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Scholars Bulletin

Abbreviated Key Title: Sch Bull
ISSN 2412-9771 (Print) | ISSN 2412-897X (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Subject Category: Medicine

Efficacy of Janus Kinase Inhibitors (JAK) in Combination with Methotrexate for Treatment of Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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DOI: https://doi.org/10.36348/sb.2024.v10i07.002 | **Received:** 14.07.2024 | **Accepted:** 19.08.2024 | **Published:** 22.08.2024

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Abstract

***Background*:** Rheumatoid Arthritis is a major public health concern, affecting 0.46% of general population. Janus kinase inhibitors (JAK) emerged as new biological drug for RA management. However, there is limited literature on effectiveness and safety of JAKi in combination therapy for RA management. We aimed to perform a meta-analysis to compare the efficacy and safety of JAKi in combination therapy with MTX as compared to MTX alone among RA patients. ***Methods*:** The recent meta-analysis of randomized controlled trials (RCT) have been conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis Protocols to fulfil research aims. Three electronic databases named as PubMed, Cochrane library and clinical trials.gov were used for research articles extraction. Primary outcomes were American College of Rheumatology criteria for 20% improvement (ACR20 response), Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire disability index (HAQ-DI), and adverse events (TEAE). The Cochrane Risk of Bias tool was used to evaluate the quality of each included randomized clinical trials. The pooled analysis was conducted by using RevMan (Review Manager) software version 5.4. ***Results*:** About 407 research articles were extracted from electronic databases and only 9 RCT's met the inclusion criteria. About 9 RCT's and 6853 RA patients met the inclusion criteria with 5040 patients receiving JAKi plus MTX in combination and 1813 patients receiving MTX in monotherapy. The pooled analysis showed that ACR20 have significantly improved among group receiving combination therapy as compared to MTX alone (Placebo) [OR: 2.44 (1.35 to 4.40) Cl: 95%] while TEAE numbers have favored the MTX alone as compared to group receiving combination therapy [RR: 1.29 (0.89 to 1.87) Cl: 95%], because number of adverse events were higher among treatment group. Moreover, the mean difference showed that HAQ DI [Mean difference: -0.53 (0.94 to -0.11) Cl: 95%], DAS28 [Mean difference: -1.85 (-2.83 to -0.86) Cl: 95%] have significantly decreased among group receiving combination therapy as compared to MTX alone (Placebo). ***Conclusion*:** Overall, the findings of recent meta-analysis revealed that JAKi in combination therapy with MTX improved the ACR20 responses, Clinical Disease Activity Index (CDAI), and mean creatinine levels, as compared to MTX alone among RA patients. However, the frequency of adverse events by JAKi plus MTX was higher as compared to MTX alone that compromised the safety profile of combination therapy.

Keywords: Rheumatoid Arthritis, Janus kinase inhibitors (JAK), monotherapy, randomized controlled trials.

1. INTRODUCTION

Rheumatoid arthritis (RA) is heterogeneous autoimmune disorder, followed by symptoms of progressive bone erosion, joint inflammation, painful deformity and immobility that affects quality of life among aged patients [1]. The quantitative data analysis and current statistical analysis demonstrate that RA is a major public health concern, imposing socioeconomic burden. About 17.6 million of people have been suffering from rheumatoid arthritis globally. In other words, global incidence of rheumatoid arthritis (RA) is reported to be 0.46% of overall population worldwide [2]. About 208 cases per 100000 people have been reported by 2021, representing an increase of 14% in global prevalence of

disorder since 1990. The ratio of prevalence was higher among females as compared to male. The mortality rates among RA patients are very low as 0.47 per 100000 population [3]. However, the increasing incidence rates have compromised the quality of life of diseased population.

As complex disorder, RA has multifactorial etiology, contributed by genetic as well as environmental factors. HLA shared epitope polymorphisms and other genetic factors contributed about 60-70% in pathophysiology of RA disease. The autoimmune responses behind disease involved the defective immune regulation, autoantibodies against citrullinated and carbamylated proteins and inflammatory cytokines like TNF-α, IL-1, and IL-17 [4]. Other environmental factors such as air pollution, diet, smoking status and demographic status triggered the RA prevalence.

In the recent years, the major advances of pharmaceutical industry have evolved the therapeutic landscape of RA. The conventional synthetic drugs including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) and disease-modifying antirheumatic drugs such as methotrexate (MTX) [5] and biologic DMARDs (bDMARDs) [6] are common for treatment of RA. But, these drugs proved ineffective for management of RA. A new class of targeted synthetic DMARD's named as Janus kinase inhibitors (JAKi) have been emerged as an effective biological drug for clinical management of RA [7, 8]. On the basis of evidences from clinical trials, the JAKi are highly recommended by the American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) rather than MTX [9]. However, if patients have been receiving MTX, the JAKi can be added to improve the poor clinical outcomes. Few key randomized controlled trials (RCTs) have been proven clinical outcomes among RA patients when JAKi combined with csDMARDs such as MTX [10].

In the pathogenesis of RA, the Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway involves four proteins such as JAK1, JAK2, JAK3, and TYK2 [10, 11]. The main functions of small molecules of JAKi are inhibition of JAK/STAT pathway and blockage of the intracellular signaling mediated pathways by infinite cytokines and other molecules, triggering the improvements in RA pathophysiology. Recently, several licensed or the Food and Drug Administration (FDA) approved JAKi drugs have been implicated for RA treatment [12]. For example, Tofacitinib, as first generation JAKi, has been approved by FDA in 2012 due to its predominant JAK1/JAK3 selectivity [13]. Other FDA approved JAKi drugs such as upadacitinib and filgotinib that inhibits JAK1, while baricitinib inhibits JAK1/JAK2 selectively [14]. JAKi have been proved to be effective with moderate tolerance for RA patients, however some adverse events such herpes infection, thromboembolism, and malignancies have been reported [15]. Some patients already receiving MTX are treated with JAKi to promote combination therapy for management of RA with effective clinical outcomes.

Additionally, results of clinical trials proved that combination therapy (JAKi plus MTX) as compared to MTX monotherapy can achieve better clinical outcomes that could disturbed by intolerance of MTX alone [16, 17]. The clinical trials involving JAKi monotherapy such as tofacitinib was proved to be effective for 60-70% of RA patients and yielded several benefits like reduced adverse events, low cost treatment and oral use [18]. Various clinical trials [19-21] have reported the improved effectiveness related clinical outcomes and safety profile of JAKi in monotherapy.

Recently, there is lack of studies proving the comparable effectiveness of JAKi in monotherapy and JAKi in combined therapy with MTX. Previous meta-analysis based study by Liu *et al.*, [22] have involved 5 RCT's and 2290 RA patients to compare the JAKi in combination therapy and MTX alone. But numbers of studies were not enough to analyze the clinical outcomes related to effectiveness and safety profile among RA patients. Another study by Solipuram *et al.*, [23] analyzed the efficacy of JAKi in combination therapy among malignancy RA patients through pooled analysis. Additionally, the numbers of studies based upon comparisons of two drugs for management of RA are rare. Therefore, we aimed to perform a meta-analysis to compare the efficacy and safety of JAKi in combination therapy with MTX and MTX alone among RA patients.

2. METHODS

The recent meta-analysis of randomized controlled trials (RCT) have been conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis Protocols [24] to fulfil research aims. There is no need of ethical consideration due to involved of already published RCT's.

2.1 PICO Framework

Among patients with Rheumatoid Arthritis (RA) what are the effectiveness and safety-related outcomes of JAKi in combination therapy with MTX and other drugs or MTX alone as placebo? The recent study used the Population Intervention Control Outcome (PICO) framework to guide the search (Table 1) [25].

Table 1: PICO framework for research question of recent study

PICO	Description
Population	Adult Patients (40-70 years old) diagnosed with rheumatoid arthritis (RA)
Intervention	JAKi (Janus kinase inhibitors) plus MTX
Control/ comparison	MTX alone or other drugs as Placebo
Outcome	American College of Rheumatology criteria for 20% improvement (ACR20 response), Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire disability index (HAQ-DI), mean creatinine levels and adverse events (TEAE)

2.2 Data Resources

The searching and selection of research articles related to PICO framework of recent meta-analysis was done to fulfil research aims. Three electronic databases named as PubMed, Cochrane library and clinical trials.gov were used for research articles extraction. The MeSH keywords used for data extraction were ("rheumatoid arthritis" OR "RA") AND ("Janus kinase inhibitors" OR "JAKi" OR "MTX" OR "Methotrexate") AND ("American College of Rheumatology criteria for 20% improvement" OR "ACR20 response" OR "Clinical Disease Activity Index" OR "CDAI" OR "Disease Activity Score in 28 joints" OR "DAS28" OR "Health Assessment Questionnaire disability index" OR "HAQ-DI" OR "mean creatinine levels" OR "adverse events" OR "TEAE"). Already published meta-analyses and their references of eligible trials were also search to reach authentic data. References were managed using EndNote (Clarivate Analytics). The timeline of research was set from 2010 to June 2024 as these JAKi drugs were approved by FDA in 2012.

2.3 Study Selection & Eligibility Criteria

The selection and screening of research articles were conducted in accordance with PRISMA guidelines. The predefined selection criteria helped in the screening of research articles. All studies were screened independently by two authors after full text review in accordance to the selection criteria.

Inclusion Criteria:

Only those research studies were included that met the following criteria:

1. Studies discussing the study population of RA patients.
2. Studies involving the RA patients receiving or received MTX as DMARD in past (6 months ago).
3. Studies that highlight the JAKi in combination therapy with MTX as intervention.
4. Studies based on randomized controlled trials, clinical trials and cohort studies.
5. Studies discussing clinical outcomes of American College of Rheumatology criteria for 20% improvement (ACR20 response), Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire disability index (HAQ-DI), mean creatinine levels and adverse events (TEAE).
6. Studies with full text and published in English.

Exclusion Criteria:

Only those studies were excluded that were:

1. Discussing population with other disease rather than RA.
2. Involving the RA patients receiving other DMARD drugs rather than MTX.
3. Discussing the other drugs for treatment of RA rather than JAKi or receiving JAKi in monotherapy.
4. Those studies were also excluded that reported outcomes rather than American College of Rheumatology criteria for 20% improvement (ACR20 response), Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire disability index (HAQ-DI), mean creatinine levels and adverse events (TEAE).
5. Already published systematic reviews, meta-analyses, scoping reviews, literature reviews, conferences, and case studies.
6. Studies with non-full-text papers or duplicated publications were published in other languages rather than English.

2.4 Data Screening & Extraction

Two authors independently screened the research articles for removal of duplicate studies and assessment of full texts of eligible research papers by reading titles and abstracts. Other disagreements were resolved through discussion. A pre-made table was used to retrieve data from the listed research. Relevant data were taken from every study that two authors included. The extracted data included author names, year of publication, country, study design, study population & sample size, study follow-up or duration, and outcomes.

2.5 Primary & Secondary Outcomes

Our main comparison was JAKi in combination therapy with MTX and MTX alone. Primary outcomes were American College of Rheumatology criteria for 20% improvement (ACR20 response), Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire disability index (HAQ-DI), and adverse events (TEAE). Secondary comparisons were mean creatinine levels and Clinical Disease Activity Index

(CDAI) between-regimens comparisons. The definitions of each outcome are given as:

ACR20: It is defined as improvements of 20% in swollen joints and number of tender and 20% improvement in three out of five criteria related to functional ability of RA patients.

DAS28: It is defined as scoring system of evaluation of disease activity and treatment response after drug among RA patients. A DAS28 score of greater than 3.2 is a well-described limit for treatment evaluation.

HAQ-DI: It is defined as health assessment questionnaire based upon 8 sections: eating, walking, dressing, arising, hygiene, grip, reach and activities that comprised of 20 questions.

CDAI: It is defined as clinical research score, used to define clinical activity and response to intervention.

2.6 Risk bias Assessment

The Cochrane Risk of Bias tool was used to evaluate the quality of each included randomized clinical trial by 2 authors independently. The risk bias of included studies was evaluated on basis of six domains; allocation concealment, blinding of participants, Selection bias, blinding of outcome assessment, selective reporting and other bias. The score or level of each included studies was categorized into Low risk, unclear and high risk [26].

2.7 Statistical Analysis

In recent meta-analysis, the pooled analysis was conducted by using RevMan (Review Manager) software version 5.4. The intervention effect for each study was estimated by calculating odds ratio (ORs) with 95% Cls. The Mantel-Hansel (M-H) random effect model was applied for evaluation of mean difference of expected outcomes after JAKi in combination therapy with MTX and odd ratio of patients showing ACR20 and adverse events were evaluated by pooled analysis. Furthermore, the I2 statistics was used to measure the heterogeneity. Heterogeneity among RCT based studies was evaluated using the Cochrane Q statistic (P values) and the inconsistency I^2 statistic. A significant difference was considered if the p-value > 0.05. If the I2 value was >50%, heterogeneity was considered significant.

3. RESULTS

3.1 Study Selection

About 407 research articles related to title "Efficacy of Janus kinase inhibitors (JAK) in combination with methotrexate for treatment of Rheumatoid Arthritis" were extracted from above mentioned electronic databases (PubMed= 85, Clinical trial gov. =116 & Cochrane library= 206). After removal of duplicates, non-full texts and irrelevant data by following PRISMA guidelines, only 209 articles were retrieved for screening. About 167 research studies were assessed for eligibility, and only 9 RCT's met the inclusion criteria, as shown in Figure 1.

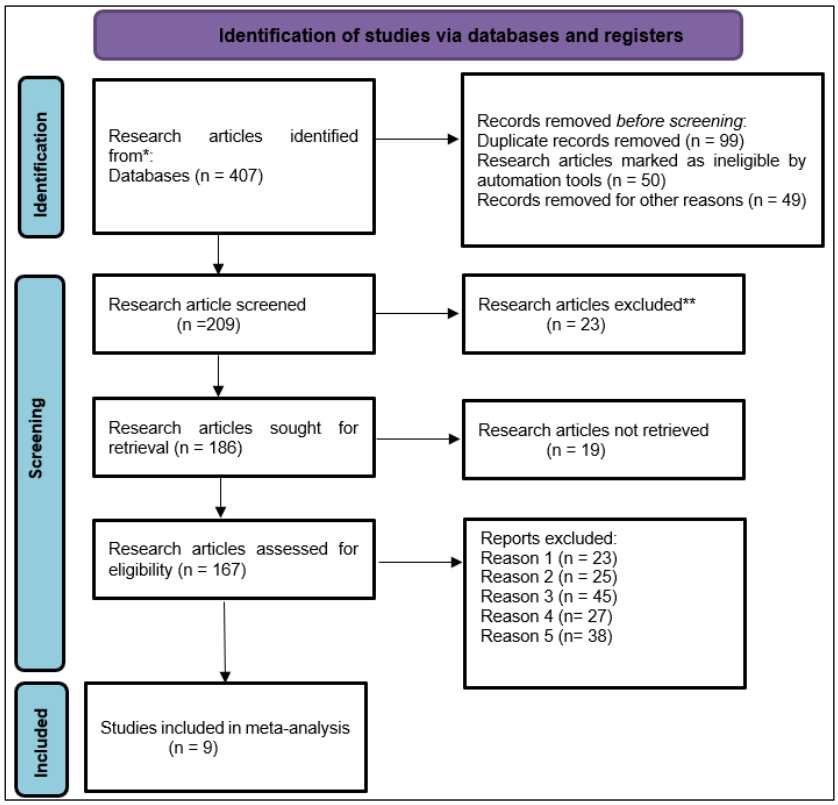

Figure 1: PRISMA flowchart for screening and selection of research articles

3.2 Risk of Bias Assessment

The Cochrane risk of bias tool was used to assess the studies, and the findings are presented in Figure 2 and 3. All our studies were considered to have minimal risk of bias, indicating a high level of reliability.

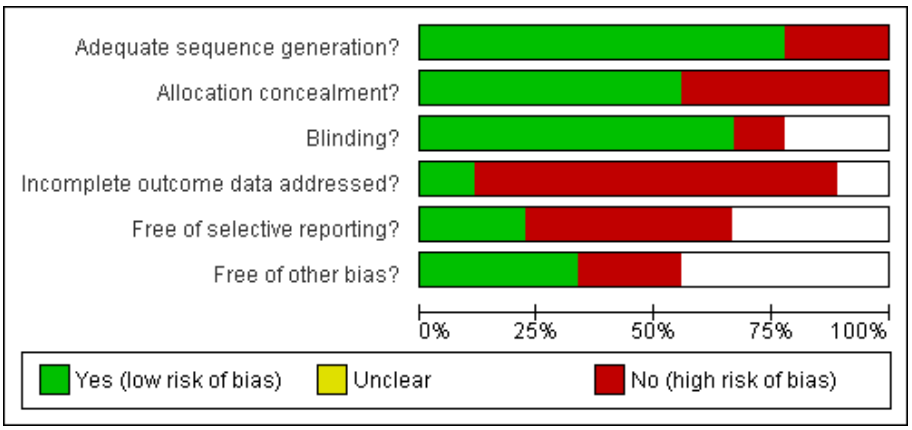

Figure 2: Graph of Risk bias of included studies

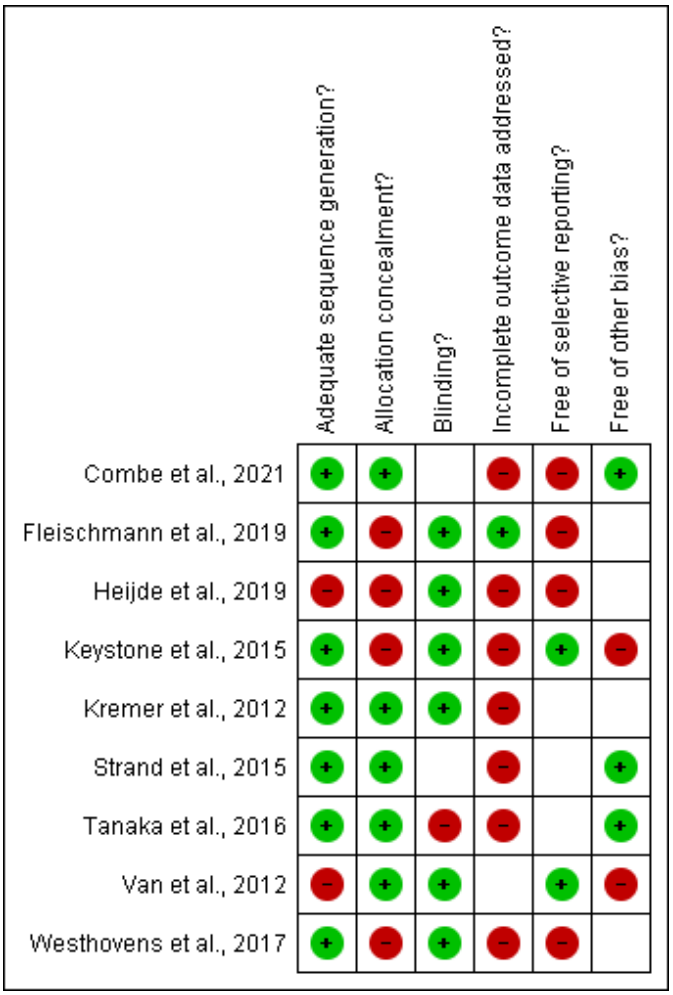

Figure 3: Graph of risk bias summary of included studies

3.3 Characteristics of included Studies

About 9 RCT's and 6853 RA patients met the inclusion criteria [16-19, 21, 27-31] with 5040 patients receiving JAKi plus MTX in combination and 1813 patients receiving MTX in monotherapy. All included RCT's were registered on clinicaltrials.gov and all studies discussed almost all primary as well as secondary outcomes of recent meta-analysis. Among included RCT's, 4 RCT's [17, 19, 27, 29] discussed tofacitinib as JAKi, 2 RCT's employed baricitinib [28, 31], and remaining three RCT's employed filgotinib [16, 18, 30]. All RA patients from included studies had exposure to

MTX previously and showed inadequate response to MTX. The maximum study follow up was 12 months and minimum study follow up was 12 weeks. The dose of MTX varied from 10 mg to 25 mg once in week while dose of JAKi drugs varied from 2mg to 20 mg twice daily for RA management. To produce heterogeneity, 9 trials belonged to 6 different countries; 4 from USA [18, 19, 27, 29], 1 from Spain [17], 1 from Canada [31], 1 from Belgium [16], 1 from France [30], and 1 from Japan [28].

Table 2: Characteristics of included studies

Author, Year	Country	Study Population & Sample size	Study Design	Study follow-up	Type of JAK drug	ACR20 response	Mean creatinine conc. (µmol/L)	TEAE	disease activity (CDAI)	HAQ-DI	mean decrease in DAS28
Westhovens *et al*., 2017 [16]	Belgium	594 RA patients; 171 in treatment & 86 in placebo	Randomized double blinded, controlled trial	24-week	50, 100 or 200 mg filgotinib twice daily	T: 113 P: 44	T: 6.1 P: 0.1	T: 85 P: 32	T: -32 P: -16	T: -0.90 P: -0.37	T: -3.2 P: -1.2
Heijde *et al*., 2019 [19]	USA	800 RA patients 432 in treatment & 107 in placebo	Randomized double blinded, controlled trial	24 months	5, 10 mg tofacitinib twice daily	T: 156 P: 74.6		T: 164 P: 39	T: 27.5 (3.0) P: 22.7 (6.5)	T: −0.7 (0.0) P: −0.6 (0.1)	T: -8.3 P: - 4.2
Kremer *et al*., 2012 [27]	USA	509 RA patients 423 in treatment 54 in placebo	Randomized double blinded, controlled trial	24 weeks	1, 3, 5, 10, 15, 20 mg tofacitinib twice daily	T: 236 P: 17		T: 111 P: 19		T: -0.53 (0.06) P: -0.16 (0.06)	T: -1.42 P: -0.84
Tanaka *et al*., 2016 [28]	Japan	145 RA patients: 94 in treatment & 48 in placebo	Randomized, placebo-controlled study	12 weeks	1 mg, 2 mg, 4 mg, or 8 mg oral baricitinib	T: 80 P: 14	T: 5.0* (–5 to 23) P: 0	T: 54 P: 26		T: -0.41 P: -0.4	T: -1.47 P: -1.01
Strand *et al*., 2015 [29]	USA	399 RA patients: 267 in treatment & 132 in placebo	Randomized, placebo-controlled study	6 months	5 mg or 10 mg of tofacitinib twice daily					T: -0.46 P: 1.63 (0.66)	
Combe *et al*., 2021 [30]	France	1759 RA patients: 1280 in treatment & 381 in placebo	Randomized, placebo-controlled study	52 weeks	100 mg, 200 mg filgotinib	T: 972 P: 190		T: 183 P: 21	T: 29.5 25.3–33.7) P: 24.2 (20.2–28.1)	T: −0.69± 0.61 P: −0.42± 0.54	T: -4.8 P: -1.4
Keystone *et al*., 2015 [31]	Canada	301 RA patients: 203 in treatment & 98 in placebo	Randomized, placebo-controlled study	24 weeks	1, 2, 4 or 8 mg baricitinib	T: 90 P: 10		T: 99 P: 45		T: −0.44 P: −0.10	

Fleischmann *et al.*, 2019 [18]	USA	1,629 RA patients 888 in treatment & 595 in placebo	Randomized, placebo-controlled study	12 weeks	15 mg of upadacitinib once daily	T: 542 P: 214	T: 0.02 P: 0.01	T: 764 P; 197		T: -0.49 P: -0.28	
Van Vollenhoven *et al.*, 2012 [17]	Spain	717 RA patients 405 in treatment 312 in placebo	Randomized, placebo-controlled study	12 months	5 mg or 10 mg of tofacitinib twice daily	T; 212 P: 125	T: 0.06 mg P: 0.02	T: 173 P: 122		T: -0.7 P: -0.4	T: -2.8 P: -2.2

CDAI: Clinical Disease Activity Index, **DAS28**: Disease Activity Score in 28 joints, **ACR20 response**: American College of Rheumatology criteria for 20% improvement, **HAQ-DI**: Health Assessment Questionnaire disability index, TEAE: Treatment emergent adverse events, T: treatment and P: placebo

3.4 Primary Outcomes

ACR20

Among 9 RCT's, 8 included studies discussed the ACR20 as primary outcome among groups receiving JAKi in combination therapy with MTX and MTX alone. The pooled analysis showed that ACR20 have significantly improved among group receiving combination therapy as compared to MTX alone (Placebo) [OR: 2.44 (1.35 to 4.40) Cl: 95%] and heterogeneity (I^2 = 95%, df= 7, p>0.00001).

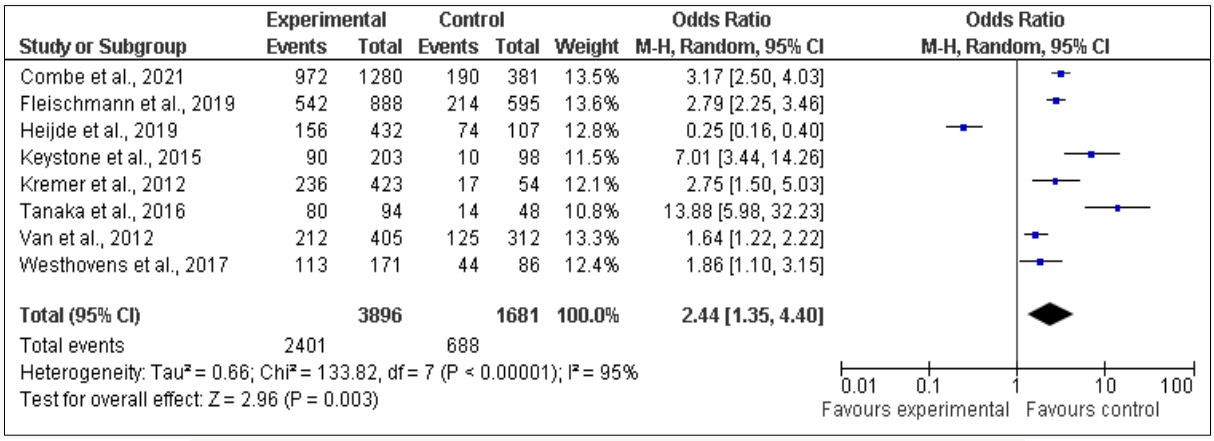

Figure 4: Forest plot of odd ratio of ACR20 among treatment and placebo groups

HAQ-DI

Among 9 RCT's, 8 included studies discussed the HAQ-DI as primary outcome among groups receiving JAKi in combination therapy with MTX and MTX alone. The mean difference showed that HAQ DI have slightly decreased among group receiving combination therapy as compared to MTX alone (Placebo) [Mean difference: -0.53 (0.94 to -0.11) Cl: 95%] and heterogeneity (I^2 = 100%, df= 7, p>0.00001).

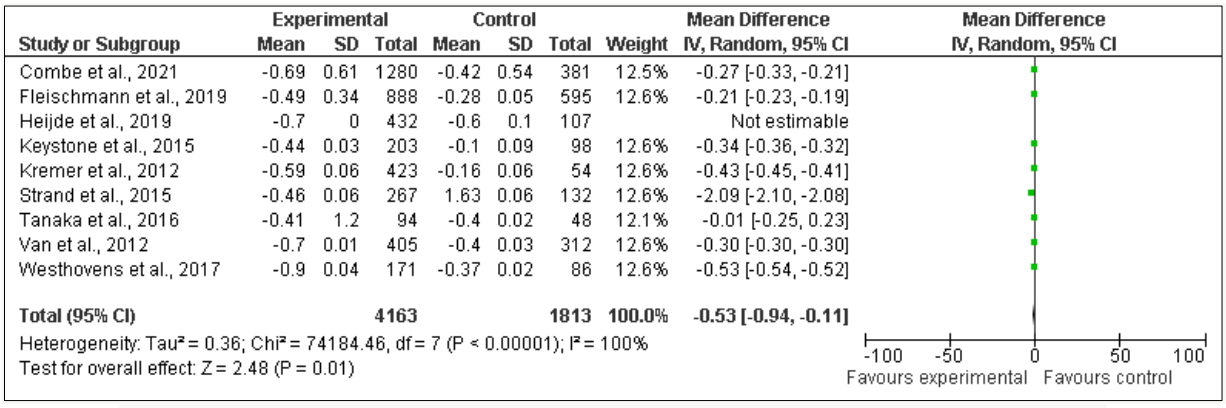

Figure 5: Forest plot of mean difference of HAQ-DI scores among treatment and placebo groups

DAS28

Among 9 RCT's, 6 included studies discussed the DAS28 as primary outcome among groups receiving JAKi in combination therapy with MTX and MTX alone. The mean difference showed that DAS28 have significantly decreased among group receiving combination therapy as compared to MTX alone (Placebo) [Mean difference: -1.85 (-2.83 to -0.86) Cl: 95%] and heterogeneity (I^2 = 100%, df= 5, p>0.00001).

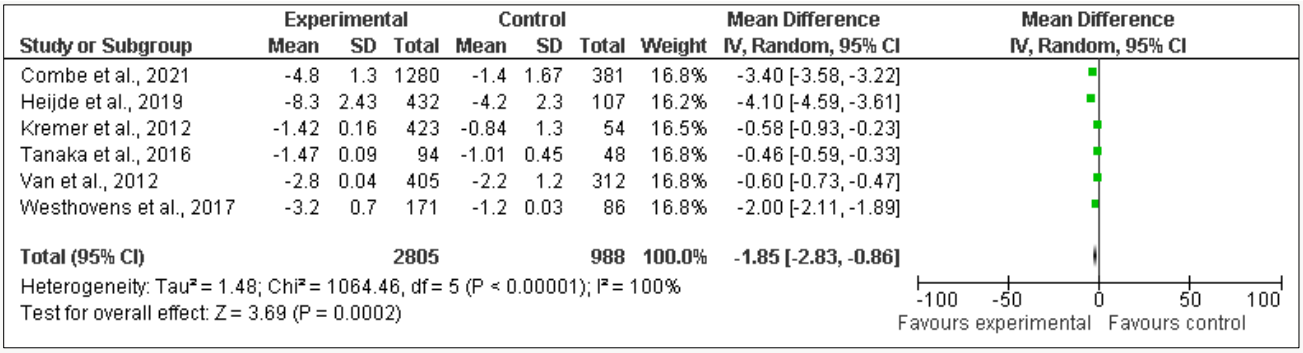

Figure 6: Funnel plot of mean difference of DAS28 scores among treatment and placebo groups

Safety Profile (TEAE)

Among 9 RCT's, 8 included studies discussed the TEAE (Treatment emergent adverse events) as primary outcome among groups receiving JAKi in combination therapy with MTX and MTX alone. The pooled analysis showed that TEAE numbers have favored the placebo group as MTX alone as compared to group receiving combination therapy [RR: 1.29 (0.89 to 1.87) Cl: 95%] and heterogeneity (I^2 = 95%, df= 7, p>0.00001).

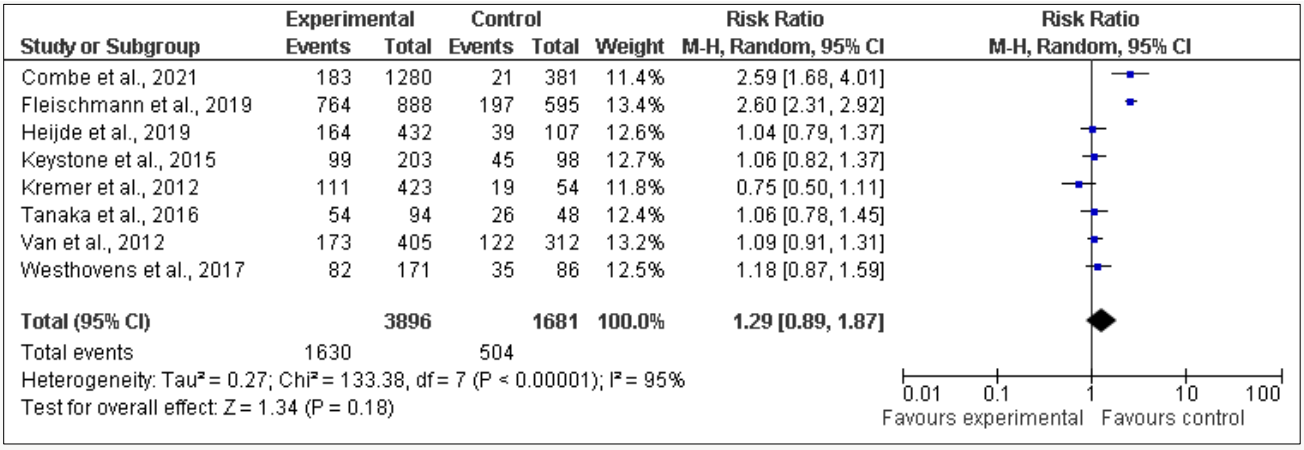

Figure 7: Forest plot of risk ratio of adverse events among treatment and placebo groups

CDAI

Among 9 RCT's, 3 included studies discussed the CDAI as primary outcome among groups receiving JAKi in combination therapy with MTX and MTX alone. The mean difference showed that CDAI scores were higher among group receiving combination therapy as compared to MTX alone (Placebo) [Mean difference: 8.71 (0.07 to 17.36) Cl: 95%] and heterogeneity (I^2 = 100%, df= 2, p>0.00001).

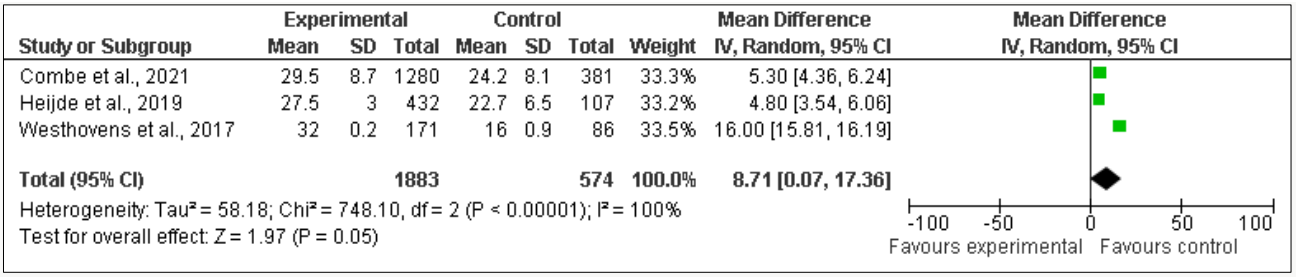

Figure 8: Forest plot mean difference of CDAI among treatment and placebo groups

Mean Creatinine Concentrations (µmol/L)

Among 9 RCT's, 4 included studies discussed the Mean creatinine concentrations (µmol/L) as primary outcome among groups receiving JAKi in combination therapy with MTX and MTX alone. The mean difference showed that mean creatinine concentration scores were increased among group receiving combination therapy as compared to MTX alone (Placebo) [Mean difference: 2.61 (0.82 to 4.40) Cl: 95%] and heterogeneity (I^2 = 100%, df= 3, p>0.00001).

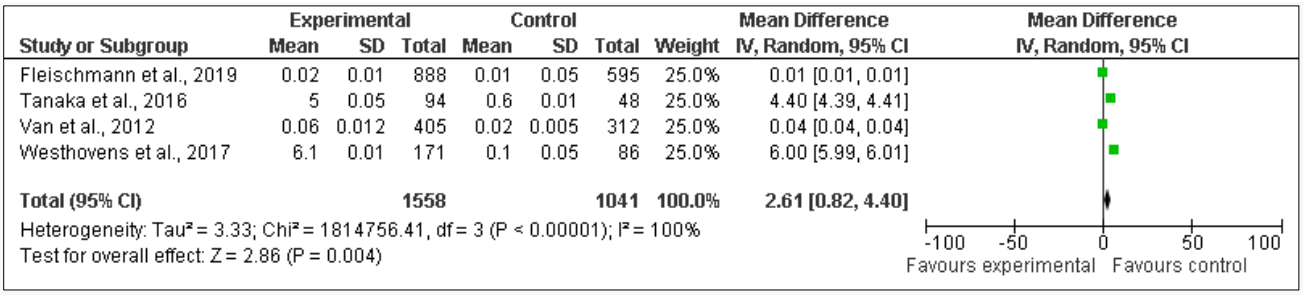

Figure 9: Forest plot mean difference of CDAI among treatment and placebo groups

4. DISCUSSION

In recent meta-analysis, about 9 RCT's and 6853 RA patients were analyzed to evaluate the efficacy and safety of JAKi in combination therapy with MTX as compared to MTX alone as placebo. The primary outcomes of American College of Rheumatology criteria for 20% improvement (ACR20 response), Clinical Disease Activity Index (CDAI), Disease Activity Score in 28 joints (DAS28), Health Assessment Questionnaire disability index (HAQ-DI), mean creatinine levels and adverse events (TEAE) were analyzed in recent study through pooled analysis. The pooled analysis showed that ACR20 have significantly improved among group receiving combination therapy as compared to MTX alone (Placebo) [OR: 2.44 (1.35 to 4.40) Cl: 95%] while TEAE numbers have favored the MTX alone as compared to group receiving combination therapy [RR: 1.29 (0.89 to 1.87) Cl: 95%], because number of adverse events were higher among treatment group. Moreover, the mean difference showed that HAQ DI [Mean difference: -0.53 (0.94 to -0.11) Cl: 95%], DAS28 [Mean difference: -1.85 (-2.83 to -0.86) Cl: 95%] have significantly decreased among group receiving combination therapy as compared to MTX alone (Placebo). The mean difference showed that CDAI [Mean difference: 8.71 (0.07 to 17.36) Cl: 95%] and mean creatinine levels [Mean difference: 2.61 (0.82 to 4.40) Cl: 95%] improved among group receiving combination therapy as compared to MTX alone.

With comparable efficacy to biological DMARDs, janus kinase inhibitors (JAKi) have become a very successful oral medication for rheumatoid arthritis (RA) [32]. The JAK-STAT pathway, which is essential for the immunological response, is disrupted by JAKi. In the UK, baricitinib, tofacitinib, upadacitinib, and filgotinib are the four JAKi that have licenses to treat RA [33]. These medications have been effective in patients who are either treatment-refractory or DMARD-naïve, with quick onset and long-lasting benefits. Though combination treatment with csDMARDs produces better results [34], JAKi monotherapy has shown to be successful. Even though JAKi are usually well tolerated, older individuals with risk factors may experience cardiovascular events and a higher risk of infection, especially herpes zoster reactivation. Even yet, JAKi has emerged as the go-to treatment for RA patients who are not responding to csDMARDs.

Overall findings of recent study was consistent with previous meta-analysis [22, 23] that exhibited the promising clinical outcomes of JAKi in combination therapy with MTX for management of RA. Another oral JAK inhibitor, tofactinib proved effective in reduction of disease activity in combination with MTX for 24 months follow up in phase 3 study [35]. As findings of 24-week phase IIb study [16], the filgotinib, as an oral JAK1 inhibitor, has improved the clinical outcomes among RA patients. When used as a monotherapy, tofacitinib performed MTX in lowering indicators of RA and preventing structural joint deterioration in patients who had never taken MTX [36]. In RA patients who did not respond well to MTX, a 24-month phase III trial demonstrated the safety, radiographic results, and therapeutic effectiveness of tofacitinib in combination with MTX. Although these JAK inhibitors shown notable advantages, certain safety issues were reported, such as elevated herpes zoster risk and modifications to laboratory markers [36].

JAKi has potential of targeting pathways behind structural damage, however, it also affects the broader pathways, leading to severe adverse events and compromised safety profile of JAKi among RA patients. The adverse events of JAKi are higher in ratio as compared to other bDMARDs, due to incidence of infections. These include cardiovascular events, malignancies and herpes virus infections [37]. With the exception of TEAEs and AEs that resulted in study removal, the incidence of adverse events was similar for JAKi safety whether MTX was used or not. This makes sense because some individuals have resistance to MTX and do not adhere to it; for these patients, JAKi monotherapy seems to be the best course of action. The

outcomes support the validity of our analysis. Although there was no apparent distinction between JAKi monotherapy and combination therapy in terms of side effects of significance (serious infections, cancer, VTE, MACE, etc.), these outcomes should be determined cautiously due to the small number of adverse events evaluated [38].

Currently, the present study is updated meta-analysis with more numbers of RCT's to evaluate the efficacy and safety of JAKi in combination therapy with MTX as compared to MTX alone among RA patients. When compared to JAKi alone, the JAKi plus MTX combination demonstrated superiority in obtaining an ACR response, improvement in HAQ-DI, low disease activity, and remission. Additionally, the JAKi combination treatment was linked to comparable tolerability when contrasted with monotherapy, with the exception of TEAEs and AEs that resulted in study cancellation.

This study offered the comprehensive and detailed pooled analysis with 9 RCT's as compared to previous studies [22, 23] to evaluate the effectiveness of JAKi combination therapy with MTX based on various clinical outcomes such as ACR20, CDAI, DAS28, HAQ-DI and safety profile of all possible therapeutic combinations. With enormous benefits, there were few limitations, there were few limitations. Firstly, the numbers of studies for subgroup analysis of drugs such as tofacitinib, baricitinib, and filgotinib, were very small to obtain absolute findings, but our study has gathered all published RCT's on JAKi combination therapy with MTX among RA patients. Secondly, the frequency of each adverse event was not identified due to limited study follow up. The meta-analysis lacked the data related to frequency of VTE or malignancy. In the future, further long-term empirical research and comparative analyses are necessary. Additionally, since the data used in this meta-analysis were from RCTs, it's possible that they can't be applied to the larger RA population, which has a variety of traits and treatment options.

5. CONCLUSION

Overall, the findings of recent meta-analysis revealed that JAKi in combination therapy with MTX improved the ACR20 responses, Clinical Disease Activity Index (CDAI), and mean creatinine levels, as compared to MTX alone among RA patients. Additionally, Health Assessment Questionnaire disability index (HAQ-DI) and Disease Activity Score in 28 joints (DAS28) scores also decreased by JAKi combination therapy with MTX as compared to MTX alone. However, the frequency of adverse events by JAKi plus MTX was higher as compared to MTX alone that compromised the safety profile of combination therapy. Further investigation on long term effects of JAKi combination therapy as well as monotherapy is needed to evaluate its safety for RA management.

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