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Author for correspondence:
Salah Ghabri, E-mail: s.ghabri@has-sante.fr

Rheumatoid arthritis treated with 6-months of first-line biologic or biosimilar therapy: an updated systematic review and network meta-analysis

Emma L. Simpson[1], Shijie Ren[1], Emma S. Hock[1], John W. Stevens[1], Aymeric Binard[2], Yves-Marie Pers[3,4], Rachel Archer[5], Suzy Paisley[5], Matthew D. Stevenson[5], Chloé Herpin[6] and Salah Ghabri[7]

[1]School of Health and Related Research (ScHARR), University of Sheffield, United Kingdom; [2]Department of Rheumatology, CHU de la Cavale-Blanche, Brest, France; [3]Clinical Immunology and Osteoarticular Diseases Therapeutic Unit, Lapeyronie University Hospital, Montpellier, France; [4]IRMB, University of Montpellier, INSERM, CHU Montpellier, Montpellier, France; [5]School of Health and Related Research (ScHARR), University of Sheffield, United Kingdom; [6]Department of Economic and Public Health Evaluation, French National Authority for Health (HAS), Saint-Denis La Plaine, France and [7]Department of Economic and Public Health Evaluation, French National Authority for Health (HAS), Saint-Denis La Plaine, France

Abstract

Objectives. The aim of this study was to estimate the effectiveness of first-line biologic disease modifying drugs(boDMARDs), and their approved biosimilars (bsDMARDs), compared with conventional (csDMARD) treatment, in terms of ACR (American College of Rheumatology) and EULAR (European League against Rheumatism) responses.

Methods. Systematic literature search, on eight databases to January 2017, sought ACR and EULAR data from randomized controlled trials (RCTs) of boDMARDs / bsDMARDs (in combination with csDMARDs, or monotherapy). Two adult populations: methotrexate (MTX)-naïve patients with severe active RA; and csDMARD-experienced patients with moderate-to-severe active RA. Network meta-analyses (NMA) were conducted using a Bayesian Markov chain Monte Carlo simulation using a random effects model with a probit link function for ordered categorical.

Results. Forty-six RCTs met the eligibility criteria. In the MTX-naïve severe active RA population, no biosimilar trials meeting the inclusion criteria were identified. MTX plus methylprednisolone (MP) was most likely to achieve the best ACR response. There was insufficient evidence that combination boDMARDs was superior to intensive (two or more) csDMARDs. In the csDMARD-experienced, moderate-to-severe RA population, the greatest effects for ACR responses were associated with tocilizumab (TCZ) monotherapy, and combination therapy (plus MTX) with bsDMARD etanercept (ETN) SB4, boDMARD ETN and TCZ. These treatments also had the greatest effects on EULAR responses. No clear differences were found between the boDMARDs and their bsDMARDs.

Conclusions. In MTX-naïve patients, there was insufficient evidence that combination boDMARDs was superior to two or more csDMARDs. In csDMARD-experienced patients, boDMARDs and bsDMARDs were comparable and all combination boDMARDs / bsDMARDs were superior to single csDMARD.

The introduction of novel targeted therapies such as biologic original disease-modifying anti-rheumatic drugs (boDMARDs) has expanded the arsenal of available drugs for rheumatoid arthritis (RA). These are usually prescribed on failure of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Biosimilars (bsDMARDs) of boDMARDs have recently been approved by the European Medicines Agency (EMA). The introduction of bsDMARDs onto the market may have the potential to provide a cheaper alternative to boDMARDs, provided they have similar effectiveness.

There are a wide range of treatment options offered, and few head-to-head randomized controlled trials (RCTs) between boDMARDs and bsDMARDs. A network meta-analysis allows a synthesis of all available evidence.

In 2017, the French national authority for health (Haute Autorité de Santé, HAS) initiated an economic evaluation of biological treatments for RA in csDMARD-experienced and methotrexate (MTX)-naïve populations. The rationale of that evaluation emphasized two issues: (i) boDMARDs place a substantial financial burden on healthcare systems and individual patients. The overall costs of boDMARDs should take into account the benefit of reducing the disease impact; however, research is required to fully assess differences in cost-effectiveness

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between the currently available treatments. (ii) A wide range of treatment options is offered, and there are few head-to-head RCTs between boDMARDs and bsDMARDs. A network meta-analysis can provide useful comparative evidence to define the best treatment strategies and a simultaneous comparison between treatments.

Unlike other reviews of biologics in RA, the current review included licensed bsDMARDs and boDMARDs compared with csDMARD therapy, and considered MTX-naive and csDMARD-experienced populations separately. Our study focused on the effectiveness criteria and aimed to estimate the short-term comparative effectiveness, on American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) responses, of first-line boDMARDs, and their EMA approved biosimilars. The choice of these outcomes was validated by the HAS clinical experts of the RA economic evaluation. Analysis of the safety outcomes were beyond the scope of this study. This will be proposed in an independent chapter of the HAS on-going cost-effectiveness report

Materials and methods

The review was conducted in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (1). The review was an update of work by Stevenson et al. 2016 (2).

Data Sources

The following electronic bibliographic databases were searched: Medline and Medline in Process (by means of Ovid SP); Embase (by means of Ovid SP); Cochrane Database of Systematic Reviews (by means of Wiley); Cochrane Central Register of Controlled Trials (by means of Wiley); Health Technology Assessment Database (by means of Wiley); Database of Abstracts of Reviews of Effect (by means of Wiley); CINAHL (by means of EBSCOhost); and Toxline (by means of ProQuest). Original searches were performed on the databases from inception until May 2013 (2) and the searches were updated on January 23, 2017. The exact search strategies are available from the authors. Electronic database searches were supplemented with searching of bibliographies of included trials, and information provided by trial authors.

Trial Selection

Study design was restricted to RCTs. Two populations of adult RA patients were included: a MTX-naïve population with severe active RA (DAS28 $\geq$ 5.1); and adults with moderate to severe active RA (DAS28 $\geq$ 3.2) previously treated with, and inadequately responded to, csDMARDs (a csDMARD-experienced population). csDMARDs included MTX, sulfasalazine, leflunomide, with MTX being most commonly used. The following boDMARDs and bsDMARDs were included, as first-line biologic treatment, prescribed in accordance with EMA licensed indications: abatacept (ABT); adalimumab (ADA); certolizumab pegol (CTZ); etanercept (ETN) and its biosimilar SB4 (Benepali); golimumab (GOL); infliximab (IFX) and its biosimilars CT-P13 (Inflectra or Remsima) and SB2 (Flixabi); and tocilizumab (TCZ). Following the date of our searches, biosimilars of adalimumab (Amgevita, Cyltezo, Imraldi, Solymbic) have been approved, however, as these were not licensed at the time of searches they were not included. boDMARDs and bsDMARDs could be delivered either as monotherapy (as allowed by current French licensed indications), or in combination with csDMARDs (biologic plus csDMARD combination therapy is illustrated by + in Tables and Figures).

Included comparators were boDMARDs or bsDMARDs compared with each other, single csDMARD treatment, or intensive csDMARDs (two or more csDMARDs). Additionally, for the MTX-naïve population, management strategies involving further conventional DMARDs (e.g. SSZ, LEF), nonsteroidal anti-inflammatory drugs, and corticosteroids. The outcomes sought were ACR responses or EULAR responses at follow-up between 22 weeks and 30 weeks. RCTs with early escape were only included if they reported a nonresponder imputation. Two reviewers independently selected trials based on the review inclusion criteria, with any discrepancy resolved by a third reviewer.

Data Collection and Assessment of Bias

One reviewer extracted data, and these data were checked by a second reviewer. Study arms where intervention treatments were administered in line with licensed indications were extracted. Where studies had treatment arms with unlicensed doses, these were not extracted. Two reviewers independently performed quality assessment based on the 2011 Cochrane risk of bias tool criteria 1.0 (3). Data extraction and quality assessment forms developed in Stevenson et al. (2) were used. Any discrepancy was resolved by a third reviewer.

Network Meta-analysis

Network meta-analyses (NMAs) of ACR and EULAR data at 22–30 weeks follow-up were conducted using Bayesian Markov chain Monte Carlo (MCMC) simulation. ACR and EULAR data were analyzed as ordered categorical data with mutually exclusive categories: ACR has four ordered categories (no response, ACR20, ACR50 and ACR70) and EULAR has three categories (no response, moderate response, and good response). Data were analyzed using a probit link function (4) a random effects model to allow for heterogeneity in treatment effects across studies and assuming an homogeneous variance. Inconsistency between direct and indirect evidence was assessed using a node-splitting method (4).

The reference treatment was defined as any single csDMARD (mostly MTX). This choice was approved by the clinical experts involved in the HAS economic evaluation of boDMARDs strategies. Meta-regression was performed to explore whether duration of disease was a treatment effect modifier. Absolute goodness-of-fit of the model was assessed using residual deviance. The analyses assumed that biosimilar treatments were not the same as their parent treatment. All the analyses were performed in OpenBUGS using the R package R2OpenBUGS (5). For each analysis, the first 180,000 iterations were discarded to allow for the number of iterations required for convergence to the target distribution, and 20,000 further iterations were used to estimate parameters. Convergence to the target distribution were checked using Gelman Rubin diagnostics (6). The most effective treatment was determined by the probability of being ranked as the best treatment, which considered the size of the treatment effect and its associated uncertainty.

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Results

Included Trials

The electronic database search identified 34,621 records and bibliography searching identified an additional eighteen records. Following title and abstract sifting, 128 studies were assessed for eligibility, and 82 studies excluded (see Supplementary Figure S1 PRISMA flow diagram (1) for reasons for exclusion). Of the seventeen trials excluded for not reporting ACR or EULAR responses within 22–30 weeks follow-up: twelve were trials with randomized phases shorter than 22 weeks; in one RCT participants in either arm could receive additional treatment at clinician's discretion after 3 months; two had unlicensed comparators; one reported EULAR Boolean 28 at 1 year follow-up, but did not report ACR or EULAR responses; and one had the primary endpoint of safety and measured efficacy as the secondary endpoints of DAS44 and the health assessment questionnaire.

There were forty-six trials meeting the review inclusion criteria, comprising ten RCTs (7–16) with a MTX-naïve population, and thirty-six RCTs (17–52) with a csDMARD-experienced population. Included trials are shown in Table 1. There was a balance across trials in terms of population characteristics and trial quality. There was some variation between trials in disease duration (Table 1), with the MTX-naïve population ranging from 5–166 weeks, and csDMARD-experienced ranging from 94–676 weeks. However, meta-regression suggested that disease duration was not a treatment effect modifier for ACR response, with the estimated coefficient of the disease duration being close to zero. The limited number of RCTs did not allow us to perform meta-regression including disease duration for EULAR response in the two selected populations. We found no evidence of selective outcome reporting in the included trials. There was a low risk of bias in terms of blinding and analyses (Supplementary Figure S2). The majority of RCTs were blinded (74 percent), and reported analyses with either intent-to-treat or modified intent-to-treat (that is, all randomized patients who received at least one dose of trial drug were included in the analyses, 87 percent of RCTs). There was a higher risk of bias regarding randomization, with unclear reporting of sequence generation and allocation concealment (54 percent and 52 percent of RCTs, respectively).

Network Meta-analyses

ACR response data were provided by ten trials of the MTX-naïve population, and thirty-four trials of the csDMARD-experienced population (Table 1). EULAR response data were provided by two trials of the MTX-naïve population and nineteen trials of the csDMARD-experienced population (Table 1). Network diagrams are shown in Supplementary Figure S3. Results are presented using medians and 95 percent credible intervals (CrI) from posterior distributions, treatment rankings. The probabilities of being the best treatment were calculated for each analysis. The models fitted the data well with the total residual deviance close to the total number of data points.

ACR Responses

Figure 1 shows the NMA for ACR responses. Results shown are the effect of each treatment relative to csDMARD on the probit scale, with negative values representing positive treatment effects (i.e. a smaller proportion of patients in the lower ACR categories).

In the MTX-naïve population, all treatments, except ADA monotherapy, were associated with beneficial median treatment effects relative to csDMARD with the greatest effect being associated with MTX plus MP (effect on probit scale -0.79, 95 percent CrI: -1.44 to -0.20) and IFX+(-0.74, 95 percent CrI: -1.14, -0.40). However, the treatment effects were superior against csDMARDs only for ADA+, ETN+, IFX+, intensive cDMARDs (two or more csDMARDs) and MTX plus MP at a conventional 5 percent level (Figure 1). Intensive cDMARDs and boDMARDs had similar responses. The difference between intensive csDMARDs and boDMARDs was not significant (data not shown). MTX plus MP was most likely to be the most effective intervention (median rank 1; probability of being the best 0.51). The estimated between-trial standard deviation was 0.10 (95 percent CrI: 0.02 to 0.34).

In the csDMARD-experienced population, all treatments, except placebo, were associated with beneficial median treatment effect relative to csDMARD with the greatest effects being associated with bsDMARD ETN (SB4)+ (-1.12, 95 percent CrI: -1.70 to -0.55), boDMARD ETN+ (-0.03, 95 percent CrI: -1.34 to -0.73), TCZ+ (-1.08, 95 percent CrI: -1.43 to -0.73), and TCZ monotherapy (-1.08, 95 percent CrI: -1.39 to -0.76). The treatment effects were superior compared with csDMARD for all interventions except for ADA (borderline nonstatistically significant) at a conventional 5 percent level (Figure 1). The treatment that was most likely to be the best was the bsDMARD of ETN (SB4) combination therapy (median rank 2; probability of being the best 0.37). The estimated between-trial standard deviation was 0.22 (95 percent CrI: 0.12 to 0.35).

EULAR Responses

Figure 2 shows the NMA for EULAR responses. Results shown are the effect of each intervention relative to csDMARDs on the probit scale, with negative values representing positive treatment.

Only two trials provided EULAR response data in the MTX-naïve population. The results showed that ADA+ and GOL+ were associated with beneficial treatment effects relative to csDMARD with the greatest effect being associated with ADA+ (-0.64, 95 percent CrI: -1.15 to -0.15). However, the treatment effect was superior only for ADA+ at a conventional 5 percent level (Figure 2). ADA+ was most likely to be the most effective intervention of the three interventions with EULAR response data (ADA+, GOL+, and csDMARD) (median rank 1; probability of being the best 0.84). The estimated between-trial standard deviation was 0.14 (95 percent CrI: 0.03 to 0.48). However, this was based on only two trials.

In the csDMARD-experienced population, all treatments, except placebo, were associated with beneficial median treatment effects relative to csDMARD with the greatest effect being associated with TCZ+(-1.56, 95 percent CrI: -2.21 to -1.01), TCZ monotherapy (-1.47, 95 percent CrI: -2.15 to -0.89), ETN+ (-1.34, 95 percent CrI: -2.55 to -0.14), and bsDMARD ETN (SB4)+ (-1.36, 95 percent CrI: -2.78 to 0.05). The treatment effects were superior only for ETN+, GOL+, IFX+, CTZ+, TCZ (with and without MTX) at a conventional 5 percent level (Figure 2). The effects of combination therapies of bsDMARDs were comparable to boDMARDs (data not shown, available from authors on request). TCZ+ was the treatment that was most likely to be the most effective intervention (median rank 2; probability of being the best 0.33) for EULAR responses. The estimated between-trial standard deviation was 0.34 (95 percent CrI: 0.15 to 0.53).

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Table 1. Included Trials

Trial	Population	Intervention (*n*)	Comparator(s) (*n*)	Disease duration (mean, weeks)	Provides data	
					ACR	EULAR
BeST	MTX-naïve	IFX+ MTX (*n* = 128)	csDMARD[a] (*n* = 126) Intensive csDMARDs[b] (*n* = 133) Step-up intensive csDMARDs[b] (*n* = 121)	24[c]	Yes	No
COMET	MTX-naïve	ETN+ MTX (*n* = 274)	MTX, PBO (*n* = 268)	78	Yes	No
Durez 2007	MTX-naïve	IFX+ MTX (*n* = 15)	MTX (*n* = 14) MTX, MP (*n* = 15)	21	Yes	No
ERA	MTX-naïve	ETN, PBO (*n* = 207)	MTX, PBO (*n* = 217)	52	Yes	No
GO-BEFORE	MTX-naïve	GOL+ MTX (*n* = 159)	MTX, PBO (*n* = 160)	166	Yes	Yes
HIT HARD	MTX-naïve	ADA, PBO (*n* = 87)	MTX, PBO (*n* = 85)	7	Yes	No
HOPEFUL1 NCT01120366	MTX-naïve	ADA+ MTX (*n* = 171)	MTX, PBO (*n* = 163)	16	Yes	Yes
IDEA NCT01308255	MTX-naïve	IFX+ MTX (*n* = 55)	MTX, MP (*n* = 57)	5	Yes	No
OPTIMA	MTX-naïve	ADA+ MTX (*n* = 515)	MTX, PBO (*n* = 517)	18	Yes	No
PREMIER	MTX-naïve	ADA, PBO (*n* = 274)	ADA+ MTX (*n* = 268) MTX, PBO (*n* = 257)	38	Yes	No
ACT-RAY	csDMARD-experienced	TCZ, PBO (*n* = 277)	TCZ+ MTX (*n* = 276)	676	Yes	Yes
ADACTA	csDMARD-experienced	ADA, PBO (*n* = 163)	TCZ, PBO (*n* = 163)	354	Yes	Yes
AIM	csDMARD-experienced	ABT i.v.+ MTX (*n* = 433)	MTX, PBO (*n* = 219)	449	Yes	No
AMPLE	csDMARD-experienced	ADA (*n* = 328)	ABT s.c. (*n* = 318)	94	Yes	No
ARMADA	csDMARD-experienced	ADA+ MTX (*n* = 67)	MTX, PBO (*n* = 62)	607	Yes	No
ATTEST	csDMARD-experienced	IFX+ MTX (*n* = 165)	ABT i.v.+ MTX (*n* = 156) MTX, PBO (*n* = 110)	405	Yes	Yes
ATTRACT	csDMARD-experienced	IFX+ MTX (*n* = 86)	MTX, PBO (*n* = 88)	NR	Yes	No
AUGUST II	csDMARD-experienced	ADA+ MTX (*n* = 79)	MTX, PBO (*n* = 76)	447	Yes	Yes
CERTAIN	csDMARD-experienced	CTZ+ csDMARDs (*n* = 98)	csDMARDs, PBO (*n* = 98)	239	Yes	Yes
CHANGE	csDMARD-experienced	ADA (*n* = 91)	PBO (*n* = 87)	477	Yes	No
DE019	csDMARD-experienced	ADA+ MTX (*n* = 207)	MTX, PBO (*n* = 200)	569	Yes	No
De Filippis 2006	csDMARD-experienced	ETN+ MTX (*n* = 16)	IFX+ MTX (*n* = 16)	NR	Yes	No
ETN Study 309	csDMARD-experienced	ETN+ SSZ (*n* = 101)	ETN, PBO (*n* = 103) SSZ, PBO (*n* = 150)	341	Yes	No
GO-FORTH	csDMARD-experienced	GOL+ MTX (*n* = 89)	MTX, PBO (*n* = 90)	455	Yes	Yes
GO-FORWARD	csDMARD-experienced	GOL+ MTX (*n* = 89)	MTX, PBO (*n* = 133)	421	Yes	Yes
CREATE-IIB	csDMARD-experienced	ETN+ csDMARD (*n* = 64)	csDMARD, PBO (*n* = 65)	419	Yes	No
JESMR	csDMARD-experienced	ETN+ MTX (*n* = 77)	ETN (*n* = 74)	485	Yes	Yes
Kim 2007	csDMARD-experienced	ADA+ MTX (*n* = 63)	MTX, PBO (*n* = 65)	356	Yes	No
LARA	csDMARD-experienced	ETN+ MTX (*n* = 281)	Intensive csDMARDs[a] (*n* = 142)	430	Yes	Yes
Moreland 1999	csDMARD-experienced	ETN, PBO (*n* = 78)	PBO (*n* = 80)	598	Yes	No
NCT00445770	csDMARD-experienced	ETN, PBO (*n* = 182)	MTX , PBO (*n* = 176)	156	Yes	No
NCT01001832	csDMARD-experienced	ABT s.c.+ MTX (*n* = 59)	ABT i.v.+ MTX (*n* = 59)	334	Yes	No
NCT01895309	csDMARD-experienced	Biosimilar[SB4] ETN+ MTX (*n* = 299)	ETN+ MTX (*n* = 297)	318	Yes	Yes
NCT01936181	csDMARD-experienced	Biosimilar [SB2] IFX+ MTX (*n* = 291)	IFX+ MTX (*n* = 293)	333	Yes	Yes

(*Continued*)

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Table 1. (*Continued.*)

Trial	Population	Intervention (*n*)	Comparator(s) (*n*)	Disease duration (mean, weeks)	Provides data	
					ACR	EULAR
PLANETRA NCT01217086	csDMARD-experienced	Biosimilar [CT-P13] IFX+ MTX (*n* = 302)	IFX+ MTX (*n* = 304)	NR	Yes	Yes
RACAT/ O'Dell	csDMARD-experienced	ETN+ MTX (*n* = 163)	Intensive csDMARDs[b] (*n* = 159)	271	Yes	No
SAMURAI	csDMARD-experienced	TCZ (*n* = 157)	csDMARDs (*n* = 145)	119	Yes	No
SATORI	csDMARD-experienced	TCZ, PBO (*n* = 61)	MTX, PBO (*n* = 64)	447	Yes	Yes
STAR	csDMARD-experienced	ADA+ csDMARDs (*n* = 318)	csDMARDs PBO (*n* = 318)	541	Yes	No
START	csDMARD-experienced	IFX+ MTX (*n* = 360)	MTX, PBO (*n* = 363)	NR	Yes	Yes
SURPRISE NCT01120366	csDMARD-experienced	TCZ i.v. (*n* = 115)	TCZ i.v.+ MTX(*n* = 118)	203	Yes	Yes
Swefot	csDMARD-experienced	IFX+ MTX (*n* = 128)	Intensive csDMARDs[b](*n* = 130)	27	No	Yes
TACIT	csDMARD-experienced	Grouped boDMARDs+ MTX (clinician's choice ADA, ETN or IFX) (*n* = 107)	Intensive csDMARDs[c] (*n* = 107)	268	No	Yes[d]
TOWARD	csDMARD-experienced	TCZ+ csDMARDs (*n* = 803)	csDMARDs, PBO (*n* = 413)	510	Yes	Yes
van de Putte 2004	csDMARD-experienced	ADA (*n* = 113)	PBO (*n* = 110)	577	Yes	Yes
Weinblatt 1999	csDMARD-experienced	ETN+ MTX (*n* = 59)	MTX, PBO (*n* = 30)	676	Yes	No

ABT, abatacept; ADA, adalimumab; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NR, not reported; PBO, placebo; TCZ, tocilizumab.
[a]Sequential monotherapy.
[b]Methotrexate, sulfasalazine and prednisone, then hydroxychloroquine for step-up group
[c]Median (mean not reported).
[d]Methotrexate, plus sulfasalazine or hydroxychloroquine.
[e]Methotrexate, sulfasalazine and hydroxychloroquine.
[f]Two to five csDMARDs.
[g]Data provided in personal communication from author.

Discussion

In this review of ten RCTs, we found that in the MTX-naïve population, MTX plus MP, or intensive csDMARDs (that is, two or more csDMARDs), were comparable to boDMARD treatment for ACR responses. Thirty-six RCTs contributed data to NMAs of the csDMARD-experienced population. For both ACR and EULAR responses in this population, the greatest effects were associated with combination therapy (with MTX) of bsDMARD ETN, boDMARD ETN, and TCZ, as well as TCZ monotherapy. The effects of combination therapies of bsDMARDs were comparable to boDMARDs (data not shown, available from authors on request). The ongoing results of the French economic evaluation of biologic treatments sequences for moderately-to-severely active RA should confirm whether bsDMARDs strategies instead of boDMARDs for a csDMARD-experienced patients are cost-effective option. However, concerning the MTX-naïve patients, the above results that showed comparable effect between boDMARDs and intensive cDMARDs at 6 months seem in line with the recent RA French guidelines which do not recommend to reimburse the use of biological treatments for this indication (except when MTX is contraindicated).

One of the strengths of our study was to adopt strict definitions of outcomes and populations that are both consistent with the therapeutic strategies of RA (as they are defined by EULAR and ACR) and the existing indications in the RA French management.

Our approach was different from other NMAs performed by HTA institutions [e.g., CADTH, 2018 (53), ICER, 2017 (54) or Cochrane of biologics, e.g., Singh et al. 2016 (55), Singh et al. 2017 (56), Hazlewood et al. 2016 (57) who included many outcomes (e.g., DAS28, remission, radiographic progression) but did not use EULAR criterion]. Moreover, the analyzed population were not often the same as the CADTH (2018) (53) and ICER (2017) (54) who focused only on clinical effectiveness for moderately-to-severely active RA for patients who had an inadequate response to prior csDMARDs.

Despite many differences in terms of exclusion criteria, inclusion of targeted synthetic DMARD (e.g., baricitinib and tofacitinib) and the number of analyzed studies, our findings on ACR criterion (e.g., ACR50) comparing boDMARDs showed similar findings for moderately-to-severely active RA as the above NMAs: most of boDMARDs (and bsDMARDs) compared with cDMARDs (i.e., MTX) showed a clinical benefit but they did not often allow to detect a significant difference when compared with each other.

Concerning MTX-naïve patients, our results were partially similar with those of Singh et al. (2017) (56) that showed that biologic with MTX were associated with statistically benefits in terms of achievement of ACR50: In our analysis, boDMARDs

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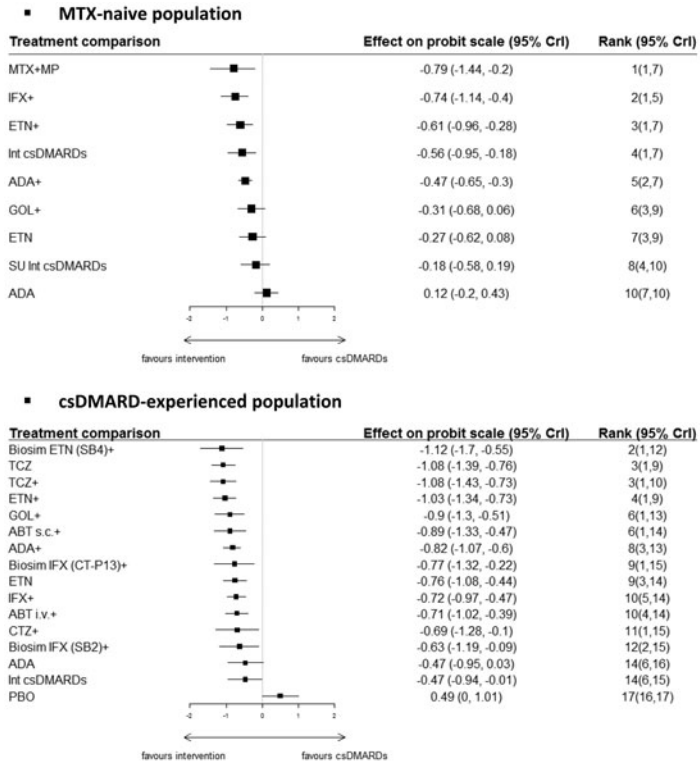

Fig. 1. ACR responses (effect and rank). ABT, abatacept; ADA, adalimumab; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NR, not reported; PBO, placebo; TCZ, tocilizumab.

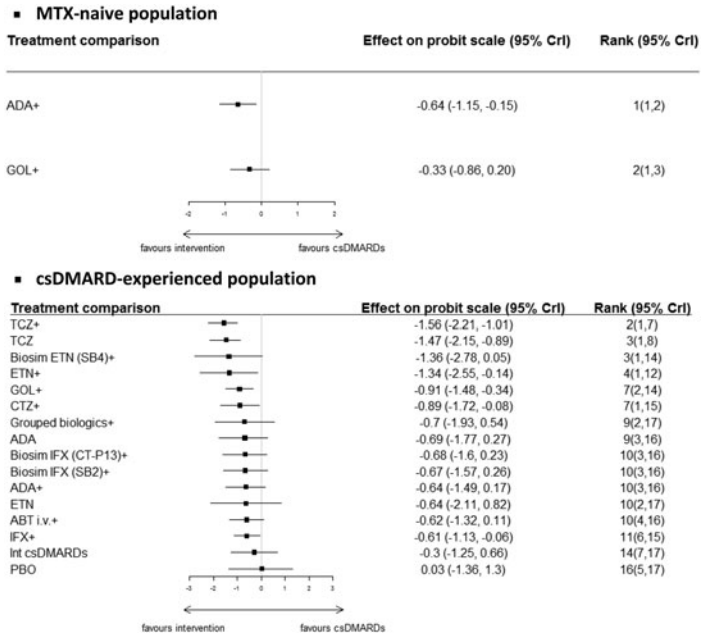

Fig. 2. EULAR responses (effect and rank). ABT, abatacept; ADA, adalimumab; CTZ, certolizumab pegol; ETN, etanercept; GOL, golimumab; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NR, not reported; PBO, placebo; TCZ, tocilizumab.

(IFX + MTX, ETN + MTX, ADA + MTX) as well as intensive cDMARDs and MTX+ MP were more effective than cDMARDs.

The review had limitations. The searches were conducted in 2017. There was limited evidence on EULAR response in MTX-naïve patients, with no bsDMARD RCTs meeting the inclusion criteria of the review, and no data for MTX plus MP or intensive csDMARDs for EULAR response. The limited number of RCTs did not allow us to perform meta-regression including disease duration for EULAR response. Only three RCTs of bsDMARDs meeting the inclusion criteria were identified. As bsDMARDs were compared only with their boDMARD, their inclusion in the NMA did not affect the results for other inventions because they did not form a closed loop in the network. Ideally, evidence synthesis based on remission or low disease activity would be used as these are established treatment targets and routinely used for monitoring patients in European clinical practice. The EMA guidelines consider that remission should be the primary endpoint in clinical trials, and can be either defined according to EULAR criteria (DAS28 < 2.6), or in accordance with the more strict EULAR–ACR criteria (Boolean or Index-based)

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(58). Nevertheless, there are few data in the RCTs on this criterion to make relevant comparisons, and so we compared the treatments on the ACR criteria, and the EULAR response, instead as these scores represent a relative change from baseline.

Our review included trials of bsDMARDs, while the majority of previous reviews have included only anti-TNF biologics. Our review differed from other reviews of biologics in RA, in that (i) it was limited to first-line biologics; (ii) it considered MTX-naive and csDMARD-experienced trials separately; (iii) it was limited to trials reporting outcomes at 22–30 weeks follow-up; (iv) it considered ACR and EULAR as ordered categorical data, whereas the reviews by Hazlewood et al. (2016) (57), Singh et al. 2016 (55), Singh et al. 2017 (56), and CADTH (2018) (53) treated these outcomes as binary which ignores the natural ordering and correlation between categories. Treating patient responses as mutually exclusive categories enables a simultaneous analysis of the data, including studies that do not provide information about some categories, and a single estimate of treatment effect.

The finding that intensive csDMARDs were comparable to boDMARDs for MTX-naïve patients (data not shown) also agreed with a previous review (57). Previous meta-analyses underscored the dearth of direct evidence of effectiveness difference between biological agents (59;60). Our findings suggested that TCZ monotherapy was most favorable for csDMARD-experienced RA patients. This result was coherent with the conclusions of a previous review (61) where TCZ was either of comparable or superior efficacy to other boDMARDs. However, this finding might be explained by the fact that, for boDMARDs with a significant effect toward inhibition of acute phase reactants (APR), such as TCZ or the Janus kinase inhibitors, DAS28 may overestimate clinical response due to the high weight of APR components in the DAS28 formula (62). Similarly C-reactive protein (CRP) level is a component of ACR response. It is commented that there may be silent residual inflammation in the joints even though CRP is low.

In clinical practice, decision making in patients with RA is not the same as in clinical trials. The choice of treatment is the result of a complex decision process that must take into account disease activity, and physician and patient characteristics. For triple intensive csDMARD therapy, despite the efficacy, the question of treatment adherence and persistence remain.

In conclusion, our findings provide data for the short term effectiveness of boDMARDs and bsDMARDs for use in the current HAS economic evaluation of DMARD strategies for RA. Adverse events were not addressed, but were in HAS's economic decision model.

For MTX-naïve patients with severe active RA, MTX plus MP or intensive csDMARDs, at six months, were comparable to boDMARDs, with all these treatments being superior to a single csDMARD. For csDMARD-experienced patients with moderate to severe active RA, bsDMARDs were comparable to their boDMARD. Combination therapy with all boDMARDs and bsDMARDs were superior to csDMARD treatment, with bsDMARD ETN, boDMARD ETN, and TCZ likely to be the most effective.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0266462318003628

Supplementary Figure 1: https://doi.org/10.1017/S0266462318003628
Supplementary Figure 2: https://doi.org/10.1017/S0266462318003628
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Author ORCIDs. Emma S. Hock, 0000-0002-8617-8875.

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Conflicts of interest. The authors declare that they have noncompeting interest.

References

1. **Moher D, Liberati A, Tetzlaff J, Altman DG and The PG** (2009) Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* **6**, e1000097.
2. **Stevenson M, Archer R, Tosh J, *et al.*** (2016) Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifying antirheumatic drugs only: Systematic review and economic evaluation. *Health Technol Assess* **20**, 1–610.
3. **The_Cochrane_Collaboration** (2011) Cochrane handbook for systematic reviews of interventions. handbook.cochrane.org (accessed December 5, 2018).
4. **Dias S, Sutton AJ, Ades AE and Welton NJ** (2013) Evidence synthesis for decision making 2: A generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* **33**, 607–617.
5. **Sturtz S, Ligges U and Gelman A** (2005) R2WinBUGS: A package for running WinBUGS from R. *J Stat Softw* **12**, 1–16.
6. **Brooks S and Gelman A** (1998) General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* **7**, 434–455.
7. **van den Broek M, Dirven L, Klarenbeek N, *et al.*** (2013) Clinical and radiological outcomes of four disease activity driven treatment strategies: 8-year results of the best study. Annals of the Rheumatic Disease [Internet], https://ard.bmj.com/content/71/Suppl_3/106.1 (accessed December 5, 2018).
8. **Emery P, Breedveld FC, Hall S, *et al.*** (2008) Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): A randomised, double-blind, parallel treatment trial. *Lancet* **372**, 375–382.
9. **Durez P, Malghem J, Toukap AN, *et al.*** (2007) Treatment of early rheumatoid arthritis: A randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis Rheum* **56**, 3919–3927.
10. **Bathon JM, Martin RW, Fleischmann RM, *et al.*** (2000) A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* **343**, 1586–1593.
11. **Emery P, Fleischmann RM, Moreland LW, *et al.*** (2009) Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III,

multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* **60**, 2272–2283.

12. **Detert J, Bastian H, Listing J, *et al.*** (2013) Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* **72**, 844–850.
13. **Takeuchi T, Yamanaka H, Ishiguro N, *et al.*** (2014) 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* **73**, 536–543.
14. **Nam JL, Villeneuve E, Hensor EM, *et al.*** (2014) Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: A double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). *Annals of the rheumatic diseases [Internet]* **73**, 75–85. http://ard.bmj.com/content/73/1/75.full.pdf (accessed December 5, 2018).
15. **Kavanaugh A, Fleischmann RM, Emery P, *et al.*** (2013) Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* **72**, 64–71.
16. **Breedveld FC, Weisman MH, Kavanaugh AF, *et al.*** (2006) The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* **54**, 26–37.
17. **Dougados M, Kissel K, Sheeran T, *et al.*** (2013) Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2 year randomized controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis* **72**, 43–50.
18. **Gabay C, Emery P, van VR, *et al.*** (2013) Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): A randomised, double-blind, controlled phase 4 trial. *Lancet* **381**, 1541–1550.
19. **Russell AS, Wallenstein GV, Li T, *et al.*** (2007) Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. *Ann Rheum Dis* **66**, 189–194.
20. **Fleischmann R, Schiff MH, Weinblatt ME, *et al.*** (2012) Effects of subcutaneous abatacept or adalimumab on remission and associated changes in physical function and radiographic outcomes: One year results from the ample (abatacept versus adalimumab comparison in biologic-naive ra subjects with background methotrexate) trial. *Arthritis Rheum* **64**, S577.
21. **Weinblatt ME, Keystone EC, Furst DE, *et al.*** (2003) Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial. *Arthritis Rheum* **48**, 35–45.
22. **Schiff M, Keiserman M, Codding C, *et al.*** (2008) Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: A phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* **67**, 1096–1103.
23. **Maini R, St Clair EW, Breedveld F, *et al.*** (1999) Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A randomised phase III trial. *Lancet* **354**, 1932–1939.
24. **van Vollenhoven RF, Kinnman N, Vincent E, Wax S, Bathon J** (2011) Atacicept in patients with rheumatoid arthritis and an inadequate response to methotrexate: Results of a phase II, randomized, placebo-controlled trial. *Arthritis Rheum* **63**, 1782–1792.
25. **Smolen J, Emery P, Ferraccioli G** (2011) Efficacy and safety of certolizumab pegol after incomplete response to DMARDS in RA patients with low moderate disease activity: Results from certain, a phase IIIb study. *Ann Rheum Dis* **70**, 259.
26. **Miyasaka N** (2008) Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: The CHANGE study. *Mod Rheumatol* **18**, 252–262.
27. **Keystone EC, Kavanaugh AF, Sharp JT, *et al.*** (2004) Radiographic, clinical, and functional outcomes of treatment with Adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: A randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* **50**, 1400–1411.
28. **De Filipis L, Caliri A, Anghelone S, *et al.*** (2006) Improving outcomes in tumour necrosis factor alpha treatment: Comparison of the efficacy of the tumour necrosis factor alpha blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. *Panminerva Med* **48**, 129–135.
29. **Combe B, Codreanu C, Fiocco U, *et al.*** (2006) Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: A double-blind comparison. *Ann Rheum Dis* **65**, 1357–1362.
30. **Tanaka Y, Harigai M, Takeuchi T, *et al.*** (2012) Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: Results of the GO-FORTH study. *Ann Rheum Dis* **71**, 817–824.
31. **Keystone E, Genovese MC, Klareskog L, *et al.*** (2010) Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* **69**, 1129–1135.
32. **Keystone EC, Wang MM, Layton M, Hollis S, McInnes IB, Study T** (2012) Clinical evaluation of the efficacy of the P2X7 purinergic receptor antagonist AZD9056 on the signs and symptoms of rheumatoid arthritis in patients with active disease despite treatment with methotrexate or sulphasalazine. [Erratum appears in Ann Rheum Dis. 2012;71:2064]. *Ann Rheum Dis* **71**, 1630–1625.
33. **Kameda H, Ueki Y, Saito K, *et al.*** (2010) Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: A randomized trial. *Mod Rheumatol* **20**, 531–538.
34. **Kim HY, Lee SK, Song YW, *et al.*** (2007) A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *J Rheumatol* **10**, 9–16.
35. **Machado D, Guzman R, Xavier R, *et al.***, editors. Combination etanercept and methotrexate therapy provides better outcomes than standard DMARD and methotrexate therapy in rheumatoid arthritis: Results from a study in the Latin America region. Presented at XVII Congress of Pan American League of Associations of Rheumatology (PANLAR); Punta Cana, Dominican Republic; 17–21 April 2012.
36. **Moreland LW, Schiff MH, Baumgartner SW, *et al.*** (1999) Etanercept therapy in rheumatoid arthritis: A randomized, controlled trial. *Ann Intern Med* **130**, 478–486.
37. **Takeuchi T, Miyasaka N, Zang C, *et al.*** (2013) A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. *Mod Rheumatol* **23**, 623–633.
38. **Matsubara T, Inoue H, Iwahashi M, Yamazaki A and Takeuchi T** (2013) A multi-center, double-dummy, double-blind study of subcutaneous (SC) abatacept (ABA) compared with intraveneous (IV) ABA in japanese rheumatoid arthritis patients with inadequate response to methotrexate. Annals of the Rheumatic Disease [Internet], 71. http://ard.bmj.com/content/71/Suppl_3/197.1.full.pdf (accessed December 5, 2018).
39. **Emery P, Vencovsky J, Sylwestrzak A, *et al.*** (2017) A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* **76**, 51–57.
40. **Choe J-Y, Prodanovic N, Niebrzydowski J, *et al.*** (2017) A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* **76**, 58–64.

https://doi.org/10.1017/S0266462318003628 Published online by Cambridge University Press

41. **Yoo DH, Hrycaj P, Miranda P, *et al.*** (2013) A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: The PLANETRA study. *Ann Rheum Dis* **72**, 1613–1620.
42. **O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, *et al.*** (2013) Therapies for active rheumatoid arthritis after methotrexate failure. The New England journal of medicine [Internet], 369:[307–18 pp.]. http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/394/CN-00876394/frame.html.
43. **Nishimoto N, Hashimoto J, Miyasaka N, *et al.*** (2007) Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): Evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. *Ann Rheum Dis* **66**, 1162–1167.
44. **Nishimoto N, Miyasaka N, Yamamoto K, *et al.*** (2009) Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): Significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. *Mod Rheumatol* **19**, 12–19.
45. **Furst DE, Schiff MH, Fleischmann RM, *et al.*** (2003) Adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: Results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* **30**, 2563–2571.
46. **Westhovens R, Yocum D, Han J, *et al.*** (2006) The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: A large, randomized, placebo-controlled trial. *Arthritis Rheum* **54**, 1075–1086.
47. **Kaneko Y, Atsumi T, Tanaka Y, *et al.*** (2016) Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a prospective, randomised, controlled study (SURPRISE study). *Ann Rheum Dis* **75**, 1917–1923.
48. **van Vollenhoven RF, Ernestam S, Geborek P, *et al.*** (2009) Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* **374**, 459–466.
49. **Scott DL, Ibrahim F, Farewell V, *et al.*** Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial. BMJ (Online) [Internet]. 2015; 350. https://www.bmj.com/content/350/bmj.h1046 (accessed December 5, 2018).
50. **Genovese MC, McKay JD, Nasonov EL, *et al.*** (2008) Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* **58**, 2968–2980.
51. **Van De Putte LBA, Atkins C, Malaise M, *et al.*** (2004) Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* **63**, 508–516.
52. **Weinblatt ME, Kremer JM, Bankhurst AD, *et al.*** (1999) A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* **340**, 253–259.
53. **CADTH Health Technology Assessment** (2018) *Drugs for the management of rheumatoid arthritis clinical evaluation*. Ottawa: CADTH
54. **ICER. Evidence report** (2017) *Targeted immune modulators for rheumatoid arthritis: Effectiveness & value*. New England: ICER
55. **Singh JA, Hossain A, Tanjong Ghogomu E, *et al.*** (2016) Biologics or tofacitinib for rheumatoid arthritis in incomplete responders to methotrexate or other traditional disease-modifying anti-rheumatic drugs: A systematic review and network meta-analysis. *Cochrane Database Syst Rev*, CD012183.
56. **Singh J, Hossain A, Mudano A, *et al.*** (2017) Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: A systematic review and network meta-analysis. *Cochrane Database Syst Rev* **13**, CD012183.
57. **Hazlewood GS, Barnabe C, Tomlinson G, *et al.*** (2016) Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: Abridged Cochrane systematic review and network meta-analysis. *BMJ* **353**, i1777.
58. **European Medicines Agency** (2015) *Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis*. Contract No.: CPMP/EWP/556/95 Rev. 2. London: European Medicines Agency.
59. **Pierreisnard A, Issa N, Barnetche T, Richez C, Schaeverbeke T** (2013) Meta-analysis of clinical and radiological efficacy of biologics in rheumatoid arthritis patients naive or inadequately responsive to methotrexate. *Joint Bone Spine* **80**, 386–392.
60. **Gaujoux-Viala C, Gossec L, Cantagrel A, *et al.*** (2014) Recommendations of the French Society for Rheumatology for managing rheumatoid arthritis. *Joint Bone Spine* **81**, 287–297.
61. **Alfonso-Cristancho R, Armstrong N, Arjunji R, *et al.*** (2016) Comparative effectiveness of biologics for the management of rheumatoid arthritis: Systematic review and network meta-analysis. *Clin Rheumatol* **36**, 25–34.
62. **Smolen JS, Aletaha D** (2011) Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: The role of acute-phase reactants. *Arthritis Rheum* **63**, 43–52.

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