Evidence for treating rheumatoid arthritis to target: results of a systematic literature search

Monika Schoels,[1] Rachel Knevel,[2] Daniel Aletaha,[3] Johannes W J Bijlsma,[4] Ferdinand C Breedveld,[2] Dimitrios T Boumpas,[5] Gerd Burmester,[6] Bernard Combe,[7] Maurizio Cutolo,[8] Maxime Dougados,[9] Paul Emery,[10] Desirée van der Heijde,[2] Tom W J Huizinga,[2] Joachim Kalden,[11] Edward C Keystone,[12] Tore K Kvien,[13] Emilio Martin-Mola,[14] Carlomaurizio Montecucco,[15] Maarten de Wit,[16] Josef S Smolen[1,3]

ABSTRACT

Objectives To summarise existing evidence on a target oriented approach for rheumatoid arthritis (RA) treatment.
Methods We conducted a systematic literature search including all clinical trials testing clinical, functional, or structural values of a targeted treatment approach. Our search covered Medline, Embase and Cochrane databases until December 2008 and also conference abstracts (2007, 2008).
Results The primary search yielded 5881 citations; after the selection process, 76 papers underwent detailed review. Of these, only seven strategic clinical trials were extracted: four studies randomised patients to routine or targeted treatment, two compared two different randomised targets and one compared targeted treatment to a historical control group. Five trials dealt with early RA patients. All identified studies showed significantly better clinical outcomes of targeted approaches than routine approaches. Disability was reported in two studies with no difference between groups. Four studies compared radiographic outcomes, two showing significant benefit of the targeted approach.
Conclusion Only few studies employed randomised controlled settings to test the value of treatment to a specific target. However, they provided unanimous evidence for benefits of targeted approaches. Nevertheless, more data on radiographic and functional outcomes and on patients with established RA are needed.

INTRODUCTION

Many new treatment options make unprecedented outcomes achievable in rheumatoid arthritis (RA).[1 2] In parallel, insights on the importance of early effective therapy[3 4] and implications of disease activity on function[5 6] and joint damage[6–8] led to paradigmatic changes in therapeutic approaches, such as frequent evaluations of disease activity to allow for timely changes of therapies.[9–13] Additionally, validated composite disease activity measures have made disease activity assessment easy.[14 15] Nevertheless, heterogeneity of therapeutic aims and patient expectations[16] characterise daily practice of RA treatment.[17] All this suggests a need to provide rheumatologists and patients with pertinent information on therapeutic targets and means to achieve them.[18 19]

Strict definitions of treatment targets intend to facilitate strategic acting in routine care and require physicians and patients to discuss and adopt therapeutic changes within distinct time frames, ideally following therapeutic algorithms. This approach has been utilised in many diseases, like diabetes,[20 21] hypertension[22–24] or hyperlipidaemia.[25] However, this policy needs to be evidence based to the best possible extent.

Here we report on a systematic review of available evidence regarding the effects of treating RA strategically according to defined outcome targets.

METHODS

Shaping the systematic literature review

As a first step, the international steering committee of the Treat-To-Target (T2T) project, comprising a group of expert rheumatologists and a patient (MdW), designed a literature search that aimed at 'treating to target'-strategy trials in RA. The search was then performed by a project fellow (MS), a control search by a second fellow (RK) and by two mentors (DA, DvdH).

The following definitions were made: (1) *strategy trial* – clinical trial of any RA drug treatment, in which a clear outcome target was the primary end point and therapeutic consequences of failing to reach the target were predefined; (2) *targets* – a target could be formulated by clinical, serological, patient-reported, functional, or radiographic variables; individual measures (eg, joint counts or acute phase reactants), composite scores (eg, disease activity score or simplified disease activity index), or response criteria (eg, those defined by the American College of Rheumatology (ACR) or the European League Against Rheumatism) were considered alike; (3) *outcomes* – Clinical, functional, serological and/or radiographic changes, as defined in the respective trials, were compared between treatment groups.

Implementation of the systematic literature review

We searched Medline, Embase and Cochrane databases from their inception until December 2008. Additionally, ACR and European League Against Rheumatism (EULAR) abstracts of 2007 and 2008 were screened. The search was limited to humans, adults and the English language. Detailed inclusion and exclusion criteria and the list of search strings are shown in supplementary tables (tables S1 and S2). We did not exclude studies based on quality.

From the identified strategy trials, data were extracted concerning definitions of targets and success rates of applied strategies.

RESULTS

We retrieved 5881 citations for further evaluation (figure 1). Title and abstract screening according to our selection criteria (supplementary table S1) left 76 papers for detailed review. Among those, 17 trials published in full and 2 abstracts addressed direct assessment of treating to target. By hand search of references, we identified three additional papers; further, one full paper and one abstract were included based on expert opinion. This gave a total of 24 publications for this review (figure 1), of which only 7 were strategic trials: 4 trials randomised patients to routine or targeted treatment,[26–29] two compared different randomised targets[30 31] and one compared targeted treatment to historical control.[32]

### Randomised strategic trials comparing targeted versus routine care

Only four trials had randomised patients to a targeted treatment algorithm versus routine care. In Tight Control of Rheumatoid Arthritis (TICORA),[26] treatment of early RA aimed at low disease activity (LDA) by Disease Activity Score (DAS), comparing DAS-driven treatment adaptations upon monthly assessments with 3-monthly routine care. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA)[27] aimed at remission of early RA, comparing monthly treatment adaptation by computerised decision if >20% (50%) reduction of several variables

was not attained with 3-monthly routine care. A cluster randomised trial by Fransen *et al*[28] compared the proportion of patients reaching LDA at the end of follow-up and the number of disease-modifying antirheumatic drug (DMARD) changes during 24 weeks (co-primary end points) in outpatient centres using systematic, DAS28-steered treatment protocols with centres providing routine care. The treatment decision in the DAS28-driven group depended on a threshold of 3.2, indicating LDA. Finally, Symmons *et al*[29] tested the effect of aggressive versus symptomatic therapy on physical outcome (*Health Assessment Questionnaire* (HAQ)) in established RA. Decisions for treatment adaption were driven by joint count- and C reactive protein (CRP) thresholds. Designs of these trials are depicted in figure 2; baseline characteristics are tabulated in supplementary table S3.

Characteristics of the core trials, including treatment targets and visit intervals, as well as clinical, functional and radiographic outcomes are summarised in table 1 and will be detailed below.

Significantly greater DAS reduction and higher likeliness to achieve remission following intensive disease management was evident in all four trials. In TICORA,[26] the primary end point, EULAR good response, as well as DAS remission were significantly more frequent upon intensive than routine care. CAMERA[27] showed significant benefits of targeted treatment regarding its primary end point, remission for 3 months.

Papers retrieved and selection process
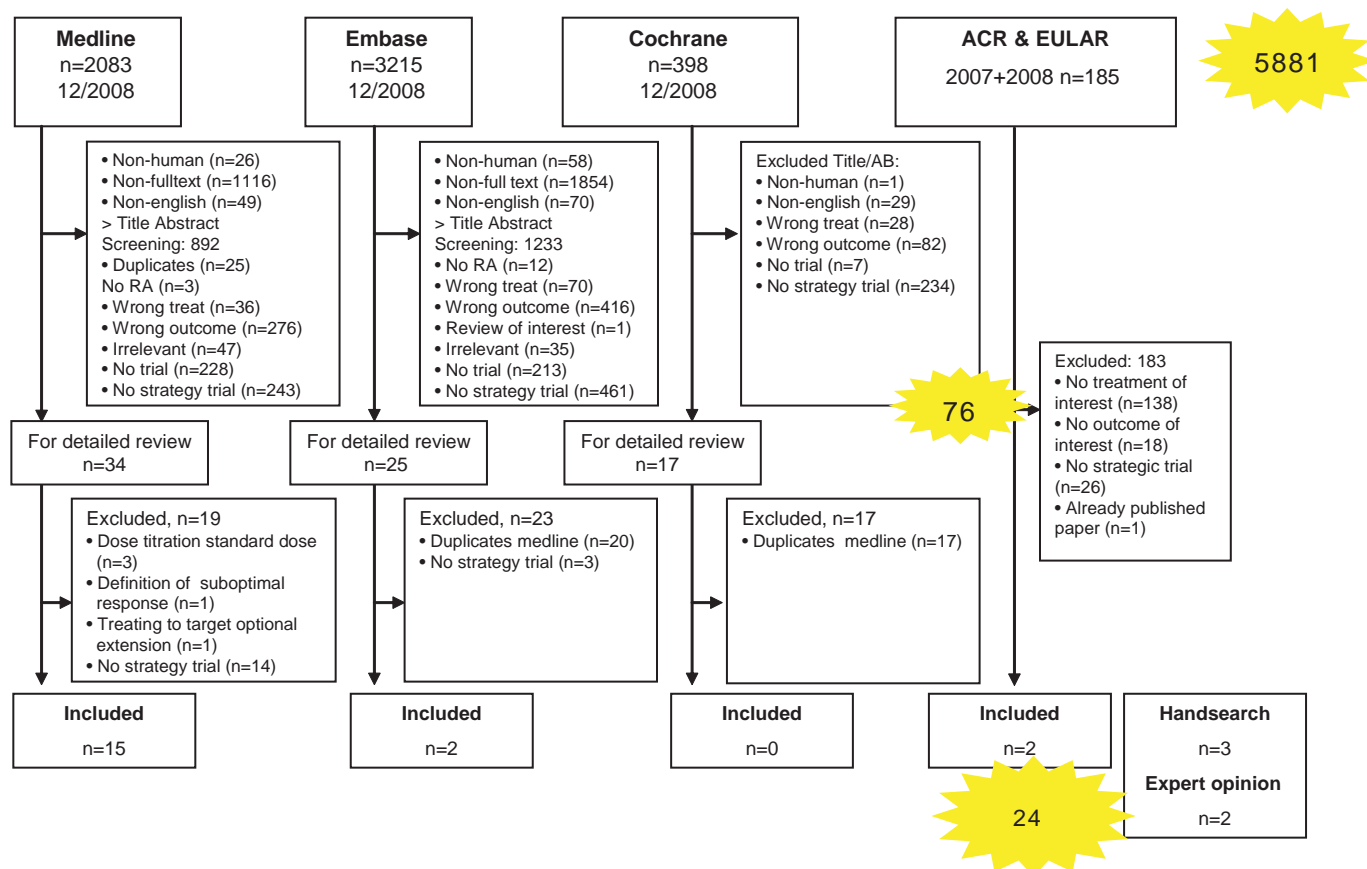
Figure 1 Flow chart of the systematic literature search. Illustrated are the results of the initial search and the selection process of abstract screening, full text review and hand search. AB, abstract; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis.
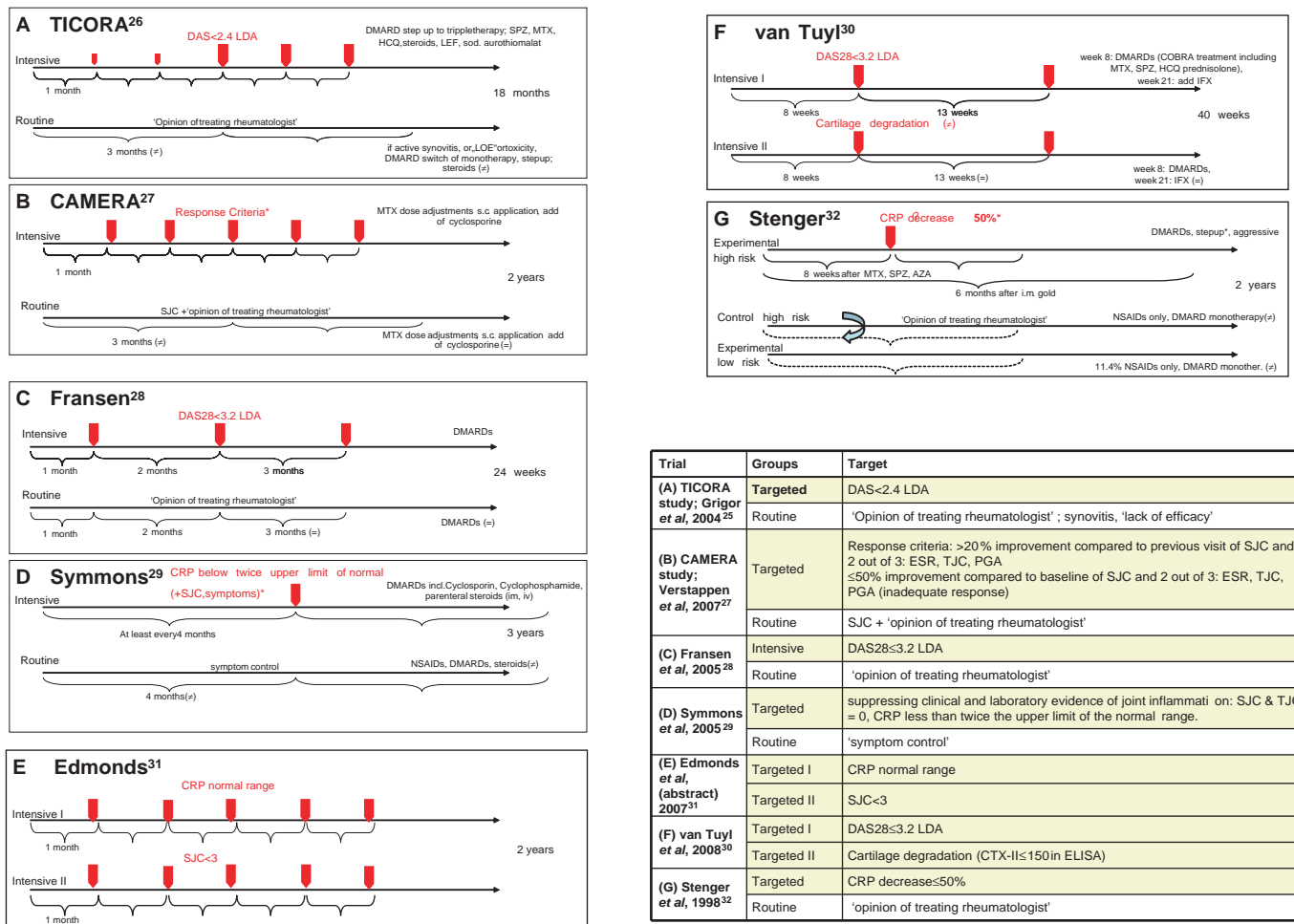
Figure 2 Design of the seven core clinical trials. (A) TICORA study (Grigor *et al* 2004)[26]; (B) CAMERA study (Verstappen *et al* 2007)[27]; (C) Fransen *et al* 2005[28]; (D) Symmons *et al* 2005[29]; (E) Edmonds *et al* 2007 (abstract)[31]; (F) van Tuyl *et al* 2008[30]; and (G) Stenger *et al* 1998.[32] Intensive and routine treatment arms are displayed, red arrows mark the scheduled intervals for target assessment. Table 1 specifies the targets of trials A–G. AZA, Azathioprine; CAMERA, Computer Assisted Management in Early Rheumatoid Arthritis; CRP, C reactive protein; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; *IFX,* ifosfamide; LDA, low disease activity; LEF, leflunomide; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; sc, subcutaneous; SJC, swollen joint count; sod., sodium; SPZ, sulfinpyrazone; TICORA, tight control of rheumatoid arthritis.

Fransen *et al*[28] showed that both the proportion of patients reaching LDA and frequency of DMARD changes during follow-up favoured a DAS28-driven DMARD strategy. Symmons *et al*[29] found significant differences in clinical outcomes in the evaluator global assessment, while other measures, including joint counts, *erythrocyte sedimentation rate* and patient global visual analogue scale, were not significantly different.

Physical function was the primary outcome in the trial by Symmons *et al*[29]; the intensive group failed to show significant differences compared to routine care regarding HAQ changes. Also CAMERA[27] did not show significant differences in functional outcomes.

Grigor *et al*[26] reported significantly less progression of radiographic changes[26] in the intensive treatment group. In contrast, no significant differences in annual radiographic progression were described in the CAMERA study.[27] Two of the studies did not report radiographic data[28][29] (table 1, figure 2).

Randomised strategic trials comparing two targeted strategies

van Tuyl *et al*[30] presented a study protocol randomising early RA patients to different targeted and tight monitoring schedules: one group aiming at DAS28 remission, the other at suppressing cartilage degradation as assessed by measuring urinary C-terminal cross-linking of type II collagen. Results did not differ significantly between the two groups with similar overall remission rates in both arms (figure 2, table 1). However, as the authors concede, this was a very small pilot study. Similarly, Edmonds *et al*[31] reported in abstract form on steering at normal CRP levels versus a joint count targeted approach. Their results suggested that targeting CRP provides better interference with radiographic damage (table 1, figure 2).

Non-randomised cohort studies comparing two targeted strategies

Stenger *et al*[32] compared an aggressive treatment protocol that stipulated change of DMARD therapy if after 8 weeks CRP decrease was less than 50% in patients with a high risk of developing aggressive disease; the comparator arm on regular therapy was a retrospectively assessed group of high risk patients. After 2 years, the area under the curve for CRP was significantly lower in the intensive treatment group than in the historic control. While no functional data were provided,

Table 1 Targets and visit intervals (left columns) and clinical, functional and structural outcomes (right columns) of core trials

Group	Treatment-decision driving target	Interval of controls	N	Outcomes/final treatment target p Values indicate differences of outcomes between the targeted (T) and the routine group (R)
(A) TICORA[26]				
Targeted group (T)	DAS<2.4 LDA	1 Month	55	Clinical outcome at 18 months
Routine control group (R)	Opinion of treating rheumatologist	1 Month	55	EULAR good response (primary outcome): OR* 5.8 (2.4 to 13.9); 82% targeted (T) versus 44% routine (R); p<0.0001 EULAR remission: OR* 9.7 (3.9 to 23.9), 64% T versus 16% R; p<0.0001 ACR70: OR* 11 (4.5 to 27), 71% T versus 18% R; p<0.0001 Functional outcome at 18 months HAQ change: −0.97±0.8 T versus −0.47±0.9 R; p=0.0025 Radiographic outcome at 18 months; median (IQR) Progression of erosion score: 0.5 (0–3.357) T versus 3 (0.5–8.5) R; p=0.002 Change in TSS: 4.5 (1–9.875) T versus 8.5 (2.0–15.5) R; p=0.02 Change in JSN: 3.25 (1.125–7.5) T versus 4.5 (1.5–9.0) R; p=0.331
(B) CAMERA[27]				
Targeted group (T)	Improvement of number of swollen joints: >20% compared to previous visit/50% compared to baseline Improvement in 2 out of 3 criteria: ESR, TJC, PGA >20% compared to previous visit	1 Month	151	Clinical outcome at 1 year† and at 2 years‡ Number of patients in remission for 3 months (primary outcome): 35% T versus 14% R; p<0.001† 50% T versus 37% R; p<0.029‡ Mean (95% CI) time until remission (months): 10.4 (9.1 to 11.7) T versus 14.3 (12.6 to 16.1) R; p<0.001 Duration (months) of all periods of remission: 11.6 (10.1–13.1) T versus 9.1 (7.6–10.6) R; p=0.025 ACR50: 58% T versus 43% R; p<0.01† 46% T versus 45% R; p=NS‡ Functional outcome at 1 year† and at 2 years‡
Routine control group (R)	Decrease of SJC, if number of SJ unchanged, assessors' judgement, looking at TJC, ESR, PGA	3 Months	148	HAQ mean±SD-change: −0.44±0.59 T versus −0.39±0.66 R; p=NS†; −0.41±0.64 T versus −0.42±0.76 R; p=NS‡ Radiographic outcome at 2 years Annual radiographic progression: median (IQR) change (units/year): 0 (0–2.0) T versus 0 (0–2.5) R; p=0.9
(C) Fransen et al[28]				
Targeted group (T)	DAS28<3.2 LDA	1 Month starting, then 2 months, then 3 months (both groups)	205	Clinical outcome at 24 weeks
Routine control group (R)	Opinion of treating rheumatologist		179	Patients in DAS28/LDA: 31% T versus 16% R; p=0.028 Mean±SD changes in DAS28: −0.4±1.0 T versus −0.14±1.2 R; p=0.36 DMARD changes: 20% T versus 9% R; p=0.013 Functional data: NR (NS) Radiographic: NR
(D) Symmons et al[29]				
Targeted group (T)	CRP<twice the upper limit of normal range TJC=0 and SJC=0 Symptom control	At least every 4 months (both groups)	233	Clinical outcome at 3 years: (adjusted mean difference (95% CI)) EGA: 3.76 (0.03–7.52); p=0.045 OSRA: 0.41 (0.01–0.71); p=0.010 SJC, TJC, ESR and PGA: p=NS Functional outcome at 3 years:
Routine control group (R)	Symptom control		233	HAQ (primary outcome): sign deterioration in both arms; mean difference between T and R: p=0.82 Radiographic outcome at 3 years: Total Larsen score: deterioration in both arms of (significant in routine group (p=0.035) but not in the targeted group (p=0.093); difference T versus R: p=NS Eroded joint count: increased slightly in both treatment arms, difference T versus R: p=NS
(E) Edmonds et al[31] (abstract)				
Targeted group I	CRP normal range	1 Month (both groups)	82	Clinical outcome at 2 years:
Targeted group II	SJC <3		85	Target 'SJC<3' was met in 29%, target 'normal CRP' in 41% of visits (p: NA) Functional outcomes: NR Radiographic outcomes at 2 years
Routine control group	–		82	Radiographic progression scores NS between study arms but: erosion progression 0.2±1.0 versus 1.0±2.5 (p<0.03), JSN 0.3±1.3 versus 1.2±2.6 (p<0.03), total score 0.5±1.6 versus 2.2±4.2 (p<0.005) if AUC-CRP target achieved, as compared to not achieved (not the case for SJC-target) (p NA).
(F) van Tuyl et al[30]				
Targeted group I	DAS28<3.2 LDA	8 Weeks, then 13 weeks (both groups)	11	Clinical outcomes at 40 weeks
Targeted group II	Cartilage degradation: CTX-II excretion ≤150 nmol/mmol creatinine		10	Remission rates: in both targeted arms: 90% (after 8 and 21 weeks: 57% and 76%) ACR20/50/70/90: 100%/95%/71%/43% Functional outcomes: NR Radiographic outcomes: NR
(G) Stenger et al[32]				
Targeted group (T)	CRP decrease >50%	8 Weeks (both groups)	139	Clinical outcomes at 1 year† and at 2 years‡ AUC-CRP (mg (week/l; median (range)): 1136 (144–3563) T versus 1836 (26–8051) R; p=0.02†; 1963 (212–8515) T versus 3025 (46–15632) R; p=0.002‡ Functional outcomes: NR Radiographic outcomes at 1 year† and at 2 years‡
Routine control group (R)	Opinion of treating rheumatologist		89	Median (range) progression rate: 17.0 (0–74) T versus 17.5 (0–130) R; p=0.22† 26.0 (0–100) T versus 35 (1–188) R; p=0.03‡

*OR (95% CI); †outcome at 1 year; ‡outcome at 2 years.
AUC, area under the curve; ACR, American College of Rheumatology; CAMERA, Computer Assisted Management in Early Rheumatoid Arthritis; CRP, C reactive protein; CTX-II, C-terminal cross-linking of type II collagen; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drugs; EGA, evaluator global assessment; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; JSN, joint space narrowing; LDA, low disease activity; NR, not reported; OSRA, overall status in rheumatoid arthritis; PGA, physician's global assessment; SJC, swollen joint count; TICORA, tight control of rheumatoid arthritis; TJC, total joint count; TSS, total Sharp score.

the reported radiographic progression favoured the intensive treatment (table 1).

Additional studies

A number of studies used the treat to target concept, but, in contrast to the mentioned papers, did not have a non-targeted control arm, since all arms pursued the same target with different treatment sequences (supplementary table S4). Likewise, several trials compared step-up with combination regimes, dose titration of agents or different therapies to reach a defined target without directly addressing the efficacy of treating to target. A description of these studies can be found in the supplementary material accompanying this manuscript.

DISCUSSION

Our review revealed that only few controlled studies investigated the value of strategic treatment schedules. Importantly, study designs and evaluated targets were very heterogeneous; for example, the Edmonds and van Tuyl studies are inherently different in design as compared to the others in that their approach compares two T2T approaches while the others compare a T2T approach with the routine approach. Nevertheless, all studies investigating early disease showed significantly better clinical outcomes of the targeted approach. Functional outcomes, reported in two trials, failed to show significant gains.[27 29] Four studies compared radiographic outcomes,[26 27 29 32] of which two showed a significant benefit of the targeted therapy.[26]

Five[26–28 30 32] studies investigated early disease (using different definitions of 'early' – see supplementary table S3). Only one trial[29] focused explicitly on late disease (duration: >5 years) and found no advantage of tight control on functional outcomes. Thus, patients with established RA seem to be underinvestigated regarding the value of treating to a target. Since longer disease duration impairs treatment outcomes,[33] extending results from early RA to the general patient population could be misleading. Furthermore, just focusing on HAQ might also be misguiding, since with increasing disease duration responsiveness of physical function to therapeutic interventions decreases (even to placebo levels).[34]

Utilised targets showed considerable heterogeneity (table 1, figure 2). Among the randomised trials comparing targeted versus routine approaches, three out of four employed state targets,[26 28 29] an approach that has been favoured as being more appropriate than assessing changes from baseline.[35] Only in CAMERA,[27] the target was formulated as reaching defined improvement criteria. Also, visit intervals were noticeably heterogenous: clinical assessments were performed from monthly[26–28 31] to every 4[29 36] months. Two trials randomised patients to different visit intervals.[26 37] In both, patients assigned to intensive strategy were seen monthly, those in routine care every 3 months.

In conclusion, only few studies have used a randomised approach to test the value of treatment to a specific target. However, all of them provided compelling evidence of clinical benefits of such an approach. However, more data are needed concerning radiographic and functional outcomes and patients with longstanding RA have not been sufficiently investigated.

Author affiliations

[1]2nd Department of Internal Medicine, Centre for Rheumatic Diseases, Hietzing Hospital, Vienna, Austria
[2]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[3]Department of Internal Medicine 3, Division of Rheumatology, Medical University of Vienna, Vienna, Austria
[4]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands
[5]Department of Internal Medicine, University of Crete Medical School, Heraklion, Greece
[6]Department of Rheumatology and Clinical Immunology, Humboldt University, Charité Hospital, Berlin, Germany
[7]Service d'Immuno-Rhumatologie, Montpellier University, Lapeyronie Hospital, Montpellier, France
[8]Research Laboratory and Academic Clinical Unit of Rheumatology, Department of Internal Medicine, University of Genova, Genova, Italy
[9]Department of Rheumatology B, René Descartes University, Cochin Hospital, Paris, France
[10]Academic Unit of Musculoskeletal Disease, University of Leeds, Leeds, UK
[11]Department of Internal Medicine III, Institute for Clinical Immunology at the Friedrich-Alexander University, Erlangen, Germany
[12]Rebecca MacDonald Centre for Arthritis and Autoimmune Disease, Mount Sinai Hospital, Toronto, Canada
[13]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[14]La Paz Hospital, Madrid, Spain
[15]Department of Rheumatology, University of Pavia, IRCCS Policlinico S. Matteo, Pavia, Italy
[16]EULAR Standing Committee of People with Arthritis/Rheumatism in Europe, Zurich, Switzerland
MS and RK Contributed equally to this study.

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