†	62 (51.5-72)†	x	3.48 (2.57-5.70)†	DAS28: 5.2 (4.4-5.9)†		x	25 (27.8%)	
Biological DMARD													
Soubrier et al, 2009 (GUEPARD)													
2.8 and 12		32	DAS28 ≤ 3.2	32	81.25	49.3 (15.2)	77.4	4.4 (3.3-5.1)	DAS28: 6.15 (0.88)		37.5	2.8: 8 (25%) 12: 19 (59.4%)† 2.8: 21 (63.6%) 12: 13 (39.4%)†	
2.8 and 12		33	DAS28 ≤ 3.2	33	78.78	46.3 (16.3)	70	4.4 (2.5-5.4)	DAS28: 6.31 (0.78)		31.25		
Tak et al, 2011 (IMAGE)													
12		249	Placebo+MTX	249	77	48.1 (12.7)	87	10.9 (13.2)	DAS28: 7.1 (1.0)		x	32 (13%)†	
12		249	Rituximab (2x500mg) + MTX	249	82	47.9 (13.4)	87	11.8 (13.2)	DAS28: 7.1 (1.0)		x	62 (25%)†	
12		250	Rituximab (2x1000mg) + MTX	250	85	47.9 (13.3)	85	11.0 (15.6)	DAS28: 7.0 (1.0)		x	78 (31%)†	
Moreland et al, 2012 (TEAR)													
24		244	DAS28 ≤ 3.2	244	74.2	50.7 (13.4)	88.5	3.5 (6.4)	DAS28: 5.8 (1.1)		3.3 (6.5)	138 (56.6%)†	
24		132	MTX+SSZ+ HCQ	132	76.5	48.8 (12.7)	91.7	4.1 (7.2)	DAS28: 5.8 (1.1)		3.3 (6.7)	78 (59.1%)†	
24		255	MTX (+ Step-up ETN)	255	69	48.6 (13.0)	91	2.9 (5.6)	DAS28: 5.8 (1.1)		2.5 (3.5)	135 (52.9%)†	
24		124	MTX (+ Step-up SSZ+HCQ)	124	70.2	49.3 (12.0)	87.1	4.5 (7.6)	DAS28: 5.8 (1.1)		3.6 (7.5)	70 (56.5%)†	
Kavanaugh et al, 2012 (OPTIMA)													
6		515	DAS28 < 3.2	515	74	50.7 (14.5)	87	4.0 (3.6)	DAS28: 6.0 (1.0)		5.4 (9.1)	175 (34%)†	
6		517	DAS28 < 3.2	517	74	50.4 (13.6)	89	4.5 (7.2)	DAS28: 6.0 (1.0)		5.1 (8.4)	88 (17%)†	

‡: Duration given in months, †: mean(sd) unless stated otherwise, x: Not available in this form in article, †: According to the ACR criteria, ∞: a swollen joint count of 0 (range 0-38 joints), and at least 2 of the following factors: tender joint count ≤ 3 (range 0-38 joints), VAS score ≤ 20mm and ESR ≤ 20mm/h, ◊: mean with range, †: median (IQR), ‡: n or (%) calculated using available data, Δ: data extracted from figure, DAS (28): Disease Activity Score (in 28 joints), RF+= positive Rheumatoid factor status, .

FIN-RACO, Finnish Rheumatoid Arthritis Combination Therapy; CAMERA-II, Computer Assisted Management in Early Rheumatoid Arthritis trial-II; GUEPARD, GUérir la PolyArthrite Rhumatoïde Débutante (cure early RA); TEAR, Triple therapy versus Etanercept plus Methotrexate in Early, Aggressive Rheumatoid Arthritis; OPTIMA, Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab

RACo) and the study of Saunders *et al.*) and in 2 studies the effects of additional prednisone to an MTX-based strategy were compared with those of the same strategy but without prednisone: the Computer-Assisted Management in Early RA (CAMERA) trial-II and the study of Montecucco *et al.*

FIN-RACo

This study from 1999 is one of the first known tight control with treat-to-target trials with a target of remission. The trial compared the results of triple combination therapy sulphasalazine (SSZ, 1g/day), MTX (max. dose 10 mg/week) and HCQ (300mg/day), combined with prednisone max. dose 7.5 mg/day) with those of sequential mono therapy: either SSZ (max. dose 3 g/day) or MTX (max. dose 15 mg/week), with or without additional prednisone (max. dose 10 mg/day). The aim was remission, according to the ACR 1987 criteria. At the end of the two year trial period, significantly more patients had met remission in the combination therapy compared to the sequential monotherapy, respectively 36 (37%) *versus* 18 (18%), ($p=0.003$). This was the only study of the 4 initial synthetic DMARD studies in which no biological agent was included as a last strategy step.

Saunders *et al.*

In 2008, the results of step-up therapy (SSZ (40 mg/kg/day), additional MTX (max. dose 25 mg/week) and additional HCQ (400 mg/day), if needed) were compared with those of combination triple therapy from start (same 3 drugs, same max. doses). In both strategy arms, intra-articular and intramuscular triamcinolone injections were allowed with a max. of 80 mg per month. The treatment aim was DAS28 <3.2. There was a not significant trend of a higher percentage of patients with DAS28 remission at 12 months in the step-up *versus* initial combination strategy: 45% *versus* 33%, respectively.

CAMERA trial-II

This second CAMERA trial (2012) used in both arms the same computer-assisted MTX-based (max. dose 30 mg/week) strategy as the tight control arm in the

first CAMERA trial (18). The difference between the 2 arms was the double-blind addition of 10 mg prednisone per day or prednisone-placebo. The target to reach was remission (defined as a swollen joint count of 0 (range 0–38 joints), and at least 2 of the following factors: tender joint count ≤ 3 (range 0–38 joints), VAS global health score ≤ 20 mm (range 0–100, 100 being the worst) and ESR ≤ 20 mm/h). In the MTX and prednisone strategy (84 (72%) had at least 1 period of sustained remission (remission for ≥ 12 weeks) *versus* 73 (61%) in the MTX and placebo strategy, $p=0.089$. The mean (SD) period until first remission was shorter in the MTX and prednisone strategy compared to the MTX and placebo strategy, 6 (5) *versus* 11 (5) months, $p<0.001$.

Montecucco *et al.*

In this 1-year study (epub ahead of print) the patients were treated according to a MTX-based (max. dose 25mg/week), step-up protocol targeted to DAS low disease activity. One treatment arm received an additional low-dose prednisone (max dose 12.5 mg/d/2weeks, tapered to 6.25 mg/d during the rest of the study). The rate of patients achieving remission was significantly higher in the MTX and prednisone strategy arm: 43 of 96 patients (45%) *versus* 25 of 90 patients (28%), $p=0.02$.

Biological DMARD studies

GUEPARD

This trial published in 2009 had two treatment arms: an initial MTX-based (max. dose 20mg/week) strategy and an initial MTX+adalimumab (max. dose 20mg/week and 40 mg/2week respectively) strategy, both aimed at low disease activity (DAS28 <3.2). Prednisone therapy was allowed, if initiated before inclusion, max. dose 10 mg/d. At week 12, there was a significant difference in remission rates (DAS28 <2.6) between the two groups in favour of MTX + adalimumab compared to initial MTX-based strategy (36% *vs.* 13%, $p=0.022$). After 12 weeks, if needed, patients in the initial MTX-based strategy additionally could get an anti tumour necrosis factor (anti-TNF) drug. After 52 weeks, there was no longer a

statistically significant difference found in remission rates (39% *vs.* 59% respectively, $p=0.15$) (see Table II).

IMAGE

In the IMAGE trial (2011) patients were assigned randomly into 3 groups: MTX with placebo-rituximab, MTX with rituximab (2x500 mg) or MTX with rituximab (2x1000 mg). Prednisolone therapy was allowed, if stable dose, max. 10 mg/d. The treatment goal was remission (DAS28 <2.6); patients not meeting this goal were retreated from week 24 with rituximab courses. Remission rates at week 52 were 13%, 25% and 31% for MTX and placebo-rituximab, MTX with lower dose rituximab and MTX with higher dose rituximab, respectively; MTX and placebo-rituximab, *versus* MTX with lower dose rituximab, $p<0.001$; MTX and placebo-rituximab *versus* MTX with higher dose rituximab, $p<0.0001$.

TEAR

The Triple therapy *versus* Etanercept plus MTX in Early, Aggressive RA trial (TEAR, epub ahead of print) included 4 arms: initial etanercept (50mg/week) +MTX (max. dose 20mg/week); initial triple therapy (MTX (max. dose 20mg/week)+SSZ (max. dose 2g/day)+HCQ (400mg/day); and MTX (with as step-up additional etanercept if the target was not reached after 24 wks); and MTX (with a step-up to triple therapy if the target was not reached after 24 wks, being DAS28 <3.2 (low disease activity). Prednisone therapy was allowed, if initiated at least 2 weeks before screening, max. dose 10 mg/d. At some point during the study of 102 weeks, about 56% of all participants were in a state of remission: 56.6%, 59.1%, 52.9% and 56.5%, respectively; no differences were seen between the 4 treatment arms.

OPTIMA

The 26-week trial OPTIMA (Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab) (2012) compared the effects of two treatment arms; an MTX (max. dose 20 mg/week) + adalimumab (40 mg/2week) strategy and an MTX (max. dose 20mg/week)

+ adalimumab placebo strategy. Patients were excluded from the study if receiving intra-articular or parenteral glucocorticoids in the 4 weeks preceding screening, but concomitant oral glucocorticoid use was allowed (max. dose not mentioned), which was the case at baseline in 41 and 46% of the patients in the strategy arms, respectively. The treatment aim was low disease activity (DAS28 with CRP <3.2). At week 26, remission rates (DAS28 <2.6) were 34% in the initial MTX + adalimumab strategy *versus* 17% in the initial MTX + adalimumab placebo strategy, $p < 0.001$.

Discussion

The 13 studies found through our search showed heterogeneity, not only in initial disease activity, study duration, patient characteristics, treatment strategies (drugs and schemes), frequency of visits (*e.g.* 1 *vs.* 3 monthly visits), but also in treatment targets (low disease activity and remission), definitions of the targets (*e.g.* for remission DAS28 based or the ACR 1987 criteria) and required duration, for instance at one visit or for ≥ 12 weeks, and reports on the outcome (remission rates at a specific point in time or rates during the study). These differences likely influence remission rates, and therefore might limit comparisons of remission rates between studies (Table II).

The meta-analysis of the 4 tight control *versus* usual care studies indicates that applying a treat to (any) target strategy increases the remission rates of the participating early RA patients, with differences that are not only statistically significant, but also clinically relevant. This conclusion appears quite robust, as all results point in the same direction, despite heterogeneity of the trials, which may compromise the procedure and reliability of the pooled estimate. The target to target trial shows that any of the RA core data set measures, and possibly a biomarker can be used as a target in a group to document that remission rates can be very high, with a very intensive treatment strategy. However, a recognised index would appear required to monitor individual patients; for instance a low level of the

ESR as treatment target would not suffice (36).

The “tight control *versus* tight control” trials indicate that, in general, the more intensive the strategy, the more strict the treatment aim and the more tight the tight control, the better the remission rates. The scope of this paper was remission only, but other reviews found similar favourable results regarding tight control strategies also on other outcomes, like disease activity (15, 22). Therefore, in agreement with recent recommendations and position papers (20, 37), there seems no doubt about effectiveness and feasibility of tight control with treat-to-target, at least in early RA. However, no single scheme has generally been accepted in daily practice. The initial strategy should at least include MTX, the anchor drug (10, 38, 39). Given the high costs and the risks of biological agents and the results of the tight control *versus* tight control trials, it does not appear obligatory to initiate a biological DMARD to see excellent results. Furthermore, based on the results, one could opt to include also a low to medium dose glucocorticoid in the initial strategy. In many trial reporting allegedly on the effect of (biological) DMARDs in fact report on the combined effects with glucocorticoids.

A consensus does not exist on which instrument to use for the treatment target remission, although recently it was concluded that DAS28, the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) would be proper instruments.(40) Seven of all 13 selected studies in our review used a DAS28-target of low disease activity or remission. But the DAS28 as a measuring tool of disease activity as basis of a treat-to-target strategy has limitations. Simple calculation is not possible, and the score gives no clinical insight into individual components, with several disease states possible for the same score. The fact that ankles and feet are not being assessed is another weakness of this instrument (and of CDAI and SDAI). Although on the group level in clinical trials this latter point seems to be no problems, on the individual patient's level it potentially

leads to misclassification of patients' disease activity level and expected future joint damage (41, 42). Furthermore, a recently published study showed that DAS28 is influenced by coexistence of tender points, even in the non-fibromyalgia range, due to the strong association of tender points with the less objective DAS28 components VAS general health and tender joint count, which has twice the weight of swollen joint count in DAS28 (43). Several studies have reported high swollen joint counts, radiological damage and other signs of active disease in patients in DAS28-defined remission (42, 44-46). Therefore, looking at the DAS28-score is not enough and a thorough look at the individual components of the DAS28 and a full clinical evaluation (including tender points) are necessary, when applying DAS28-guided individual treatment strategies (43). The same would apply other composite index scores. In the 2011 Boolean-based remission criteria (19), there can be only one swollen joint in the remission state; this is a clear advantage to the remission definition of DAS28, at which patients can have several swollen joints (42).

There are some limitations to our study. As our topic was outcome in terms of remission, tight control with treat-to-target studies that did not report on this specific outcome or did not provide numeric results were not included, as were studies which did not specify clearly the target of treatment. For example, rescue medication following non-response was not regarded as treat-to-target. Also, trials without a comparison of a tight control arm with a control arm or second tight control arm were excluded. The screening of the titles and abstracts was performed by one person; however, there was full consensus among all authors on the included studies.

More research is needed to elucidate which target is optimal for each individual patient, with which kind of tight control strategy; the strategy seems to be more important than the agents used (47). Tight control with treat-to-target should also be studied in patients with longstanding RA, with different levels of disease activity, and with different preset targets and with different medical

regimens. It can be hypothesised that in longstanding RA remission is not always possible and that low disease activity would be a more realistic target. Furthermore, the outcome of the same level of remission might be different at different treatment regimens, as it has been shown that in patients in remission on conventional DMARDs, radiographic damage may slowly progress, in contrast to in patients in remission on anti-TNF. However, research has to establish how clinically relevant this is.

Conclusion

Tight control with treat-to-target results in higher percentages of remission in patients with RA. This is a feasible and rewarding principle in clinical trials and daily practice. Nonetheless, more research is needed to optimise the strategies for specific individual patients.

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