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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

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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 2013[3] and 2016[4]) 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 procedures[7] 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 *et al*[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
			56	No intervention				223.8 (184.1; 263.5)	+3.7 (−20.6, 28.0)	
Mathieux *et al*[12]	1c	RA of ≤2 years' duration	30	Education and practice regarding joint protection with hand and wrist exercises	0.5 day	Handgrip strength at week 12	Measured by an air dynamometer in kPa	Mean (SD) 37.9 (21.7)	3-month value: 53.9 (24.2)†	Unclear
			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	Population and controls	Intervention	Time point	Clinical outcomes		Radiographic progression (SHS change >0.5)	Risk of bias
Verschueren *et al*[16]	CareRA	2c	43 pts with low risk† ERA	PRED from 30 to 0 mg/day in 34 weeks	16 weeks	Remission DAS28-CRP	65.1%[$]	NA	High‡
			47 pts with low risk† ERA	No GC			46.8%		
De Jong *et al*[17]	tREACH	1b	91 pts with ERA	Intramuscular: MP 120 or TRIAM 80 mg at inclusion	1 year	Remission DAS	61%	21%	High§
			93 pts with ERA	Oral: PRED from 15 to 0 mg/day in 10 weeks			54%	24%	
Menon *et al*[18]		2c	25 pts with ERA	TRIAM 40 mg in every SJ at baseline	12 weeks	ACR20/50/70	100*/60**/36**	NA	High‡
			25 pts with ERA	No GC			84/20/0		

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 trial[34] and the COBRA-light study[35] 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	n	DMARD start	End point	Functional outcomes	Radiographic outcomes
Bosello *et al* (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%
			77	≥3 months			45.4%
Gremese *et al* (2b)[25]	Consecutive patients attending 3 early arthritis clinics	RA with duration <12 months	105	<3 months	12-month HAQ <0.5	62.7%	
			376	≥3 months		41.3%	
Lukas *et al* (2b)[26]	ESPOIR	Arthritis with duration <6 months	140	<3 months	12-month mean radiographic progression		0.8 units/year *,†
			521	≥3 months			1.7 units/year
Weng *et al* (2b)[32]	Western Consortium of Practicing rheumatologist study	RF+RA within 16 months from symptoms onset to DMARD initiation	42	<3 months	2-year changes in HAQ and mTSS progression	−0.63±0.58	4.62±8.46 units/year
			3	≥10 months		−0.35±0.61	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 *et al* (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
			NA	n=85	MTX+PBO		37%		6.4*	
Atsumi *et al* (1b)[44]	C-OPERA	Yes	Week 52	Pts with high risk† ERA n=108	CZP+MTX	SDAI remission at week 104	41%	Percentage of patients with year 2 ΔmTSS ≥0.5	16%	Unclear‡
			NA	n=71	MTX+PBO		29%*		32%***	
Hørslev-Petersen *et al* (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 *et al* (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 *et al* (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 *et al* (1b)[48]	IDEA	55	IFX+MTX	IFX dose increase	Week 26	DAS44 <1.6	48%	ΔmTSS at week 50	1.2	Low
		57	MTX+MP+PBO	csDMARD combination			36%		2.8	
Ter Wee *et al* (1b)[49]	COBRA-light	81	MTX+SSZ+GC	MTX dose increase, then ETN.	Week 26	DAS44 <1.6	47%	ΔmTSS at week 52	0.5 ±1.6	High†
		81	MTX +GC	ETN			38%		0.6 ±1.4	
Axelsen *et al* (1b)[50] Hørslev-Petersen *et al*[51]	OPERA	89	ADA+MTX	csDMARD combination or bDMARD	Week 12	DAS28CRP <2.6	74%	mTSS at week 52	5.0 ±5.2	Low
		91	PBO+MTX	csDMARD combination, then ADA			49%***		5.5 ±6.2	
De Jong *et al* (1b)[17]	tREACH	91	csDMARD combination +Intramuscular-GC	MTX+ETN, then MTX+ADA	Week 12	DAS <1.6	61%	ΔmTSS at week 52	0.1 (0.0–1.0)	High‡
		93	csDMARD combination +oral GC	MTX+ETN, then MTX+ADA			54%		0.0 (0.0–1.0)	
		97	MTX+ oral GC	MTX+ETN, then MTX+ADA			51%		0.0 (0.0–1.0)	
Atsumi *et al* (2c)[44]	C-OPERA	159	CZP+MTX	open label CZP +MTX	Week 24	DAS28 <2.6	57%	ΔmTSS at week 52	0.4 ±2.7	Low
		157	PBO+MTX	CZP+MTX			37%***		1.6 ±4.9	
Bijlsma et al (1b)[42 52]	U-ACT-EARLY STRATEGY STUDY	106	TCZ+MTX	TCZ+MTX+HCQ, then TNFi+MTX		DAS28 <2.6 with SJC ≤4, for ≥24 weeks[$]	86%	ΔmTSS at week 52	0.5 ±1.5	Low
		103	TCZ+PBO	TCZ+HCQ, then TCZ+MTX			88%		0.8 ±3.2	
		108	MTX+PBO	MTX+HCQ, then MTX+TCZ			77%		1.0 ±2.9*	

Results are expressed in %; means±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]

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