SYSTEMATIC REVIEW

Response Comparison of Disease Modifying Anti-rheumatic Drugs for Ankylosing Spondylitis: Systematic Review of Network Meta-analyses

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ABSTRACT

Introduction: Ankylosing spondylitis (AS) presents challenges in selecting first-line biologic disease-modifying anti-rheumatic drugs (b-DMARDs) due to uncertainty about their effectiveness. Additionally, new research has introduced targeted synthetic DMARDs (ts-DMARDs) as treatment options. This systematic review compares the effectiveness of various DMARDs, both biologic and targeted, for AS patients.**Materials and methods:** A literature search was performed in several databases with the keywords "ankylosing spondylitis", "DMARDs", "efficacy", and "network meta-analysis" with its synonym applied. Inclusion criteria were network meta-analysis (NMAs), ≥18-year-old patients with AS, and language in Bahasa or English. Critical appraisal of selected NMAs was carried out according to the ISPOR guideline for NMA. This study is registered in PROSPERO with the ID of CRD42024563670. **Results:** Eleven NMAs based on randomized clinical trials were included. Infliximab was found to have the greatest probability of eliciting a response across various assessments (ASAS 20, ASAS 40, BASDAI 50, and BASFI). Among subcutaneous biologics, Golimumab demonstrated the highest probability of response. The evidence for ts-DMARDs, such as JAK inhibitors, indicates they may be viable alternatives if established treatments do not achieve remission. However, these results should be interpreted with caution due to statistical insignificance in several NMAs, likely from limited direct comparisons between DMARDs. **Conclusion:** Infliximab appears to have a higher likelihood of achieving responses in various assessments, and Golimumab may be considered for those preferring subcutaneous administration. Both treatments may be promising options for first-line therapy, but these conclusions should be viewed cautiously until future RCTs provide more robust comparative data on DMARDs.
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Keywords: Ankylosing spondylitis, DMARD, Effectivity, Systematic review, Network meta-analysis

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INTRODUCTION

Ankylosing spondylitis (AS) is an autoimmune condition primarily affecting the spine, though it can also involve peripheral joints. Research has identified HLA-B27 as a significant genetic marker linked to an increased risk of developing the disease, suggesting potential familial patterns. However, the precise relationship between this gene and the onset of ankylosing spondylitis remains unclear. Only a small proportion of patients achieve low disease activity with conventional disease-modifying antirheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs (NSAIDs).(1) Hence, needing modern DMARDs, various options are available including biologic DMARDs (b-DMARDs) such as TNF-α inhibitors (e.g., infliximab, adalimumab, certolizumab, golimumab), IL-6 inhibitors (e.g., tocilizumab), IL-17 inhibitors (e.g., secukinumab, ixekizumab), and IL-23 inhibitors (e.g., risankizumab, ustekinumab). Conversely, targeted synthetic DMARDs (ts-DMARDs) consist of Janus kinase (JAK) inhibitors, which include agents such as upadacitinib and tofacitinib that are administered orally.(2) TNF-α inhibitors and IL-17 inhibitors are well-established treatments. While others are not recommended yet and are still widely understudied. Although still studied, ts-DMARDs have the potential, a recent NMA by Deodhar (2020) provides its potential efficacy compared to the two established treatment groups.(3)

The wide variety of modern DMARDs can be confusing for physicians when recommending first-line treatment and when patients want to change their previous medication due to remission failure. Physicians also face challenges in providing recommendations due

to limited comparison among these DMARDs. Most studies, especially randomized controlled trials (RCTs), compare DMARDs with placebos rather than with each other, resulting in very limited direct comparison data. Furthermore, RCTs that directly compare various DMARDs require large patient sample sizes to identify differences in efficacy, leading to high costs.

Due to the scarcity of direct comparison data between b-DMARDs and ts-DMARDs, network meta-analysis (NMA) is the most suitable statistical method. NMA can estimate several parameters from studies that make similar comparisons and obtain new and relevant data by assembling and analyzing data from multiple studies on the same subject. In this context, NMA can include studies comparing modern DMARDs with placebos and use placebo as a common reference to enable comparisons between DMARDs. Although a few published NMAs exist, their results vary. For instance, a study by Chen et al.(4)(2016) showed that Infliximab has the highest probability of achieving ASAS 20, while Liu et al.(5) (2016) found that Adalimumab has the highest probability. Another NMA by Deodhar et al.(3)(2020) indicated that tocilizumab has the highest probability. These differences in NMA results can make choosing the appropriate modern DMARDs challenging. Furthermore, another systematic review of NMAs by Migliore et al.(1) (2021), did not include the newer type of DMARDs which is the ts-DMARDs that might be a potential new treatment for AS patients with a more comfortable route of administration.

To address this challenge, this systematic review aims to synthesize evidence from all published NMAs comparing the efficacy of b-DMARDs and ts-DMARDs. The goal is better to understand the differences in effectiveness among the available modern DMARDs, aiding physicians in making more informed treatment decisions.

MATERIALS AND METHODS

Materials & Method

Our review was conducted in accordance with the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (6.2) and reported using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Upon completion and finalization, we register it with the International Prospective Register of Systematic Reviews (PROSPERO) with an ID of CRD42024563670.

Search Strategy

A comprehensive literature search was performed by two independent reviewers in various databases, such as PubMed, Scopus, Cochrane, Embase, and Wiley, up to May 9th, 2024. The keywords used in the pursuit were ankylosing spondylitis, DMARDs, and network meta-analysis, along with their synonyms. When applicable and available in each database, advanced search techniques were used to make the search more precise.

Study Eligibility Criteria

Studies were screened according to the following inclusion and exclusion criteria: Our inclusion criteria were: (1) NMA of RCTs; (2) >18 years old patients with AS: (3) Language in Bahasa or English. Exclusion criteria: (1) studies with qualitative outcome data only; (2) Other study design besides NMA. The planned procedure is illustrated in Figure 1.

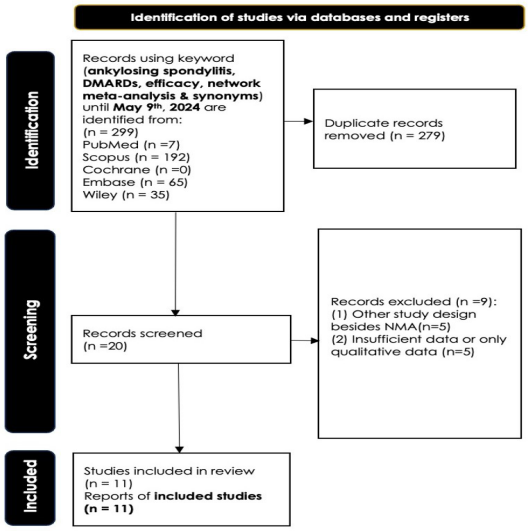

Figure 1: PRISMA Diagram

Data extraction and risk of bias

We predetermined the outcome sheet in tabular form (MS Excel® for Mac; Microsoft Corporation, Redmond, WA, 2018) to include the following data to be extracted: (1) author and year of publication; (2) study characteristics, including study design, NMA model, random/fixed effects, amount of RCTs included, type of patients population, and total amount of sample included; (3) type of modern DMARDs used; (4) treatment duration; (5) assessment applied; (6) interpretation of results; (7) ISPOR guideline adherence: (8) reported bias about consistency and homogeneity.

All the NMAs were appraised using the ISPOR guideline with details listed in the results table. Two reviewers did the quality assessment blind to each other's scores and then discussed until a consensus was reached.

RESULTS

Study selection

We identified 299 studies through the search strategy. After deduplicating and excluding irrelevant studies, our final search resulted in eleven NMAs. The result of the study selection process is shown in Figure 1.

Study characteristics and design

All included NMAs used the Bayesian model to perform the analysis. Ten out of eleven included NMAs used random effects to minimize the heterogeneity. Majorities also used a mixed population rather than biologically naive. All the characteristics details are listed in Table I.

Table I: Characteristic of included NMAs

No	Author, year	Study design	Random/Fixed effects	Number of studies included	Population based on the new relativity to treatment	Sample (n)
1	Chen et al, 2016	NMAs of RCTs	Random Effects	14	Mixed population	2672
2	Liu et al, 2016	NMAs of RCTs	Random Effects	16	Mixed population	2574
3	Deodhar et al, 2020	NMAs of RCTs	Random Effects	30	Mixed population	6711
4	Machado et al, 2013	NMAs of RCTs	Random Effects	27	Mixed population	2820
5	Cao et al, 2022	NMAs of RCTs	Random Effects	39	Mixed population	8995
6	Migliore et al, 2012	NMAs of RCTs	Fixed Effects	3	Biologically naive	871
7	Shu et al, 2013	NMAs of RCTs	Random Effects	14	Mixed population	2.514
8	Baji et al, 2014	NMAs of RCTs	Random Effects	5	Mixed population	2575
9	Migliore et al, 2015	NMAs of RCTs	Random Effects	5	Mixed population	642
10	Betts et al, 2016	NMAs of RCTs	Random Effects	15	Mixed population	3094
11	Wang et al, 2018	NMAs of RCTs	Random Effects	20	Mixed population	3220

Quality of study

All NMAs have followed the ISPOR guidelines which are standard guidelines for making NMAs and the majority have homogeneous & consistent populations, although some NMAs (the majority of publications >10 years ago) do not provide information on the homogeneity & consistency of loops.

Response comparison between DMARDs

All DMARDs showed significant better response compared to placebo except for IL-16 and IL-23 inhibitors. For the b-DMARDs group, one of which Infliximab (INF) IV at a dose of 5 mg/kg consistently achieve higher rank of obtaining response in ASAS 40, BASDAI 50, BASFI, and most ASAS 20 assessments. However, three network meta-analyses (NMAs) identified various modern DMARDs could have the highest probability to obtain response for ASAS 20 and BASFI.(3,6,7)When considering only subcutaneous (SC) administration, Golimumab achieved the highest rankings of obtaining response in ASAS 40, BASDAI 50, BASFI, and most ASAS 20 assessments. Nonetheless, two NMAs indicated that Adalimumab outperformed the probability of Golimumab in obtaining responses in the ASAS 20 assessment.(5,8) While, for the ts-DMARDs that consist of the JAK inhibitors group, only two NMAs have researched this group and NMA with more recent publication year. An NMA by Deodhar et al. (2020) suggested that Tofacitinib as part of JAK inhibitors may achieve higher probability in obtaining response compare to b-DMARDs in ASAS 20, although in other assesment such as BASFI, Golimumab IV and Infliximab IV is still ranked better.

While newer NMA by Cao et al. (2022)2 did not include tofacitinib as one of the five medications that have the highest probability of achieving responses. However, this NMA performed analysis of the big groups (TNF-α inhibitor, IL-17 inhibitors, etc), the results showed that the JAK inhibitors group always ranked after the TNF-α inhibitor and IL-17 inhibitors group and even ranked the second for the improvement in daily living function. While for other group of medications which are the IL-6 and IL-23 inhibitors, same to JAK inhibitors only NMA by Cao et al and Deodhar et al., that analyzed them, both stated that these two groups have lower probability in obtaining response compared to others. Furthermore, NMA by Cao el al., stated that these two groups did not gave significant difference with the placebo. All the details are listed in Table II.

Table II: Results reported from NMAs

No	Author, year	DMARDs	Treatment duration (week)	Assessment	Results	Reported bias about consistency and homogeneity	ISPOR Guidelines of NMA	Safety of DMARDS
1	Chen et al, 2016 (4)	Pla, Eta 25 mg, Inf 5mg/kgbb, Ada, Eta 50mg QW, Eta 25mg BIW, Eta 50mg BIW, Gol 50 mg, Gol 100mg, Sec, Toc	12 & 14	**ASAS 20** **Placebo as reference** Rank 1: Inf 5mg: 7.36 (3.57 - 16.45) Rank 2: Ada : 4.41 (2.65 - 7.09) Rank 3: Eta 50mg QW : 4.38 (2.28 - 8.72) Rank 4 : Gol 100mg : 4.31 (2.17 - 9.68) Rank 5 :Eta 25 mg BIW : 3.96 (2.45 - 6.66)	Inf 5 mg/kg has the highest response probability rank when compared to all of the treatments that have been included and it is the only b-DMARDs that is significant compared to tocilizumab, but there is no significant difference to other b-DMARDs.	Consistency was checked using P value in the node-splitting method (Non discontinuous) was found) and Heterogeneity was assessed with Cochran's Q-statistic and a P-value (Highly Heterogeneous).	This NMA included only high-quality RCTs and other aspects of the ISPOR guideline are fulfilled except for sensitivity analysis. In addition, there is no subgroup anaylsis or meta regression performed.	N/A
2	Liu et al, 2016(5)	Pla, Gol 50mg Q4W, Eta 25 nf BIW, Inf 5mg/kg, inf 3mg/kgEta 25 mg BIW, Eta 50 mg QW, Ada 40 mg Q2W,	N/A	**ASAS 20** **NMA with SUCRA:** Rank 1: Ada : 71% Rank 2: Eta : 71% Rank 3: Inf : 64% Rank 4: Gol : 44% **Placebo as reference** Rank 1: Ada : 5.00 (3.14, 8.33) Rank 2: Eta : 4.98 (3.45, 7.26) Rank 3: Inf : 4.69 (3.03, 7.43) Rank 4: Gol : 3.89 (2.35, 6.72) **ASAS 40** **NMA with SUCRA** Rank 1: Inf : 88% Rank 2: Gol: 67% Rank 3: Ada : 57% Rank 4: Eta: 36% **Placebo as reference** Rank 1: Inf : 11.23 (3.89, 45.10) Rank 2: Gol : 6.94 (2.10, 37.14) Rank 3: Ada : 5.89 (1.63, 21.25) Rank 4: Eta: 3.69 (0.96, 13.48) **BASDAI 50:** **NMA with SUCRA** Rank 1: Inf : 89% Rank 2: Gol: 60% Rank 3: Eta: 54% Rank 4: Ada: 47% **Placebo as reference** Rank 1: Inf : 9.15 (4.27, 18.55) Rank 2: Gol: 5.67 (2.02, 18.20) Rank 3: Eta: 5.37 (2.95, 10.79) Rank 4: Ada: 4.63 (2.35, 9.61)	In ASAS20 the highest probability response comes from Ada. However, in ASAS 40 and BASDAI 50 Inf show its highest probability rank with also lower side effects. However, comparisons between b-DMARDs were not statistically significant.	Consistency was checked using P value in the node-splitting method (generally consistent) and Heterogeneity was assessed by Cochran's Q-statistic and a P-value (Low Heterogenous).	This NMA included only high-quality RCTs and other aspects of the ISPOR guideline are fulfilled except for sensitivity analysis. In addition, there is no subgroup anaylsis or meta regression performed.	Placebo as reference from most side effect to least (statistically insignificant) Rank 1 : Inf : 4.00 (0.50 – 68.0) Rank 2: Eta : 3.40 (0.62 -27.0) Rank 3: Ada: 0.87 (0.10 -7.7) Rank 4: Gol : 0.70 (0.05 – 10.0)

CONTINUE

Table II: Results reported from NMAs (CONT.)

No	Author, year	DMARDs	Treatment duration (week)	Assessment	Results	Reported bias about consistency and homogeneity	ISPOR Guidelines of NMA	Safety of DMARDS
3	Deodhar et al, 2020(3)	Pla, Ada 40mg, Cer 200mg, Czp 400mg, Eta 25mg, Eta 50mg, Inf 5mg,kg, Gol 50mg, Gol 2 mg/kg, Gol SC 100, Sec SC 75mg, Sec SC 150mg, Sec SC 150 mg, Sec IV 75mg, Sec IV 150mg, Apr 30 mg,Tof 10 mg, Tof 5 mg, Tof 2 mg,Fil 200mg, Ris 90mg, Ris 18 mg, Ris 180mg,Ust, 45mg, Ust 90mg, Ixe 80mg Q4W, Ixe 80 mg Q2W	12-16	**ASAS 20** **SUCRA score** Rank 1: Tof 5mg : 93% Rank 2: Gol IV 2mg/kg : 90% Rank 3: Fil 200mg : 86% Rank 4: Eta 50mg : 84% Rank 5: Inf 5 mg/kg : 80% **Placebo as reference** Rank 1: Tof 5mg : 4.24 (1.55, 11.79) Rank 2: Gol IV 2mg/kg : 3.55 (1.32, 10.74) Rank 3: Fil 200mg : 3.15 (1.26, 8.25) Rank 4: Eta 50mg : 2.82 (1.28, 6.68) Rank 5: Inf 5 mg/kg : 2.49 (1.01, 6.87) **BASFI:** **SUCRA score** Rank 1: Gol IV 2mg/kg :81% Rank 2: Inf 5mg/kg : 80% Rank 3: Gol 100mg : 69% Rank 4: Sec SC 150mg : 67% Rank 5: Gol 50 mg : 67% **Placebo as reference** Rank 1: Gol IV 2mg/kg : -1.9 (-3.34, -0.49) Rank 2: Inf 5mg/kg : -1.8 (-2.9, -0.75) Rank 3: Gol 100mg : -1.54 (-2.86, -0.22) Rank 4: Sec SC 150mg : -1.5 (-2.89, -0.05) Rank 5: Gol 50 mg : -1.46 (-2.46, -0.45)	ASAS20 shows Tof 5mg as part of JAK inhibitor to has the highest response probability and in BASFI Gol IV 2mg/kg also shows its highest rank. Most TNF-α inhibitors showed superiority compared to subcutaneous sec 75 mg and tofacitinib 2 and 10 mg	Consistency was checked using P value in the node-splitting method (Inconsistent) and Heterogeneity was assessed with Cochran's Q-statistic and a P-value (Moderate Heterogenous).	This NMA included only high-quality RCTs and other aspects of the ISPOR guideline is fulfilled. However, this NMA did not performed meta regression or subgroup analysis.	N/A
4	Cao et al, 2022(2)	Pla, Sec, Ixe, Net, Bim, Fil, Tof, Upa, Eta, Inf, Ada, Cer, Gol:.	N/A	**ASAS 40** **NMAs with SUCRA** Rank 1: Inf: 89.8% Rank 2: cer: 89.5% Rank 3: bim: 83.3% Rank 4: Gol: 69.2% Rank 5 : Ada: 66.3 % **Placebo as reference** Rank 1: Inf: 3.63 (2.23-5.91) Rank 2: cer: 3.58 (2.37-5.39) Rank 3: bim: 3.44 (1.53-7.76) Rank 4: Gol: 2.52 (1.89 - 3.38) Rank 5 : Ada: 2.44 (1.80 - 3.31)	In ASAS 40, Inf shows the highest response probability and it is tolerability is good also. Both ts and b-DMARDs are significant compared to placebo except for IL-16 and 23 inhibitors.	Consistency was checked using P value in the node-splitting method (Inconsistency was found)	This NMA included only high-quality of RCTs but did not state any statistical method to assess the inconsistency in the network loop. But, other aspects of the ISPOR guideline are fulfilled. However, this NMA did not performed meta regression or subgroup analysis.	IL-23 inhibitors were the most likely to have the highest tolerability (SUCRA = 76.4%), while IL-17AF inhibitors had the lowest likelihood of serious adverse events (SAEs) (SUCRA = 83.9%). Additionally, TNFiFMA exhibited the greatest potential as both the most effective and best-tolerated treatment.

CONTINUE

Table II: Results reported from NMAs (CONT.)

No	Author, year	DMARDs	Treatment duration (week)	Assessment	Results	Reported bias about consistency and homogeneity	ISPOR Guidelines of NMA	Safety of DMARDS
5	Migliore et al, 2012(10)	Pla, Inf, Eta, Ada	24	**ASAS 20** **Placebo as reference** Rank 1: Inf : 6.88 (3.66-13.46) Rank 2: Eta : 4.95 (2.71-8.16) Rank 3 : Ada : 4.48 (2.63 - 9.16)	Inf has the highest response probability 72%. However, the comparison between therapies was not statistically significant. All b-DMARDs have similar efficacy.	N/A	This NMA included only high quality of RCTs, but did not stated any statistical method to assess the homogenity & consistency in the network loop. Although, it stated that their study population is homogeneous. But, other ascpets in the ISPOR guideline is fulfilled. However, this NMA did not performed sensitivity analysis, meta regression or subgroup analysis.	N/A
6	Shu et al, 2013(11)	Pla, Eta 50mg, Gol 50mg, Gol 100mg, Inf 5mg/kg, Inf 3 mg/kg, Ada 40mg	12	**ASAS 20** **Placebo as reference** Rank 1: Inf 5mg/kg : 6.65 (3.36, 11.97) Rank 2: Gol 100mg : 6.22 (2.34, 13.6) Rank 3: Gol 50mg : 6.04 (2.29, 13.04) Rank 4: Ada 40 mg : 6.03 (2.52, 12.56) Rank 5: Eta 50mg : 5.94 (3.55, 9.27)	Inf has highest response probability than other treatments. However, it is not significant when compared with other treatments. All b-DMARDs have similar efficacy.	N/A	This NMA included only high quality of RCTs, but did not stated any statistical method to assess the homogenity & consistency in the network loop. But, other ascpets in the ISPOR guideline is fulfilled. However, this NMA did not performed sensitivity analysis, meta regression or subgroup analysis.	N/A
7	Baji et al, 2014(12)	Pla, inf dyyb 5mg/kgBB, Ada 40mg, Eta 25mg, Eta 50mg, Gol 50mg, Gol 100mg	12 & 24	**ASAS 20 12 weeks** **Placebo as reference** Rank 1: Inf dyyb: 6.74 (3.81-11.3) Rank 2: Gol : 5.7 (288-10.44) Rank 3: Ada : 4.65 (3.29–6.43) Rank 4: Eta : 4.35 (3.09–5.96) **ASAS 20 24 weeks** **Placebo as reference** Rank 1: Inf dyyb: 7.2 (3.68–13.19) Rank 2:Ada : 4.81 (2.67–8.18) Rank 3: Eta: 4.76 (2.73–7.81) Rank 4: Gol : 4.53 (2.32–8.22)	Inf has the highest response probability in ASAS 20 at 12 and 24 weeks. All b-DMARDs are significant compared to placebo	N/A	This NMA included only high quality of RCTs, but did not stated any statistical method to assess the homogenity & consistency in the network loop. However other ascpets in the ISPOR guideline is fulfilled. Additionally, this NMA did not performed sensitivity analysis, meta regression or subgroup analysis.	Placebo as reference from most side effect to least (statistically insignificant) Rank 1 : Inf dyyb : 2.31 (0.17 – 11.43) Rank 2: Ada: 1.57 (0.27 -5.72) Rank 3: Gol : 0.69 (0.14 – 2.1)

CONTINUE

Table II: Results reported from NMAs (CONT.)

No	Author, year	DMARDs	Treatment duration (week)	Assessment	Results	Reported bias about consistency and homogeneity	ISPOR Guidelines of NMA	Safety of DMARDS
8	Migliore et al, 2015(6)	Pla, Eta, Ada, Gol, Cer	24	**ASAS20** **SUCRA score:** Rank 1: Gol: 41.28% Rank 2: Ada:29.91 % Rank 3: Eta: 28.74 % Ranks 4: Cer: 0.07 %	All treatment shows effects better than placebo with Gol has the highest response probability to others. Ada, Gol, and Eta is significantly more effective than Cer.	N/A	This NMA included only high quality of RCTs, but did not stated any statistical method to assess the homogenity & consistency in the network loop. Although, it stated that their study population is homogeneous. But, other ascpets in the ISPOR guideline is fulfilled. However, this NMA did not performed sensitivity analysis, meta regression or subgroup analysis.	N/A
9	Betts et al , 2016(8)	Pla, Ada 40mg, cer 200mg, cer 400mg, eta 25 mg, eta 50mg, Inf 5mg/kg, Gol 50mg, Sec 75mg, Sec 150mg	12	**ASAS20** **SUCRA SCORE** Rank 1:Inf : 71.7% Rank 2: Ada : 63.6% Rank 3: Eta : 62.0% Rank 4: Sec : 60.3% Rank 5 : Gol 60.2% **ASAS40** **SUCRA SCORE** Rank 1: Inf : 51.5% Rank 2:Ada : 49.2% Rank 3: Sec: 42.4% Rank 4: Eta : 41.4% Rank 5 : Gol : 38.6%	Inf has the highest response probability in ASAS 20 and ASAS40 followed by Ada. All b-DMARDs are significant compared to placebo.	N/A	This NMA included only high quality of RCTs, but did not stated any statistical method to assess the homogenity & consistency in the network loop. However other ascpets in the ISPOR guideline is fulfilled. Additionally, this NMA did not performed sensitivity analysis, meta regression or subgroup analysis.	N/A

CONTINUE

Table II: Results reported from NMAs (CONT.)

No	Author, year	DMARDs	Treatment duration (week)	Assessment	Results	Reported bias about consistency and homogeneity	ISPOR Guidelines of NMA	Safety of DMARDS
10	Wang et al , 2018(13)	Pla, Ada 40mg, Cer 200mg, Cer 400MG, Eta 25mg, Eta 50mg, Gol 50mg, Gol 100mg,Inf 5mg/kg, Inf 3mg/kg, Inf-dyyb(biosimilar) 5 mg/kg	12 &24	**BASDAI 12 weeks** **Placebo as reference** Rank 1: Inf dyyb : 2.7 (1.3–3.9) Rank 2: Inf : 2.7 (1.3–3.9) Rank 3: Gol : 1.5 (0.9–2.2) Rank 4: Eta : 1.5 (1–2) Rank 5: Cer : 1.5 (0.6–2.3) **BASDAI 24 weeks** **Placebo as reference** Rank 1: Inf dyyb : 3 (1.5–4.2) Rank 2: Inf : 2.4 (1.4–3.1) Rank 3: Cer : 1.8 (1.0–2.6) Rank 4: Ada : 1.7 (0.9–2.6) Rank 5: Eta : 1.7 (0.7–2.4) **BASFI 12 weeks** **Placebo as reference** Rank 1: Inf : 2 (1.4–2.5) Rank 2: Inf dyyb: 1.8 (0.8–2.7) Rank 3: Gol : 1.6 (1.1–2.1) Rank 4: Eta : 1.4 (1.1–1.8) Rank 5: Ada : 1.4 (1.0–1.8) **BASFI 24 weeks** **Placebo as reference** Rank 1: Inf dyyb : 2 (0.10–3.9) Rank 2: Ada: 1.7 (0.5–2.8) Rank 3: Inf : 1.6 (0.5–2.6) Rank 4: Cer: 1.4 (0.2–2.6) Rank 5: Gol : 1.3 (0.5–2.1)	Inf has the highest response probability in most of the assessments, biosimilar Inf also shows a similar outcome. Inf was superior to the other TNF-α inhibitor in decreasing BASDAI at 12 weeks, but not at 24 weeks.	N/A	This NMA included only high quality of RCTs, but did not stated any statistical method to assess the homogenity & consistency in the network loop. However other ascpets in the ISPOR guideline is fulfilled. Additionally, this NMA did not performed sensitivity analysis, meta regression or subgroup analysis.	N/A

Pla: placebo; Sec: secukinumab; Ixe: ixekizumab; Net: netakimab; Bim: bimekizumab; Fil: filgotinib; Tof: tofacitinib; Upa: upadacitinib; Eta: etanercept; Inf: infliximab; Inf dyyb: Infliximab biosimilar; Ada: adalimumab; Cer: certolizumab pegol; Gol: golimumab.

Safety comparison between DMARDs

TNF-α inhibitor groups showed the highest response probability and best-tolerated treatment. Although, if the efficacy is not being counted, IL-23 inhibitors were the most likely to have the highest tolerability (SUCRA = 76.4%), while IL-17AF inhibitors had the lowest likelihood of serious adverse events (SAEs) (SUCRA = 83.9%) as was being showed by NMA by Cao et al (2022).(2) While in the TNF-α inhibitor groups itself, the one with the less side effect is Golimumab, followed by Adalimumab, Etarnecept, and Infliximab. Although, the differences is insignificant, Infliximab is associated with highest adverse event rates despite achieving highest response probability.

DISCUSSION

DMARDs are classified into conventional and modern types. Conventional DMARDs, utilized historically, possess complex mechanisms of action, including inhibiting DNA synthesis, affecting cell replication, modulating the immune system, and reducing cell proliferation. Examples of these drugs include methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, and cyclosporine. In contrast, modern DMARDs target specific components of the immune system, resulting in improved therapeutic responses and outcomes. As also aforementioned most AS patients require modern DMARDs to achieve remission. These include biological ones that consist of TNF-α inhibitors, IL inhibitors, B-cell inhibitors, T-cell inhibitors, and target selected (ts) consisting of JAK inhibitors.(1,9)

Hence, our systematic review investigates the use of modern DMARDs (biologic and target selected) in AS patients through the compilation of various NMAs, that facilitate both indirect and direct comparisons of various DMARDs for AS with multiple assessments, which are ASAS 20, ASAS 40, BASDAI 50, and BASFI. We summarized all data of NMAs about the efficacy of DMARDs for AS, to obtain response primarily at 12 and 24 weeks. All treatments show a significant better outcome than placebo.(2–8,10–13)

Our systematic review showed that infliximab achieved the highest probability to obtain response in large varieties of assessments such as ASAS 40, BASFI, and BASDAI 50, and the majority of ASAS 20 in 12 and 24 weeks. Infliximab is usually given as an infusion at weeks 0, 2, and 6, and then every 6–8 weeks with the fastest onset of effect observed on 2-4 weeks. Other than that, a study by Maini et al, 1998, shows that infliximab typically shows a clinical response within 1 to 2 weeks after the first infusion with the full therapeutic effect often observed within 6 to 12 weeks of treatment.(14) Some patients may experience symptom improvement as early as the first week. Our study displayed similar results with clinical response in 12 weeks, but there is a longer period of response found in 24 weeks. Another systematic review by Migliore et al. (2021) also analyzed several previous NMAs and found that infliximab had the highest probability of achieving ASAS20 and ASAS40 responses in AS patients within the same period, strengthening our results.(1). Although, if compared to other intravenous drugs, which is Golimumab IV, one NMA by Deodhar et al.(3), stated that it was ranked higher compared to Infliximab in ASAS 20 and BASFI. Unfortunately, only one NMAs compared the efficacy of Golimumab IV which indicated more research need to be conducted to further validate this result. In term of cost itself, infliximab is considered a relatively expensive DMARD, with an annual cost of approximately $23,448. However, infliximab biosimilars may serve as a more cost-effective alternative, as highlighted by Wang et al. (2018)(13) and Baji et al (2014)(12), the biosimilar has shown similar efficacy to its reference product and other DMARDss. These biosimilars offer a more cost-effective alternative, priced at nearly half the cost of the original infliximab, making treatment more accessible to patients.(15)

If considering only subcutaneous administration, Golimumab has the highest likelihood to achieve response in ASAS 40, BASDAI 50, BASFI, and the majority of ASAS 20 in 12 weeks. A study by Deodhar et al (2015) shows that likelihood period to give a response is at 24 weeks of treatment and can have the same response until 5 years.(16) On the other side, some NMAs, Chen et al (2016), Liu et al (2016), Baji et al (2014) , dan Betts et al (2016), showed the higher probability to obtain response of adalimumab compared to golimumab in ASAS 20.(4,5,8,12) However, the majority of the study still concluded a higher probability of golimumab than adalimumab in achieving various assessments as previously mentioned. The systematic review by Migliore et al, also highlighted that when considering subcutaneous (SC) administration only, golimumab ranked highest response probability using the same assessment criteria, same to our review. (1) A study by Hebeisen et al (2019) also showed that golimumab has a better response probability than adalimumab in axial spondylitis. (17)As our review gave more updated studies, similar results with Migliore might give a probability, without future RCTs to give more direct comparison data, this systematic review will still serve as a valuable reference for a long period, this is also due to more complicated factors to performed RCTs such as large fund, etc. Although Golimumab is associated with highest probability of efficacy compared to other subcutaneous DMARDs, its cost-effectiveness was lower compared to other drugs. Golimumab is more expensive than several other subcutaneous DMARDs, with an annual cost of $18,666—approximately 1.5 to 2 times higher than other comparable subcutaneous options.(15)

While, for the ts-DMARDs that consist of the JAK

inhibitors group, only two NMAs have researched this group and we reported conflicting findings. An NMA by Deodhar et al. (2020) suggested that Tofacitinib as part of JAK inhibitors may have higher probability to other b-DMARDs.(3) While newer NMA by Cao et al. (2022)2 did not include tofacitinib or upadacitinib as part of JAK inhibitor group as one of the five medications that have the highest probability of achieving response. However, this NMA also performed analysis of the big groups (TNF-α inhibitor, IL-17 inhibitors, etc), the results showed that the JAK inhibitors group always ranked after the TNF-α inhibitor and IL-17 inhibitors group and even ranked the second for the improvement in daily living function.(4)Due to NMA by Deodhar et al., stated that Tofacitinib ranked the highest, while NMA by Cao et al., showed it ranked after the two established treatment, it is safe to conclude that the current evidence suggest that JAK inhibitors could be the alternative choice, if TNF-α and IL-17 inhibitors have insignificant response from the patient. Other than that, a comparison to other studies by Strand et al, 2015, also shows that tofacitinib has the same significance as TNF-α Inhibitors.(18) It is advised to perform more RCTs to further validate these results due to limited direct comparison between the JAK inhibitors group for AS, to provide more statistical significance and provide more clarity. JAK inhibitors that may serves as an alternative from other DMARDs have been shown to be relatively affordable, with an annual cost ranging from $17,490 to $17,770. This makes this drugs a more cost-effective alternative option compared to intravenous DMARDs and subcutaneous Golimumab.(15)

While for other choice of medications, the IL-6 and IL-23 inhibitors, same to JAK inhibitors only NMA by Cao et al and Deodhar et al., that analyzed them, both stated that these two groups have lower efficacy compared to others.(2,3) Furthermore, NMA by Cao el al., stated that these two groups did not gave significant difference with the placebo.(2) Other study by McGonagle et al (2021) and Zhang et al (2022) also shown that IL-23 inhibitors to be ineffective.(19,20) Study by Sieper et al. (2015) and Sieper et al.(21,22) (2014) shown that IL-6 inhibitors are insignificant in treatment of ankylosis spondylitis.

As it was mentioned aboved, although the effectiveness of DMARDs is crucial to determined the treatment options, cost also plays a crucial role. Cost analysis indicates that subcutaneous administration is generally more affordable than intravenous (IV) administration. Among the options with highest response probability, infliximab is the most expensive, priced at $23,448, followed by subcutaneous golimumab at $18,666. In contrast, infliximab biosimilar presents the most cost-effective alternative, with prices ranging from $11,832 to $12,600. Similarly, a biosimilar of golimumab has been identified and evaluated, showing comparable efficacy to standard golimumab, but due to its recent appearance, its cost-effectiveness has not studied yet. However, biosimilar products usually offer more cost-effectiveness compared to its reference product.(23,24) This represents a promising alternative, offering a cost-effective alternative without compromising therapeutic efficacy. Therefore, cost remains a key factor in determining the most suitable DMARD for patients.(15)

The choice of administration route can be offered to the patients based on their most preferred comfort and price, but if all administration routes are considered, infliximab still has higher response probability compared to golimumab. While for the oral route of JAK inhibitors, the current evidence suggest that it could be an alternative treatment if the both established treatment groups failed to bring remission. As aforementioned, interpretation needs to be cautiously performed due to most NMAs stating statistical insignificance through these ranking results, this may stem from limited directed comparison data from modern DMARDs.

Strengths and limitations

This study's systematic review approach is a significant strength of this study, which comprehensively analyzes all available NMAs and synthesizes evidence comparing modern DMARDs for ankylosing spondylitis. NMAs are particularly valuable in this context as they allow for indirect comparisons between different modern DMARDs, even in the absence of direct comparative studies. Most existing studies primarily compare b-DMARDs to placebos, creating a gap in direct comparative data. By leveraging indirect comparison data, NMAs can provide meaningful insights into the relative efficacy of various modern DMARDs, thus enhancing our understanding and informing clinical decision-making. Although most NMAs did not show statistically significant differences in effectiveness between modern DMARDs. This lack of significant differences is largely due to the limited or absent direct comparison data between modern DMARDs in the existing literature. Additionally, some older NMAs (>10 years old) did not explicitly assess the transitivity assumption, leaving a potential risk of bias unaddressed.

CONCLUSION

Our systematic review of NMAs indicates that infliximab has the highest probability of achieving responses in various assessments (ASAS 20, ASAS 40, BASDAI, and BASFI) at both 12 and 24 weeks. When considering only subcutaneous administration, golimumab shows the highest probability of achieving clinical response. While, for ts-DMARDs, the current evidence suggest it could be an alternate choice if both established treatment groups failed to bring remission. The findings of this study should be interpreted with caution due to the limited direct comparison data between modern DMARDs, which often results in statistical insignificance in NMAs. Despite these limitations, our results provide a valuable reference for selecting DMARDs until future

randomized controlled trials (RCTs) can provide more direct comparison data, thereby achieving greater statistical significance.

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