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REVIEW ARTICLE

# A Bayesian mixed treatment comparison of efficacy of biologics and small molecules in early rheumatoid arthritis

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## Abstract

The current paradigm in the management of rheumatoid arthritis (RA) is to treat patients in the early stage of the disease (ERA). Previous meta-analysis-based mixed treatment comparisons (MTCs), aimed to identify the most effective drugs in ERA, are biased by the wide "window" of early definition, ranging from 6 months to 2 years. The aim of this study was to estimate through a Bayesian Network Meta-Analysis which biologics or small molecules are more likely to achieve a 1-year good clinical response in ERA patients with disease duration < 1 year. According to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement, randomized controlled trials (RCTs) of biologic agents and small molecules in combination with MTX to treat patients affected with ERA lasting < 1 year were searched through MEDLINE, EMBASE, Cochrane Library, and Clinicaltrials.gov between 1990 and September 2017. The outcome of interest was the achievement of American College of Rheumatology (ACR) 50 and ACR 70 response at 1 year. WinBUGS 1.4 software (MRC Biostatistics Unit, Cambridge, UK) was used to perform the analyses, using a fixed effect model. Fourteen studies were included in the analysis. Tofacitinib (64.83%) followed by Etanercept (23.26%) were the drugs with the highest probability of achieving ACR50 response. Rituximab showed the highest probability of inducing ACR70 response (52.81%) followed by Etanercept (26.85%). This is the first MTC involving only RCTs on ERA patients with disease duration < 1 year. Tofacitinib and rituximab were the drugs ranked first in inducing 1-year ACR50 and ACR70 response, respectively.

**Keywords** Early · Efficacy · Meta-analysis · Rheumatoid arthritis · Rituximab · Tofacitinib

## Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterized by a chronic synovitis, releasing inflammatory cytokines and degradative mediators which cause pain, joint damage, and subsequent disability. RA affects 0.5 to 1.0% of the population [1] and frequently leads to health-related quality of life impairment [2]. Current treatments aim at controlling inflammation, improving pain, and maintaining physical function by slowing radiographic progression [3].

It is widely accepted in the rheumatology community that a "therapeutic window of opportunity" exists for patients with RA, and prompt treatments within this window can reset the disease's long-term trajectory while delayed treatments would be less effective [4, 5]. In order to make an early diagnosis of RA, efforts have been made by reviewing classification criteria to improve sensitivity for early disease [6, 7], as well as by focusing randomized controlled trials (RCTs) on the treatment of RA at this stage. Several biologic drugs, in combination or not with methotrexate (MTX), are licensed for treatment in RA, both in established disease and in early RA (ERA) [8–10].

Despite some studies have indirectly compared biologic therapies in combination with MTX either in patients affected

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with established RA [11], in inadequate responders to MTX [12] or in MTX naïve patients [13], to date, only two studies reported indirect comparisons of biologic drugs associated to MTX specifically in ERA [14, 15]. The latter, however, were devoted to a limited number of biologics, while the small molecules approved for the treatment of RA were not taken in account. Nevertheless, the major criticism in these studies is to analyze clinical trials enrolling ERA patients with a high variance of definition of early disease, thus entailing a meaningful bias in comparing the clinical outcomes. Ideally head-to-head comparisons would be required to estimate which treatment is the most effective in certain diseases. Alternatively, indirect comparisons that use a common comparator may be also useful [16]. The use of all available data from both direct and indirect comparisons is the essence of mixedtreatment comparison (MTC), an extension of meta-analysis. It allows to make multiple pairwise comparisons across a range of different treatments in a Bayesian framework, reflecting a prior belief of the possible values of the model parameters of interest whose likelihood distribution is based on the observed data, and shaping a posterior probability distribution [17].

In the most recent RCTs, there is the trend toward identifying the early stage of disease in a period of time varying from 6 to 12 months since the symptoms onset, which is approximately the time lag from onset to therapy in real life settings [18]. Therefore, we purposed to perform a MTC of RCTs on all current available biologics or small molecules in combination with methotrexate (MTX), in patients affected with RA, whose disease duration was < 1 year, considering as outcome of interest of the clinical response at 1 year.

## Methods

An extensive literature search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for transparent reporting of systematic reviews and meta-analysis [19] to identify results of RCTs that evaluated clinically biologic agents and small molecules at licensed doses to treat patients affected with ERA. MEDLINE, EMBASE, Cochrane Library, and Clinicaltrials.gov were searched for all RCTs published ranging from 1990 to September 2017. The search terms included "Rheumatoid Arthritis" and "randomized controlled trial," and "early." During the search time frame, complete reports published in English were reviewed (letters and abstracts were excluded). Patients enrolled in RCTs had to fulfill the ACR 1988 revised criteria for classified RA [20] and/or the 2010 ACR/EULAR criteria for classified RA [7].

According to our protocol, we included all completed and available RCTs, whose treatment arms consisted of biologics or small molecules at approved dose for RA in combination with MTX, with MTX alone as control arm, administered with placebo or in combination with other biologics or small molecules, in patients whose RA had mean duration from the clinical onset of less than 1 year. In addition, as a further inclusion criterion, outcomes had to be evaluated after 1 year of continuous treatment both in active and in placebo branches. The selected studies had to report on efficacy, which was defined as rates of American College of Rheumatology (ACR) 50% response. The secondary outcome of interest was ACR 70% response. Data on patient demographics, disease duration, and ACR response rates were also extracted.

### Data analysis

For each analysis, we used the reported number of patients in each response category in the treatment and placebo groups in each included trial. Bayesian methods involve a formal combination of a prior probability distribution (that reflects a prior belief of the possible values of the pooled effect) with a likelihood distribution of the pooled effect based on the observed data to obtain a posterior probability distribution of the pooled effect. In order not to influence the observed results by the prior distribution, a non-informative prior distribution was used for the pooled treatment effect. With such a flat prior, it is assumed that before seeing the data, any value for the pooled effect is equally likely to occur; as a consequence, posterior results are not influenced by the prior distribution but totally driven by the data as with a conventional frequentist meta-analysis. Determining whether a fixed effects model or a random effects model is appropriate to pool individual study results is extremely important. For such a reason, the ascertainment is obtained by comparing the residual deviance of the models using random or fixed effects. Given the similarity of residual deviance between those two models, the fixed effects one should be considered, as in this MTC. In order to limit the risk of disconnected networks and to justify quantitative synthesis [21], RCTs reporting on the same agent but different administration route were lumped considering them as the same treatment node.

The MTC results are reported as the odd ratio (OR) for a response with every single treatment compared with the comparator used in all RCTs—in this case MTX—and the OR for a response emerging from each pairwise combination of the combination treatment (biologic plus methotrexate). Furthermore, the probability for each analyzed agent of being the most effective and the relative rank for each of them have been provided. A known OR is a relative measure of the effect, which allows comparison of the treatment group and the control group in a study. An OR > 1 means that the treatment has a greater effect than the control, in this case, MTX + placebo; the 95% confidence interval (95% CI) is reported to indicate the level of uncertainty around the measure of the effect. The first 50,000 simulations to allow for model

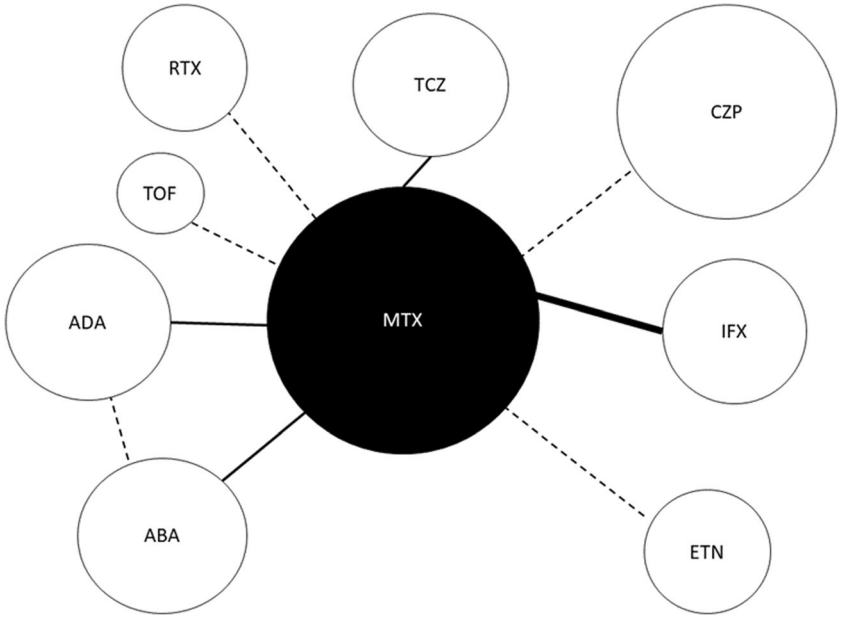


**Fig. 1** Mixed treatment comparison design. Reference treatment is methotrexate + placebo. A connection line means there is a RCT which compared circled agents. Dashed lines indicate that a single RCT evaluating the specified comparison was included. Solid thin lines mean that two RCTs compared the connected items, while solid thick lines account for three RCTs. The width of each circle is proportional to the cumulative amounts of patients randomized for the specified agent. ABA abatacept, ADA adalimumab, CZP certolizumab pegol, ETN etanercept, IFX infliximab, MTX methotrexate + placebo, RTX rituximab, TCZ tocilizumab, TOF tofacitinib

convergence were discarded, while additional 200,000 simulations were run to estimate the posterior probabilities. Satisfactory convergence was verified by trace plots, monitoring the Monte Carlo error, and with Gelman-Rubin diagnostics.

To demonstrate consistency assumption, a fixed effect network meta-analysis consistency model with a binomial likelihood and logit link was fitted to the data taking MTX as the reference treatment, and was then compared to a fixed effects inconsistency unrelated mean relative effect (UME) model fitting to the same data and estimating independent mean treatment effects. WinBUGS 1.4 software (MRC Biostatistics Unit, Cambridge, UK) was used to perform the analyses.

## Results

A total of 2508 scientific papers were extracted from Embase, Medline, Clinicaltials.gov and Cochrane Library. Of these records, after a check for duplicates carried out by two

**Table 1** Demographic characteristics of patients of the enrolled studies. Data about age and disease duration are expressed as mean ± SD unless otherwise stated

| | | | Treatment + MTX arm | | | MTX + placebo arm | | |
|---|---|---|---|---|---|---|---|---|
| Study | Agent | Follow-up period (weeks) | *n* | Age (years) | Mean disease duration (months) | *n* | Age (years) | Mean disease duration (months) |
| St Claire et al. [24] | IFX | 54 | 359 | 51 ± 12 | 9.6 ± 8.4 | 282 | 50 ± 13 | 10.8 ± 8.4 |
| Durez et al. [22] | IFX | 52 | 15 | 50 ± 9.9 | 4.32 ± 3.72 | 14 | 53.8 ± 15.2 | 9.6 ± 10.8 |
| Quinn et al. [23] | IFX | 54 | 10 | 51.3 ± 9.5 | 7.4 ± 4.6 | 10 | 53.1 ± 13.7 | 6 ± 3.7 |
| Emery et al. [27] | ETN | 52 | 274 | 50.5 ± 0.9 | 8.8 ± 0.4 | 260 | 52.3 ± 0.8 | 9.3 ± 0.4 |
| Breedveld et al. [25] | ADA | 108 * | 268 | 51.9 ± 14 | 8.4 ± 9.6 | 257 | 52 ± 13.1 | 9.6 ± 10.8 |
| Bejarano et al. [26] | ADA | 56 | 75 | 47 ± 9 | 9.5 ± 6 | 73 | 47 ± 9 | 7.9 ± 5.4 |
| Westhovens et al.[31] | ABA | 54 | 256 | 50.1 ± 12.4 | 6.2 ± 7.5 | 253 | 49.7 ± 13 | 6.7 ± 7.1 |
| Emery et al. [32] | ABA | 104* | 119 | 46.4 ± 13.2 | 6.96 ± 6 | 116 | 49.1 ± 12.4 | 6 ± 5.88 |
| Schiff et al. [35] | ABA/ADA | 104* | 71 | 50 (19; 80)*** | 3.6 ± 1.2 | 70 | 52 (22; 75)*** | 3.6 ± 1.2 |
| Emery et al. [28] | CZP | 52 | 655 | 50.4 ± 13.6 | 2.9 ± 4.6 | 213 | 51.2 ± 13.0 | 2.9 ± 2.9 |
| Burmester at al. [30] | TCZ | 104* | 292 | 49.5 ± 13.70 | 6 ± 6.24 | 287 | 49.6 ± 13.10 | 4.8 ± 5.76 |
| Burmester et al. [29] | TCZ | 104* | 106 | 53 (46–60) *** | < 1** | 108 | 53.5 (44.5–62)*** | < 1** |
| Conaghan at al. [33] | TOFACITINIB | 52 | 36 | 47.8 ± 12.3 | 9.6 (1.2; 26.4)*** | 37 | 47.8 ± 11.6 | 7.2 (1.2; 22.8)*** |
| Tak e t al. [34] | RTX | 52 | 250 | 47.9 ± 13.3 | 11.0 ± 15.6 | 249 | 48.1 ± 12.7 | 11.0 ± 13.2 |

*Clinical outcomes also reported at 1-year follow-up. **precise measures of dispersion not available. ***mean (range)

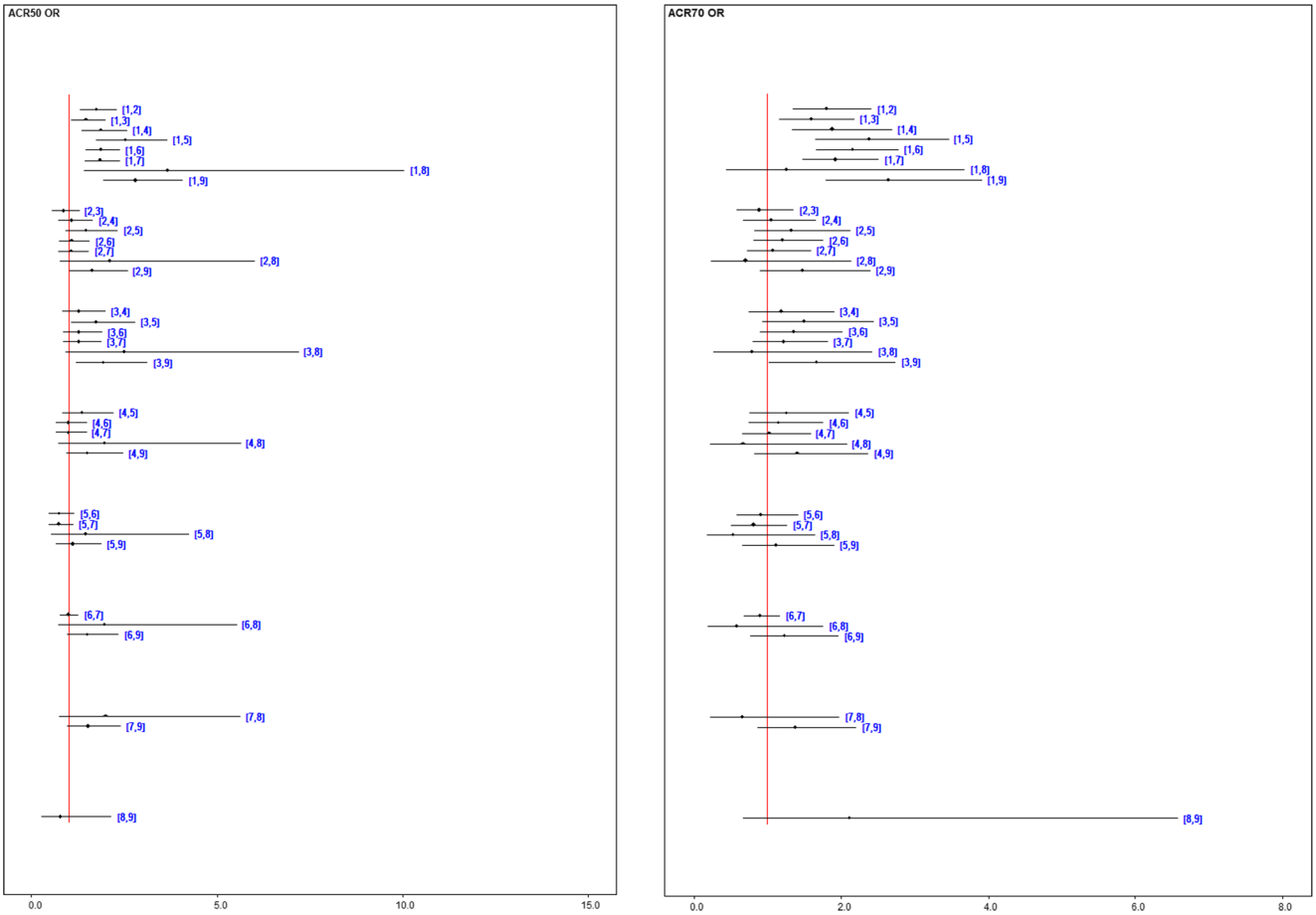


**Fig. 2** On the left, caterpillar plot for posterior mean OR of reaching ACR 50 response at 1-year follow-up for each possible comparison; on the right, the same plot is reported for ACR70 response. Methotrexate + placebo is the reference treatment; an OR > 1 favors comparator agent. 95% confidence intervals containing 1 indicate that the relative OR cannot be considered significant. 1 methotrexate, 2 tocilizumab, 3 certolizumab pegol, 4 infliximab, 5 etancercept, 6 abatacept, 7 adalimumab, 8 tofacitinib, 9 rituximab

authors independently, 158 papers remained for abstract screening. The latter abstracts were examined by three authors independently, and only RCTs in early RA that reported on the use of biologic drugs or small molecules administered at licensed doses with MTX in the active arm were retained for further analysis. Of the 158 abstracts examined, only 22 studies remained as candidates for inclusion in the analysis. For the 22 remaining studies, the full text of each paper was analyzed by three authors independently and, in the end, 14 were included in the analysis. A flow chart of the study selection process is shown in Fig. 3. All were RCTs, ten out of 14 reported outcomes at follow-up period of 52 weeks, one at follow-up period of 48 weeks, two at follow-up period of 54 weeks, and one at follow-up period of 56 weeks.

Among the studies whose comparator was MTX plus placebo, three reported data on use of infliximab (IFX) [22–24], two on adalimumab (ADA) [25, 26], one on etanercept (ETN) [27], one on certolizumab pegol (CZP) [28], two on tocilizumab (TCZ) [29, 30], two on abatacept (ABA) [31, 32], one on tofacitinib (TOF) [33], and one on Rituximab (RTX) [34] all in combination with MTX. Only one study reported on head-to-head comparison of subcutaneous ABA and subcutaneous ADA, both administered in combination with MTX [35] (Fig. 1, Table 1).

HIT HARD study [36] was not included as ADA in the interventional arm was administered for 24 weeks only. OPTIMA study [37], as well as GO-BEFORE [38] trials were not taken into account respectively for not reporting outcomes of interest at 1 year of continuous treatment and because of the long mean disease duration of enrolled patients, exceeding 1 year. GUEPARD trial from Soubrier et al. [39] was discarded for its design requiring ADA discontinuation at week 12 if DAS28-based low disease activity had been already achieved. The ORAL start trial [40] as well as the ORAL strategy trial [41] assessing TOF efficacy were not included because mean disease duration of enrolled patients exceeded 1 year. For the same reason, RA-BEGIN trial on baricitinib [42] was excluded. EMPIRE trial [43] was not included as ACR responses were not reported.

Samples of patients affected with ERA from the selected studies were similarly represented in terms of sex distribution

**Table 2** Mean Posterior Probability of reaching either ACR50 (top panel) or ACR 70 (bottom panel) response at 1 year follow-up for each agent. Treatment have been ranked according to higher probability

| | Mean | sd | MC error | Rank |
|---|---|---|---|---|
| ACR50 RESPONSE | | | | |
| TOF | 0.6483 | 0.4775 | $9.283\ 10^{-4}$ | 1 |
| RTX | 0.2326 | 0.4225 | $7.907\ 10^{-4}$ | 2 |
| ETN | 0.1115 | 0.3148 | $5.372\ 10^{-4}$ | 3 |
| ABA | 0.001275 | 0.03568 | $5.043\ 10^{-5}$ | 4 |
| IFX | 0.004238 | 0.06496 | $9.241\ 10^{-5}$ | 5 |
| ADA | 0.001227 | 0.035 | $4.942\ 10^{-5}$ | 6 |
| TCZ | $8.0\ 10^{-4}$ | 0.02827 | $3.833\ 10^{-5}$ | 7 |
| CZP | $8.5\ 10^{-5}$ | 0.009219 | $1.346\ 10^{-4}$ | 8 |
| MTX | 0.0 | 0.0 | $7.454\ 10^{-14}$ | 9 |
| ACR70 RESPONSE | | | | |
| RTX | 0.5281 | 0.4992 | 0.001059 | 1 |
| ETN | 0.2685 | 0.4432 | $9.113\ 10^{-4}$ | 2 |
| ABA | 0.07129 | 0.2573 | $4.856\ 10^{-4}$ | 3 |
| ADA | 0.013 | 0.1133 | $1.738\ 10^{-4}$ | 4 |
| IFX | 0.03368 | 0.1804 | $3.16\ 10^{-4}$ | 5 |
| TCZ | 0.01047 | 0.1018 | $1.585\ 10^{-4}$ | 6 |
| CZP | 0.002302 | 0.04792 | $8.107\ 10^{-5}$ | 7 |
| TOF | 0.07258 | 0.2594 | $4.777\ 10^{-4}$ | 8 |
| MTX | 0.0 | 0.0 | $7.454\ 10^{-14}$ | 9 |

*ABA* abatacept, *ADA* adalimumab, *CZP* certolizumab pegol, *ETN* etanercept, *IFX* infliximab, *MC* Monte Carlo, *MTX* methotrexate, *RTX* rituximab, *TCZ* tocilizumab, *TOF* tofacitinib, *sd* standard deviation

and disease duration. The notion of inconsistency was not supported as the UME model allowing inconsistency, fitted worse the data than the original fixed effect model (Table A.1).

### ACR50 response

All the biologic DMARDs as well as TOF showed greater odds than MTX plus placebo of inducing an ACR50 Response at 12-month follow-up. The results of the evaluations of each drug in combination with MTX versus MTX plus placebo and the comparisons between biologic agents and TOF in inducing an ACR50 response are showed by caterpillar plot in Fig. 2 (extensively reported in Table A.2). TOF was the most effective overall probability of being the best treatment: (64.83%) while among biologics, RTX showed the highest probability (23.26%) of inducing an ACR50 response in patients affected with ERA (Table 2).

### ACR70 response

Data regarding comparisons of different biologic agents in inducing an ACR70 response in patients affected by ERA are showed by a caterpillar plot in Fig. 2 (extensively reported in Table A.3). The agent with the highest probability of inducing an ACR70 response at 12 months in ERA patient was RTX (52.81%) followed by ETN (26.85%) (Table 2). However, all compared biologics in combination with MTX were statistically superior to MTX alone in inducing an ACR70 response. Posterior OR for TOF seemed to indicate a trend toward a better ACR70 response than MTX, although this was not statistically significant.

## Discussion

Shutting down the immune-inflammation characterizing RA is the ultimate aim of modern Rheumatology, and the "treat to target" strategy along with an early therapeutic intervention can entail to achieve the best outcomes [8, 44, 45]. Therefore, despite the availability of effective drugs, such as biologic DMARDs and novel small molecules, defining an early stage of RA and calibrating treatment to achieve remission, is a demanding issue. This "quest for the best" was actually the *primum movens* of our analysis.

Previous network meta-analysis [14] considered as affected with ERA patients with high variance of disease duration and pooled together the clinical outcomes recorded at different follow-up periods. Furthermore, systematic reviews carried out on RCTs of agents administered to patients naive to MTX [13] could be marginally taken into account for decision making strategy as bDMARDs and novel agents are usually given in MTX inadequate responders in real world settings. Nevertheless, given the existence of a certain "window of opportunity," it appears more reasonable to compare treatments administered in patients with similar disease duration. Furthermore, as efficacy is time-dependent, the comparisons would be more reliable if only studies whose outcomes are recorded at the same time points are considered. As mentioned above, the strict inclusion criteria of our protocol were intended to extrapolate from RCTs information as close as possible to real life settings, where patients with arthritis of recent onset are diagnosed with RA in the first 12 months on average [18].

According to our analysis, TOF seems to be the drug with the highest probability of inducing ACR50 response (probability rate of 64.83%) followed by RTX, (23.26%), but the analyzed dose of TOF was 10 mg bid, a therapeutic scheme which may not be available on the market in all countries. However, all bDMARDs given in combination with MTX showed a superior weighted effect to MTX in achieving ACR50 response at 12 months. In addition, RTX and ETN were ranked as the best bDMARD in achieving ACR70 response at 12-month follow-up. Of note, all the analyzed bDMARDs performed better than MTX + placebo in achieving such goal in the considered follow-up period, but TOF +

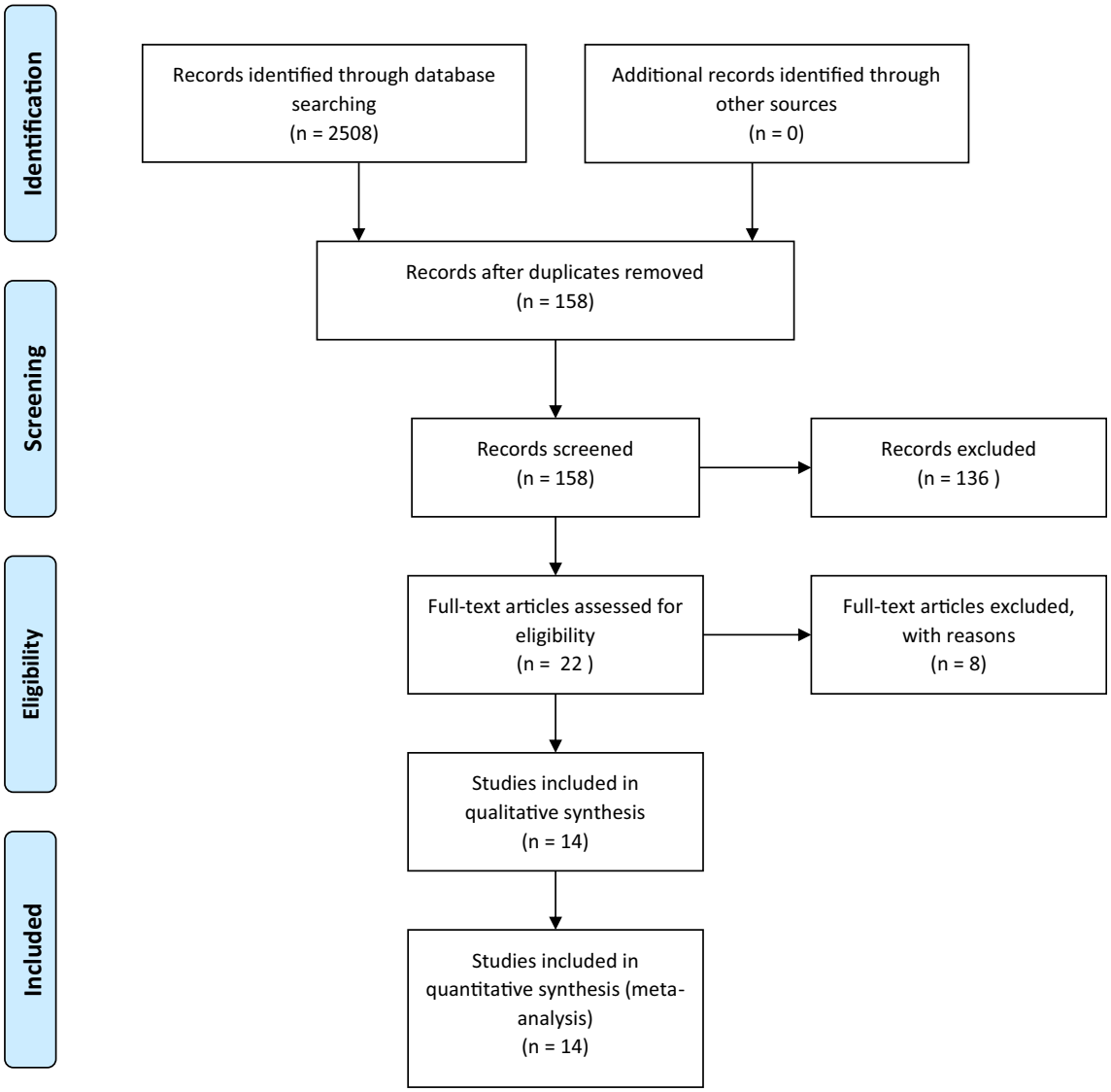


**Fig. 3** Flow diagram of the research strategy carried out, according to PRISMA recommendations [19]

MTX was found to be not superior to MTX plus placebo in achieving ACR70 response at 12 months. This may be due to the fact that the only study comparing TOF plus MTX to MTX plus placebo included in this MTC meta-analysis enrolled few patients.

In the end, TOF, RTX, and ETN in combination with MTX seem to be more effective in patients with ERA with disease duration < 1 year. These finding are worthy also in the perspective of saving direct costs [46]. Of note, the very good odds of RTX of inducing ACR50 and ACR70 response do clash with the limited possibility of administering it in biologic-naïve ERA patients, as per international recommendations [8].

Most of the limitations of our study are related to our search protocol, which may be considered as a double-edged sword. On one hand, the strict inclusion criteria should fit well the need to analyze RCTs involving patients whose disease duration better resembling the modern meaning of "early" RA. On the other hand, these stringent criteria restricted the number of eligible trials, possibly penalizing posterior distribution of effect for those agents analyzed in single small-sized trial with high variability in term of outcome of interest Fig. 3. Another drawback of our study could be figured by the variability in dose and administration routes of MTX that could have biased ACR50 and ACR70 responses in each included trial. A further limitation of this analysis is the lack of clinical response in a shorter period, e.g., 6 months, due to the scarcity of data in the selected RCTs.

## Conclusions

The findings of the present MTC show that TOF, ETN and RTX are the agents with the highest probability of inducing an

ACR50 or ACR70 responses at 12 months in ERA patients with disease duration < 1 year. Further RCTs, possibly considering head-to-head comparisons and encompassing radiological along with clinical outcomes, on RA patients with accurate time definition of early disease are warranted.

## Compliance with ethical standards

**Disclosures** None.

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