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Research Article

Evaluation of the Efficacy and Safety of Abatacept Combined with Methotrexate in the Treatment of Patients with Rheumatoid Arthritis: A Meta-Analysis and Systematic Review

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Abstract

Objectives: The goal of this study was to directly compare the efficacy and safety of Abatacept (ABA) plus Methotrexate (MTX) with the control group which includes placebo plus MTX or only MTX in slowing Rheumatoid Arthritis (RA) progression.

Methods: A systematic review (up to October 2019) of the literature of double-blind, Randomized Controlled Trials (RCTs) was conducted by searching for Pubmed, Cochrane, Embase and Clinical trials.gov. The efficacy was evaluated based on the rates in the DAS28 defined remission, ACR20/ACR50/ACR70, SDAI $\leq$ 3.3 and HAQ-DI > 0.3; safety was assessed based on rates of Adverse Events (AEs), infections and malignancies. In the end, ten studies met the inclusion criteria, comprising 2949 patients. The results were analyzed using meta-analysis methods that enabled the calculation of an estimate for the expected relative effect of comparative treatments. Analysis results were expressed as the difference in Odds Ratio (OR) of achieving outcomes and associated 95% Credible Intervals (CI).

Results: For all of the efficacy parameters, the ABA group was more efficacious than MTX monotherapy group, however, the level of benefits was significant differed in MTX-naive and MTX-experienced subgroups. At the same time, there was no significant difference between groups in terms of safety in the incident rates of AEs, infections, and malignancies.

Conclusion: Our meta-analysis demonstrated that the ABA plus MTX combination therapy presented favorably compared to the MTX monotherapy. Both MTX-naive and MTX-experienced groups benefit from the ABA combination therapy to some different extent.

Keywords: Abatacept; Methotrexate; Rheumatoid Arthritis; Meta-Analysis; Systematic Review

Introduction

Rheumatoid Arthritis (RA) is a chronic, progressive, multisystem disorder of unknown etiology, characterized by chronic destructive synovitis. RA is a common disease that occurs throughout the world. Older age, female gender, genetic factors, and lifestyle are risk factors both for the development of RA and for a worse outcome [1]. Recent therapeutic strategies focusing on the introduction of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) have led to improved physical, functional, and structural outcomes for patients with rheumatoid arthritis. Methotrexate (MTX), as monotherapy is usually part of the first-line treatment based on its efficacy, safety, the feasibility to individualize dose and method of administration as well as relatively low cost. However, inadequate response and patient intolerance are common reasons for discontinuation [2]. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, when poor prognostic factors are present, the addition of a biological(b) DMARD should be considered, such as abatacept, tocilizumab and rituximab [3]. Abatacept (ABA), a recombinant soluble fusion protein, consists of the extracellular

domain of human cytotoxic T lymphocyte-associated antigen 4 linked to the modified Fc portion of human immunoglobulin G1 and has a high affinity to CD28. It is the first agent to target and thus interfere with full T cell activation by competing with CD28 for binding of CD80 and CD86 [4]. Its initial role is likely to be an alternative to anti-TNFα agents for patients who fail to respond or have a contraindication such as an overlap with connective tissue disease [5]. There has been recent evidence for the use of abatacept in lupus and primary Sjögren's syndrome [6,7].

Although ABA had a relatively more acceptable efficacy, safety and tolerability profile than other biologic DMARD [8,9]. The use of ABA still has the potential to fulfill a unique role in a wide variety of immunological problems. A couple of studies in early RA patients confirm, in this population, the results demonstrated that ABA with background MTX significantly slowed radiographic progression in patients with active RA who had inadequate response or intolerance to other DMARDs, including MTX or anti-TNFα [10-12]. While generally clinically effective, these trials have varying results, the magnitude of benefit and safety is hard to draw conclusions, especially, such malignancy as a kind of low probability adverse event need to be detected based on a large population.

Therefore, the aim of this paper was to review the evidence for the efficacy of ABA-MTX combination therapy in rheumatoid arthritis by calculating standardized outcomes, so that different trails could be pooled and compared according to their effect on reducing disease activity. The aim of the study was to estimate the relative efficacy of abatacept in combination with MTX in Disease Activity Score in 28 joints (DAS28) defined remission (< 2.6), Health Assessment Questionnaire disability index(HAQ-DI)> 0.3, 20/ 50/70% improvement in American College of Rheumatology criterion (ACR20/ACR50/ACR70) and Simple Disease Activity Index (SDAI) ≤ 3.3. As a secondary aim, we studied safety in terms of incident rates of the Adverse Events (AEs), infections and malignancies.

Materials and Methods Literature Search and Study Selection

A comprehensive search of randomized clinical trials was conducted utilizing the advanced search functions of the Cochrane controlled trials register, Medline, and Embase up to July 2019. The keywords used were "abatacept" or "orencia". Search filters were applied to identify the most relevant results. This was supplemented by manually searching the bibliographies of relevant published reviews and papers and clinicaltrials.gov which is a database of privately and publicly funded clinical studies conducted around the world in the field. The last search was conducted in June 2019. The study design and report adhered to the PRISMA Statement guidelines (PRISMA S1). The search strategy was conducted as the study selection flow diagram Figure 1.

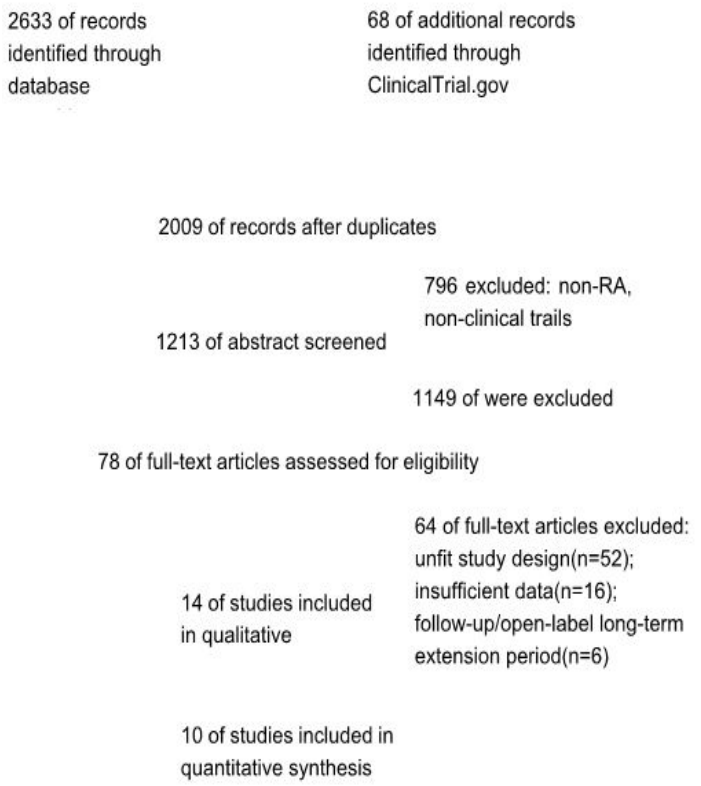

Figure 1: Study selection flow diagram.

Data Extraction

In order to minimize errors in data extraction, efficacy data were extracted from the relevant reports by two authors (AL, YJX) working independently. The reviewers examined all publications for duplication of study populations, discussed publications that were considered to be potentially relevant and came to a consensus on inclusion based on the inclusion criteria. Afterward, the results of data extraction were compared, and any disagreements were resolved by discussions between the two to come to an agreement in case of discrepancies. The full-text articles were assessed for inclusion according to the following selection criteria: (1) only randomized, controlled trials that treatment with combination of abatacept with MTX in comparison with MTX or Placebo + MTX in adult patients with RA were included, for the iv and sc maintain dose of abatacept should be around 10mg/kg/4 weeks or 125mg/week respectively; (2) the selected studies had to report on efficacy, which was defined as DAS28 < 2.6, SDAI ≤ 3.3 and rates of ACR 20%, 50%, and 70% response as well as other non-RA clinical endpoints of HAQ-DI > 0.3. All patients were monitored for the occurrence of AEs. Additional details were collected on pre-specified AEs of special interest (such as infections and malignancies).

Study Assessments

The two review authors independently assessed the risk of bias of each trial using Risk of Bias Assessment such as the one provided by Cochrane. We explicitly assessed each of these domains as being at 'low' or 'high' risk of bias; where insufficient information was available, or there was uncertainty over the potential for bias, we rated the study as being at 'unclear' risk of bias in that domain. Revman 5.3 was used to record the review authors' judgments about each risk of bias item presented as percentages across all included studies in the risk of bias graph Figure 2.

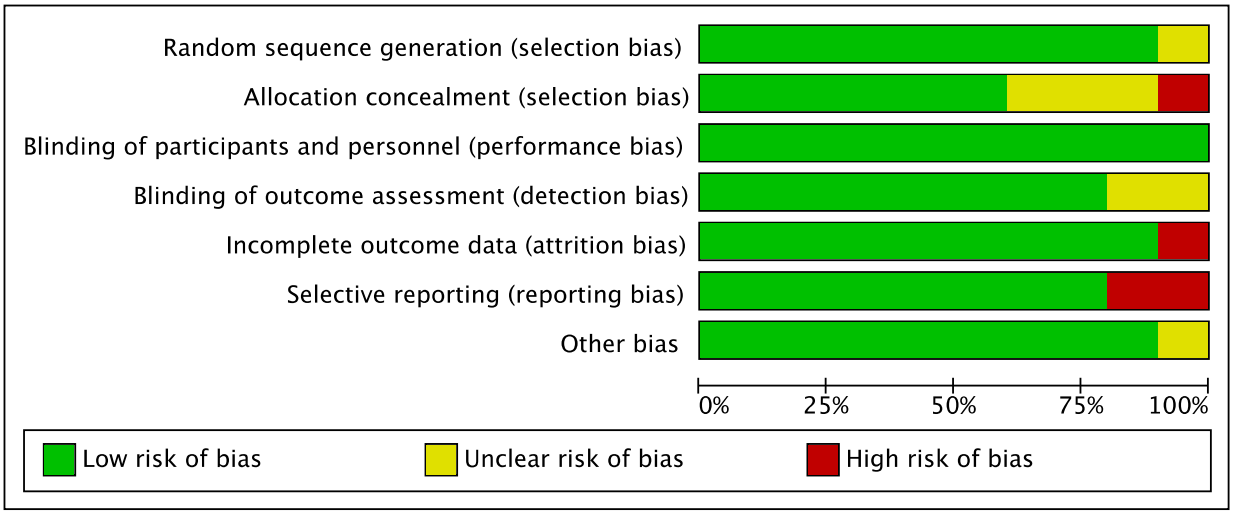

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Statistical Analysis

Patient characteristics were reported descriptively as either mean (SD) or n (%). Summary statistics are presented by treatment group (abatacept or control) for all abatacept-treated patients combined, regardless of dose levels or formulation. Using a placebo in combination with MTX or just MTX as the common comparator. We performed the meta-analysis by combining trials of the various drugs compared with the control group to obtain mutually independent Odds Ratios (ORs). For each trial, the effect was plotted according to its standard error in a forest plot showing a graphical overview of the results. A P-value equal to or less than 0.1 was considered statistically.

For drug efficacy outcomes, analyses were performed for the endpoints of DAS28 < 2.6 response rates, HAQ-DI > 0.3, SDAI ≤ 3.3 and ACR20/ACR50/ACR70(dichotomous outcomes) significant. For an indirect analysis, the homogeneity of the study population and that of the treatment and control arms are necessary to allow comparison of treatment arms across different studies. Therefore, we examined clinical heterogeneity by assessing the baseline characteristics of the study population. The Cochrane Q statistic was used to test for heterogeneity between studies, where P<0.10 indicates significant heterogeneity. The proportion of variability between studies due to heterogeneity instead of chance was assessed using the I^2, where $I^2 > 50\%$ indicates significant heterogeneity. If $I^2 > 50\%$, we choose a random effects model; conversely, then choose fixed effects model. When the $I^2 > 50\%$, each study was removed individually to check if this study is the main source of significant heterogeneity.

Results

Study Selection

Data were pooled from the ten clinical trials of abatacept (IV or SC) treatment in patients with RA that were randomized, controlled. Background therapy was permitted in all arms. In total, 1626 patients received MTX with abatacept and 1323 received MTX with or without a placebo. The mean duration of exposure to abatacept was 10.9 months with a total of 1481 patient years (py) of exposure versus the placebo duration of 10.6 months with a total of 1175 py of exposure. The groups were well matched for demographics and disease characteristics at baseline. The patient characteristics, duration of double-blind treatment, and sample size for each study are outlined in Table 1.

RCTs (Ref.)	Year	Registration No.	Way	Age (years)	Female (%)	Study Duration	Patients (n)	Compared interventions
Conaghan [13]	2013	NCT00420199	iv	51.7/52.5	59.3/69.6	4m	26/23	PLA+MTX(>=6mg/w)
Emery [14]	2015	NCT01142726	sc	46.4/49.1	79.8/76.7	12m	119/116	MTX (15~20mg/w)
Emery [15]	2018	NCT02504268	sc	50/50	75.6/80.7	52w	225/150	MTX
Kaine [16]	2012	NCT00533897	sc	48.9/49.1	85/83.8	12W	40/80	PLA+MTX(>=10mg/w)
Kremer [17,18]	2005	NCT00162266	iv	55.8/54.7	75/66	12m	115/119	PLA+MTX (10~30mg/w)
Kremer [19]	2006	NCT00048568	iv	51.5/50.4	77.8/81.4	1y	433/219	PLA+MTX(>=15mg/w)
Matsubara [20]	2018	NCT01758198	iv	56.6/54.8	81.3/86.6	52w	203/202	PLA+MTX(>=6mg/w)
Schiff [21]	2008	NCT00095147	iv	49.0/49.4	83.3/87.3	197d	156/110	PLA+MTX(>=15mg/w)
Shim [22]	2010	NCT00409838	iv	47.4/49.2	84.9/88.5	6m	55/57	PLA+MTX(~25mg/w)
Westhovens[23]	2009	NCT00122382	iv	50.1/49.7	76.6/78.7	1y	256/253	PLA+MTX(~20mg/w)

Table 1: Overview of trail designs.

Meta-Analysis Results for Efficacy

For evaluation of the efficacy of ABT plus MTX, the following data were extracted from the studies: the proportion of patients who achieved DAS28 < 2.6, HAQ-DI > 0.3, SDAI ≤ 3.3 and ACR20/50/70 response rates.

1. DAS28 defined remission (DAS28 < 2.6)

Considering the DAS28 outcomes, all studies provided data on the outcomes within the treatment. The experimental group was found to result in more patients with DAS28 defined remission than the control group, with an OR of 3.54 (95% CI: 2.27, 5.54). The DAS28 defined remission significantly differed between MTX-naive (MTX naive or received MTX for ≤ 4 weeks with 1month MTX wash-out period prior to enrolment) and MTX-experienced subgroups. Figure 3 shows the sample size and effect size characteristics of DAS28 defined remission in subgroups. From the forest plot, the effect size in these RCTs which include MTX naive RA patients with an OR of 2.06 (95%1.60, 2.66) was significantly lower than in the MTX-experienced subgroup, with an OR of 5.01(95%3.01, 8.32). Nevertheless, these results need to be interpreted with caution. It doesn't mean ABA combination therapy less likely to achieve a DAS28 defined remission in MTX-naive subgroup, the proportion of DAS28 defined remission responders for abatacept were comparable in MTX naive subgroup and MTX experienced subgroup (32.3%; 37.6%). The differences of effect size results from the MTX control group, MTX naive subgroup showed significantly higher remission response than MTX-experienced.

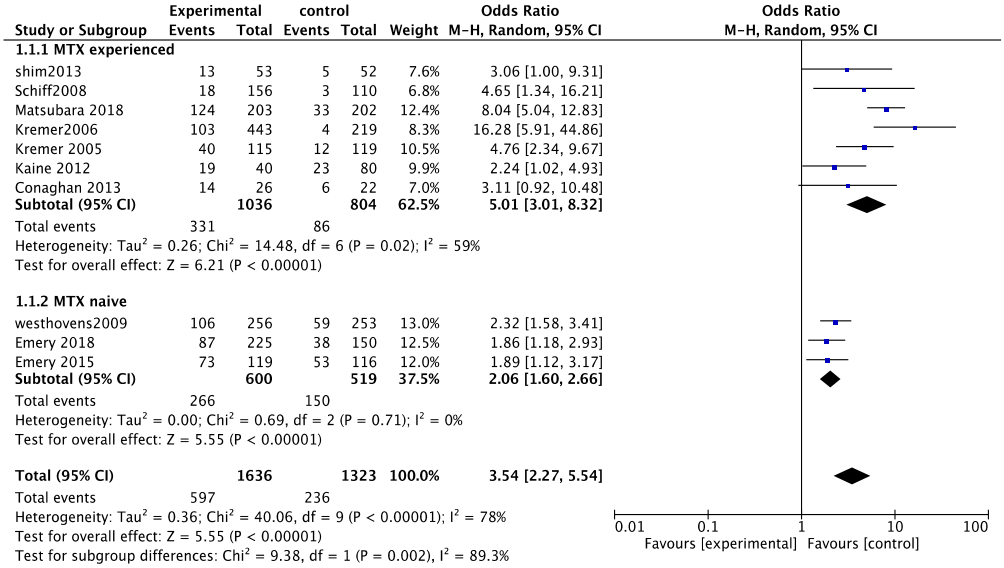

Figure 3: Forest plot reporting the effect size values for Disease Activity Score in 28 joints (DAS28) defined remission (< 2.6).

2. HAQ-DI > 0.3

Considering the proportion of patients who showed an improvement of 0.3 or more in the HAQ-DI scale, five studies provided data on the outcomes within the double-blinded treatment [19,21,22,24-26]. Abatacept in combination with MTX was found to be more effective than the control group in improving functional status, with an OR of 2.77 (95% CI: 1.69, 4.55), Figure 4A illustrates the weight of each RCT in relative efficacy. It is notable that one study [19-22,24]. had relatively higher odds ratio, there is no significant difference in the design of the methods except the study was conducted in Asian patients. These differences may be partly ascribable to variations in geographic areas and genetic susceptibility factors.

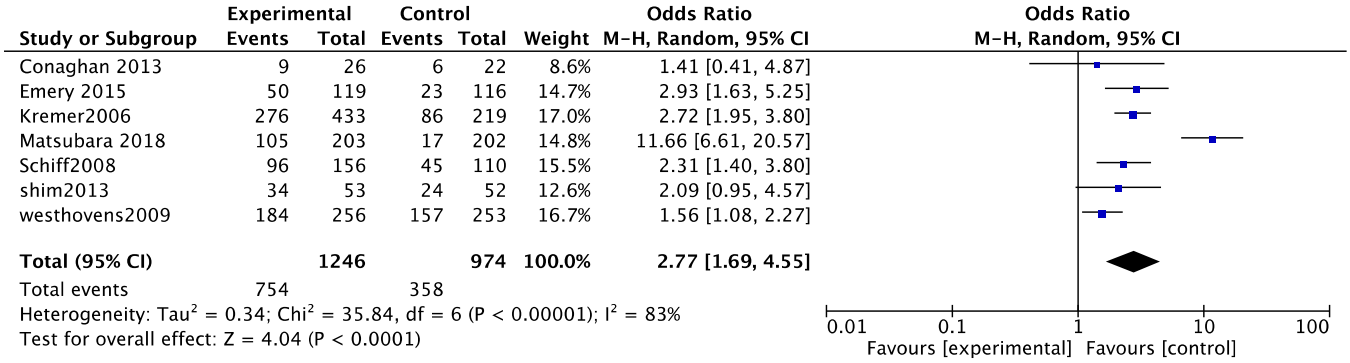

Figure 4: Forest plot reporting the Health Assessment Questionnaire disability index (HAQ-DI) > 0.3 (A) and Simplified Disease Activity Index (SDAI) ≤ 3.3 (B).

3. SDAI≤ 3.3

Considering the SDAI outcomes, four studies provided data on the outcomes within the treatment. ABA plus MTX was found to result in more patients with SDAI ≤ 3.3 than MTX monotherapy, with an OR of 3.06 (95% CI: 1.54, 6.06). The forest plot of SDAI outcomes can be seen in Figure 4B.

4. ACR-20/50/70 response rates

Abatacept combined MTX demonstrated a higher proportion of ACR-20/50/70 responders than monotherapy. The ORs comparing experimental arms versus the control arms were as follows: 3.20 [1.98, 5.16] for ACR20, 3.11 [2.00, 4.85] for ACR50 and 3.77 [2.27, 6.27] for ACR70 (Figure 5A-5C). In total, 71.08% of the patients achieved ACR20 after treatment with experimental arm compared to 40.46% of the control arm. For ACR50 and ACR70, the values were 51.09% and 32.26% for the ABA arm and 25.62% and 12.65% for the control arm, respectively. There is a trend that differences between ABA arm and control arm are increasing when realizing higher scores of ACR response. The ABA arm was 2.55 times more than the control arm in the ACR70 response rate compared to 1.77 times in the ACR20 response rate. The use of ABA combination therapy is associated with a significantly higher likelihood of achieving improvement in American College of Rheumatology criterion especially in a high level of improvement.

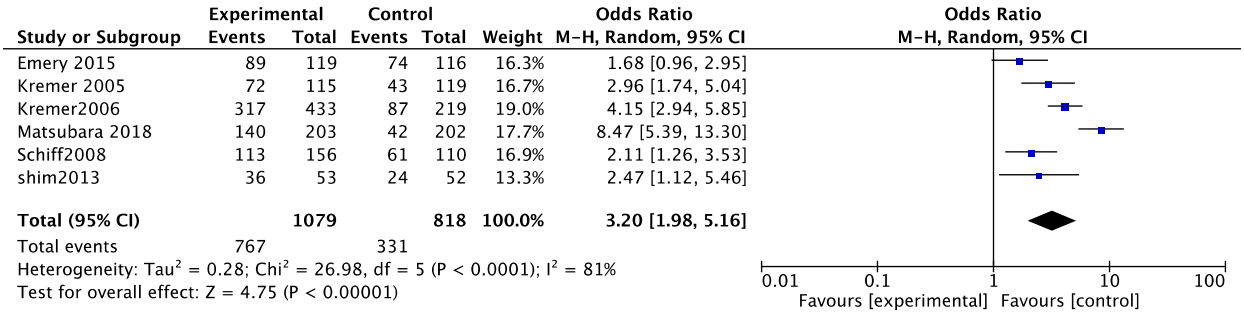

Figure 5: Forest plot reporting the 20/ 50/70% improvement in American College of Rheumatology criterion (ACR20/ACR50/ACR70). (A) ACR20; (B)ACR50; (C)ACR70.

Meta-analysis results for safety

The overall AE profiles, including AEs, infections, and malignancies, were comparable between groups. The pooled OR of AEs in patients with RA using ABA combination therapy vs MTX monotherapy was 1.14 [0.88, 1.46]. Statistical heterogeneity was low (I^2 = 0%) and not beyond variations that could be due to chance (P = 0.87), shown in Figure 6A.

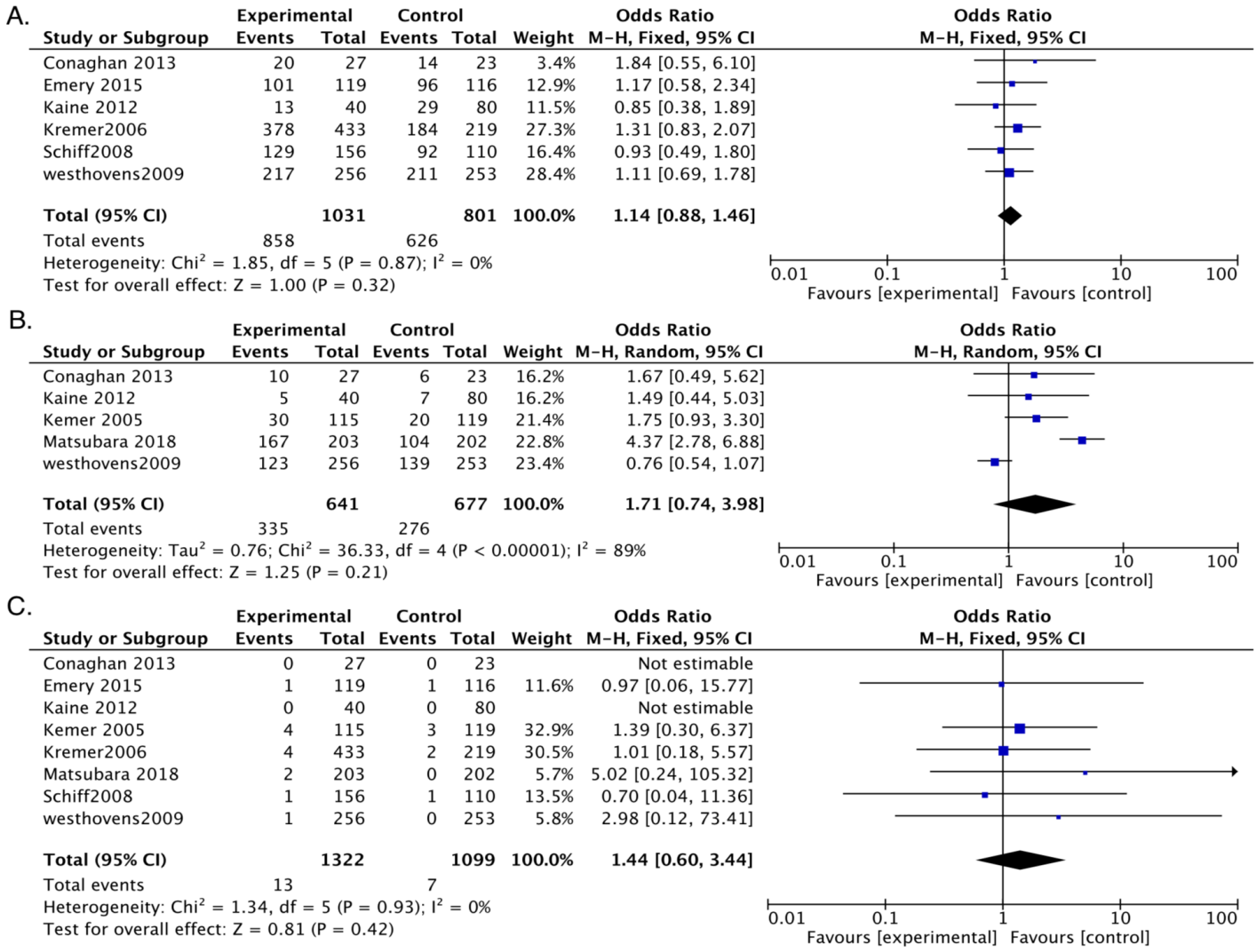

Figure 6: Forest plot reporting the effect size values for incident rates of adverse events (A), infections (B) and malignancies (C).

A total of 335 (52%; IR: 64 [95% CI:22, 105]) infections reported in the ABA arm compared with 276 (41%; IR: 47 [95% CI:19, 76]) in the control group. The risk of infection was slightly pronounced in ABA arm than control (pooled OR 1.71, 95% CI 0.74 to 3.98) (Figure 6B). The most frequent infections in both groups were upper respiratory tract infection, nasopharyngitis, urinary tract infection, and pharyngitis.

Direct comparisons of the two groups to each other show no statistically significant differences for patients attaining malignancy rates (pooled OR 1.44, 95% CI: 0.60, 3.44) (Figure 6C). Hence, Abatacept arm showed comparable malignancies rate relative to the control group.

Sensitivity analyses

High statistical heterogeneity among the studies ($I^2 > 50$ %) was observed for the six outcomes (HAQ-DI > 0.3, SDAI ≤ 3.3, ACR20, 50, 70 and infection). When each study was removed from the comparison respectively, the heterogeneity of all the outcomes was most caused by one study [20], which had ABT + MTX versus placebo + MTX as the intervention. The values included in the meta-analysis resulted in a difference, favoring the ABT group. The proportions of patients were biologic-naive with less than 2 years of mean RA disease duration and it's the only inclusive study bring Asian (Japanese) into study. Both the incidence and the prevalence of RA vary widely across geographic areas. These differences may be partly ascribable to variations in genetic susceptibility factors and to lifestyle [27]. By excluding this trial, the heterogeneity reduced and goodness of fit statistics suggested the use of a fixed effects model. This resulted in smaller credible intervals around the point estimates. Removing this trial did not significantly impact the findings for all outcomes and there wasn't enough study to compare subgroups of race, so we still keep this trial in our meta-analysis.

Discussion

Based on its efficacy and safety as well as relatively low costs, MTX continues to be the anchor ('first') drug for patients with RA both as monotherapy as well as in combination with other drugs [3]. Unfortunately, there is great person-to-person variability in the physiological response to MTX, with up to 50% of patients showing little response to the medication [27]. Recent studies showed the effectiveness of a combination of biologics DMARDs and MTX for the treatment of RA [28,29] and ABA monotherapy had a relatively more acceptable efficacy, safety and tolerability profile than other biologic disease-modifying antirheumatic drugs (bDMARDs) [9,21]. Thus, a meta-analysis based on a systematic review of the literature was performed to estimate the relative efficacy and safety of abatacept in combination with MTX compared with placebo plus MTX or only MTX in the treatment of RA patients.

The primary problem this study addressed is the effectiveness which is identified from the result of various parameters (DAS28 < 2.6, SDAI ≤ 3.3, ACR20/50/70 response rate and HAQ-DI> 0.3). Not all trials reported findings on all evaluated endpoints. The decision was made to include all available data leading to differences in evidence used across endpoints. In this study, the ABT arm consistently demonstrated efficacy benefits over the control after the treatment of the DB period was observed, including reduced disease activity measures and improvements in physical function and health-related quality of life.

Our meta-analyses included the results of studies involving patients with early RA and patients with longer disease duration (with a mean duration of disease varying from 0.54 years to 9.6 years). The remission of the disease is partly elevating when ABA is used in the early stages of RA [30]. There is a rationale for the use of ABA in early RA, due to a greater impact on naive T cells, since T-cells are thought to be involved in the initiation of RA [24]. In this study, only four trials [13,15,20,24]. included patients who were within less than 30 months of disease duration. The rate of DAS28 < 2.6 in the patients whose disease duration < 30 months is 52% which is almost twice than 28% in disease duration > 30 months.

Another issue that we do not address is the MTX-resistant population of RA patients. ACR guidelines mentioned for the treatment of RA specifies a trial of a DMARD before initiating a biologic agent except in patients with active disease and poor prognosis in which case a DMARD plus a biologic can be used. MTX-resistant individuals represent a significant portion of the patients who are often offered a biologic in order to achieve maximum control of their disease. The previous study has already evaluated with a meta-analysis [31] which has also shown benefits associated with the use of ABA with the background of MTX in MTX-resistant patients, which involves three studies [17,18,21] that were cited by our analysis as well. Abatacept was found to result in more patients with DAS28 defined remission than placebo, with an OR of 4.77 (95% CI: 1.60; 15.78).

We also evaluated adverse events, infections, and malignancy, which should inform physicians with regard to their choice of agents to treat patients with RA, making second-order considerations more important. The safety showed no differences between the groups with regard to AEs and malignancy, while the incident rate of the infections in the ABA group is subtle superior to the control group. In pooled RCTs data have confirmed a low cumulative incidence of malignancy, cancer incidence in ABA group was 1.3 per 100 py compare to 0.9 per 100 py in control group including basal cell carcinoma, pulmonary carcinoid tumor, bladder cancer, B-cell lymphoma and endometrial carcinoma that does not increase with increasing exposure to ABA arms. Infections are the most common AEs reported in RCTs, some of the common infections recorded in the studies were nausea, nasopharyngitis, headache and upper respiratory tract infection [16,18,32]. Serious AEs were not included in our study due to the small number of RCT involved, but the Cochrane collaboration has performed a network meta-analysis [33] revealing that ABA was associated with a significantly lower risk of serious adverse events compared to most other biologics. There are infusion reactions (acute and peri-infusional) that occurred with the ABA arms [19,22,34]. There were patients experienced hypersensitivity (rash and chest pain), and severe hypotension after the infusion. Nevertheless, these events resolved shortly after cessation of infusions.

Above all, there are some potential limitations to this study. Firstly, patients were also permitted to treat with oral corticosteroids and non-biological Disease-Modifying Antirheumatic Drugs (DMARD) in most of the trials. However, patients receiving these drugs were required to be on a stable dose at initiation and to maintain that dose until the end of the DB period. Secondly, for MTX-resistant patients, ABA therapy should be used in combination with MTX, when possible; due to superior efficacy of this combination over monotherapy [35], it seems to be a superior strategy to MTX monotherapy in non-MTX-resistant

patients. A caveat here is that because of the use of corticosteroids and NSAIDs, it is difficult to determine what a minimal clinically significant difference is.

Lastly, this study included some important clinical efficacy outcomes, however, other safety outcomes could not be analyzed (such as SAEs, death, severe infections) because they were less often included in the reviewed RCTs. Only RCT was included in this study for the evaluation of outcomes. However, long-term observational studies can provide a more realistic long-term estimation of the outcomes, especially the safety-related ones, reflecting the risks of ABT in the "real world".

Conclusion

Our meta-analyses provided a comprehensive picture of the clinical efficacy and safety of ABT in combination with a background of MTX, which presented a higher efficacy for all considered parameters (DAS28 < 2.6, HAQ-DI > 0.3, SDAI ≤ 3.3 and ACR20/50/70) compared to MTX monotherapy. Pool analysis has also shown that ABA arm is safe and well-tolerated, with no significant difference in the incident rates of AEs, infections, and malignancies compared with the control arm, demonstrating a favorable benefit-risk profile.

Lastly, there is also a growing movement to perform the trails on a more specific patient population divided by ACPA (anti-citrullinated protein antibody) level, RF (rheumatoid factor) level, DMARD-naive or resistant and race. We recommend future studies to perform analysis on DMARD inadequate responders, the major group of patients for whom a biologic agent is recommended. On the other hand, for observational studies, real-world observational analyses with larger patient samples and higher incidence of measured outcomes, are needed to further examine the incident rates of specific infection or malignancy.

Supporting Information

PRISMA S1. The PRISMA checklist contains items pertaining to the content of reviewed papers which include the title, abstract, methods, results, discussion, and funding. The author thanks Exploration of the World Funding, for the funding support.

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