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ORIGINAL ARTICLE

Indirect comparisons of the efficacy of biological agents in patients with active ankylosing spondylitis: a systematic review and meta-analysis

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Abstract Patients with ankylosing (AS) often do not have a satisfactory response to, or could not tolerate, non-steroidal anti-inflammatory drugs (NSAIDs). Several biologic agents are available for such patients. However, the comparative efficacy of these treatments remains unknown as head-to-head randomized controlled trials (RCTs) are not available. RCTs examining the efficacy of biologic agents in patients with AS who had inadequate response to, or could not tolerate, NSAIDs were identified. If at least two RCTs were available for a given biologic agent, the pooled odds ratio (OR) and 95% confidence interval (CI) of achieving 20% improvement according to the Ankylosing Spondylitis Assessment Study group response criteria 20 (ASAS20) across trials were calculated. The pooled OR for each biologic agent was then compared to each other using the indirect comparison technique. A total of 14 RCTs of older TNF inhibitors, two RCTs of secukinumab, one RCT of certolizumab, and one RCT of tofacitinib were identified. No significant difference in any indirect comparisons was observed with the *p* values ranging from 0.12 to 0.74. The likelihood of achieving the ASAS20 response in patients AS who failed or could not tolerate NSAIDs was not significantly different between older TNF inhibitors, secukinumab, certolizumab, and tofacitinib. However, the analysis is limited by the small sample size with only one RCT for certolizumab and tofacitinib.

Keywords Ankylosing spondylitis · Biologic agents · Meta-analysis · Systematic review · TNF inhibitors

Introduction

Ankylosing spondylitis (AS) is a chronic systemic arthritis with a strong association with HLA-B27, characterized by the presence of enthesitis and arthritis of the axial joints [1]. AS affects males more often than females, with a male-to-female ratio of approximately 3 to 1. It is a disease of young adults with the peak incidence between 20 and 30 years old [2–4].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line pharmacological therapy for AS. The efficacy of NSAIDs to improve AS symptoms and to slow down radiographic progression has been demonstrated in several clinical studies [5, 6]. Nonetheless, response to NSAIDs is not universal with the failure rate of approximately 20–30% [6]. In addition, side effects from NSAIDs, such as gastrointestinal ulcer, acute kidney injury, and cardiovascular disease, are common and lead to discontinuation of the medications in significant amount of patients [7–9]. Thus, non-NSAIDs treatments are often required. Unfortunately, studies have shown that traditional non-synthetic disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, are not effective for AS [10, 11].

With the better understanding of the molecular pathogenesis of AS and other systemic autoimmune disorders, over the

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past few decades, a novel class of medication called biologic agent has been developed. In early 2000s, tumor necrosis factor (TNF) inhibitors were initially approved for treatment of rheumatoid arthritis (RA) and were subsequently approved for treatment of AS. The current American College of Rheumatology (ACR) guideline for management of AS [12] recommends treatment with TNF inhibitors for patients who fail or could not tolerate NSAIDs. The guideline does not prefer a specific TNF inhibitor over the others as there is no head-to-head randomized trial comparing efficacy between two TNF inhibitors. In addition, a 2015 indirect comparison meta-analysis from the Cochrane collaboration did not find a significant difference for the efficacy (defined by Ankylosing Spondylitis Assessment Study [ASAS] group response criteria) between older TNF inhibitors (infliximab, adalimumab, golimumab, and etanercept) [13].

Since the publication of that meta-analysis, studies of one more TNF inhibitor (certolizumab) and few non-TNF inhibitor biologic agents (secukinumab, apremilast, and tofacitinib) have been published. Those trials have demonstrated the superior efficacy of the medications compared to placebo. Whether these newer agents are more effective compare with older TNF inhibitors is not known due to the lack of head-to-head controlled trial. The current study aims to compare the efficacy of certolizumab and non-TNF inhibitor biologic agents to older TNF inhibitors in patients who are biologic agent-naïve using indirect comparison technique.

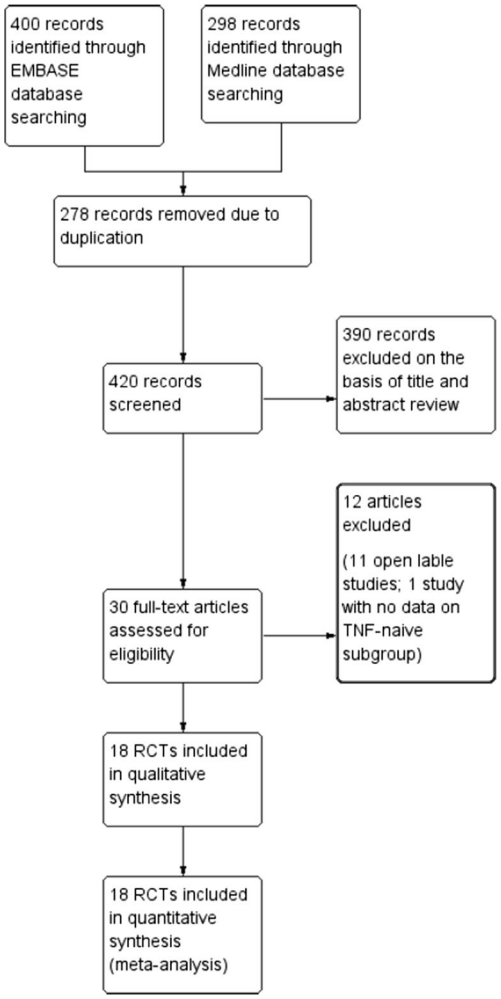

Fig. 1 Outline of literature review and study identification process

Material and methods

Search strategy

An experienced medical librarian (PJE) in consultation with the two investigators (P.U. and M.K.) searched for published studies indexed in Ovid Medline, Ovid CENTRAL, and Ovid EMBASE database from inception to January 2017 using the search terms described in the supplementary data 1. These terms included the controlled vocabulary of each database and text words (names of individual biologic agents and terms for ankylosing spondylitis). No language limitation was applied. The search retrievals were imported into EndNote X7, and duplicates removed. Search in clinicaltrials.gov was also performed to look for any additional unpublished studies. The bibliographies of selected review articles and the previous meta-analysis by the Cochrane collaboration were also manually searched.

Inclusion criteria

The following criteria were used to determine the eligibility of each study. (1) Eligible studies had to be randomized controlled trials (RCTs). (2) They had to compare the efficacy of biologic agents to placebo in patients with active AS who have failed or could not tolerate NSAIDs therapy. (3) Duration of studies was between 12 weeks to 30 weeks. (4) Ankylosing Spondylitis Assessment Study group response criteria 20 (ASAS20) was the primary or one of the major secondary outcomes. ASAS20 response is defined as at least 20% improvement in at least three of our four evaluated domains (patient global, pain, function, and inflammation) without worsening of more than 20% of the remaining domain [14]. The same two investigators independently determined the study eligibility. Different determinations were resolved by discussion.

Data extraction

A standardized data collection form was used to extract the following information from each study: first author, title of the article, year of publication, countries where the study was conducted, study design, inclusion and exclusion criteria, duration of treatment and follow-up, number of participants in

Table 1 Characteristics of included RCTs

	Braun et al. [20]	van der Heijde et al. (ASSERT) [21]	Marzo-Ortega et al. [22]	Inman et al. [23]	Maksymowych et al. [24]	van der Heijde et al. (ATLAS) [25]	Lambert et al. [26]	Huang et al. [27]	Inman et al. [28]	Bao et al. [29]
Year of publication	2002	2005	2005	2010	2010	2006	2007	2013	2008	2014
Intervention	Infliximab infusion 5 mg/kg at weeks 0, 2, and 6	Infliximab infusion 5 mg/kg at weeks 0, 2, 6, 12, and 18	Infliximab infusion 5 mg/kg at week, 0, 2, 6, 14, and 22	Infliximab infusion 3 mg/kg at weeks, 0, 2, and 6	Infliximab infusion 3 mg/kg at weeks 0, 2, and 6	Adalimumab 40 mg SC every other week	Adalimumab 40 mg SC every other week	Adalimumab 40 mg SC every other week	Golimumab 50 mg SC every 4 weeks	RCT, double-blinded
Country where study was conducted	Germany	Europe, USA, and Canada	UK	Canada	Canada	USA and Europe	Canada	China	USA, Canada, Europe, and Asia	Golimumab 50 mg SC every 4 weeks
Inclusion criteria	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VA-S ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VA-S ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (spinal pain VAS ≥ 3/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate response or intolerance to NSAIDs	Placebo
Concomitant therapy	Stable dose of NSAIDs was allowed during the study. DMARDs and corticosteroids were not allowed.	Stable dose of NSAIDs was allowed during the study. DMARDs and corticosteroids were not allowed.	Stable dose of NSAIDs and corticosteroids was allowed during the study. Methotrexate at 10 mg per week was given to both groups. Other DMARDs were not allowed.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.	China
Outcome	ASAS 20 response at week 12	ASAS 20 response at week 24	ASAS 20 response at week 30	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 12	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Never received biologic therapy 5. History of an inadequate

Table 1 (continued)

	Braun et al. [20]	van der Heijde et al. (ASSERT) [21]	Marzo-Ortega et al. [22]	Inman et al. [23]	Maksymowych et al. [24]	van der Heijde et al. (ATLAS) [25]	Lambert et al. [26]	Huang et al. [27]	Inman et al. [28]	Bao et al. [29]
										response or intolerance to NSAIDs
Number of treatment group	34	201	28	39	18	208	38	229	138	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during study.
Number of control group	35	78	14	37	18	107	44	115	78	ASAS 20 response at week 12
Percentage of male in treatment and control group	68/63	78/87	82/79	82/78	78/78	76/74	76/82	81/83	74/71	108
Average age of treatment and control group (year)	40.6/39.0	40.0/41.0	41.0/39.0	44.0/39.0	43.6/41.7	41.7/43.4	41.9/40.0	30.1/29.6	38.0/41.0	105
Average duration of disease of treatment and control group (year)	16.4/14.9	7.7/13.2	8.0/10.0	18.7/18.6	12.0/14.3	11.3/10.0	14.5/12.1	3.0/3.0	5.2/7.3	90/87 30.5/30.6 4.2/3.7

	Davis et al. [30]	Calin et al. [31]	van der Heijde et al. [32]	Dougados et al. (SPINE) [33]	Baeten et al. (MEASURE 1) [34]	Sieper et al. (MEASURE 2) [35]	Landewe et al. [36]	van der Heijde et al. [37]
Year of publication	2003	2004	2006	2011	2015	2017	2013	2017
Intervention	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded	RCT, double-blinded
Country where study was conducted	Etanercept 25 mg SC twice weekly	Etanercept 25 mg SC twice weekly	Etanercept 50 mg SC weekly	Etanercept 50 mg SC weekly	Secukinumab infusion 10 mg/kg at weeks 0, 2, and 4 followed by secukinumab SC at 75 mg or 150 mg every 4 weeks	Secukinumab 75 or 150 mg SC at weeks 1, 2, 3, 4, and then every 4 weeks	Certolizumab 400 mg SC at weeks 0, 2, and 4 then either 200 mg SC every 2 weeks or 400 mg SC every 4 weeks	Tofacitinib 10 mg oral twice daily
Inclusion criteria	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Concomitant therapy	USA, Canada, the Netherlands, Germany, and France	USA and Europe	Europe	Europe	Europe, Asia, North America, and South America	Europe, Asia, North America, and South America	Europe, North America, and Latin America	Europe, North America, and Asia
Outcome	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (spinal pain VAS ≥ 4/10)	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (spinal pain VAS ≥ 3/10)	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (spinal pain VAS ≥ 3/10)	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Previous exposure to TNF inhibitor was allowed (but	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Previous exposure to TNF inhibitor was allowed (but	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (BASDAI ≥4 and spinal pain VAS ≥ 4/10) 4. Previous exposure to TNF inhibitor was allowed (but	1. At least 18 years old 2. Fulfilled the modified NY criteria for AS 3. Active AS (spinal pain VAS ≥ 4/10)

Table 1 (continued)

	Davis et al. [30]	Calin et al. [31]	van der Heijde et al. [32]	Dougados et al. (SPINE) [33]	Baeten et al. (MEASURE 1) [34]	Sieper et al. (MEASURE 2) [35]	Landewe et al. [36]	van der Heijde et al. [37]
	spinal pain VAS ≥ 3/10) 4. No previous exposure to TNF inhibitor 5. History of an inadequate response or intolerance to NSAIDs	4. No previous exposure to TNF inhibitor 5. History of an inadequate response or intolerance to NSAIDs	4. No previous exposure to TNF inhibitor 5. History of an inadequate response or intolerance to NSAIDs	4. No previous exposure to TNF inhibitor 5. History of an inadequate response or intolerance to NSAIDs	subgroup analysis on patients who were TNF inhibitor naïve) 5. History of an inadequate response or intolerance to NSAIDs	subgroup analysis on patients who were TNF inhibitor naïve) 5. History of an inadequate response or intolerance to NSAIDs	subgroup analysis on patients who were TNF inhibitor naïve) 5. History of an inadequate response or intolerance to NSAIDs	4. No previous exposure to TNF inhibitor 5. History of an inadequate response or intolerance to NSAIDs
Number of treatment group	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.	Stable dose of NSAIDs, DMARDs, and corticosteroids was allowed during the study.
Number of control group	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 12	ASAS 20 response at week 16	ASAS 20 response at week 16	ASAS 20 response at week 12	ASAS 20 response at week 12
Percentage of male in treatment and control group	138	45	155	39	182	89	101	52
Average age of treatment and control group (year)	139	39	51	43	89	45	41	51
Average duration of disease of treatment and control group (year)	76/76	80/77	70/78	95/91	69/70	64/78	62/61	73/63
	42.1/41.9 10.1/10.5	45.3/40.7 15.0/9.7	41.5/40.1 9.0/8.5	46.0/48.0 19.0/23.0	40.7/43.1 7.2/8.3	43.8/43.5 4.9/3.9	39.5/39.9 7.5/7.7	41.6/41.9 1.5/3.0

RCT randomized controlled trial, *AS* ankylosing spondylitis, *ASAS* Ankylosing Spondylitis Assessment Study, *SC* subcutaneous, *DMARDs* Disease modifying anti-rheumatic drugs, *NSAIDs* non-steroidal anti-inflammatory drugs, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *VAS* visual analogue scale

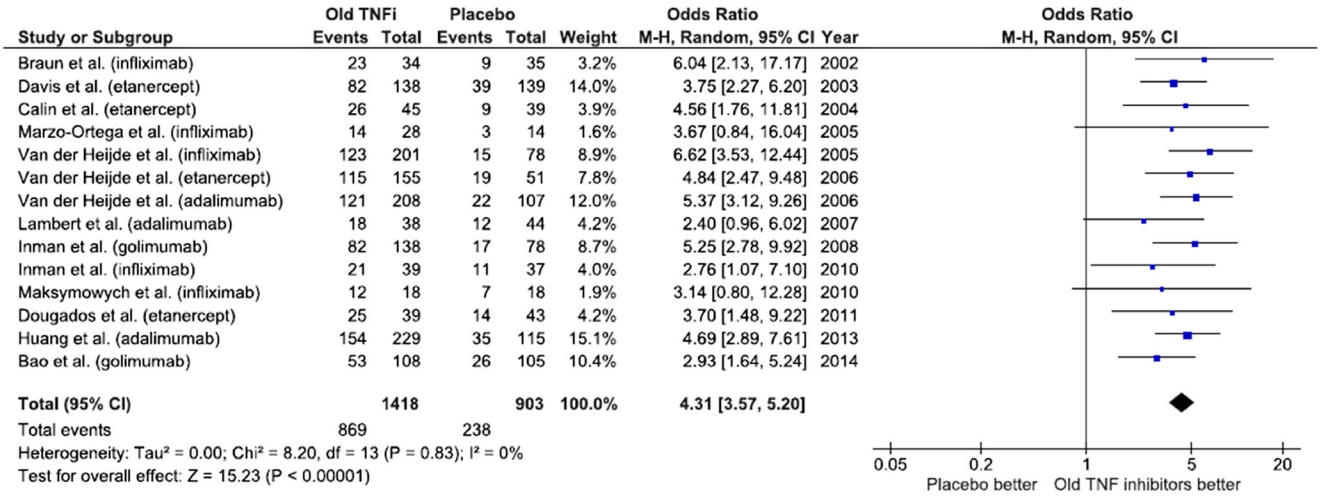

Fig. 2 Forest plot of older TNF inhibitors

treatment and placebo arm, baseline characteristics of participants, study interventions, concomitant treatments, and number of participants who achieved ASAS20 response in each arm.

To ensure the accuracy of the data extraction, this process was also independently performed by the two investigators. Any discrepancy was resolved by referring back to the original studies.

Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, UK). If at least two RCTs were available for a given biologic agent, the pooled odds ratio (OR) of achieving ASAS20 response and 95% confidence interval (CI) across studies were calculated using a random effect, Mantel–Haenszel analysis [15]. Effect estimates from intention-to-treat analysis were used in this meta-analysis. Random effect model, rather than fixed effect model, was used due to the difference in baseline characteristics of participants in each study. Cochran's Q test was used to assess statistical heterogeneity of the ASAS20 response rate for each biologic agent. This statistic was complemented with the I^2 statistic, which quantifies the percentage of total variation across studies that is due to true heterogeneity rather than chance. A value of I^2 of 0 to 25% represents insignificant heterogeneity; >25% but ≤50%, low heterogeneity; >50% but ≤75%, moderate heterogeneity; and >75%, high heterogeneity [16].

Indirect comparison technique as described by Bucher et al. [17] and Song et al. [18] was then utilized to compare the relative efficacy of these biologic agents. This indirect comparison is made through a common comparator (placebo group). The efficacy of two biologic agents was considered significantly different if the 95% CI did not contain OR of one (which would correspond to the p value of less than 0.05).

Evaluation for bias

Risk of bias for individual study was evaluated in six domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Visualization of funnel plot and Egger's regression test were used for the evaluation of publication bias. Comprehensive Meta Analysis version 2.2 software (NJ, USA) was used to perform the Egger's regression test.

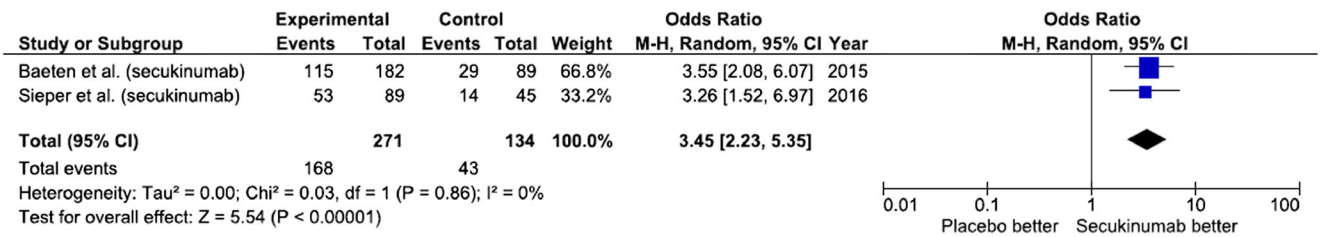

Fig. 3 Forest plot of secukinumab

Table 2 Indirect comparison between four treatments

Indirect comparison (ASAS20 response)	OR (95% CI)	*p* value
All older anti-TNF/certolizumab	1.84 (0.86–3.94)	0.12
All older anti-TNF/tofacitinib	1.47 (0.64–3.34)	0.36
All older anti-TNF/secukinumab	1.25 (0.78–2.01)	0.35
Secukinumab/certolizumab	1.47 (0.63–3.43)	0.37
Secukinumab/tofacitinib	1.17 (0.47–2.92)	0.74
Tofacitinib/certolizumab	1.26 (0.42–3.73)	0.68

ASAS Ankylosing Spondylitis Assessment Study, *OR* odds ratio, *CI* confidence interval, *TNF* tumor necrosis factor

Results

Systematic review of the literature

The search strategy yielded 698 potentially relevant articles (400 articles from EMBASE and 298 articles from Medline). After exclusion of 278 duplicate articles, 420 articles underwent title and abstract review. Three hundred and ninety articles were excluded at this stage as they were clearly not RCTs of biologic agents in AS, leaving 30 articles for full-length article review. Eleven of them were excluded at this stage as they were open-label extension phase of the original RCTs. One study (which is the only available study on apremilast) was excluded as it included both biologic agent experience and naïve patients and did not report ASAS20 response among the subgroup of patients who were biologic agent naïve [19]. Thus, 18 RCTs met the eligibility criteria and were included in our data analyses [20–37]. Additional search in clinicaltrials.gov and bibliographies of selected articles did not yield any other additional studies. The literature review process is summarized in Fig. 1. The methodology and baseline characteristics of participants of the included studies are illustrated in Table 1. It should be noted that the inter-rater agreement for eligibility of studies was high with the kappa statistics of 0.62.

Efficacy of biologic agents in active AS

We included 14 trials of older TNF inhibitors (2321 patients) [20–33], two trials of secukinumab (405 patients) [34, 35], one trial of certolizumab (142 patients) [36], and one trial of tofacitinib (103 patients) [37]. Baseline characteristics of participants were similar across these trials with similar female-to-male ratio, average age, and baseline disease activity as reflected by similar Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). All studies used modified New York criteria to classify participants with AS. The definitions of active AS were consistent across studies (i.e., BASDAI ≥4 and spinal pain VAS ≥ 3 or 4). All studies allowed concomitant use of stable dose of NSAIDs, DMARDs, and steroid at the dose of not more than 10 mg daily of prednisone or equivalent. Nonetheless, the duration of disease varied considerably across the studies, ranging from 1.5 to 18.7 years.

First, the results of 14 trials of older TNF inhibitors were pooled together. The pooled OR of achieving ASAS20 response among older TNF inhibitor-treated patients compared with placebo-treated patients was 4.31 (95% CI, 3.57–5.20). The statistical heterogeneity was low with I^2 of 0%. Forest plot of older TNF inhibitors is shown as Fig. 2. Funnel plot was used to evaluate publication bias. The plot was symmetric and did not provide a suggestive evidence of publication bias (supplementary Fig. 1). Egger's regression test was also not statistically significant ($p = 0.56$) which did not suggest the presence of publication bias.

Second, the results of two trials of secukinumab were pooled together. The pooled OR of achieving ASAS20 response among secukinumab-treated patients compared with placebo-treated patients was 3.45 (95% CI, 2.23–5.35). The statistical heterogeneity was low with I^2 of 0%. Forest plot of secukinumab is shown as Fig. 3. Evaluation for publication bias for secukinumab was not performed as there were only two eligible studies.

The four treatments were then compared to each other using placebo as the common comparator. The OR from the certolizumab study and the OR from the tofacitinib study were used for this analysis to indirectly compare with the aforementioned pooled ORs of older TNF inhibitors and secukinumab. There was no significant difference in any comparisons with the *p* values ranging from 0.12 to 0.74. The ORs with the corresponding 95% CIs and *p* values for every comparison are shown in Table 2.

Risk of bias

Risk of bias for individual study is shown in supplementary Fig. 2. The risk was low except for unclear risk of selection bias as most studies did not report the process of randomization in detail.

Discussion

Over the past three decades, biological agents were discovered and approved for clinical use. This meta-analysis aimed to answer a common clinical question in everyday practice. What would be the most effective biological agent for AS after the patients fail or could not tolerate NSAIDs? As there is no available direct head-to-head comparison between those agents, indirect comparison technique was utilized. Older TNF inhibitors, secukinumab, certolizumab, and tofacitinib were compared and their likelihood of achieving ASAS20 response was not significantly different from each other. Thus, from an efficacy standpoint, any one of them could be used as the first line therapy following NSAIDs failure. Of

course, safety profile and cost-effectiveness need to be considered as well. For instance, congestive heart failure or history of multiple sclerosis is contra-indications for the use of TNF inhibitors [38]. As such, patients with these conditions should receive either secukinumab or tofacitinib.

Nevertheless, we acknowledge that there are several limitations in this study. Therefore, the results should be interpreted with caution.

The first limitation is inherent to indirect comparison technique as this analysis assumes that the common comparator (in this case, placebo) is transitive, which means that the placebo arms are adequately similar across the included RCTs [39]. This assumption is not always true if characteristics at study entrance of participants, additional treatments, compliance, and follow-up protocol are not similar across studies which would result in uneven distribution of certain confounders or effect modifiers across sets of comparisons. This uneven distribution can still occur even though this study included only RCTs since participants are randomized to treatment/placebo arms within a single trial but are not randomized to different trials.

The second limitation is related to the number of included studies as there is only one study available for certolizumab and tofacitinib. Therefore, the comparisons relied on limited number of participants and it is possible the analyses were underpowered to detect statistical significance. For instance, the upper bound of the CI of the OR of indirect comparison between older TNF inhibitors and certolizumab was 3.94 which means that the odds of achieving ASAS20 response may be as high as four times higher by older TNF inhibitors than certolizumab. Nonetheless, with the wide CI, statistical significance could not be established.

In conclusion, the current meta-analysis demonstrated that the odds of achieving an ASAS20 response in patients with AS who did not have an adequate response to, or could not tolerate, NSAIDs were not significantly different between older TNF inhibitors, secukinumab, certolizumab, and tofacitinib. However, the interpretation of the results was limited by the small number of included RCTs. Head-to-head RCTs are still required to establish the comparative efficacy.

Authors' contribution Patompong Ungprasert: Study design, literature search, statistical analysis, and writing manuscript.

Patricia J. Erwin: Literature search and approval of manuscript.

Matthew J. Koster: Study design, literature search, and approval of manuscript.

Compliance with ethical standards

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Disclosures None.

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