CONCISE REPORT

Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of The EULAR recommendations for the management of rheumatoid arthritis

Katerina Chatzidionysiou,[1] Sharzad Emamikia,[1] Jackie Nam,[2] Sofia Ramiro,[3] Josef Smolen,[4] Désirée van der Heijde,[3] Maxime Dougados,[5] Johannes Bijlsma,[6] Gerd Burmester,[7] Marieke Scholte,[8,9] Ronald van Vollenhoven,[1,10] Robert Landewé[10]

Handling editor Dr. Francis Berenbaum

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2016-210711).

For numbered affiliations see end of article.

Correspondence to
Dr Katerina Chatzidionysiou, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), Rheumatology Department, Karolinska University Hospital, The Karolinska Institute, Stockholm 171 76, Sweden; aikaterini.chatzidionysiou@karolinska.se

Received 21 October 2016
Revised 26 January 2017
Accepted 28 February 2017
Published Online First 29 March 2017

► http://dx.doi.org/10.1136/annrheumdis-2016-210715
► http://dx.doi.org/10.1136/annrheumdis-2016-211005

To cite: Chatzidionysiou K, Emamikia S, Nam J, *et al*. *Ann Rheum Dis* 2017;**76**:1102–1107.

ABSTRACT

Objectives To perform a systematic literature review (SLR) informing the 2016 update of the recommendations for the management of rheumatoid arthritis (RA).

Methods An SLR for the period between 2013 and 2016 was undertaken to assess the efficacy of glucocorticoids (GCs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs) (tofacitinib and baricitinib) in randomised clinical trials.

Results For GCs, four studies were included in the SLR. Patients without poor prognostic factors experienced benefit when GCs were added to methotrexate (MTX). Lower doses of GCs were similar to higher doses. For csDMARDs, two new studies comparing MTX monotherapy with combination csDMARD were included in the SLR. In the tREACH trial at the end of 12 months no difference between the groups in disease activity, functional ability and radiographic progression was seen, using principles of tight control (treat-to-target). In the CareRA trial, combination therapy with csDMARDs was not superior to MTX monotherapy and monotherapy was better tolerated.

For tsDMARDs, tofacitinib and baricitinib were shown to be more effective than placebo (MTX) in different patient populations.

Conclusions Addition of GCs to csDMARD therapy may be beneficial but the benefits should be balanced against the risk of toxicity. Under tight control conditions MTX monotherapy is not less effective than combination csDMARDs, but better tolerated. Tofacitinib and baricitinib are efficacious in patients with RA, including those with refractory disease.

INTRODUCTION

The landscape of rheumatoid arthritis (RA) treatment has unquestionably changed dramatically during the last decade. The development and introduction to daily clinical practice of disease modifying antirheumatic drugs (DMARDs) as well as earlier diagnosis and treatment, and well defined goals of treatment, have contributed to this treatment revolution. Despite this progress, there are still unmet needs, and a better application of the currently available treatments as well as better treatment strategies are needed. Practical recommendations based on the existing evidence are appropriate tools for the rheumatologists. In 2013 a European League Against Rheumatism (EULAR) task force has revised the previous recommendations on RA treatment.[1] A revision of the 2013 recommendations was now undertaken.

The aim of this review was to inform the new EULAR recommendations[2] on the management of RA on efficacy of glucocorticoids (GCs), conventional synthetic DMARDs (csDMARDs) and two targeted synthetic DMARDs (tsDMARDs), tofacitinib and baricitinib based on new evidence accrued since 2013.[3] The results of this and two other systematic literature reviews (SLRs)[4 5] provided the task force with the current state of evidence.

METHODS

An SLR using MEDLINE, EMBASE and the Cochrane CENTRAL library was performed from January 2013 until February 2016, based on a prespecified PICOS statement: P=population, I=interventions, C=comparators, O=outcomes and S=study design. The population was 'adult RA patients'; the intervention was (1) GCs, (2) csDMARDs (methotrexate (MTX), leflunomide, sulfasalazine, hydroxychloroquine, intramuscular gold, auranofin, azathioprine, ciclosporine, minocycline, D-penicillamine, cyclophosphamide, chlorambucil, mycophenolate, tacrolimus), (as monotherapy or combination therapy) and (3) tsDMARDs (tofacitinib and baricitinib); the comparator was patients not receiving the abovementioned treatments; the outcome pertained to efficacy on disease activity, function, patient reported outcomes (PROs) and structural damage; and the study design always was 'randomised controlled trials' (RCTs). Risk of bias (RoB) was assessed using the Cochrane RoB assessment tool (Cochrane Handbook for Systematic Reviews of Interventions V.5.1.0 March 2011 (cited September 2016); available from: http://handbook.cochrane.org/). ORs for dichotomous measures were

determined to assess the magnitude of treatment effect. The DerSimonian and Laird random-effects model was used to pool the data when possible, allowing for both within-study and between-study variations. Statistical heterogeneity among studies was evaluated using the I^2 statistic and χ^2 test where a p value <0.10 was considered to be statistically significant. A value of above 50% for I^2 was considered to be high. Details about the search and the studies included can be found in the online supplementary material. The selected group of patients included in RCTs as well as the relatively short duration of RCTs, makes addressing long-term safety of drugs in RCTs difficult. For this reason, safety aspects of GCs and csDMARDs were addressed in a separate SLR based on observational studies coming from registries.[5] Some safety issues regarding tsDMARDs will be discussed here, since real life data of tsDMARDs are still lacking.

RESULTS

Efficacy of addition of GCs to csDMARDs

Of 348 hits, 4 studies were included in the analysis (table 1). The selection of articles is shown in online supplementary figure S1. A small study by Menon *et al*[6] showed greater efficacy of a combination of csDMARDs with intra-articular GCs than with csDMARDs alone in patients with RA with less than 2 years disease duration, but this was an open label study with high RoB. In the CareRA trial patients with early RA, but without poor prognostic factors, benefited from the addition of GCs (COBRA-slim) to MTX with no differences in safety observed.[7] The primary end point of this study was not met, since the percentage of patients achieving remission at week 16 was only numerically but not significantly higher in the GC group (65.1% vs 46.8%, p=0.08). However, this substudy analysis did not have sufficient statistical power and had a high RoB, primarily due to lack of blinding.

A non-inferiority trial compared two different GC strategies; the COBRA-light strategy (prednisolone at 30 mg/day, tapered to 7.5 mg/day in 9 weeks) in combination with MTX; and the COBRA strategy, using prednisolone at 60 mg/day (tapered to7.5 mg/day in 6 weeks) in combination with both MTX and sulfasalazine. The lower dose of GCs was efficacious in suppressing clinical disease activity and improving functional ability, but non-inferiority could not be claimed formally.[8 9] The degree of radiographic progression was similar in the two groups (COBRA and COBRA-light). However, this study also had a high RoB (open design), and no comparison with application of conventional GCs was performed.

In a double-blind RCT with patients with established RA, low-dose prednisone with modified release ('chronotherapy') added to existing DMARD treatment in patients with active disease had a significant effect on disease activity and health-related quality of life compared with placebo.[10]

A pooled analysis could not be performed because of significant heterogeneity of the studies regarding designs, patient populations, doses and routes of administration of GCs, and outcome measures. The results of the newer RCTs are in accordance with the previously formulated standpoint that GC when added to csDMARD therapy may have beneficial effects. Safety aspects, as addressed in a separate SLR, have to be taken into consideration.[5] Level of evidence (LOE): 1a.

Efficacy of csDMARDs and csDMARD combinations

In total 518 studies were screened. The selection of articles is shown in online supplementary figure S2. Only two new studies comparing MTX monotherapy with MTX in combination with another csDMARD without differences in GC usage were

Table 1 Randomised controlled trials of glucocorticoids (GCs) added to csDMARDs in RA

Study	Study design	RoB	Disease duration (years)	N. patients	GC regimen	Control group	Primary outcome	Result in GC group	Result in control group	p Value
Menon *et al*[6]	Superiority, open	High	<2	56	i.a. triamcinolone acetonide	No i.a. GCs	DAS28 at week 12 ACR 20/50/70 at week 12*	3.39 100/60/36	4.99 84/20/0	0.001 <0.05
CareRA, Verschueren *et al*[7]	Superiority, open	High	≤1	90	p.o. Prednisolone (step-down from 30 mg/day)	No oral GCs	DAS28 (CRP) <2.6 at week 16	65.1%	46.8%	0.08
CAPRA-2. Buttgereit *et al*[10]	Superiority, double-blind	Low	Mean 8	350	MR prednisone (5 mg/day)	Placebo	ACR20 at week 12	48%	29%	<0.001
den Uyl *et al*[8]† ter Wee *et al*[9]†	Non-inferiority, open	High	≤2	164	COBRA light (step-down from 30 mg/day)	COBRA (step-down from 60 mg/day)	mean ΔDAS44 at week 26	−2.18 (SD 1.1) in COBRA light	−2.50 (SD 1.21) in COBRA	0.08

*Composite primary end point.
†Two separate publications based on the same study.
ACR, American College of Rheumatology; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS, Disease Activity Score; i.a., intra-articular; MR, modified release; p.o., per os; RA, rheumatoid arthritis; RoB, risk of bias.

included in the SLR. In the tREACH trial, that applied tight control principles, at 12 months, disease activity, functional ability and radiographic progression were similar in the two groups who received csDMARD combination therapy (MTX, sulfasalazine and hydroxychloroquine) with either oral GCs or intramuscular GCs and the group that received MTX monotherapy (see online supplementary table S1). GCs were given either intramuscularly (methylprednisolone 120 mg or triamcinolone 80 mg) or in an oral tapering scheme (weeks 1–4: 15 mg/day, weeks 5–6: 10 mg/day, weeks 7–8: 5 mg/day and weeks 9–10: 2.5 mg/day). In addition, a higher number of medication adjustments due to adverse events (AEs) were applied in the combination group.[11 12] Interestingly, for the two groups on combination therapy, intramuscular and oral GCs were similarly effective as modes of bridging therapy.

In the CareRA trial (in a different subpopulation than the one described above in a different part of the CareRA trial) patients with early RA and risk factors for more aggressive disease did not benefit from combination of MTX with other csDMARDs in comparison to MTX monotherapy (both combined with GCs) (see online supplementary table S1). In these arms GCs were dosed orally using a weekly step-down scheme (30–20–12.5–10–7.5–5 mg prednisone). Monotherapy with MTX was better tolerated.[13] The CareRA trial has a high RoB (open label).

The results of the newer RCTs are in accordance with the previously formulated standpoint that combination of csDMARDs is not better than monotherapy with MTX. The need for more optimal use of csDMARDs, particularly regarding the dose of csDMARDs, however, is obvious. One double-blind RCT failed to show differences between two starting doses of MTX, namely 7.5 mg and 15 mg weekly.[14] In the CONCERTO trial initiating adalimumab+MTX combination therapy, the efficacy of 10 mg/week and 20 mg/week MTX was not statistically different in patients with early RA.[15] One study compared a loading dose of leflunomide (100 mg×1 for 3 days) with a fixed dose of 20 mg daily and did not show differences in efficacy but a better safety profile for the fixed dose.[16] A weekly dose of 50 mg leflunomide showed similar benefits to a daily dose of 10 mg leflunomide for the treatment of mild-to-moderate early RA.[17] The latter however was an open superiority study with a high RoB and 10 mg leflunomide daily is considered a suboptimal dose.

Efficacy of tsDMARDs (tofacitinib and baricitinib)

From the 134 hits on tofacitinib 9 were identified as RCTs (table 2).[18–26] Efficacy of tofacitinib, both as monotherapy and in combination with MTX, was formally proven in different patient populations (MTX-naïve, csDMARD and biological DMARD (bDMARD) inadequate responders) compared with placebo (background MTX). For baricitinib the literature search yielded eight new RCTs (two of them had PROs as main study outcomes) (table 3).[27–34] Similar clinical efficacy of baricitinib in monotherapy and in combination with MTX has been suggested, but only the combination (baricitinib+MTX) significantly inhibited radiographic progression.[29] In the MTX-IR (inadequate responder) RA-BEAM study, comparing adalimumab+MTX versus baricitinib+MTX versus placebo+MTX, showed small but significantly lower responses for adalimumab +MTX versus baricitinib+MTX, but both were higher than placebo+MTX (Disease Activity Score 28-C reactive protein <2.6 19% vs 24% vs 4%) at week 12.[30]

Importantly, baricitinib has now shown efficacy in a refractory RA population after failure of both antitumour necrosis factor (anti-TNF) and non-anti-TNF bDMARDs.[16] All studies had low RoB. The selection of articles for tofacitinib and baricitinib is shown in online supplementary figures S3 and S4, respectively.

No meta-analysis could be performed due to the heterogeneity between the studies. The most commonly found laboratory abnormalities with tofacitinib were mild decreases in neutrophil and lymphocyte counts and mild increases in aminotransferase and creatinine levels, while baricitinib was associated with reductions in haemoglobin levels. The relative risks for serious AEs with tofacitinib and baricitinib compared with placebo were 0.8 (95% CI 0.5 to 1.3) and 1.0 (95% CI 0.6 to 1.7), respectively. However, a significantly increased risk of herpes infection was seen (RR=3.1, 95% CI 1.1 to 8.5) with tofacitinib.

The results of the newer RCTs are in accordance with the previously formulated standpoint that the tsDMARDs (tofacitinib and baricitinib) are effective and safe in the short term. (LOE: 1A)

DISCUSSION

Overall, the results of this review confirmed the previous SLR and expanded the overall insights. Although the evidence on efficacy of short-term GCs when added to csDMARDs is robust and undisputed, there are still concerns regarding long-term safety (such as infections, diabetes, osteoporosis, and gastrointestinal and cardiovascular events). Preliminary long-term results of the CAMERA II trial showed a low occurrence of AEs but suggested for the first time an increased cardiovascular risk for the patients with early RA treated with 10 mg/day prednisone for at least 2 years.[35] These results are still unpublished (abstract in American College of Rheumatology 2015). A separate SLR focusing on the safety of GCs has been performed in order to inform the task force and enable the formation of the recommendations.[5] GC safety aspects have also been addressed in a separate paper prior EULAR activity.[36] Clear consensus regarding the dose and tapering of GCs is still lacking. New data have suggested that short-term lower doses of GCs (starting at 30 mg prednisone per day with rapid tapering), as in the COBRA-light regimen, might be a feasible alternative to the higher doses (starting at 60 mg/day) as in the COBRA regimen, although formal non-inferiority was not proven. In fact, this trial did not fulfil the inclusion criteria for the SLR, since there was no comparator group (group without GCs according to the PICO). However, we decided to include it in the SLR since the question posed is highly clinically relevant.

Interestingly, the tREACH trial has suggested that the efficacy of oral GCs as bridging treatments was not superior to intramuscular GCs. Two new studies were published regarding chronotherapy and intra-articular GC therapy, thus answering one of the research questions posed in 2013. The latter however was a high RoB study.

Regarding the choice of csDMARD combination therapy over monotherapy, again—and in contradiction with the perception of many clinicians—we could not substantiate clear evidence in favour of combination therapy with csDMARDs. Neither the 1-year results of the tREACH, nor those of the CARERA study, showed clear evidence that MTX monotherapy is inferior to combination therapy with csDMARDs when used in combination with GCs and when a tight treat-to-target approach is employed. Importantly, monotherapy was generally better tolerated than combination therapy in these studies. Generally, the complexity of the design of pragmatic trials and certain methodological issues, such as high dropout rates and change of primary end point, make the interpretation of the results challenging.

Table 2 Randomised controlled trials of tofacitinib in RA

Study	Study design	N patients	Patient population	Primary outcome	Tofacitinib monotherapy or in combination with csDMARDs	Comparator arm	Result in tofacitinib arm (5 mg×2)	Result in tofacitinib arm (10 mg×2)	Result in comparator arm	p Value
Lee *et al*[23] ORAL start	Superiority, double-blind	958	DMARD-naive	ACR70 and mean change from baseline SHS at month 6	Monotherapy	MTX	25.5% least-squares mean (±SE)=0.2±0.1	37.7% least-squares mean (±SE)=<0.1 ±0.1	12% least-squares mean (±SE)=0.8 ±0.2	p<0.001 for either dose vs MTX p<0.001 (both tofacitinib groups vs placebo)
Kremer *et al*[22] ORAL sync	Superiority, double-blind	795	csDMARDs and/or bDMARDs IR	ACR20 at month 6 Change in HAQ at month 3 Remission at month 6	Combination with csDMARDs	Placebo with csDMARDs	52.1% −0.44 8.5%	56.6% −0.53 12.5%	30.8% −0.16 2.6%	<0.001 <0.001 <0.005
Van der Heijde *et al*[20] ORAL scan	Superiority, double-blind	800	MTX IR§	ACR20 at month 6	Combination with MTX	Placebo with MTX	51.5%	61.8%	25.3%	<0.001 for both tofacitinib doses vs placebo
				Change in SHS at month 6			0.12	0.06	0.47	<0.05 only for 10 mg tofacitinib vs placebo
				ΔHAQ at month 3			−0.4	−0.54	−0.15	<0.0001 (10 mg)*
				Remission at month 6			7.2%	16%	1.6%	<0.001 (10 mg)*
Burmester *et al*[21] ORAL step	Superiority, double-blind	399	TNFis IR+##	ACR20 at month 3 ΔHAQ at month 3 Remission at month 3	Combination with MTX	Placebo with MTX	41.7% −0.43 6.7%	48.1% −0.46 8.8%	24.4% −0.18 1.7%	<0.001† <0.0001† <0.05†
Tanaka *et al*[24]	Superiority, double-blind	318	csDMARDs and/or bDMARs IR	ACR20 at month 3	Monotherapy	Placebo	73.1%	84.9%	15.4%	<0.0001 both groups vs placebo
Strand *et al*[18] ORAL solo	Superiority, double-blind	611	csDMARDs and/or bDMARDs IR	Multiple PROs	Monotherapy	Placebo	Tofacitinib > placebo			
Strand *et al*[19] ORAL step	Superiority, double-blind	399	≥1 TNFi*	Multiple PROs	Combination with MTX	Placebo with MTX	Tofacitinib > placebo			
Wallenstein *et al*[25]	2 Phase-IIb studies, double-blind	507 (combination with MTX) 384 (monotherapy)	MTX IR	Multiple PROs	Both in combination with MTX and in monotherapy	Placebo	Tofacitinib > placebo (both as monotherapy and in combination with MTX)			
Strand *et al*[26] ORAL standard	Superiority, double-blind	717	MTX IR*	Multiple PROs	Combination with csDMARDs	Placebo	Tofacitinib+MTX > control group			

*Since tofacitinib at 5 mg twice daily failed to be statistically significant for radiographic progression, and due to the step-down procedure applied to primary efficacy end points, significance was not declared for the HAQ DI score or remission (DAS28-ESR <2.6) for tofacitinib at 5 mg twice daily.
†For both groups versus placebo.
ACR, American College of Rheumatology; bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IR, inadequate responder; MTX, methotrexate; PROs, patient reported outcomes; RA, rheumatoid arthritis; SHS, van der Heijde modification of the total Sharp Score; TNFi, tumour necrosis factor inhibitor.

Table 3 Randomised controlled trials of baricitinib in RA

Study	Study design	N patients	Patient population	Primary outcome	Baricitinib arm(s)	Comparator arm	Result in baricitinib arm (4 mg)	Result in comparator arm	p Value
Fleischmann *et al*[29] RA-begin*	Phase III, non-inferiority	584	DMARD naive	ACR20 at week 24	Monotherapy or in combination with MTX	MTX	77% (both as monotherapy or in comb with MTX)	62%	<0.01
Keystone *et al*[27]	Phase II, superiority	301	MTX IR	ACR20 at week 12	Baricitinib+MTX	Placebo+MTX	76%	41%	<0.001
Tanaka *et al*[29]	Phase II, superiority	145	MTX IR	ACR20 at week 12	Baricitinib+MTX	Placebo+MTX	77%	31%	<0.001
Taylor *et al*[30] RA-beam	Phase IIII, (Superiority design for baricitinib vs placebo)	1305	MTX IR	ACR2o at week 12	Baricitinib+MTX	Placebo+MTX ADA+MTX	70%	40% in the placebo arm 61% in the ADA arm	<0.001 vs placebo <0.05 vs ADA
Genovese *et al*[31] Smolen *et al*[33] RA-beacon‡	Phase III, superiority	527	bDMARDs IR	ACR20 at week 12 Several PROs	Baricitinib+MTX	Placebo+MTX	55% Baricitinib+MTX>placebo+MTX	27%	<0.001
Dougados *et al*[34] Emery *et al*[32] RA-build	Phase III, superiority	684	csDMARDs IR	ACR20 at week 12 Several PROs	Baricitinib+csDMARD	Placebo +csDMARD	62% Bari>placebo	39%	<0.001

The primary objective evaluated non-inferiority of baricitinib 4 mg monotherapy to MTX on ACR20.
†38% of the patients had a history of treatment with at least one biologic DMARD that was not a TNFi.
ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biological DMARD; csDMARD, conventional synthetic DMARD; DMARD, disease-modifying antirheumatic drug; IR, inadequate responder; MTX, methotrexate; PROs, patient-reported outcomes; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

There is a clear need for studies addressing the optimal use of csDMARDs. No new studies fulfilling the inclusion criteria regarding dose and route of administration of MTX were identified. A previous SLR by Visser and van der Heijde[37] had addressed this issue.

Tofacitinib is the first JAK inhibitor approved for the treatment of RA in many countries and baricitinib is under regulatory evaluation. This SLR confirmed that tofacitinib has beneficial effects on disease activity, physical function, radiographic progression and PROs, both in patients with early RA who are DMARD-naive and in patients with established disease who have failed csDMARDs and/or bDMARDs. Baricitinib was found to be effective in MTX-naïve patients and also after failure of drugs with multiple modes of action. Data on long-term safety of this new class of DMARDs from real life observational studies are needed. Until then, rheumatologists are advised to take into account safety data obtained through RCTs and follow the labels of each drug, including AEs and lab monitoring.

Author affiliations
[1]Karolinska Institute, Stockholm, Sweden
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[3]LUMC, Leiden, The Netherlands
[4]Medical University of Vienna, Vienna, Austria
[5]Paris Descartes University, Paris, France
[6]Utrecht University Medical Center, Utrecht, The Netherlands
[7]Charité University Hospital, Berlin, Germany
[8]Department of Psychology, Health and Technology, University of Twente, Enschede, The Netherlands
[9]EULAR Standing Committee of People with Arthritis/Rheumatism in Europe
[10]Amsterdam Rheumatology and Immunology Center, Amsterdam, The Netherlands

Contributors All authors contributed and finally approved the current manuscript.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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