

ORIGINAL ARTICLE

Non-pharmacological and pharmacological interventions in patients with early arthritis: a systematic literature review informing the 2016 update of EULAR recommendations for the management of early arthritis

Claire Immediato DAIEN,¹ Charlotte HUA,¹ Bernard COMBE,¹ Robert LANDEWE²

To cite: DAIEN CI, HUA C, COMBE B, *et al.* Non-pharmacological and pharmacological interventions in patients with early arthritis: a systematic literature review informing the 2016 update of EULAR recommendations for the management of early arthritis. *RMD Open* 2017;**3**: e000404. doi:10.1136/rmdopen-2016-000404

► Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2016-000404>).

Received 13 November 2016
Accepted 9 December 2016



► <http://dx.doi.org/10.1136/rmdopen-2016-000406>



CrossMark

For numbered affiliations see end of article.

Correspondence to

Dr Claire Immediato DAIEN;
cidaen@gmail.com

ABSTRACT

Objective: To perform a systematic literature review (SLR) on pharmacological and non-pharmacological treatments, in order to inform the European League Against Rheumatism (EULAR) recommendations for the management of early arthritis (EA).

Methods: The expert committee defined research questions concerning non-pharmacological interventions, patient information and education, non-steroidal anti-inflammatory drug, glucocorticoid (GC) and disease-modifying antirheumatic drugs (DMARDs) use, as well as on disease monitoring. The SLR included articles published after the last EULAR SLR until November 2015 found in the MEDLINE, EMBASE and Cochrane databases and abstracts from the 2014 and 2015 American College of Rheumatology and EULAR conferences.

Results: Exercise programmes may improve pain and physical function in patients with EA. Patients with EA treated within the first 3 months of symptoms have better clinical and radiological outcomes than those treated beyond 3 months. The clinical and radiological efficacy of GCs is confirmed, with similar efficacy of oral and parenteral administrations. Long-term data raise concerns regarding cardiovascular safety when using GCs. Step-up DMARD therapy is as effective as intensive DMARD therapy ‘ab initio’ for the long-term outcome of EA. Short-term superiority of intensive therapy with bDMARDs is not maintained on withdrawal of bDMARD. Patients with early psoriatic arthritis have better skin and joint outcomes when tight control is used compared to standard care.

Conclusions: The findings confirm the beneficial effect of exercise programmes and the importance of early drug therapy and tight control. They support the use of methotrexate and GCs as first-line drugs, although the long-term use of GCs raises safety concerns.

Key messages

What is already known about this subject?

- Systemic glucocorticoids (GC) reduce pain and swelling and should be considered as part of the disease-modifying antirheumatic drugs strategy.
- Methotrexate is an effective and safe therapy in patients with early arthritis at risk of developing persistent disease.
- Targeting at early remission may lead to a better outcome than targeting at low disease activity.

What does this study add?

- GCs are efficacious drugs with regard to clinical and radiological outcomes, but their long-term use still raises safety concerns.
- Patients with early psoriatic arthritis have better skin and joint outcomes when tight control is used compared to standard care.
- Biomarkers to predict response to a first-line therapy are lacking.

How might this impact on clinical practice?

- This systematic literature review highlights the need for early treatment in patients with early arthritis with glucocorticoids and methotrexate. The long-term use of GCs still raises safety concerns.

INTRODUCTION

The management of patients with early arthritis (EA) has changed considerably in the past few years under the influence of new therapies. The latest version of the European League Against Rheumatism (EULAR) recommendations for the management of EA was published in 2007.¹ A systematic literature review (SLR) underlying the 2007 EULAR

recommendations had included studies published up to January 2005.¹ However, between 2005 and 2015, many new studies in patients with EA have been published. In 2010, EULAR has published recommendations for the management of rheumatoid arthritis (RA)² (updated in 2013³ and 2016⁴) and for the management of psoriatic arthritis.⁵ The aim of this SLR was to inform the update of the EULAR recommendations for EA management on new evidence for non-pharmacological interventions, patient information and education, and for pharmacological therapy in patients with EA.⁶

METHODS

The expert committee selected the following topics of interest: the recognition (1) and referral (2) of patients with EA, the diagnosis of EA (3), its prognosis (4), its classification (5), patient information and education (6), non-pharmacological interventions (7), pharmacological treatments (8), monitoring of the disease course (9) and prevention (10). The research questions were framed, defined and structured according to the EULAR standardised operating procedures⁷ using the 'Patients, Intervention, Comparator or Control, Outcome, Type of study (PICOT)-format'. The results of the SLR for recognition of arthritis, referral, diagnosis, prognosis and classification were summarised in a separate article.⁸ This article reports the results on non-pharmacological and pharmacological interventions, monitoring and prevention of EA.

Research questions

Research questions and PICOTs are provided in the online supplementary file.

Research questions dealing with non-pharmacological interventions aimed at addressing the clinical effects (disease activity and patient-reported outcomes) and radiological effects of exercise therapy. Impact of coping strategies, psychological intervention and strategies to promote DMARD adherence was also addressed. Influence of smoking cessation on early arthritis outcomes was assessed. Research questions dealing with non-steroidal anti-inflammatory drugs (NSAIDs) aimed at comparing the efficacy and safety of NSAIDs with those of simple analgesics.

Research questions dealing with glucocorticoids (GCs) aimed at assessing the efficacy and safety of systemic GCs (versus no GCs); of prolonged oral GCs versus parenteral GC administration; and of intra-articular GCs compared to no GCs.

Research questions dealing with DMARDs aimed at:

- I. Finding evidence for the existence of a window of opportunity and for its optimal duration.
- II. Establishing the efficacy and safety of a combination of conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs) and biological DMARDs (bDMARDs) 'ab initio', as compared to csDMARD monotherapy

III. Assessing predictive factors of response to first-line csDMARDs

For disease monitoring, we searched for randomised controlled trials (RCT) that had compared patients who were regularly monitored using a predetermined target level for disease activity versus patients who had not been treated according to such a tight monitoring strategy.

Study selection

A skilled librarian performed a systematic search of articles in the MEDLINE, EMBASE, Cochrane, Central, DARE, Health Technology Assessment and National Health Service databases. The start date was the lock date of the previous Cochrane or EULAR SLRs (depending on the topic of interest: between 2005 and 2013). The lock date of this SLR was November 2015. In addition, two fellows (CID and CH) manually searched the proceedings of the 2014 and 2015 American College of Rheumatology (ACR) and EULAR annual meetings for abstracts.

Inclusion criteria are described in online supplementary files according to PICOTs. All articles published in English were included. For efficacy and safety questions, only RCTs were included. Articles had to include adults (at least 18 years old) with a clinical diagnosis of EA or early RA. The detailed search strategies are presented in the online supplementary file.

Data extraction

Two fellows assessed each title and abstract for inclusion in the review, according to the predetermined selection criteria, followed by a full-text article review where applicable. Data regarding inclusion and exclusion criteria, follow-up time, characteristics of study population, outcome definition, interventions and outcome measures were extracted using a standardised data extraction form. Risk of bias was assessed using The Cochrane Collaboration's tool covering selection, performance, detection, attrition, reporting and other biases. Level of evidence, for each selected study, was determined according to the standards of the Oxford Centre for Evidence-Based Medicine.⁹

RESULTS

Non-pharmacological interventions, information and education

Among the 1260 articles published after the latest SLR,¹⁰ only 2 met the inclusion criteria.^{11 12} Both suggested a benefit of exercise programmes on hand function (table 1).

Studies designed to assess the effect of smoking cessation as an intervention on EA outcomes were not found. Three studies compared outcomes in current versus former smokers,^{13–15} but this comparison did not allow any conclusion regarding the effect of smoking cessation as part of the therapeutic management of patients with EA.

Table 1 Impact of exercise programme on hand function in patients with recent RA

Study	LoE	Population	n	Intervention	Intervention duration	Primary end point	Dominant hand grip	Baseline	Three months	Risk of bias
Manning <i>et al</i> ¹¹	1c	RA of ≤5 years' duration	52	Education, Self-Management, and Upper Extremity Exercise Training	2 weeks	Change in Hand questionnaire DASH at week 12	Measured by a hydraulic handgrip dynamometer in Newton	Mean (95% IQR) 184.8 (144.1; 225.5)	3-month change*: +16.8 (-8.2, 41.7)	Unclear
Mathieux <i>et al</i> ²	1c	RA of ≤2 years' duration	30	No intervention	0.5 day	Handgrip strength at week 12	Measured by an air dynamometer in kPa	223.8 (184.1; 263.5)	+3.7 (-20.6, 28.0)	Unclear
			30	Education and practice regarding joint protection with hand and wrist exercises				Mean (SD) 37.9 (21.7)	3-month value: 53.9 (24.2) [†]	
			30	No intervention				35.7 (24.0)	37.3 (22.9)	

*Comparison between intervention and non-intervention changes p=0.36.

[†]Comparison between intervention and non-intervention changes p<0.05.

DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; LoE, level of evidence; RA, rheumatoid arthritis.

We did not find studies addressing the effects of psychological interventions and strategies for promoting DMARD adherence.

The new RCTs are in accordance with the previously formulated standpoint that non-pharmaceutical interventions such as dynamic exercises can be applied as adjuncts to pharmaceutical interventions in patients with early arthritis.

NSAIDs in EA

Among 422 screened records, new RCTs assessing the efficacy of NSAIDs in patients with EA were not found.

GCs in EA

Of 350 screened records, 42 were fully reviewed and 7 RCTs and 1 meta-analysis met the inclusion criteria. The key efficacy data are shown in [table 2](#).

Efficacy of systemic GCs

A recent meta-analysis of 10 trials with low-dose (≤10 mg/day prednisone) and 4 trials with high-dose GC regimens has shown a doubling of the likelihood of achieving 28-joint Disease Activity Score (DAS28)-remission in patients treated with GCs, as compared to those not treated with GCs (OR 2.46 (95% CI 1.51 to 4.00), 2.14 (1.40 to 3.27) and 3.54 (2.03 to 6.19) at 6, 12 and 24 months, respectively).¹⁹

The CareRA RCT showed that patients without poor prognostic factors (see [table 1](#)) who took an oral GCs bridging therapy (COBRA-slim) did not have a statistically significant benefit in the DAS28 improvement and DAS28 remission rate at week 16 compared with patients treated with methotrexate (MTX) without oral GC.¹⁶ While this subanalysis did not have sufficient statistical power and the study was not blinded, the primary end point (percentage of patients achieving remission at week 16) was numerically higher in the GC group (65.1% vs 46.8%, p=0.08).

Efficacy of prolonged oral GCs as compared with parenteral GC administration

The tREACH trial has suggested that oral prednisone with a tapering scheme over 10 weeks and a single subcutaneous injection with GCs leads to similar clinical and radiographic outcomes after 1 year.¹⁷

Efficacy of intra-articular GCs compared with no GCs

One small RCT has shown higher ACR20/50/70 responses in patients who had received initial intra-articular injections of all swollen joints in addition to their usual DMARD use than in those who had not.¹⁸

Safety of systemic GCs

The short-term safety of systemic GCs was assessed in two RCTs and one meta-analysis.^{16 20 21} In the meta-analysis of eight studies with low-dose GCs (≤10 mg/day) and four studies with high-dose GCs, the number of adverse events (AEs) was similar with and

Table 2 Efficacy of GCs in patients with early arthritis

Study	Trial	LoE controls	Population and LoE controls	Intervention	Time point	Clinical outcomes	Radiographic progression (SHS change >0.5)	Risk of bias
Verschueren <i>et al</i> ¹⁶	CareRA	2c	43 pts with low risk† ERA 47 pts with low risk† ERA	PRED from 30 to 0 mg/day in 34 weeks No GC	16 weeks	Remission DAS28-CRP	65.1% [§] NA 46.8%	High†
De Jong <i>et al</i> ¹⁷	tREACH	1b	91 pts with ERA	Intramuscular: MP 120 or TRIAM 80 mg at inclusion Oral: PRED from 15 to 0 mg/day in 10 weeks	1 year	Remission DAS	61% 21%	High§
Menon <i>et al</i> ¹⁸		2c	93 pts with ERA 25 pts with ERA	TRIAM 40 mg in every SJ at baseline No GC	12 weeks	ACR20/50/70	54% 100*/60**/ 36** 84/20/0	High†

Intervention versus controls p values: [§]p=0.08; *p<0.05; **p<0.01.
†Low risk definition: (1) No erosion+rheumatoid factor (RF)/ACPA negative or (2) No erosion+RF and/or ACPA positive+DAS28-CRP≤3.2 or (3) Erosion+RF/ACPA negative+DAS28-CRP≤3.2.
‡Open design.
§Assessor single-blind trial.
ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; CRP, C reactive protein; DAS28, Disease Activity Score 28 joints; ERA, early rheumatoid arthritis; GCs, glucocorticoids; LoE, level of evidence; MP, methylprednisolone; NA, not available; NS, not significant; PRED, prednisone; TRIAM, triamcinolone.

without GCs, except for epigastric pain, which was more frequent with GCs (HR 1.76 (1.05 to 2.95)).²⁰ In the CareRA trial, the proportion of patients with 'serious-AEs' or 'any' AEs at 4 months was similar in patients treated with and without GCs.¹⁶ In the tREACH trial, short-term safety was similar in patients treated with Intramuscular-GC administration or prolonged oral GCs.¹⁷

Two studies reported long-term safety of GCs in early RA. Patients initially randomised to oral GCs 7.5 mg/day in BARFOT had an increased number of cerebrovascular events at 10 years (10/112) compared to those initially randomised to no GC group (5/111) (HR after adjustment for age: 3.7 (1.2 to 11.4)).²² Preliminary results from the CAMERA-II trial suggest that, after a mean follow-up of 7 years, cardiovascular events were more frequent in the early patients with RA treated with 10 mg/day prednisone (10/57) for at least 2 years than in the non-GC group (3/61; p=0.04).²³

The results of the latest RCTs are in accordance with the previously formulated standpoint that systemic GCs reduce pain and swelling and should be considered as adjunctive treatment, as part of the DMARD strategy and that intra-articular GC injections should be considered for the relief of local symptoms of inflammation. These RCTs also support the statement that, in view of their cumulative side effects, GCs should be used at the lowest dose necessary and as temporary adjunctive treatment.

DMARDs in EA

Of the 1848 screened articles, 353 were fully reviewed and 11 prognostic studies with prospective follow-up were considered suitable to examine the window of opportunity concept. Twenty-five RCTs were relevant for efficacy and safety and 48 prognostic studies with prospective follow-up met the inclusion criteria concerning the prediction of therapeutic response.

Nine studies with prospective follow-up, assessing the impact of early treatment on long-term outcomes, were found. Eight of them were compatible with a window of opportunity theory: they all suggested a better prognosis with an early rather than delayed treatment start.^{24–31} The most frequently studied cut-off duration for treatment start was 3 months.^{24–27} Studies comparing functional and radiographic outcomes between patients with early versus late DMARD start are summarised in table 3.

The symptom duration with optimal likelihood to achieve drug-free remission was between 11.4 and 19.1 weeks, depending on the population studied.³³

We did not find any new trial comparing combinations of csDMARDs or tsDMARDs to MTX monotherapy in patients with EA or early RA. The CareRA trial³⁴ and the COBRA-light study³⁵ compared MTX monotherapy with csDMARD combination therapy, but the doses of GCs in the combination csDMARD arm and in the monotherapy arm were markedly different, making a

Table 3 Window of opportunity: impact of early treatment start on functional and radiographic outcomes

Reference (LoE)	Data source	Population	DMARD n	DMARD start	End point	Functional outcomes	Radiographic outcomes
Bosello <i>et al</i> (2b) ²⁴	Consecutive patients attending early arthritis clinic	RA with duration <12 months	44	<3 months	Presence of at least one erosion at 12 months	27.1%	
Gremese <i>et al</i> (2b) ²⁵	Consecutive patients attending 3 early arthritis clinics	RA with duration <12 months	77 105	≥3 months <3 months	12-month HAQ <0.5	62.7%	45.4%
Lukas <i>et al</i> (2b) ²⁶	ESPOIR	Arthritis with duration <6 months	376 140	≥3 months <3 months	12-month mean radiographic progression	41.3%	0.8 units/year*,†
Weng <i>et al</i> (2b) ³²	Western Consortium of Practicing rheumatologist study	RF+RA within 16 months from symptoms onset to DMARD initiation	521 42 3	≥3 months <3 months ≥10 months	2-year changes in HAQ and mTSS progression	-0.63±0.58 -0.35±0.61	1.7 units/year 4.62±8.46 units/year 1.77±2.75 units/year

*Comparison early versus late DMARD start: p<0.05.

†Propensity analysis. Data are expressed in means±SD or in percentage.

DMARD, disease-modifying antirheumatic drug; ESPOIR, Evaluation et Suivi de Polyarthrites Indifférenciées Récentes; HAQ, Health Assessment Questionnaire; LoE, level of evidence; mTSS, modified total Sharp score; RA, rheumatoid arthritis.

valid comparison of csDMARDs arms with respect to the effectiveness of treatment intensity hazardous. The two studies comparing tsDMARD to MTX included patients with MTX-naïve RA, but were not limited to early RA and were thus excluded from this SLR (mean RA duration 2.7–3.4 years in the tofacitinib study and from 1.3 to 1.9 years in the baricitinib study depending on groups).^{36–38}

Seven of nine new RCTs confirmed the clinical^{34 35 39–43} and radiological^{34 35 40 41} superiority of bDMARDs over MTX monotherapy. These data are summarised in online supplementary table S1.

Five studies compared a temporary intensive treatment with bDMARDs plus MTX followed by a maintenance therapy with MTX monotherapy to MTX monotherapy from the start, with end points assessed after the step-down strategy (table 4).

The step-down strategy was either applied to all patients from the intensive arm^{39 44} or to those reaching low disease activity.^{43 45 46} Two studies showed that the clinical benefit of intensive therapy was not maintained after its withdrawal^{39 45 47} and three others showed a small difference between groups. The radiographic evaluation conducted in four trials revealed a significant structural benefit in only two trials.^{45 46}

We also evaluated the efficacy of intensive therapy with bDMARDs or a combination of csDMARDs ‘ab initio’ compared to delayed intensification of therapy in a treat-to-target approach. We found eight studies with an end point assessed after the intensification phase. Three studies involved only completers or did not apply imputation of missing data and were thus excluded. The five remaining studies are summarised in table 5.

Three of them^{17 48 49} did not show any clinical or radiological benefit of early intensive therapy compared to delayed treatment intensification (‘step-up’). In the U-Act-Early RCT, the primary analysis found a higher sustained remission rate in the TCZ+MTX and TCZ monotherapy groups than in the MTX monotherapy group (86% vs 84% vs 44%), but these differences were no longer observed at the end of the entire study period when patients were allowed to escalate therapy (86% vs 88% vs 77%),⁴² although a small radiological benefit remained. In general, ‘ab-initio’ intensive therapy did not have radiographic benefits compared to delayed intensive therapy in treat-to-target strategy trials.

All safety data are summarised in online supplementary table S2. Three trials compared the safety of csDMARD monotherapy versus csDMARDs combination therapy. In the CareRA trial,⁵³ patients on MTX monotherapy had less AEs than those treated with csDMARD combination therapies, but patients on MTX monotherapy had also received less GCs. The COBRA-light trial did not show differences in safety between MTX monotherapy and csDMARD combination therapy.^{49 54} In the tREACH trial,¹⁷ the number of AEs was similar in the three groups, but medication adjustments because of AEs were more frequent in patients on csDMARD combination

Table 4 Comparison of induction therapy with bDMARD±MTX followed by step-down and MTX monotherapy on clinical and radiographic outcomes in patients with early arthritis

Study (LoE)	Trial	Systematic bDMARD withdrawal	Withdrawal from	Population (DMARD naïve)	Initial therapy	Clinical outcome after step-down	Radiographic outcome after step-down	Risk of bias	
Detert <i>et al</i> (1b) ³⁹	HIT HARD	Yes	Week 24	Pts with ERA n=87	ADA+MTX	DAS28 remission at week-48 42%	Week-48 mTSS	2.6	Low
Atsumi <i>et al</i> (1b) ⁴⁴	C-OPERA	Yes	NA	n=85	MTX+PBO	37%	Percentage of patients with year 2 ΔmTSS ≥0.5	6.4*	Unclear‡
			Week 52	Pts with high risk† ERA n=108	CZP+MTX	SDAI remission at week 104 41%		16%	
Hørslev-Petersen <i>et al</i> (2b) ⁴⁵	OPERA	LDA only	Week 54	Pts with ERA n=89	ADA+MTX	DAS28CRP <2.6 at 24 months 69%	Per centage of pts with year 2 ΔmTSS ≥1	84%	Low
			NA	n=91	MTX+PBO	66%		80%	
Smolen <i>et al</i> (2b) ⁴⁶	OPTIMA	LDA only	Week 26	Pts with ERA n=102	ADA+MTX	DAS28CRP <2.6 at 78 weeks 66%	Percentage of pts with week78 ΔmTSS ≥0.5	81%	Low
			NA	n=112	MTX+PBO	68% **		78%	
Emery <i>et al</i> (2b) ⁴³	AVERT	LDA only	Week 54	Pts with ACPA +ERA n=119	ABA+MTX	DAS28-CRP <2.6 at 18 months 18%	None		Low
			Week 54	n=116	ABA+PBO	12%			
			NA	n=116	MTX+PBO	9%*			

p Value for comparison bDMARD+MTX versus MTX *<0.05; **<0.01; ***<0.001.

†High-risk ERA defined as high titres of ACPA/RF or erosions.

‡Abstract only.

ACPA, anticitrullinated protein antibody; ADA, adalimumab; CZP, certolizumab-pegol; DB, double-blind; ERA, early rheumatoid arthritis; LDA, low disease activity; LoE, level of evidence; MTX, methotrexate; NA, not applicable; pts, patients; RF, rheumatoid factor; SJC, swollen joint count; SSZ, sulfasalazine; ΔmTSS, variations in modified total Sharp score.

Table 5 Treat-to-target strategy trials comparing ab initio versus delayed intensive therapy in terms of efficacy in patients with early arthritis

Study (LoE)	Trial	n	Initial arms	Type of intensification	Step-up from	Twelve-month remission		Radiographic outcome after step-down	Risk of bias		
Nam J <i>et al</i> (1b) ⁴⁸	IDEA	55	IFX+MTX	IFX dose increase csDMARD combination	Week 26	DAS44 <1.6	48%	Δ mTSS at week 50	1.2 2.8	Low	
		57	MTX+MP+PBO				36%				
Ter Wee <i>et al</i> (1b) ⁴⁹	COBRA-light	81	MTX+SSZ+GC	MTX dose increase, then ETN. ETN	Week 26	DAS44 <1.6	47%	Δ mTSS at week 52	0.5 \pm 1.6	High†	
		81	MTX +GC				38%				0.6 \pm 1.4
Axelsen <i>et al</i> (1b) ⁵⁰ Hørslev-Petersen <i>et al</i> ⁵¹	OPERA	89	ADA+MTX	csDMARD combination or bDMARD csDMARD combination, then ADA	Week 12	DAS28CRP <2.6	74%	mTSS at week 52	5.0 \pm 5.2	Low	
		91	PBO+MTX				49%***				5.5 \pm 6.2
De Jong <i>et al</i> (1b) ¹⁷	tREACH	91	csDMARD combination +Intramuscular-GC	MTX+ETN, then MTX+ADA	Week 12	DAS <1.6	61%	Δ mTSS at week 52	0.1 (0.0– 1.0)	High‡	
		93	csDMARD combination +oral GC				54%				0.0 (0.0– 1.0)
		97	MTX+ oral GC				51%				0.0 (0.0– 1.0)
Atsumi <i>et al</i> (2c) ⁴⁴	C-OPERA	159	CZP+MTX	open label CZP +MTX CZP+MTX	Week 24	DAS28 <2.6	57%	Δ mTSS at week 52	0.4 \pm 2.7	Low	
		157	PBO+MTX				37%***				1.6 \pm 4.9
Bijlsma <i>et al</i> (1b) ^{42 52}	U-ACT-EARLY STRATEGY STUDY	106	TCZ+MTX	TCZ+MTX+HCQ, then TNFi+MTX TCZ+HCQ, then TCZ+MTX MTX+HCQ, then MTX+TCZ		DAS28 <2.6 with SJC \leq 4, for \geq 24 weeks [§]	86%	Δ mTSS at week 52	0.5 \pm 1.5	Low	
		103	TCZ+PBO				88%				0.8 \pm 3.2
		108	MTX+PBO				77%				1.0 \pm 2.9*

Results are expressed in %; means \pm SD or medians (IQR).

Comparison of ab initio versus delayed intensive therapy *p<0.05; ***p<0.001.

†Open label trial.

‡Single-blinded trial.

ADA, adalimumab; bDMARD, biological DMARD; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS, Disease Activity Score; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; LoE, level of evidence; MP, methylprednisolone; MTX, methotrexate; mTSS, variation of modified total Sharp score; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitors.

therapy than in those on MTX monotherapy (n=60/93 vs n=44/97; p=0.008).

Among the 10 studies comparing bDMARDs and csDMARDs in early RA, the rate of infections was numerically higher with bDMARDs in 2 studies (1.2 to 2.9-fold) and the withdrawal for safety numerically higher with bDMARDs in 4 studies (1.2 to 2.0-fold).

The results of these RCTs are in accordance with the previously formulated standpoint that among the DMARDs, MTX is considered the anchor drug, and should be used first in patients at risk of developing persistent disease.

Predictors of primary failure, predictors of therapeutic response and predictors of remission achievement in patients treated with a first-line csDMARD

Many clinical and biological biomarkers have reportedly been associated with primary failure, and considered as predictors of therapeutic response, or predictors of remission in patients treated with a first-line csDMARD. These are listed in online supplementary table S3. While three studies reported statistically significant associations between body mass index (BMI) and remission, predictive values of a high BMI at baseline were either not available or lower than 40% (see online supplementary table S4).^{55–58} Current smoking was associated with lower response to a first-line DMARD in four studies, with positive predictive value ranging from 38% to 71% (see online supplementary table S4).^{59–62} Otherwise, published associations between therapeutic response and other biomarkers have not been replicated yet.

Disease monitoring

Of the 1872 records screened, only 1 met the inclusion criteria.⁶³ The TICORA study conducted in early psoriatic arthritis randomised patients to receive either tight control (monthly review with escalation of therapy if the target was not achieved) or standard care (3 monthly review). The proportion of patients achieving an ACR20 response at 48 weeks (primary outcome) was higher in the tight control arm compared to the standard care arm (55/89 vs 37/84; OR 1.9 (1.0 to 3.5); p=0.04).

The results of this RCT are in accordance with the previously formulated standpoint that in EA, disease activity should be assessed at 1–3-month intervals for as long as remission is not achieved.

DISCUSSION

This SLR was performed to inform the EULAR task force involved in the update of the recommendations for the management of EA. Overall, this SLR reinforces the data provided by the SLRs performed in 2005 and 2013 on pharmacological and non-pharmacological interventions.^{1 64}

With regard to non-pharmacological interventions, exercise programmes may improve pain and function.^{11 12 65}

With regard to pharmacological interventions, GCs may help improve clinical and radiographic

outcomes^{16 19} but raise concerns about long-term safety, especially on cardiovascular outcomes.^{22 23} Prolonged oral GC administration and parenteral GC administration (injections) give similar results.¹⁷ Robust data regarding the dose and the ideal tapering schedule of GCs are still lacking.

Recent studies have convincingly demonstrated the need for an early start of DMARDs, which gives a better long-term outcome with a ‘window of opportunity’ estimated at ~3 months after the start of symptoms.^{24–26}

Recent data for DMARDs did not show convincing evidence for a benefit of csDMARDs combination over MTX monotherapy.^{53 54 66} bDMARDs, usually combined with csDMARDs, are more efficacious than MTX monotherapy in early RA, but also have more side effects and are far more expensive.^{67 68} Reports on the efficacy of tsDMARDs in EA are limited and long-term safety from real-life observational studies is still lacking. A delayed start of bDMARDs in combination with MTX (only in those patients who need it) does not seem to be associated with worse long-term outcomes than bDMARDs ‘ab initio’ as long as a rigorous treat-to-target strategy is pursued, and is far cheaper. Short-term superiority of treatment with bDMARDs was not maintained on withdrawal of the bDMARD. Thus, escalating csDMARD therapy and adding a bDMARD in cases of non-response seems to be a rational approach.

Biomarkers that can predict a failure to first-line therapy with MTX would be useful to propose intensive therapy ‘ab initio’ in selected cases. However, such a biomarker is currently not available. Further research is warranted.

Prospective longitudinal studies evaluating the impact of smoking cessation on the outcome of EA as well as the efficacy of psychological interventions and strategies to promote DMARD adherence are currently lacking and should be added to the research agenda.

The main limitation of this SLR is the lack of studies including patients with early undifferentiated arthritis, since most of the literature refers to patients with early RA. Another limitation is that the analysis on DMARD safety in this SLR was limited to safety reported in RCTs. However, a recent SLR conducted by EULAR had a broader focus on safety of DMARD in RA.⁸

Author affiliations

¹Rheumatology department, Lapeyronie Hospital, Montpellier University, Montpellier, France

²Department of Clinical Immunology & Rheumatology, Amsterdam Rheumatology Center, Amsterdam & Zuyderland Medical Centre, Heerlen, The Netherlands

Acknowledgements The authors thank Louise Falzon (Columbia University Medical Center, Colombia, USA) for conducting the literature search, Cédric Lukas (Montpellier, France) and Sofia Romero (Leiden, the Netherlands) for expert advice and EULAR for supporting this systematic literature research.

Contributors CID and CH performed the systematic literature review and wrote the manuscript. BC and RL defined the research questions, supervised the work and revised the manuscript.

Funding EULAR.

Competing interests The individual declaration of conflicts of interest is available on demand at the EULAR secretariat and is summarised below: CID has received honoraria from BMS, MSD, Pfizer, Roche-Chugai and UCB, and research grants from MSD, Pfizer, Roche-Chugai and UCB. BC has received honoraria from BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche-Chugai and UCB, and research grants from Pfizer, Roche-Chugai and UCB. RL has received honoraria and/or research grants from AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Celgene, Janssen, Galapagos, Glaxo-Smith-Kline, Novartis, Novo-Nordisk, Merck, Pfizer, Roche, TiGenix and UCB. RL is director of Rheumatology Consultancy BV.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- Combe B, Landewe R, Lukas C, *et al.* EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCI-SIT). *Ann Rheum Dis* 2007;66:34–45.
- Smolen JS, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
- Smolen JS, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
- Smolen J, Landewé R, Bijlsma J, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017. In press.
- Gossec L, Smolen JS, Ramiro S, *et al.* European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016;75:499–510.
- Combe B, Landewé R, Daien CI, *et al.* 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis* 2016;[Epub ahead of print 15 Dec 2016]. doi: 10.1136/annrheumdis-2016-210602.
- van der Heijde D, Aletaha D, Carmona L, *et al.* 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- Hua C, Daien CI, Combe B, *et al.* Diagnosis, prognosis and classification of early arthritis: results of a systematic review informing the 2016 update of the EULAR recommendations for the management of early arthritis. *RMD Open* 2016;2:e000406.
- OCEBM Levels of Evidence. CEBM. 2016 [cited 3 May 2016]. <http://www.cebm.net/ocebm-levels-of-evidence>
- Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, *et al.* Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev* 2009;(4):CD006853.
- Manning VL, Hurley MV, Scott DL, *et al.* Education, self-management, and upper extremity exercise training in people with rheumatoid arthritis: a randomized controlled trial. *Arthritis Care Res* 2014;66:217–27.
- Mathieux R, Marotte H, Battistini L, *et al.* Early occupational therapy programme increases hand grip strength at 3 months: results from a randomised, blind, controlled study in early rheumatoid arthritis. *Ann Rheum Dis* 2009;68:400–3.
- Manfredsdottir VF, Vikingsdottir T, Jonsson T, *et al.* The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:734–40.
- Westhoff G, Rau R, Zink A. Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. *Rheumatol Oxf Engl* 2008;47:849–54.
- Andersson ML, Bergman S, Söderlin MK. The effect of stopping smoking on disease activity in rheumatoid arthritis (RA). Data from BARFOT, a Multicenter Study of Early RA. *Open Rheumatol J* 2012;6:303–9.
- Verschueren P, De Cock D, Corluy L, *et al.* Patients lacking classical poor prognostic markers might also benefit from a step-down glucocorticoid bridging scheme in early rheumatoid arthritis: week 16 results from the randomized multicenter CareRA trial. *Arthritis Res Ther* 2015;17:97.
- de Jong PH, Hazes JM, Han HK, *et al.* Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. *Ann Rheum Dis* 2014;73:1331–9.
- Menon N, Kothari SY, Gogna A, *et al.* Comparison of intra-articular glucocorticoid injections with DMARDs versus DMARDs alone in rheumatoid arthritis. *J Assoc Physicians India* 2014;62:673–6.
- Gaujoux-Viala C, Mitrovic S, Barnetche T, *et al.* Efficacy of glucocorticoids for early rheumatoid arthritis (RA): a meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2014;73:218.
- Mitrovic S, Fardet L, Vatié C, *et al.* THU0142 Safety of glucocorticoids for early rheumatoid arthritis: a meta-analysis of randomised controlled trials. *Ann Rheum Dis* 2014;73:228.
- Ding CZ, Yao Y, Feng XB, *et al.* Clinical analysis of Chinese patients with rheumatoid arthritis treated with leflunomide and methotrexate combined with different dosages of glucocorticoid. *Curr Ther Res Clin Exp* 2012;73:123–33.
- Ajeganova S, Svensson B, Hafström I, *et al.* Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. *BMJ Open* 2014;4:e004259.
- de Hair M, Ijff N, Jacobes J. Long-term adverse events after daily concomitant treatment with 10 mg prednisone in the 2-year computer assisted management in early rheumatoid arthritis trial-II. *Arthritis Rheumatol* 2015;67(Suppl 10) <http://acrabstracts.org/abstract/long-term-adverse-events-after-daily-concomitant-treatment-with-10mg-prednisone-in-the-2-year-computer-assisted-management-in-early-rheumatoid-arthritis-trial-ii/> (accessed 21 Dec 2016).
- Bosello S, Fedele AL, Peluso G, *et al.* Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression. *Ann Rheum Dis* 2011;70:1292–5.
- Gremese E, Salaffi F, Bosello SL, *et al.* Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. *Ann Rheum Dis* 2013;72:858–62.
- Lukas C, Combe B, Ravaut P, *et al.* Favorable effect of very early disease-modifying antirheumatic drug treatment on radiographic progression in early inflammatory arthritis: data from the Etude et Suivi des polyarthrites indifférenciées récentes (study and follow-up of early undifferentiated polyarthritis). *Arthritis Rheum* 2011;63:1804–11.
- Söderlin MK, Bergman S, BARFOT Study Group. Absent 'Window of Opportunity' in smokers with short disease duration. Data from BARFOT, a multicenter study of early rheumatoid arthritis. *J Rheumatol* 2011;38:2160–8.
- Kyburz D, Gabay C, Michel BA, *et al.* The long-term impact of early treatment of rheumatoid arthritis on radiographic progression: a population-based cohort study. *Rheumatology (Oxford)* 2011;50:1106–10.
- Moura CS, Abrahamowicz M, Beauchamp ME, *et al.* Early medication use in new-onset rheumatoid arthritis may delay joint replacement: results of a large population-based study. *Arthritis Res Ther* 2015;17:197.
- van der Woude D, Young A, Jayakumar K, *et al.* Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. *Arthritis Rheum* 2009;60:2262–71.
- van der Kooij SM, le Cessie S, Goekoop-Ruiterman YPM, *et al.* Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2009;68:1153–8.
- Weng HH, Ranganath VK, Khanna D, *et al.* Equivalent responses to disease-modifying antirheumatic drugs initiated at any time during the first 15 months after symptom onset in patients with seropositive rheumatoid arthritis. *J Rheumatol* 2010;37:550–7.
- van Nies JA, Tsonaka R, Gaujoux-Viala C, *et al.* Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. *Ann Rheum Dis* 2015;74:806–12.
- Emery P, Bingham C, Burmester GR. The first study of certolizumab pegol in combination with methotrexate in DMARD-naïve early rheumatoid arthritis patients led to sustained clinical response and inhibition of radiographic progression at 52 weeks: the C-EARLY

- randomized, double-blind, controlled phase 3 study. *Ann Rheum Dis* 2015;74(Suppl 2):712.
35. Burmester GR, Rigby WF, van Vollenhoven RF, *et al.* Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis* 2016;75:1081–91.
 36. Lee EB, Fleischmann R, Hall S, *et al.* Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377–86.
 37. Fleischmann R, Takeuchi T, Schlichting DE. Baricitinib, methotrexate, or baricitinib plus methotrexate in patients with early rheumatoid arthritis who had received limited or no treatment with Disease-Modifying Anti-Rheumatic Drugs (DMARDs): phase 3 trial results. *Arthritis Rheumatol* 2015;67(Suppl 10). <http://acrabstracts.org/abstract/baricitinib-methotrexate-or-baricitinib-plus-methotrexate-in-patients-with-early-rheumatoid-arthritis-who-had-received-limited-or-no-treatment-with-disease-modifying-anti-rheumatic-drugs-dmards-p/> (accessed 21 Dec 2016).
 38. Fleischmann R, Schiff M, van der Heijde D, *et al.* Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Rheumatol* 2016; doi:10.1002/art.39953 [Epub ahead of print].
 39. Detert J, Bastian H, Listing J, *et al.* Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naïve patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–50.
 40. Takeuchi T, Yamanaka H, Ishiguro N, *et al.* Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. *Ann Rheum Dis* 2014;73:536–43.
 41. Atsumi T, Yamamoto K, Takeuchi T, *et al.* FRI0278 The first early rheumatoid arthritis, certolizumab pegol, multicenter, double-blind, randomized, parallel-group study: C-Opera, in patients fulfilling the 2010 ACR/EULAR classification criteria, demonstrates inhibition of joint damage progression. *Ann Rheum Dis* 2014;73:484.
 42. Bijlsma JW, Welsing PM, Woodworth TG, OP0033 Rapid and sustained remission in early rheumatoid arthritis (RA) treated to target with tocilizumab, methotrexate, or their combination: the U-Act-Early Strategy Study. *Ann Rheum Dis* 2015;74:77–8.
 43. Emery P, Burmester GR, Bykerk VP, *et al.* Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis* 2015;74:19–26.
 44. Atsumi T, Yamamoto K, Takeuchi T. Clinical benefit of 1-year certolizumab pegol treatment in mtx-naïve, early rheumatoid arthritis patients is maintained after discontinuation up to 1 year. *Arthritis Rheumatol* 2016;75:75–83.
 45. Hørslev-Petersen K, Hetland ML, Ørnberg LM, *et al.* Clinical and radiographic outcome of a treat-to-target strategy using methotrexate and intra-articular glucocorticoids with or without adalimumab induction: a 2-year investigator-initiated, double-blinded, randomised, controlled trial (OPERA). *Ann Rheum Dis* 2016;75:1645–53.
 46. Smolen JS, Emery P, Fleischmann R, *et al.* Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. *Lancet Lond Engl* 2014;383:321–32.
 47. Durez P, Depresseux G, Nzeusseu Toukap A. Rate of remission by tocilizumab or methotrexate induction therapy in early active rheumatoid arthritis: results of the Tomera trial. *Ann Rheum Dis* 2013;72(Suppl 3):623.
 48. Nam JL, Villeneuve E, Hensor EM, *et al.* Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naïve, rheumatoid arthritis (the IDEA study). *Ann Rheum Dis* 2014;73:75–85.
 49. ter Wee MM, den Uyl D, Boers M, *et al.* Intensive combination treatment regimens, including prednisolone, are effective in treating patients with early rheumatoid arthritis regardless of additional etanercept: 1-year results of the COBRA-light open-label, randomised, non-inferiority trial. *Ann Rheum Dis* 2015;74:1233–40.
 50. Axelsen MB, Eshed I, Hørslev-Petersen K, *et al.* A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. *Ann Rheum Dis* 2015;74:867–75.
 51. Hørslev-Petersen K, Hetland ML, Junker P, *et al.* Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. *Ann Rheum Dis* 2014;73:654–61.
 52. Bijlsma JW, Welsing PM, Woodworth TG, *et al.* Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. *Lancet Lond Engl* 2016;388:343–55.
 53. Verschueren P, De Cock D, Corlyu L, *et al.* Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. *Ann Rheum Dis* 2015;74:27–34.
 54. den Uyl D, ter Wee M, Boers M, *et al.* A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. *Ann Rheum Dis* 2014;73:1071–8.
 55. Heimans L, Van Den Broek M, Le Cessie S, *et al.* Association of high body mass index with decreased treatment response to combination therapy in recent-onset rheumatoid arthritis patients. *Arthritis Care Res* 2013;65:1235–42.
 56. Sandberg MEC, Bengtsson C, Källberg H, *et al.* Overweight decreases the chance of achieving good response and low disease activity in early rheumatoid arthritis. *Ann Rheum Dis* 2014;73:2029–33.
 57. Wevers-De Boer K, Visser K, Heimans L, *et al.* Extended report: remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). *Ann Rheum Dis* 2012;71:1472–7.
 58. Mirpourian M, Salehi M, Abdolahi H, *et al.* The association of body mass index with disease activity and clinical response to combination therapy in patients with rheumatoid arthritis. *J Res Med Sci Off J Isfahan Univ Med Sci* 2014;19:509–14.
 59. Saevarsdotir S, Rezaei H, Geborek P, *et al.* Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial. *Ann Rheum Dis* 2015;74:1509–14.
 60. Saevarsdotir S, Wedrén S, Seddighzadeh M, *et al.* Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. *Arthritis Rheum* 2011;63:26–36.
 61. Rojas-Serrano J, Pérez LL, García CG, *et al.* Current smoking status is associated to a non-ACR 50 response in early rheumatoid arthritis. A cohort study. *Clin Rheumatol* 2011;30:1589–93.
 62. Wessels JAM, van der Kooij SM, le Cessie S, *et al.* A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. *Arthritis Rheum* 2007;56:1765–75.
 63. Coates LC, Moverley AR, McParland L, *et al.* Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet Lond Engl* 2015;386:2489–98.
 64. Gaujoux-Viala C, Nam J, Ramiro S, *et al.* Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:510–15.
 65. Orlova EV, Karateev D, Denisov L. Comparative efficacy of two exercises programs in patients with early rheumatoid arthritis: 6-month randomized controlled trial. *Ann Rheum Dis* 2015.
 66. O'Dell JR, Curtis JR, Mikuls TR, *et al.* Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. *Arthritis Rheum* 2013;65:1985–94.
 67. Joensuu JT, Huoponen S, Aaltonen KJ, *et al.* The cost-effectiveness of biologics for the treatment of rheumatoid arthritis: a systematic review. *PLoS ONE* 2015;10:e0119683.
 68. Finckh A, Bansack N, Marra CA, *et al.* Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents: a cost-effectiveness analysis. *Ann Intern Med* 2009;151:612–21.