Review

Comparative efficacy and safety of current therapies for early rheumatoid arthritis: a systematic literature review and network meta-analysis

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ABSTRACT

Objective. *This systematic literature review (SLR) and network meta-analysis (NMA) was aimed at comparing the relative efficacy and safety of abatacept (ABA) with other currently recommended therapies for patients with early RA.*

Methods. *An SLR (January 1998 to June 2018) was conducted including MEDLINE®, Embase, and CENTRAL databases, and grey literature. Population was adults with active RA for ≤2 years treated with biologic DMARDs as monotherapy or in combination with conventional DMARDs. A Bayesian NMA was performed using randomised controlled trials (RCTs) and comparisons for ACR50, DAS28 remission, withdrawal due to adverse events and total withdrawal where reported.*

Results. *Ninety publications pertaining to 69 studies (43 RCTs and 26 observational studies) were identified. Twenty-eight RCTs were eligible to be included in the NMA. ABA as monotherapy was similar to the combination of ABA+methotrexate (MTX) for ACR50 (RR: 0.82 [95% CI 0.51–1.35]), and DAS28 remission (RR: 0.69 [95% CI 0.37–1.3]), as well as for withdrawal due to AEs (RR: 2.35 [95% CI 0.69–7.38]) and all-cause withdrawal (RR: 1.73 [95% CI 0.905–3.35]). ABA as monotherapy and ABA+MTX were both comparable to all other therapies for the main efficacy and safety outcomes. Observational study data reported was congruous with the RCT analysis.*

Conclusion. *The results of this NMA show similar efficacy and safety between ABA (as monotherapy or in combination with MTX) and other biologics in early RA. Further comparison of different treatment options for early RA is warranted as growing research provides evidence for the application of new novel therapies for RA.*

Introduction

Rheumatoid arthritis (RA) is a widespread and debilitating disorder that is becoming increasingly prevalent globally in the growing and aging population. It is characterised by inflammation, swelling, and pain in the joints caused by an autoimmune response in which the body begins to attack the synovium surrounding the joints. Left untreated, RA may damage cartilage and bone through erosion, leading to premature mortality and disability. Early identification and treatment of RA is critical for preventing disability and joint damage (1, 2).

Pharmacological treatments for RA include disease-modifying anti-rheumatic drugs (DMARDs) which may be non-biologic (nbDMARDs) or biologic (bDMARDs). Non-biologic DMARDs may be further classified as conventional synthetic DMARDs (csDMARDs) such as leflunomide, and targeted synthetic DMARDs (tsDMARDs) such as baricitinib. Biologic DMARDs are categorised as TNF inhibitors (TNFi) and non-TNF inhibitors (non-TNFi). Current guidelines from the American College of Rheumatology (ACR) (1) and European League Against Rheumatism (EULAR) (2) recommend initial treatment with csDMARDs. Patients typically begin with methotrexate (MTX), with limited use of bDMARDs and other novel therapies within first year of diagnosis. However, many patients fail to reach remission or low disease activity with csDMARDs such as MTX alone (2), and thus, the use of other DMARDs early in the course of disease can be investigated.

This SLR and NMA aimed to compare the relative efficacy of ABA alone and in combination with MTX to other currently recommended therapies for patients with early RA defined as RA disease duration less than 2 years from diagnosis (3).

Methods

Study eligibility

Study identification and eligibility criteria were developed using the Population, Intervention, Comparator, and Outcome (PICO) framework as described by Cochrane Collaboration's handbook for Systematic Reviews of Interventions. Studies evaluating efficacy and safety of treatments for adult patients with early RA who were treated with DMARDs as monotherapy or in combination with conventional DMARDs were included. Patients were required to have at least 3 months of outpatient treatment in order to capture the full effect of treatment, similar to what was done in previous SLRs (4). RCTs and observational studies (with population of n ≥100) were included for review.

Search methods

The searches for the review were conducted from January 1998 (date of first biologic approval for RA in the US) to June 2018 on main databases (MEDLINE®, Embase, Cochrane), and January 2014 to July 2018 (EULAR and ACR conference proceedings via Embase) to include grey literature. United States and European clinical trials registries were searched to capture ongoing clinical trials with unpublished study results from 10 years preceding June 2018. A hand-search was also performed on the reference lists of previously published SLRs on the same topic and eligible articles were screened through a main database search to capture additional eligible studies that were missed during the main database search. Search strategies for MEDLINE®, Embase, and Cochrane are available in the online supplementary material (Appendix Tables 1-3).

Study selection

Two investigators reviewed all abstracts identified in the SLR. PICO criteria were applied, and abstracts deemed eligible for inclusion were advanced to full-text screening. Full-text articles were screened by two investigators. At each stage of the screening process, discrepancies were identified and resolved by an independent investigator. Articles deemed eligible after full-text screening were included in the SLR.

Data extraction

Data were extracted by two investigators for the included studies. The Digital Outcome Conversion (DOC) Data version 2.0 software platform (Doctor Evidence, LLC, Santa Monica, CA, USA) was used to store and manage data.

Extraction included trial characteristics, interventions, patient characteristics, as well as efficacy and safety outcomes. Characteristics of interest were race/ethnicity, RA duration, rheumatoid factor positivity, anti-CCP positivity, and baseline disease activity scores. ACR50 and DAS28 remission were the primary efficacy outcomes of interest for this review and analysis. Primary safety outcomes included total withdrawal and withdrawal due to adverse events (AEs). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials was used to assess the included studies with a randomised study design. This instrument is used to evaluate seven domains of bias: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias (other bias). Each domain was evaluated as high, low, or unclear when the study did not provide adequate information or there was uncertainty over the potential for bias. Assessments were conducted by two independent reviewers with disagreements resolved by discussion or the senior author.

Statistical analysis

A Bayesian NMA was run using the R package "gemtc" which utilises jags and has been validated by running examples found in the National Institute for Health and Clinical Excellence Decision Support Unit, Technical Support Documents (NICE DSU TSD) series. RCTs comparing at least two different active treatment regimens with comparable baseline characteristics were used. A random effects model with one parameter for the between-study heterogeneity was chosen, assuming that the between-study heterogeneity was the same for each intervention relative to the overall reference treatment of choice.

Outcomes were included if reported with adequate information for analysis at ±4 weeks of the desired timepoints of 6 months, 1 year, or 2 years. If multiple timepoints were reported, the longest follow-up in which patients were being actively treated was analysed. In studies with multiple dosing groups for the same regimen, the group that received the highest dose was analysed. Timepoint sensitivity analysis was performed wherever feasible for 6-month, 1-year, and 2-year timepoints.

Analysis of binary outcomes, such as ACR50, was performed based on the proportion of patients experiencing the event of interest using the standard general linear model (GLM) of a binomial likelihood and logit link. Normal non-informative prior distributions for the parameters were used with a mean of 0 and a variance of 10,000. Relative treatment effects were expressed as risk ratios (RR).

Results

A total of 15,866 records were returned from main database and grey literature searches for screening process (Fig. 1), of which 14,405 records were excluded during title/abstract screening and 1,371 references during full-text screening with reason for exclusion being primarily due to populations of established RA (defined as >2 years from diagnosis). In total, 90 publications (66 journal articles, 16 meeting abstracts and 8 clinicaltrials.gov records) pertaining to 69 studies were identified and included in this review. 43 studies were RCTs and 26 observational.

28 RCTs (46 references) met the previously described criteria for inclusion in NMA. Trials evaluated methotrexate monotherapy [MTX]

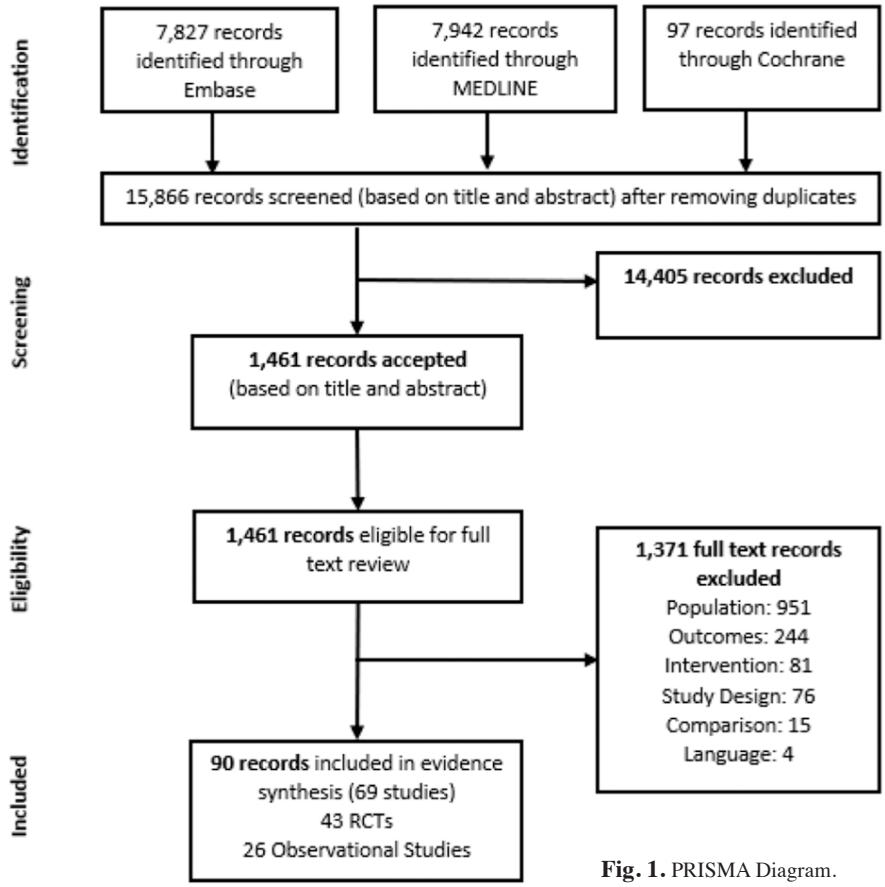

Fig. 1. PRISMA Diagram.

(n=21), adalimumab plus methotrexate [ADA+MTX] (n=6), infliximab plus methotrexate [IFX+MTX] (n=4), prednisone plus methotrexate [Pred+MTX] (n=4), sulfasalazine monotherapy [SSZ] (n=4), abatacept plus methotrexate [ABA+MTX] (n=2), certolizumab plus methotrexate [CTZ+MTX] (n=2), methylprednisolone plus methotrexate [MPred+MTX] (n=2), prednisone plus sulfasalazine plus methotrexate [Pred+SSZ+MTX] (n=2), sulfasalazine plus methotrexate [SSZ+MTX] (n=2), tocilizumab monotherapy [TCZ] (n=2), tocilizumab plus methotrexate [TCZ+MTX] (n=2), tofacitinib monotherapy [TOF] (n=2), tofacitinib plus methotrexate [TOF+MTX] (n=2), abatacept monotherapy [ABA] (n=1 trial), etanercept monotherapy [ETN] (n=1), etanercept plus methotrexate [ETN+MTX] (n=1), hydroxychloroquine plus sulfasalazine plus methotrexate [HCQ+SSZ+MTX] (n=1), hydroxychloroquine plus sulfasalazine plus prednisone plus methotrexate [HCQ+SSZ+Pred+MTX] (n=1), methylprednisolone plus prednisone plus methotrexate [MPred+Pred+MTX] (n=1), and prednisone monotherapy [Pred] (n=1). Appendix Figure 1 shows the network of all 28 studies with multi-dosage arms pooled.

Appendix Table 4 summarises patient characteristics of the analysed studies. Mean age ranged from 36 years (5) to 59.5 years (6), patients were predominately female (56% (7) to 86.5% (8)) and disease duration ranged from a median of 26 days (9, 10) to 9 months (11-13). Patients had high disease activity with baseline DAS28 ranging from 5 (14) to 6.7 units (15).

Information regarding the characteristics and safety and efficacy outcomes in observational studies and RCTs excluded from the NMA can be found in Appendix Tables 5-6.

The Cochrane Collaboration risk of bias assessment found that overall, analysed studies generally had low or unclear risk of bias (Appendix Table 7). Sixteen studies had low risk of selection bias (6, 7, 9, 12, 16-27) while 12 had unclear risk due to lack of information on the randomisation procedure (5, 8, 14, 15, 28-35). One trial evaluating ETN and MTX had high risk of allocation concealment since both patients and the clinician were aware of the treatment allocation (33), while 14 trials had unclear risk (5, 6, 8, 9, 14, 15, 26, 28-32, 34, 35), and 13 were low risk (7,12,16-25,27). Seven trials were considered high risk for performance bias as patients and/or investigators were not blinded, comparing MTX+Pred *vs*. MTX+Pred+SSZ, ETN *vs*. MTX, MTX+ Pred *vs*. MTX, HCQ+MTX+Pred+SSZ *vs*. SSZ, ABA+MTX *vs*. ADA+MTX, SSZ *vs*. Pred, and IFX+MTX *vs*. HCQ+MTX+SSZ (6, 14, 19, 24, 27, 33, 34). In 13 studies this risk was unclear (5, 8, 15, 17, 20-22, 26, 29-32, 35) and was considered low risk in 8 studies (7, 9, 12, 16, 18, 23, 25, 28). Risk of detection bias was high in 4 trials comparing MTX+Pred *vs*. MTX+Pred+SSZ, HCQ+MTX+Pred+SSZ *vs*. SSZ, SSZ *vs*. Pred, and IFX+MTX *vs*. HCQ+MTX+SSZ as outcome assessors were not blinded (14, 19, 24, 27, 36). However, in 9 trials risk was unclear (5, 8, 15, 16, 20-22, 32, 34) and risk was low in 15 trials (6, 7, 9, 12, 17, 18, 23, 25, 26, 28-31, 33, 35). Five trials had unclear risk of attrition bias due to lack of information on method of handling missing data (5, 8, 15, 31, 32) while 23 trials had a low risk (6, 7, 9, 12, 14, 16-30, 33-35). All studies were determined to have a low risk of reporting bias and other sources of bias. Appendix Figure 2 is a visual representation of risk of bias across studies included in the analysis for each of the domains in the instrument.

ACR50

Twenty-three studies (n=2,112 patients) were included in the ACR50 analysis. Response rates varied between 17% (Pred+MTX) (37) to 80% (IFX+MTX) (26) of patients (Appendix Table 8). Monotherapies of csDMARDs yielded highly variable ACR50 rates between 22% (MTX) (36) to 63% (MTX) (38), while non-TNFi and tsDMARD monotherapies yielded rates between 53.1% (TCZ) (36) to 55% (TCZ) (9), and 50% (TOF) (18), respectively. ACR50 response rates varied greatly across combination therapies, csDMARD combi-

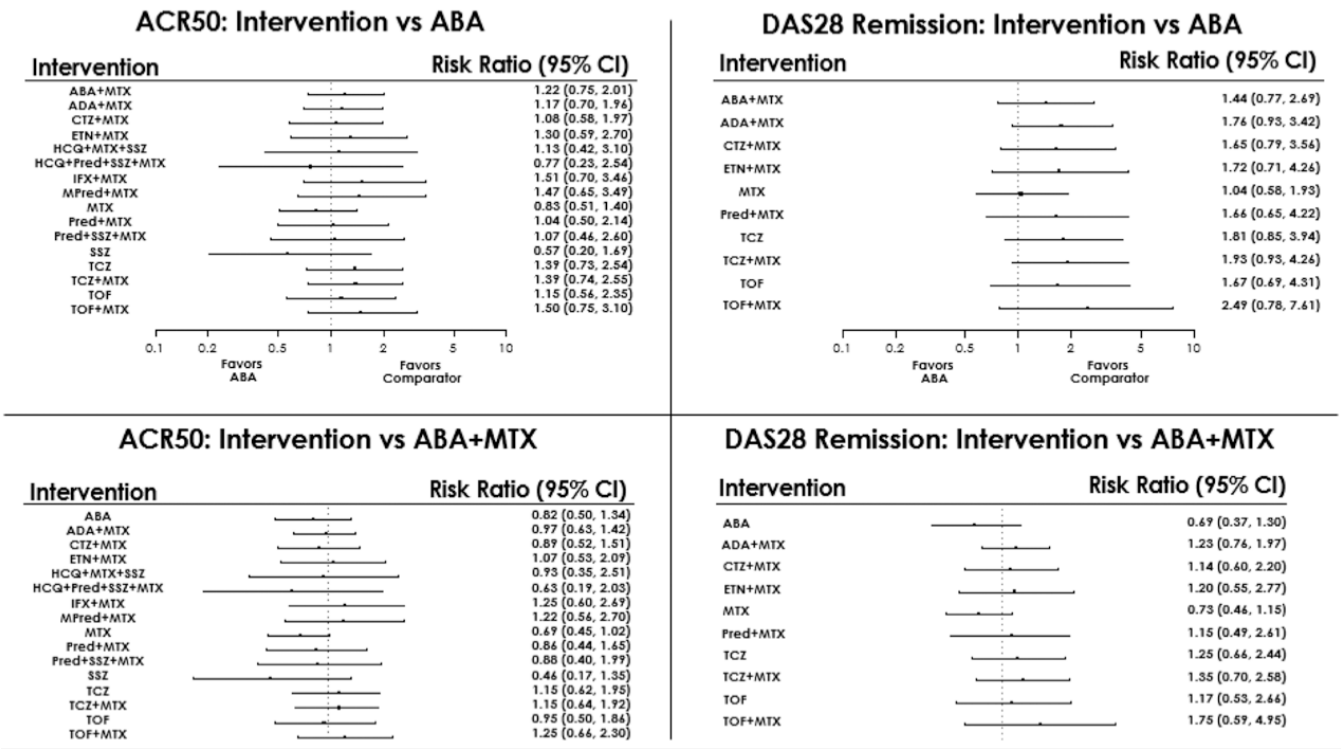

Fig. 2. Efficacy analysis obtained with network meta-analysis: ABA and ABA+MTX *versus* treatment.

nation (HCQ+SSZ+MTX) yielded 22% (39) and csDMARD and steroid combinations yielded 17% (Pred+MTX) (37) to 75.9% (HCQ+Pred+SSZ+MTX) (24). Combination therapies of MTX with other DMARD classes also yielded heterogeneous rates of response: tsDMARDs+MTX showed 65.7% (TOF+MTX) (18), TNFi+MTX yielded 30% (IFX+MTX) (39) to 80% (IFX+MTX) (26), and non-TNFi+MTX ranged from 42.3% (ABA) (34) to 63% (ABA+MTX) (20).

Results of the ACR50 NMA relative to ABA and ABA+MTX are shown in Figure 2. ABA monotherapy had a similar response rate to the combination of ABA+MTX (RR: 0.82 [95% CI 0.51–1.35]). Both ABA monotherapy and in combination with MTX were comparable to all other treatment regimens in the network.

NMA results comparing other therapies to each other also showed the benefit of early biologic intervention, with respect to achievement of ACR50 (Appendix Table 9). The TNF inhibitors ADA and IFX, as well as the non-TNF inhibitor TCZ, and the targeted synthetic nbDMARD TOF in combination with MTX had a higher treatment response than MTX alone (range of RR: 1.40 [95% CI 1.13–1.75] to 1.80 [95% CI 1.01–3.47]). Additionally, TCZ monotherapy showed significantly higher response rate than MTX (RR: 1.66 [95% CI 1.14–2.41]).

A timepoint sensitivity analysis (Appendix Tables 10-12) produced similar results.

DAS28 remission

The NMA of DAS28 remission included 15 studies (n=2128 patients) reporting remission rates ranging from 11.2% (MTX) (32) to 74% (ADA+MTX) (21). Remission rates for MTX monotherapy ranged from 11.2% (32) to 58.6% (9). Other monotherapies reported DAS28 remission between 42.5% (ABA) (40) and 70.5% (TCZ) (9) for patients receiving non-TNFi monotherapy, and between 19.4% (TOF) (41) and 21.7% (TOF) (32) of those using tsDMARD monotherapy. Rates of DAS28 remission in patients receiving combination therapy with MTX were reported for TNFi (34% [ADA+MTX] (22) to 74% [ADA+MTX] (21)), non-TNFi (42.6% [ABA+MTX] (34) to 74% [TCZ+MTX] (9)), and tsDMARD (32.4% [TOF+MTX] (41)).

The results of the NMA for DAS28 remission relative to ABA and ABA+MTX are shown in Figure 2. Monotherapy and combination therapy of ABA and MTX were comparable, with a RR of 0.69 (95% CI 0.37–1.3). Abatacept alone and in combination with MTX was comparable to all other treatment regimens in the network.

Relative to other therapies early biologic intervention was beneficial in inducing remission (Appendix Table 13). The combination of ADA+MTX and TCZ+MTX resulted in a higher treatment response than MTX alone (RR: 1.70 [95% CI 1.28–2.23] and 1.86 [95% CI 1.19–2.95], respectively). Tocilizumab as monotherapy also demonstrated a superior treatment response to MTX, with a RR of 1.78 (95% CI 1.12–2.75).

A timepoint sensitivity analysis (Appendix Tables 14-16) produced similar results.

Withdrawal

Twenty-three studies (n=2,364 patients) were included in the all-cause withdrawal NMA with rates ranging from 0% (ETN, MTX) (26,33) to 71.4% (MTX) (16). Monotherapies reporting withdrawal rates in-

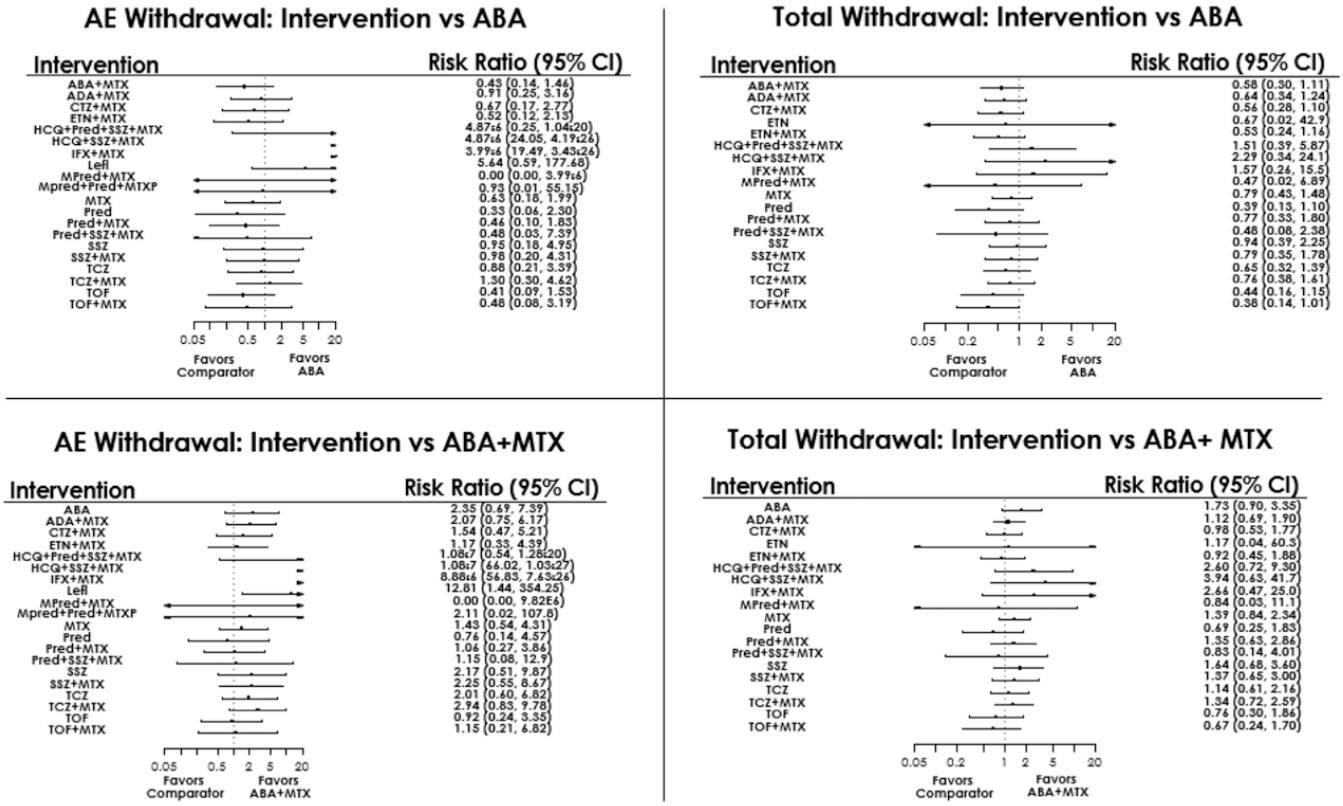

Fig. 3. Safety Analysis Obtained with Network Meta-analysis: ABA and ABA+MTX versus Treatment.

cluded steroids (19% [Pred] (14)), csDMARDs (0% [MTX] (26) to 71.4% [MTX] (16)), which differed from TNFi (0% [ETN] (33)), non-TNFi (19.18% [TCZ] (15) to 21.6% [ABA] (40), and tsDMARDs (25% [TOF] (18)). Combination therapies reported rates ranging from 21.1% (SSZ+MTX) (5) to 43.1% (HCQ+SSZ+MTX) (39) for csDMARDs and from 3.7% (Pred+SSZ+MTX) (37) to 27.4% (Pred+MTX) (28) in patients taking steroids in combination with csDMARDs. Additionally, MTX combinations reported all-cause withdrawal rates ranging from 5.8% (ADA+MTX) (29) to 56.2%(CTZ+MTX) (16) for TNFi, 13.5% (ABA+MTX) (40) to 26.4% (TCZ+MTX) (9) for non-TNFi, and 22.2% (TOF+MTX) (18) for tsDMARD treated patients.

The results of the NMA on the total withdrawal relative to ABA and ABA+MTX are shown in Figure 3. Abatacept monotherapy had similar withdrawal compared to ABA+MTX (RR: 1.73 [95% CI 0.905–3.35]). Both ABA monotherapy and in combination with MTX were comparable to all other treatment regimens in the network. When other therapies were investigated, NMA results showed few significant differences between treatments (Appendix Table 17). Prednisone was favoured over SSZ (RR: 0.419 [95% CI 0.233–0.740]) and the combination of HCQ+Pred+SSZ+MTX (0.263 [95% CI 0.084–0.815]). Additionally, there were fewer all-cause withdrawals with CTZ+MTX (RR: 0.717 [95% CI 0.491–0.935]) than with MTX alone.

The NMA of withdrawal due to AEs included 24 studies (n=2,487 patients) with remission rates ranging from 0% (MTX (26,31), SSZ (24), Pred+MTX (8), MPred+MTX (31), HCQ+Pred+SSZ+MTX (24)) to 33.3% (SSZ) (14) (Appendix Table 18). Adverse event withdrawal rates for monotherapies were described for steroids [11.5% (Pred)] (14), csDMARDs [0% (MTX (26, 31), SSZ (24)) to 33.3% (SSZ) (14)], non-TNFi [6.9% (ABA) (20) to 11.6% (TCZ) (15)], and tsDMARDs [5.6% (TOF) (18) to 10.1% (TOF) (32)]. Rates reported for combination therapy of csDMARDs ranged from 13.2% (SSZ+MTX) (30) to 21.1% (SSZ+MTX) (5) and from 0% (Pred+MTX (8), MPred+MTX (31), HCQ+Pred+SSZ+MTX (24)) to 16.9% (HCQ+SSZ+MTX) (39) for combinations of csDMARDs and steroids. There was variation in reported rates of withdrawal due to AEs among MTX combinations, with MTX+TNFi having withdrawals reported ranging from 2.3% (ADA+MTX) (21) to 14.8% (IFX+MTX) (39), MTX+non-TNFi ranging from 2.8% (ABA+MTX) to 20.3% (TCZ+MTX) (15), and MTX+tsDMARDs with 11.1% (TOF+MTX) of patients withdrawn due to AEs (18).

Results of the AE withdrawal NMA relative to ABA and ABA+MTX are shown in Figure 3. Monotherapy and combination therapy of ABA and MTX were comparable with an RR of 2.35 (95% CI 0.69–7.38). Abatacept alone and in combination with MTX, were found to have a statistically significant benefit compared to IFX+MTX, HCQ+SSZ+MTX, and leflunomide. However, these comparisons should be interpreted with caution due to excessively large point estimates and

credible intervals, *e.g.* $9.18x10^6$ (95% CI 57–7.73 $x10^{26}$). These values were skewed by a few small studies reporting statistically significant differences between groups such as Quinn (2005) (26), comparing MTX (n=10) and IFX+MTX (n=10), and Durez (2007) (31) which evaluated MTX (n=14), IFX+MTX (n=15) and MPred+MTX (n=15). These results underscore the need for a more robust network to balance these outliers.

Discussion

This SLR and NMA was conducted to assess the comparative efficacy and safety of drug therapies for adults with early RA. A similar review on early RA was recently published by the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI) (4). There are several differences between the AHRQ/PCROI report and this review, one being the definition of early RA. The AHRQ/PCORI report defined early RA as <1 year from the time of diagnosis while this review used ≤2 years. There is a lack of consensus around the definition of early RA. It has recently been defined as <6 months from onset of symptoms (1) and within 3 months of onset of symptoms (2). Previous to these definitions, early RA was defined as ≤2 years from diagnosis. This definition is still used by the NICE guidelines on the management and treatment of RA (3) and encompasses the therapeutic window to prevent joint damage. We believe limiting the definition of early RA to 1 year does not encompass all of the available research on this topic and expanding the limit to 2 years is not only clinically appropriate, but the inclusion of these additional trials improves precision of the estimates without unduly affecting validity.

Additionally, in the AHRQ/PCORI report, the authors did not conduct a formal grey literature search of the major rheumatology conferences proceedings published in the past 2-3 years, as is common practice for conducting major systematic literature reviews. One such example of missing evidence in this review is a poster presented at the 2014 EULAR conference which stratified patients by less than or greater than 6 months of disease duration, and discusses clinical outcomes in patient with early RA using data from the AMPLE trial (34).

The statistical significance of several ABA comparisons was impacted by the differences between this report and the AHRQ/PCORI report. This analysis found no significant difference between ABA and IFX+MTX for ACR50 (RR: 1.51 [95% CI 0.699–3.45)]) where the AHRQ/PCORI report favoured the comparator (RR: 1.36 [95% CI 1.02–1.84]). All-cause withdrawal was also found to have non-significant differences between ADA+MTX, CTZ+MTX, ETN, and ETN+MTX (RR: 0.642 [95% CI 0.344–1.24]; 0.564 [95% CI 0.274–1.10]; 0.665 [95% CI 0.0218–43.1]; 0.527 [95% CI 0.236–1.16]) which significantly favoured the comparator in the AHRQ/PCORI analysis (RR: 0.51 [95% CI 0.27–0.96]; 0.44 [95% CI 0.24–0.77]; 0.38 [95% CI 0.20–0.73]; 0.51 [95% CI 0.28–0.91]).

Other analyses, such as one performed on data from the RECord-linkage on Rheumatic Diseases (RECORD) study, have found that RA patients using ABA therapy had a significantly lower risk of infection compared to those using ETN therapy (HR: 0.29 [95% CI: 0.100.82]) (42). MTX+bDMARD therapy decreased the risk of infection (HR: 0.72 [95% CI: 0.52–0.99]) relative to bDMARD therapy (42). Additionally, RECORD study analysis was not performed solely on patients with early RA and the results suggested that combination therapy may have a better safety profile compared to monotherapies.

Two recent reviews (43, 44) also discussed discoveries in treatment of RA from papers published in 2018 and 2019. Both reviews did not include an NMA component but provided descriptive results based on RCTs on early RA which were similar to the current review.

Current ACR and EULAR guidelines recommend monotherapy with a csDMARD, such as MTX, as initial treatment for early RA patients even when disease activity is moderate or high and only incorporate bDMARD upon initial treatment failure. The findings of this review suggest that patients may see a clinical benefit in achieving ACR50 or DAS28 remission with combination therapy of a bDMARD or tsDMARD along with MTX without increasing their risk for withdrawal. The discrepancy in findings may be due to population differences as this review analysed patients with moderate to high disease activity while patients with early RA may clinically present with lower disease severity. Additionally, the guideline recommendations take into consideration patients' values and preferences as well as the relative benefits and harms of the treatment options. As some patients respond to initial monotherapy, patients may be hesitant to begin with combination therapy. A better understanding of the prognostic factors for initial treatment failure could help identify patients in which bDMARD initial therapy may be the most beneficial.

The primary limitation of this review was the limited network of RCTs on early RA (≤2 years), with many connections made with only one or two trials. There was a lack of studies on some therapies and drug classes in early RA such as rituximab, sarilumab, baricitinib, or biosimilars despite their common use in patients with RA. As rituximab is one of the non-TNF options used in RA, absence of its use in early RA limits our understanding of bDMARDs for this particular population.

The results of this review underscore the need for more comprehensive research into biologic treatment in the early RA population. Future research should aim to better understand all treatment options for this critical time that may change the course of a patient's disease.

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