

Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis

R Knevel,¹ M Schoels,² T W J Huizinga,¹ D Aletaha,³ G R Burmester,⁴ B Combe,⁵ R B Landewé,⁶ J S Smolen,³ T Sokka,⁷ D M F M van der Heijde¹

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¹Department of Rheumatology, Leiden University Medical Centre, Leiden, The Netherlands;

²2nd Department of Medicine, Centre for Rheumatic Diseases, Hietzing Hospital, Vienna, Austria;

³Division of Rheumatology, Department of Internal Medicine 3, Medical University of Vienna, Austria;

⁴Humboldt University, Department of Rheumatology and Clinical Immunology, Charite Hospital, Berlin, Germany;

⁵Service d'Immuno-Rhumatologie, Montpellier I University, Lapeyronie Hospital, Montpellier, France;

⁶Department of Rheumatology, University Hospital Maastricht, The Netherlands;

⁷Department of Rheumatology, Jyväskylä Central Hospital, Jyväskylä, Finland

Correspondence to

Ms Rachel Knevel, Department of Rheumatology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, Albinusdreef 2, The Netherlands; r.knevel@lumc.nl

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ABSTRACT

Objectives To perform a systematic literature review of effective strategies for the treatment of rheumatoid arthritis (RA).

Methods As part of a European League Against Rheumatism (EULAR) Task Force investigation, a literature search was carried out from January 1962 until February 2009 in PubMed/Ovid Embase/Cochrane and EULAR/American College of Rheumatism (ACR) abstracts (2007/2008) for studies with a treatment strategy adjusted to target a predefined outcome. Articles were systematically reviewed and clinical outcome, physical function and structural damage were compared between intensive and less intensive strategies. The results were evaluated by an expert panel to consolidate evidence on treatment strategies in RA.

Results The search identified two different kinds of treatment strategies: strategies in which the reason for treatment adjustment differed between the study arms ('steering strategies', n=13) and strategies in which all trial arms used the same clinical outcome to adjust treatment with different pharmacological treatments ('medication strategies', n=7). Both intensive steering strategies and intensive medication strategies resulted in better outcome than less intensive strategies in patients with early active RA.

Conclusion Intensive steering strategies and intensive medication strategies produce a better clinical outcome, improved physical function and less structural damage than conventional steering or treatment. Proof in favour of any steering method is lacking and the best medication sequence is still not known.

INTRODUCTION

The treatment of rheumatoid arthritis (RA) has undergone tremendous changes. Most clinical trials compare medical treatment according to rigid protocols. These trials are useful to assess efficacy of drugs, but do not give information on the order in which treatment should be given, nor when and how treatment regimens should be adjusted. Studies examining the effect of treatment strategies were designed.^{1–3} Our systematic literature search focused on these strategic trials. The aim of the search was to define what

medication sequence or adjustment methods should be started or modified and how patients should be monitored to obtain low disease activity or remission, good physical function and low progression of joint damage most effectively in patients with RA.

METHODS

Systematic literature search

An international steering committee consisting of 29 experts defined the scope of an extensive literature search in order to give recommendations for the treatment of RA.⁴ A subgroup of this steering committee (see author list) focused on strategy trials.

In collaboration with a librarian the project fellow (RK) searched Pubmed, Ovid Embase and Cochrane from January 1962 until February 2009 and in European League Against Rheumatism (EULAR) and American College of Rheumatism (ACR) abstracts of 2007–8. The search was performed using an extended combination of search strings (see online supplementary table 1). Inclusion criteria were RA, adults and medical treatment. Publications without an abstract or in a language other than English were excluded. Trials were included when they met the following definition of strategy:

A strategic trial is a clinical trial of any treatment of RA in which at least one arm consists of medication adjustment according to protocol, based on clinical outcomes aiming at a specific target.

Relevant articles were selected in a three-step approach. First, titles and abstracts of identified references were screened to exclude articles that did not deal with the topic of interest. Second, the full paper of selected articles was reviewed. Lastly, references of the finally selected articles and relevant reviews were hand searched for additional relevant publications. EULAR and ACR abstracts were searched by hand and with a simplified search string.

Data extraction

A standard form was used to extract study design and outcome data on three domains: clinical

Table 1 Baseline characteristics of patients and treatment strategies in steering strategy trials

Study	Arms (n)	Adjustment if	Frequent visits	Median (IQR)/mean age ± SD at inclusion	Women (%)	Median (IQR)/mean ± SD disease duration since diagnosis	RF+ (%)
TICORA ⁵	Intensive (55)	DAS > 2, 4	Monthly	51 ± 15	71	19 ± 16 months	75
	Conventional (55)	Judgment of rheumatologist	3-Monthly	54 ± 11	69	20 ± 16 months	73
CAMERA ⁶	I (151)	No SJC + 2 of: ≤ 3 TJC, ≤ 20 ESR, ≤ 20 VAS _{pt global}	Monthly	54 ± 14	69	< 1 year	66
	Conventional (148)	Judgment of rheumatologist	3-Monthly	53 ± 15	66	< 1 year	62
Fransen <i>et al</i> ⁷	DAS guided (79)	DAS ₂₈ ≥ 3.2	Monthly	57 ± 11	67	6 (3–14) years	84
	Conventional (75)	Judgment of rheumatologist	N/A	57 ± 10	62	4 (2–10) years	87
BROSG ⁸	Aggressive care by rheumatologist (233)	CRP > 2 × normal	4-Monthly	60.4 ± 11.1	68	12.6 ± 6.7 years	N/A
	Symptomatic care (233)	Based on nurse interview	4-Monthly	60.8 ± 11.3	68	12.5 ± 6.8 years	N/A
van Hulst <i>et al</i> ¹⁰	DAS steered (144)	DAS ₂₈ > 3.2	3-Monthly	58	60	9 years	75
	Conventional (104)	Judgment of rheumatologist	3-Monthly	60	65	6 years	79
Allaert <i>et al</i> ¹¹	DAS steered (arm 1 and 2 BeSt) (247)	DAS > 2, 4	3-Monthly	54 ± 13 and 54 ± 13	68 and 71	2 (1–5) and 2 (1–4) weeks	65
	Conventional (N/A)	Judgment of rheumatologist	N/A	N/A	N/A	N/A	N/A
Stenger <i>et al</i> ¹²	Intensive high risk (78)	< 50% CRP decrease	N/A	58 (20–72)	65	6.5 ± 3, 2 months	91
	Intensive low risk (61)			49 (18–72)	75	7.0 ± 3.4	69
	Routine care high risk (42)	Judgment of rheumatologist		54 (24–72)	67	7.5 ± 3.3	100
	Routine care low risk (47)			46 (17–70)	68	7.0 ± 3.6	79
van der Woude <i>et al</i> ¹³	DAS steered (all arms BeSt) (508)	DAS > 2, 4	3-Monthly	N/A	N/A	Longer	N/A
	Conventional (410)	Judgment of rheumatologist	–			Shorter	
van Tuyl <i>et al</i> ¹⁴	DAS steered (11)	If goal not met	2-Monthly	52 ± 14	73	2 ± 2 months	73
	CTX-II steered (10)			50 ± 13	60	4 ± 6 months	78
Edmonds <i>et al</i> ¹⁵	SJC steered (85)	SJC ≥ 3	N/A	56 ± 12 years	N/A	7.2 ± 6.6 months	N/A
	CRP steered (82)	Elevated CRP					
Brenol <i>et al</i> ³¹	Conventional (82)	Judgment of rheumatologist					
	Intensive (241)	DAS ₂₈ < 2.6 or < 3.2 CDAI < 2.8 or < 10	Minimum 4 monthly	54.9 ± 11.89	85	10 years	N/A
Proudman <i>et al</i> ³²	Intensive (61)	Based on SJC ESR/CRP; TJC fatigue	N/A	56 ± 14	76	< 24 weeks	61
Kuper <i>et al</i> ³³	Intensive (190)	DAS ₂₈ < 2.6	N/A	57.3 ± 13.7	64	16 (1–52) weeks	53

BROSG, British Rheumatoid Outcome Study Group; CAMERA, Computer Assisted Management for Early Rheumatoid Arthritis; CRP, C reactive protein; CDAI, *Crohn's Disease Activity Index*; CTX-II, C-terminal cross-linked telopeptide of type II collagen (marker for cartilage degradation); DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; N/A, not applicable; RF, rheumatoid factor; SJC, swollen joint count; TICORA, Tight Control of Rheumatoid Arthritis; TJC, tender joint count; VAS, visual analogue scale.

efficacy, functional and structural outcome (online supplementary table 2). Since the published data were heterogeneous it was not possible to make comparisons with summarising statistics. However, the studies most often compared an intensive strategy with a conventional strategy, which could be used as the main comparison between the trials. To make this comparison, data were extracted at approximately 2 years of follow-up.

RESULTS

The search retrieved 6464 papers and abstracts for further evaluation (online supplementary figure 1), resulting in a selection of 17 comparative strategy trials from 23 published articles and three abstracts.^{5–30} Extension of the search to the inclusion of non-comparative trials resulted in three additional papers.^{31–33}

Close study of the literature disclosed two different types of strategy studies: (1) steering studies—same treatment but different target (eg, Disease Activity Score (DAS)-steered versus clinical judgment) or different follow-up (eg, routine outpatient vs intensive follow-up); (2) medication studies—same target (eg, low disease activity) and strategy (eg, adjustment every 3 months) with different treatments (online supplementary

figure 2). Since these differences provide answers to different questions, the retrieved literature is analysed using this dichotomy.

Steering strategies

Thirteen trials studied the effect of steering methods.^{5–15 31–33} Seven of these were randomised controlled trials (RCTs) comparing intensive with conventional steering.^{5–10 14 15} Three non-randomised controlled trials were included.^{11–13} Finally, three non-comparative studies investigating the effect of intensive steering in daily practice were included.^{31–33} Detailed information is provided in table 1 (baseline characteristics and treatment target) and table 3 (outcome) and online supplementary table 3 (design).

Three of the five RCTs, TICORA (Tight Control of Rheumatoid Arthritis)⁵ CAMERA (Computer Assisted Management for Early Rheumatoid Arthritis)⁶ and Fransen *et al*,⁷ showed significantly better results for the intensively treated arm than for the conventionally treated arm on clinical outcome in patients with early RA. TICORA also observed a difference in progression of structural damage. Such a difference was not found by CAMERA while Fransen *et al* did not assess progression of structural damage.

Table 2 Baseline characteristics of patient in medication strategy trials

Study	Arms	Adjustment if (target)	Adjustment to	Mean age (SD) at inclusion	Women (%)	Median (range)/mean \pm SD disease duration since diagnosis	RF+ (%)
FIN-RACo ¹⁶	SSZ+MTX+HCQ	Int ACR remis criteria* not met	Dose increase	47 \pm 10	n=56	7.3 (2–22) months	70
	SSZ		Dose increase	48 \pm 10	n=65	8.6 (2–23) months	66
NEO-RACo ²¹	SSZ+MTX+HCQ+IFX	Int ACR remis criteria* not met	Dose increase	46 \pm 10	67	4 (2–6) months (symptom duration)	68
	SSZ+MTX+HCQ+placebo		Dose increase				
BeSt ²²	Seq mono	DAS ₄₄ > 2.4	MTX \rightarrow SSZ \rightarrow Lef	54 \pm 13	68	2 (1–5) weeks	67
	Step up		MTX \rightarrow + SSZ \rightarrow + HCQ	54 \pm 13	71	2 (1–4)	64
	MTX+SSZ+pred		\rightarrow MTX + CsA	55 \pm 14	65	2 (1–4)	65
	MTX+IFX		Dose increase	54 \pm 14	66	3 (1–5)	64
GUEPARD ²⁷	MTX+ada	DAS ₂₈ \geq 3.2	Ada dose increase	47.8 \pm 15.7	80	< 6 months	74
	MTX		Add ada				
Saunders <i>et al</i> ²⁸	Step-up	DAS ₂₈ \geq 3.2	SSZ \rightarrow + MTX \rightarrow + HCQ	55 \pm 11	79	13 \pm 12 months	72
	Triple therapy		MTX + SSZ + HCQ \rightarrow dose \uparrow	55 \pm 15	76	10 \pm 9	69
Ferraccioli <i>et al</i> ²⁹	MTX	ACR ₅₀ not met	+ CsA \rightarrow + SSZ	59 \pm 0, 7	86	1.2 \pm 0.8 years	73
	CsA		+ MTX \rightarrow + SSZ	54 \pm 14	84	1.0 \pm 0.8	52
	SSZ		Dose increase	59 \pm 15	86	2.0 \pm 1.0	55
Verschueren <i>et al</i> ³⁰	Step-down	Based on DAS and CRP	SSZ+MTX+step-down pred	45 \pm 17	63	0.7 \pm 0.6 months	79
	Step-up		SSZ \rightarrow + MTX \rightarrow + HCQ \rightarrow + aza \rightarrow add other	55 \pm 15	65	0.8 \pm 0.7	52

*The criterion 'no fatigue' was omitted.

\rightarrow +, add following; \rightarrow , change to following; dose \uparrow , dose increase.

ACR, American College of Rheumatology; Ada, Adalimumab; aza, azathioprine; CRP, C-reactive protein; CsA, ciclosporin; DAS, Disease Activity Score; FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy; GUEPARD, GUérir la PolyArthrite Rhumatoïde Débutante (cure early RA); HCQ, hydrochloroquine; IFX, infliximab; Int ACR remis, intensifies ACR remission criteria; Lef, leflunomide; MTX, methotrexate; pred, prednisone; seq mono, sequential monotherapy; SSZ, sulfasalazine.

The other two RCTs found no difference: BROSG (British Rheumatoid Outcome Study Group),^{8,9} which in contrast to the RCTs mentioned above, examined patients with established RA; van Hulst *et al*¹⁰ found that since the doctors were not obliged to adjust treatment in their study, the frequency of treatment adjustments was similar in both arms, resulting in no difference in clinical outcome.

All non-randomised studies used historical data as a comparison. Two of these studies concluded in favour of the intensive treatment arms. Allaart *et al*¹¹ observed better clinical outcomes for the DAS₄₄-steered patients than for conventionally treated patients. Remarkably, the latter had less severe joint damage. The authors attributed this effect to the differences in DAS₄₄ at baseline. Stenger *et al*¹² observed significantly lower area under the curve values of C-reactive protein and progression of joint damage in the high-risk intensive treatment group versus the high-risk historic control group. This difference was not seen in the low-risk group. Finally, van der Woude *et al*¹³ did not find a difference in remission rate between BeSt-patients and Emotional Approach Coping Scale-patients. However, the studies by Allaart *et al* and van de Woude *et al* were not randomised.

RCTs analysing the best target to use did not come to definitive conclusions.^{14,15} The three non-comparative trials observed significant benefits on all three outcome measures (structure, function, signs and symptoms), concluding that strategy was effective in daily practice.^{31–33}

Medication strategies

Seven comparative trials investigated patients with different medication sequences but with similar treatment goals and adjustment criteria.^{16,21,22,27–30} Six trials were RCTs^{16,21,22,27–29} and one had a prospective cohort design.³⁰ Detailed information is provided in table 2 (baseline characteristics and treatment target) and table 3 (outcome) and supplementary table 3 (design).

Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo)^{16–20} and BeSt^{22–26} found significantly more rapid improvement in clinical and functional outcome in the combination groups than in the initial monotherapy groups. Although, the difference in clinical response decreased over time, a difference in structural damage favouring combination therapy was still seen after 5 years in BeSt and FIN-RACo. The difference in structural damage developed during the first period of the study with a relatively constant difference over time. Adding infliximab in the first 6 months to FIN-RACo combination therapy, carried out by Neo Rheumatoid Arthritis Combination Therapy (Neo-RACo)²¹ resulted in higher remission rates and more patients without radiological damage than adding placebo.

GUEPARD (GUérir la PolyArthrite Rhumatoïde Débutante (cure early RA))²⁷ found the same faster response of DAS for the initial combination group of methotrexate (MTX) plus adalimumab versus MTX only, resulting in a higher DAS area under the curve for the latter. However, unique in this study was the quick addition of adalimumab to MTX after 3 months if the

Table 3 Outcome of steering and drug strategy trials

Steering trials		
RCTs		
TICORA⁵ (DAS-steered vs routine care)		
C	EULAR good response at 18 months (primary outcome): OR=5.8 (95% CI 2.4 to 13.9); 82% vs 44%	p<0.0001
	EULAR remission at 18 months: OR=9.7 (3.9 to 23 to 9), 64% vs 16%	p<0.0001
	ACR70 at 18 months OR=11 (95% CI 4.5 to 27), 71% vs 18%	p<0.0001
F	NA	
R	Median (IQR) change in total Sharp Scores at 18 months 4.5 (1–9.87) vs 8.5 (2–15.5)	p=0.02
CAMERA⁶ (intensive steering based on SJC, TJC, ESR and VAS_{pt}-pain vs routine care)		
C	Number of patients in remission for 3 months (primary outcome)	
	During the first year: 35% vs 14%	p<0.001
	During second year: 50% vs 37%	p<0.0029
	TJC AUC after 2 years 3.6 (1.9 to 6.0) vs 5.5 (2.8 to 9.2), p=0.001	p<0.001
	SJC AUC after 2 years 2.7 (1.5 to 5.2) vs 4.7 (2.8 to 7.6)	p<0.001
	ESR AUC after 2 years 17.7 (10.2 to 27.6) vs 21.6 (13.0 to 33.6)	p=0.007
	ACR50 at	
	1 year: 58% vs 43%	p<0.01
	2 years: 43% vs 45%	NS
F	HAQ-AUC	NS
R	Annual radiographic progression	NS
	Median (IQR) change over 2 years 0 (0–2.0) vs 0 (0–2.5) units per year	
Fransen <i>et al</i>⁷ (DAS-steered vs routine care)		
C	DAS ₂₈ ≤3.2 at 24 weeks: 31% vs 16% (primary outcome)	p<0.028
	DMARD changes: 20% vs 9% (primary outcome)	p<0.05
F	NA	
R	NA	
BROSG⁸ (intensive care vs symptomatic care)		
C	SJC, TJC, ESR and PGA	NS
F	HAQ (primary outcome): sign deterioration in both arms: NS between treatment arms	NS
R	Larsen score	NS
van Hulst <i>et al</i>¹⁰ (DAS-guided vs routine care)		
C	DAS ₂₈ mean change after 18 months 0.5 vs 0.65	NS
F	NA	
R	NA	
Non-randomised comparative trials		
Allaert <i>et al</i>¹¹ (DAS-steered vs routine treatment)		
C	ESR median (IQR) at 1 year –19 (–6 to –37) vs –13 (–3 to –28)	p=0.011
	DAS ₂₈ (target) mean at 1 year –2.7±1.5 vs –1.9±1.5	p=0.001
F	HAQ mean change after 1 year –0.7±0.7 vs –0.5±0.7	p=0.029
R	NA	
Stenger <i>et al</i>¹² (CRP-steered high-risk/low-risk vs routine care high-risk/low-risk)		
C	AUC for CRP (target) lower in intensive group after 2 years	
	High-risk patients	p=0.002
	Low-risk patients	p=0.20
F	NA	
R	SHS median (IQR) progression rate after 2 years	
	High-risk patients 26.0 (range 0–100) vs 35 (1–188)	p=0.03
	Low-risk patients 11.0 (0–87) vs 8.0 (0–99)	p=0.36
van der Woude <i>et al</i>¹³ (DAS-steered vs routine care)		
C	DAS<1.6 (remission) after 5 years 9% vs 11%	NS
F	NA	
R	NA	

Continued

Table 3 continued

RCTs comparison of steering methods		
van Tuyl <i>et al</i>¹⁴ (DAS-steered vs CTX-steered)		
C	DAS <1.6 (remission) 57%, 76% and 90% after 8, 21 and 40 weeks in both targeted arms	NS
F	NA	
R	NA	
Edmonds <i>et al</i>¹⁵ (SJC-steered vs CRP-steered vs routine care)		
C	CRP, SJC	NA
F	NA	
R	SHS progression CRP group that met CRP target vs patients who did not meet CRP target: 0.53±1.57 vs 2.15±4.18	p=0.005
Non-comparative trials		
Brenol <i>et al</i>³¹ (baseline vs 14 months)		
C	SJC, TJC and VAS _{pt} -pain and VAS _{pt} -global health assessment baseline vs 12–14 m	p<0.05
	DAS ₂₈ total 12–14 m 4.64±1.57 vs 3.99±1.45	p<0.005
	DAS ₂₈ <2.6 12.6% vs 20.4%	p<0.001
	CDAI<2.8 8.6% vs 14.2%	p<0.001
F	HAQ total 12–14 m 1.45±0.86 vs 1.31±0.81	p=0.002
R	NA	
Proudman <i>et al</i>³²		
C	CRP median baseline vs 24 months 14 (6–31) vs 4 (3–4)	p<0.05
	ESR median baseline vs 24 months 39 (24–54) vs 11 (5.5–18.75)	p<0.05
	DAS ₂₈ (primary outcome) mean score baseline vs 24 months 5.3±1.1 vs 2.7±1.4	p<0.05
F	HAQ mean baseline vs 24 months 0.9±0.5 vs 0.2±0.3	p<0.05
R	SHS modified median (IQR) total score baseline vs 24 m 8 (5 to 15) vs 13 (8–12)	p<0.05
Kuper <i>et al</i>³³		
C	DAS ₂₈ <2.6 (remission) after 48–52 weeks 51%	NA
F	NA	
R	NA	
Medication trials		
RCTs		
FIN-RACo^{16–20} (combination vs monotherapy)		
C	Remission (primary outcome, ACR definition of remission) 2 years 37% vs 18%	p=0.003
	DAS ₂₈ median at 2 years 2.0 vs 3.1	p=0.005
	ACR ₅₀ , ESR, SJC, TJC, VAS _{pt} -global health	NS
F	Mean change in HAQ	NS
R	Increase in Larsen score after 2 years 4 vs 12	p=0.002
NEO-RACo²¹ (combination+IFX vs combination+placebo)		
C	Remission (primary outcome) after 2 years 70% vs 53%	p=0.08
F	NA	
R	SHS=0 after 2 years 54% vs 41%	p=0.005
BeSt^{22–26} (sequential monotherapy; step-up monotherapy; combination therapy+prednisone; combination therapy with IFX)		
C	DAS≤2.4 (target) after	
	1 year 53%; 64%; 71%; 74%	p<0.01 (1 vs 3 and 1 vs 4)
	2 years 75%; 81%; 78%; 82%	NS
	VAS _{pt} -pain change	
	After 6 months with baseline –17.4; –25.5; –30.3; –30.2	p=0.001 (1 vs 3+4)
	After 2 years –28.2; –27.3; –26.9; –32.6	NS
	VAS _{pt} -global health assessment after 2 years –26.4; –25.6; –23.9; –31.8	NS
	F	
	HAQ mean improvement	

Continued

Table 3 continued

	After 12 months 0.7; 0.7; 0.9; 0.8	p=0.031 (1 vs 3+4)
	After 24 months 0.7; 0.8; 0.9; 0.9	NS
	R	
	SHS mean increase after 2 years 2.0; 2.0; 1.0; 1.0 (9.0; 5.2; 2.6; 2.5)	p=0.005 (1+2 vs 3+4)
GUEPARD²⁷ (initial MTX vs initial combination MTX with ADA)		
C	DAS ₂₈ AUC at 1 year 164.6 vs 186.7	0.049
F	HAQ increase at 1 year -0.51 vs -0.82	0.26
R	SHS increase 1.8±4.7 vs 1.9±4.0	NS
Saunders <i>et al</i>²⁸ (step-up vs parallel)		
C	Mean difference	
	After 1 year SJC, TJC, CRP, ESR, VAS _{pt} -pain, -global health assessment, DAS ₂₈	NS
	After 1 year OR ACR ₂₀ 0.9 (0.3–1.6); OR ACR ₅₀ 0.7 (0.3–1.6); OR ACR ₇₀ 0.6 (0.2–1.5)	NS
	After 1 year OR EULAR remission 0.6 (0.3–1.4)	NS
F	HAQ mean difference	NS
R	SHS mean difference	NS
Ferraccioli <i>et al</i>²⁹ (MTX adding CsA; CsA adding MTX; SSZ monotherapy)		
C	SJC mean (95%CI) increase	
	After 18 months -6.3 (-3.1 to -9.5); -5.0 (-2.8 to -7.8); -3.7 (-0.6 to -6.9)	p=0.04 (1 vs 3)
	18–36 months -2.2 (-1.3 to -3.2); -3.1 (-1.9 to -4.3); -1.8 (-0.6 to -3.1)	NS
	TJC mean (95%CI) increase	
	After 18 months -5.8 (-2.7 to -8.9); -5.7 (-2.8 to -8.7); -2.2 (0.8 to -5.3)	p=0.001 (1 vs 3 and 2 vs 3)
	18–36 months -1.7 (-0.5 to -2.9); -4.8 (-3.6 to -6.1); -2.8 (-1.5 to -4.1)	p=0.02 (1 vs 2)
	CRP mean (95%CI) increase	
	After 18 months -23 (-13.5 to -33.3); -9.0 (-6.4 to 11.6); -11.8 (0.4 to -23.9)	p=0.001 (1 vs 3)
	18–36 months -1.8 (2.3 to -5.9); -9.0 (-6.4 to -11.6); -0.9 (2.9 to -4.8)	p=0.01 (1 vs 2); p=0.03 (2 vs 3)
	VAS _{pt} mean (95%CI) increase	
	After 18 months -4.2 (-3.7 to -4.7); -4.4 (-1.9 to -7.0); -2.3 (-1.9 to -2.7)	p=0.001 (1 vs 3 and 2 vs 3)
	18–36 months -1.3 (-0.9 to -1.7); -0.6 -0.4 to -0.9); -0.6 (-0.3 to -0.9)	p=0.001 (1 vs 2)
	ACR ₅₀ (target) after 18 months 90%; 88%; 24%	NS
F	NA	
R	NA	
Non-randomised comparative trials		
Verschuere <i>et al</i>³⁰ (step-down vs step-up)		
C	DAS ₂₈ <2.4 percentage after 4 months 63.2% vs 36.4%	p=0.049
	After 12 months	NS
F	HAQ >0.22 increase after 4 months	p=0.010
R	NA	

Published data after approximately 2 years. Data are sorted according to intensive treatment compared with less intensive treatment. ACR, American College of Rheumatism; ADA, adalimumab; AUC, area under the curve; BROSG, British Rheumatoid Outcome Study Group; C, clinical outcomes; CAMERA, Computer Assisted Management for Early Rheumatoid Arthritis; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; CsA, ciclosporin; CTX, C-terminal cross-linked telopeptide; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; F, functional outcome; FIN-RACO, Finnish Rheumatoid Arthritis Combination Therapy; GUEPARD, GUÉrir la PolyArthrite Rhumatoïde Débutante (cure early RA); HAQ, Health Assessment Questionnaire; IFX, infliximab; MTX, methotrexate; PGA, patient global assessment; R, radiographic outcome; RCT, randomised controlled trial; SJC, swollen joint count; SSZ, sulfasalazine; TICORA, Tlght CControl of Rheumatoid Arthritis; TJC, tender joint count; VAS, visual analogue scale.

target was not reached, which apparently led to similar functional and radiological outcomes in both groups.

The small study by Saunders *et al*²⁸ found neither a difference in clinical outcome nor in physical functional or structural damage in the comparison of step-up versus initial triple therapy. Ferraccioli *et al*²⁹ observed better clinical response in the two intensively treated arms than in the arm treated with monotherapy. The difference in clinical outcome between the two

intensively treated arms was inconclusive. Finally, Verschuere *et al*³⁰ observed quicker clinical response in the intensively treated group, although they had higher disease activity at baseline.

DISCUSSION

The conclusions of the steering and medication trials are remarkably consistent: Five trials showed significant benefits

for intensive steering on clinical outcome, physical function and structural damage.^{5-8 12 13} The trials that found no differences studied patients with established RA, and one of the trials did not demand treatment adjustment.^{8 10} These results lead to the conclusion that patients with early active RA benefit from active steering. Proof in late disease is lacking. Additionally, protocol-based adjustment appears to be required. Regardless of the steering method used, active steering resulted in better outcomes, suggesting that the method is less important than the active steering itself. Almost all successful studies used a composite index as steering method. Based on these data in early RA, a prompt start and active steering of medication is advisable.

The medication sequence used, the allowance of prednisone use and the lack of appropriate comparisons across strategies make it impossible to prioritise a particular sequence. The results of FIN-RACo¹⁶ and BeSt²² favoured initial combination therapy. However, the combination treatment of BeSt consisted of prednisone or antitumour necrosis factor (anti-TNF), which does not answer the question as to whether a combination of conventional disease-modifying antirheumatic drugs (DMARDs) is better than initial monotherapy. FIN-RACo compared sequential monotherapy with combination therapy. Saunders *et al*²³ compared step-up therapy with combination therapy and found no difference between the treatment arms. Although this could be caused by a difference in sulfasalazine dose, it suggests that rather than starting with combination therapy, it was the prompt adjustment of treatment for non-optimal response that made the difference. This is underlined by the conclusion of GUEPARD, that initial anti-TNF does not give better outcomes than prompt adjustment to anti-TNF when MTX treatment fails after 3 months.

CONCLUSION

Patients with early active disease may benefit substantially from an immediate start of treatment, active steering and prompt adjustment of treatment intensity. Proof in favour of any steering method is lacking and the best medication sequence is still not known. The benefits of intensive treatment of patients with established RA should be further explored.

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