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The comparative safety of biological treatment in patients with axial spondylarthritis: a meta-analysis of randomized controlled trials with placebo

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Abstract. – OBJECTIVE: To evaluate the comparative safety of biological treatment in patients with axial spondyloarthritis (axSpA) enrolled in randomized controlled trials (RCTs) with placebo.

MATERIALS AND METHODS: Studies were systematically retrieved from the Web of Science, PubMed, Cochrane Library, and Embase databases. The last search was performed on 8 June 2020. The primary outcome measures were adverse events (AEs), serious AEs, infection, serious infection, and discontinuation due to AEs. This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

RESULTS: A total of twenty-two trials, including 2599 participants treated with biologics and 1547 participants treated with placebo, met the inclusion criteria. There was a significantly higher risk of infection, AEs, and discontinuation due to AEs in the biologics groups compared to the placebo groups [risk ratio (RR) = 1.38, 95% confidence interval (95% CI) = 1.22-1.57, $p < 0.01$; RR = 1.17, 95% CI = 1.10-1.25, $p < 0.01$; and RR = 1.72, 95% CI = 1.03-2.87, $p = 0.04$, respectively], and low heterogeneity was found among the included studies ($I^2 = 0\%$, $p = 0.49$; $I^2 = 29\%$, $p = 0.10$; and $I^2 = 0\%$, $p = 0.79$, respectively). The risk of serious infection and serious AEs was not significantly different between axSpA patients treated with biologics and those treated with placebo [RR = 1.62, 95% CI = 0.54-4.90, $p = 0.39$ and RR = 1.17, 95% CI = 0.79-1.73, $p = 0.44$]. Low heterogeneity was found among the included studies ($I^2 = 0\%$, $p = 0.94$ and $I^2 = 0\%$, $p = 0.69$). The subgroup analyses based on tumour necrosis factor inhibitors and interleukin antagonists did not yield significant differences.

CONCLUSIONS: This meta-analysis is the first comprehensive assessment of the safety of various biological agents in axSpA patients. The use of biological agents in axSpA is generally safe and tolerable.

Key Words:
Axial spondyloarthritis, Safety, Biologics, Meta-analysis.

Introduction

Axial spondylitis (axSpA) is a chronic inflammatory disease that can eventually lead to disability. The development of axSpA predominantly affects the axial bone and may develop into the stiffness of the associated joints and lead to progressive functional limitations[1]. AxSpA comprises ankylosing spondylitis [AS or radiographic axSpA (r-axSpA)] and non-radiographic axSpA (nr-axSpA)[2]. It develops much more often in the second or third decade of life among males and has a strong association with HLA-B27 positivity[3].

There is no effective method to completely cure axSpA, and three main types of drugs are currently used to relieve the symptoms of axSpA. Nonsteroidal anti-inflammatory drugs

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are the first-line medication recommended for axSpA due to their extensive anti-inflammatory and suppressive structural injury effects[4]. However, serious gastrointestinal and cardiovascular complications limit their long-term application[5]. Conventional disease-modifying antirheumatic drugs (cDMARDs), such as sulfasalazine can improve the symptoms of some axSpA patients to a limited extent, evidence[6] has shown that cDMARDs have little benefit for axial symptoms. Biologics, as a class of disease-modifying drugs with broad potential for the therapeutic management of axSpA, have made notable progress in recent years.

The biologics currently used to treat patients with axSpA include tumour necrosis factor inhibitors (TNFis), interleukin inhibitors, and Janus kinase inhibitors. Numerous published randomized controlled trials[7-9] (RCTs) based on biological treatment in axSpA have revealed that biological agents have a better profile in relieving disease activity. The safety of the use of biologics for patient management deserves the attention of clinicians, although these drugs are generally considered safe. Khraishi[10] indicates that infection, infusion, or injection reactions are the main adverse events (AEs) caused by biological agents. Other relatively rare AEs include the development of anti-drug antibodies, demyelinating syndromes and lupus-like syndromes[11]. In previous studies, different results have been observed on the safety of biological agents in patients with axSpA, and most of the studies mainly focused on a single type of biological agent and a subgroup of axSpA[12]. Moreover, no systematic review has been conducted to assess the safety of all types of biologics versus placebo in axSpA patients.

In this study, we focused on the safety of all types of biological treatments in patients with axSpA. In contrast to previous studies, we included available RCTs using all types of biologics compared with placebo. We sought to assess the overall safety of biologics in axSpA patients.

Materials and Methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[13]. As the included studies were approved by the Ethics Committees of their research institutes, this meta-analysis did not require further approval.

Search Strategy

We systematically searched the Web of Science, PubMed, Cochrane Library, and Embase databases for relevant literature. The last search was performed on 8 June 2020. The search strategy was conducted by the following keywords: (“axial spondyloarthritis” OR “ankylosing spondylitis” OR “non-radiographic axial spondyloarthritis” AND “biological” OR “biologics” AND “safety” OR “adverse event” OR “infection” AND “randomized controlled trial” OR “double blind” AND “Adalimumab” OR “Ixekizumab” OR “Sarilumab” OR “Tocilizumab” OR “Infliximab” OR “Golimumab” OR “Etanercept” OR “Certolizumab pegol”). The filters were as follows: controlled clinical trials and randomized controlled trials. A free word retrieval strategy was applied, supplemented by hand searching to identify any eligible studies.

Study Selection Criteria

The inclusion criteria were as follows: (1) research involving the safety-related evaluation and analysis of biologics, including AEs, serious AEs, infection, serious infection, and discontinuation due to AEs; (2) research involving the use of a certain type of biological agent in comparison with a placebo; (3) security-related data can be obtained directly from published articles. The exclusion criteria were as follows: (1) open-label data of studies after a control group; (2) reviews, meta-analyses, and editorials; (3) data could not be extracted from the original published study.

Data Extraction and Quality Evaluation

According to the above search strategies and criteria, two reviewers independently drew preliminary conclusions based on the titles and abstracts of the studies. If the conclusions were inconsistent, all authors discussed whether the article should be included in this study. Relevant information and data from the included studies, including first author, publication year, disease characteristics, type and dosage of biological agents, information of cases in the treatment group and control group, duration of the trial, and safety-related indicators based on the inclusion criteria, were extracted. The methodological quality of the trials was evaluated according to the methods recommended by the Cochrane Collaboration[14].

Statistical Analysis

The definitions of AEs, serious AEs, infection, serious infection, and discontinuation due to AEs were consistent with the definitions within each included study. The safety indicator of biologics/placebo in patients with axSpA, as dichotomous data, was quantified using the pooled risk ratio (RR) and 95% confidence interval (95% CI). A random-effects model was adopted in this study, as it is more suitable in the case of large heterogeneity when merging data. When RR > 1, biological treatment was considered a risk factor for the related safety events compared to placebo. The 95% CI was used to estimate the overall parameters. The narrower the 95% CI range is, the better the reliability of estimating population parameters. A p-value < 0.05 was considered a statistically significant difference in the meta-analysis. The determination of heterogeneity was similar to that in traditional studies[15]. The heterogeneity was expressed by I^2. I^2 < 25%, I^2 = 25%–50%, and I^2 > 50% were considered to indicate low, moderate, and large heterogeneity, respectively. Subgroup analyses based on TNFi and interleukin antagonists were also performed. A p-value < 0.01 was considered a statistically significant difference in the subgroup analysis. Additionally, funnel plots were used to assess potential publication bias in this meta-analysis.

The statistical analyses were performed using Review Manager software (RevMan, Version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

Results

Literature Search and Study Characteristics

A total of 606 published studies were first identified. Then, 487 studies were excluded after screening titles and abstracts, and 68 were excluded after full-text reviews. Finally, twenty-two studies published between 2002 and 2019 were included in this meta-analysis. A flow chart of the study selection process is shown in Figure 1.

A total of 4687 patients, including 2993 treated by biologics and 1694 treated by placebo, were included this study. The duration of the trials ranged from 12 weeks to 52 weeks (average 19.9 weeks). A total of 2041 patients were treated with TNF inhibitors (adalimumab, tocilizumab, infliximab, golimumab, etanercept, and certolizumab pegol). A total of 702 patients were treated with anti-IL-17A antibodies (secukinumab and ixekizumab). A total of 250 patients were treated with anti-IL-6 antibody (sarilumab). Table I shows the basic characteristics of the included studies[16-37].

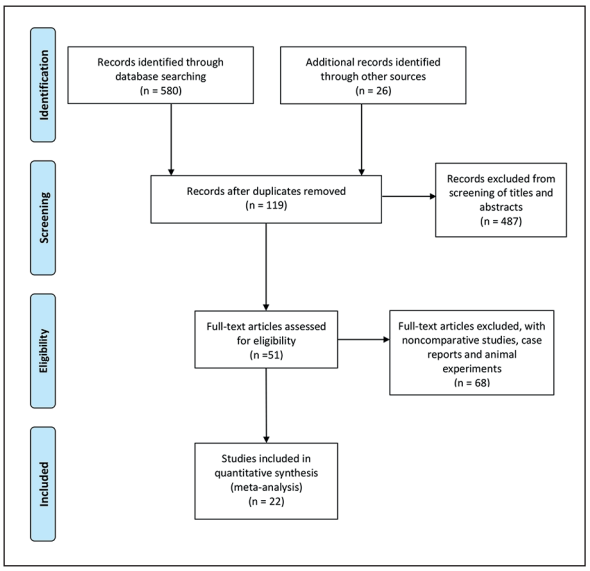

Figure 1. Flow diagram of study selection.

The quality of the included literature was acceptable, and Figure 2 shows the risk of bias graph and the risk of bias summary.

Infection and Serious Infection

Eighteen trials, including 2879 patients treated with biologics and 1566 patients treated with placebo, reported data about infection. Infections were reported in 714 patients in the biologic groups and 253 patients in the placebo groups. The meta-analysis showed that there was a significantly higher risk of infection between the biologics groups and the placebo groups [RR = 1.38, 95% CI = 1.22-1.57, p < 0.01], and low heterogeneity was found among the included studies (I^2 = 0%, p = 0. 62) (Figure 3A).

Eight trials, including 1414 patients treated with biologics and 783 patients treated with placebo, reported data about serious infections. There was no significant difference in the risk of infection between the two groups [RR = 1.62, 95% CI = 0.54-4.90, p = 0.39], with low heterogeneity among the included studies (I^2 = 0%, p = 0.94) (Figure 3B).

AEs and Serious AEs

Twenty-two trials, including 2599 patients treated with biologics and 1547 patients treated with placebo, provided data about AEs. AEs were reported in 1625 and 776 patients in the biologic

Table I. Characteristics of randomized controlled trials included in the meta-analysis.

Authors	Year	Disease characteristics	Treatment group			Control group			Duration of trial (week)
			Cases (N)	Male, n (%)	Dosage	Cases (N)	Male, n (%)	Dosage	
Adalimumab									
Sieper[16]	2013	Active nr-axSpA	91	44 (48)	40 mg every other week	94	40 (43)	Placebo	12
van der Heijde[17]	2006	Active AS.	208	157 (75.5)	40 mg every other week	107	79 (73.8)	Placebo	24
Haibel[18]	2008	Active nr-axSpA	22	13 (59)	40 mg every other week	24	12 (50)	Placebo	12
Horneff[19]	2012	Juvenile onset AS	17	10 (59)	40 mg every other week	15	7 (47)	Placebo	12
Huang[20]	2012	Active AS	229	185 (80.8)	40 mg every other week	115	95 (82.6)	Placebo	12
van der Heijde[21]	2018	AS or radiographic axSpA	90	73 (81)	40 mg every other week	86	64 (77)	Placebo	16
Ixekizumab									
Deodhar[22]	2019	Active nr-axSpA	96	50 (52)	80 mg every 4 weeks	104	44 (42)	Placebo	52
			92	49 (48)	80 mg every 2 weeks				
Deodhar[23]	2019	Active radiographic ax-SpA	98	75 (76.5)	80 mg every 2 weeks	104	87 (83.7)	Placebo	16
			114	91 (79.8)	80 mg every 4 weeks				
van der Heijde[21]	2018	AS or radiographic ax-SpA	82	64 (77)	80 mg every 2 weeks	86	64 (77)	Placebo	16
			82	68 (84)	80 mg every 4 weeks				
Sarilumab									
Sieper[24]	2013	Active AS	49	30 (61.2)	100 mg every 2 weeks	50	38 (76)	Placebo	12
			50	34 (68)	150 mg every 2 weeks				
			51	37 (71.2)	100 mg every 2 weeks				
			50	40 (80)	200 mg every 2 weeks				
			50	39 (78)	150 mg once a week				
Secukinumab									
Baeten[25]	2013	Active AS	24	14 (58)	2×10 mg/kg at day1and day 22	6	5 (83)	Placebo	28
Pavelka[26]	2017	Active AS	57	50 (65.8)	10 mg/kg at baseline and 2 and 4 weeks, followed 300 mg every 4 weeks starting at week 8	76	40 (52.6)	Placebo	16
			57	46 (62.2)	10 mg/kg at baseline and weeks 2 and 4, followed 150 mg every 4 weeks starting at week 8				

Table Continued

Table I *(Continued)*. Characteristics of randomized controlled trials included in the meta-analysis.

Authors	Year	Disease characteristics	Treatment group			Control group			Duration of trial (week)
			Cases (N)	Male, n (%)	Dosage	Cases (N)	Male, n (%)	Dosage	
Tocilizumab									
Sieper[27]	2013	Active AS	51	36 (71)	8 mg/kg every 4 weeks	51	40 (78)	Placebo	12
Infliximab									
van der Heijde[28]	2004	Active AS	202	157 (78.1)	5 mg/kg at 0, 2, 6, 12, and 18 weeks	75	68 (87.2)	Placebo	24
Braun[29]	2003	Active AS	34	22 (63)	5 mg/kg at 0, 2, and 6 weeks	34	22 (63)	Placebo	12
Marzo-Ortega[30]	2005	Active AS	28	23 (82.1)	5 mg/kg at 0, 2, 6, 14, and 22 weeks +MTX 7.5 mg once a week	14	11 (78.6)	Placebo + MTX 7.5 mg once a week	30
Sieper[31]	2014	Active ax-SpA	105	72 (68.6)	5 mg/kg at 0, 2, 6, 12, and 18 weeks +NPX 1000 mg daily	52	40 (78.4)	Placebo + NPX 1000 mg daily	28
Golimumab									
Deodhar[32]	2017	Active AS	105	86 (81.9)	2 mg/kg at 0, 4, and 12 weeks	103	77 (74.8)	Placebo	16
Etanercept									
Davis[33]	2003	Active AS	138	105 (76)	25 mg subcutaneously twice weekly+ DMARDs	139	105 (76)	Placebo +DMARDs	24
van der Heijde[34]	2006	Active AS 150	155	108 (69.7)	50 mg once weekly	51	40 (78.4)	Placebo	12
Dougados[35]	2011	Active AS	39	37 (91)	50 mg once weekly	43	39 (91)	Placebo	12
Certolizumab pegol									
Landewé[36]	2013	Active ax-SpA	111 107	67 (60.4) 68 (63.6)	200 mg every 2 weeks 400 mg every 4 weeks	107	65 (60.7)	Placebo	24
Deodhar[37]	2019	Active ax-SpA	159	78 (49)	200 mg every 2 weeks and their current nonbiologic background medication	158	76 (48)	Placebo and their current nonbiologic background medication	52

Notes: AS, ankylosing spondylitis; nr-axSpA, non-radiographic axial spondyloarthritis; axSpA, axial spondyloarthritis; MTX, methotrexate; NPX, naproxen; DMARDs, disease-modifying anti-rheumatic drugs.

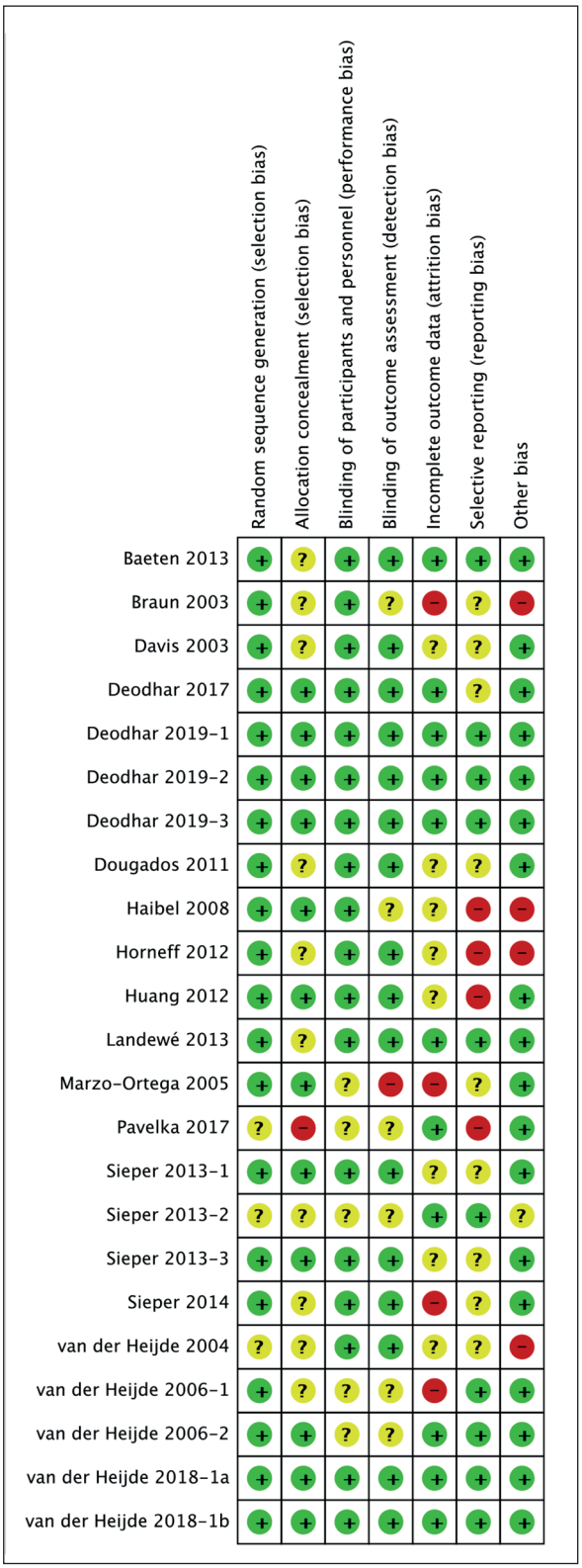

Figure 2. Risk of bias graph and risk of bias summary. The review authors' assessments for each risk of bias in the trials included the following: (+): low risk of bias; (?): unclear risk of bias; and (-): high risk of bias

and placebo groups, respectively. The risk of AEs in patients treated with biologics was significantly higher than that in patients treated with placebo [RR = 1.17, 95% CI = 1.10-1.25, $p < 0.01$], and low heterogeneity was found among the included studies ($I^2 = 29\%$, $p = 0.10$) (Figure 4A).

Twenty trials, including 2698 patients treated with biologics and 1643 patients treated with placebo, reported data about serious AEs. There was no significant difference in the risk of serious AEs between the two groups [RR = 1.17, 95% CI = 0.79-1.73, $p = 0.44$], with low heterogeneity among the included studies ($I^2 = 0\%$, $p = 0.69$) (Figure 4B).

Discontinuation due to AEs

Of the fourteen total trials, discontinuation due to AEs was reported in 2712 patients in the biologic groups and 1687 patients in the placebo groups. Seventy-five patients in the biologic groups and 19 patients in the placebo groups experienced treatment interruption during their trials. The risk of discontinuation due to AEs was significantly different between axSpA patients treated with biologics and those treated with placebo [RR = 1.72, 95% CI = 1.03-2.87, $p = 0.04$], and low heterogeneity was found among the included studies ($I^2 = 0\%$, $p = 0.71$) (Figure 5).

Subgroup Analysis and Publication Bias

Subgroup analysis for these safety indicators was performed based on TNFi and interleukin antagonists. Overall, the subgroup analyses did not reveal significant differences between groups (Table II). The funnel plot was symmetrical for each safety indicator (Figure 6A-E).

Discussion

The safety of biological agents is the main concern of clinicians; however, the safety of biological treatments for axSpA patients is not completely clear. With the completion of more clinical trials in recent years, more reliable research results with larger samples can be obtained and analysed. Previous studies[12,38] on biological agents in axSpA are mostly aimed at a single type of biological agent and a subgroup of axSpA, but there is no overall evaluation of the safety of all types of biological agents used by axSpA patients. This meta-analysis is the first comprehensive assessment of the safety of various biological

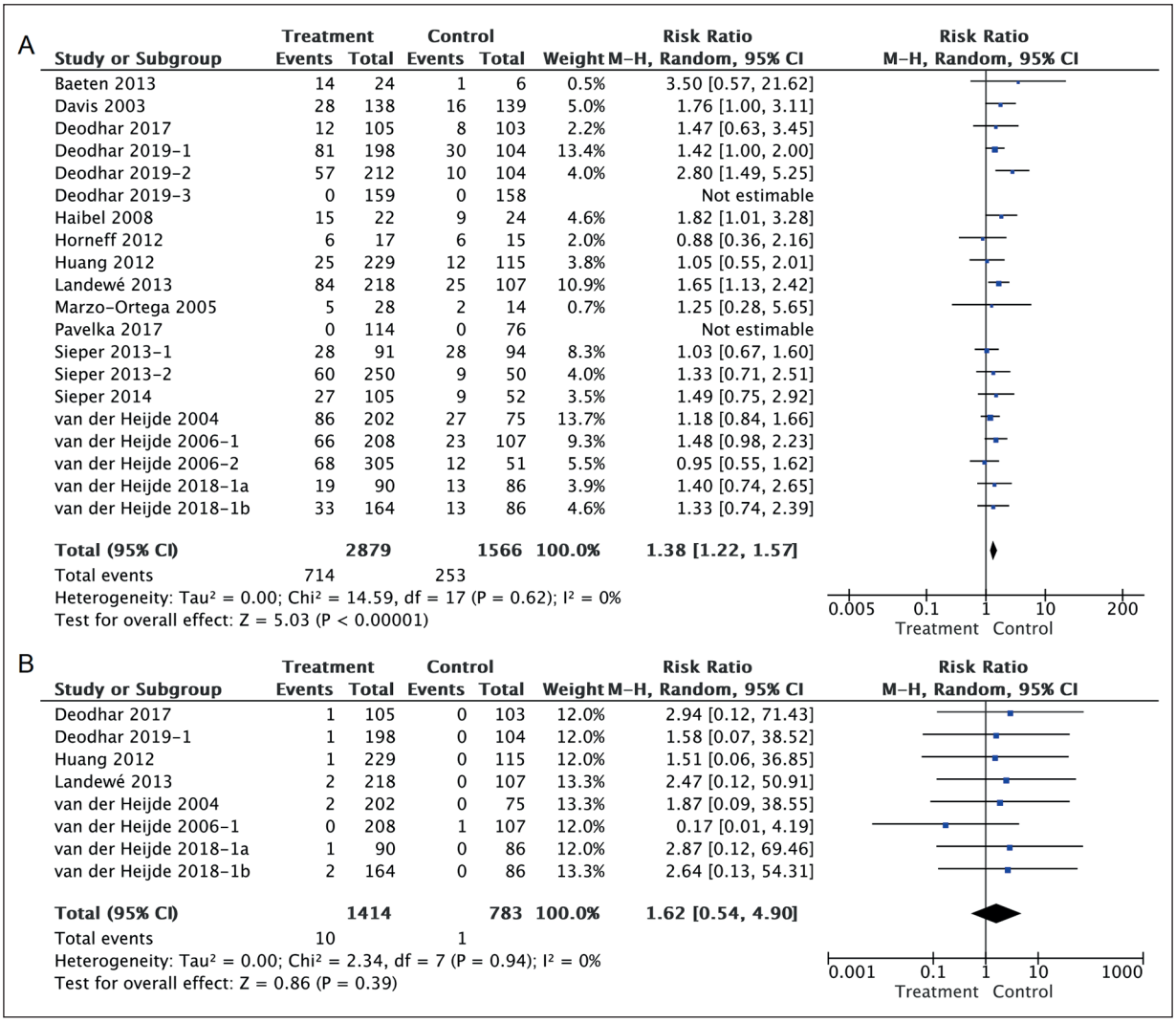

Figure 3. Forest plots estimated for the risk of infection and serious infection in biological treatment versus placebo. (**A**) For infection and (**B**) for serious infection. Deodhar 2019-1, 2019-2, and 2019-3 were for references 22, 23, and 37, respectively. Sieper 2013-1 and 2013-2 were for references 16 and 24, respectively, and van der Heijde 2006-1 and 2006-2 were for references 17 and 34, respectively. Both van der Heijde 2018-1a and van der Heijde 2018-1b were for reference 21 because Adalimumab and Ixekizumab were independently used in different treatment groups in this trial, respectively. These notes are also applied to Figures 4 and 5.

agents in the treatment of axSpA and includes the latest literature to evaluate the safety of all biologics based on randomized controlled trials with placebo.

Our study reveals a significantly higher risk of infection, AEs, and discontinuation due to AEs in axSpA patients receiving biologics compared with those receiving placebo. Moreover, the subgroup analysis results based on TNFi and interleukin antagonists did not appear to differ substantially. Part of the results of our study updates the published meta-analysis results. Hou et al[39] reported the discontinuation due to AEs in patients treated with TNFis were not significantly different from those treated with placebo. Additionally, some results further confirm the previous conclusion. Wang et al[40] and Fouque-Aubert et al[41] reported that at the early stage, there was no significant correlation between the use of biological agents and the increased risk of serious infection in axSpA patients. Our results suggest that clinicians should carefully consider the risk of infection and AEs when using biological agents in patients with axSpA and make a timely choice of drug withdrawal if necessary. In addition, our study revealed that there was no significant difference

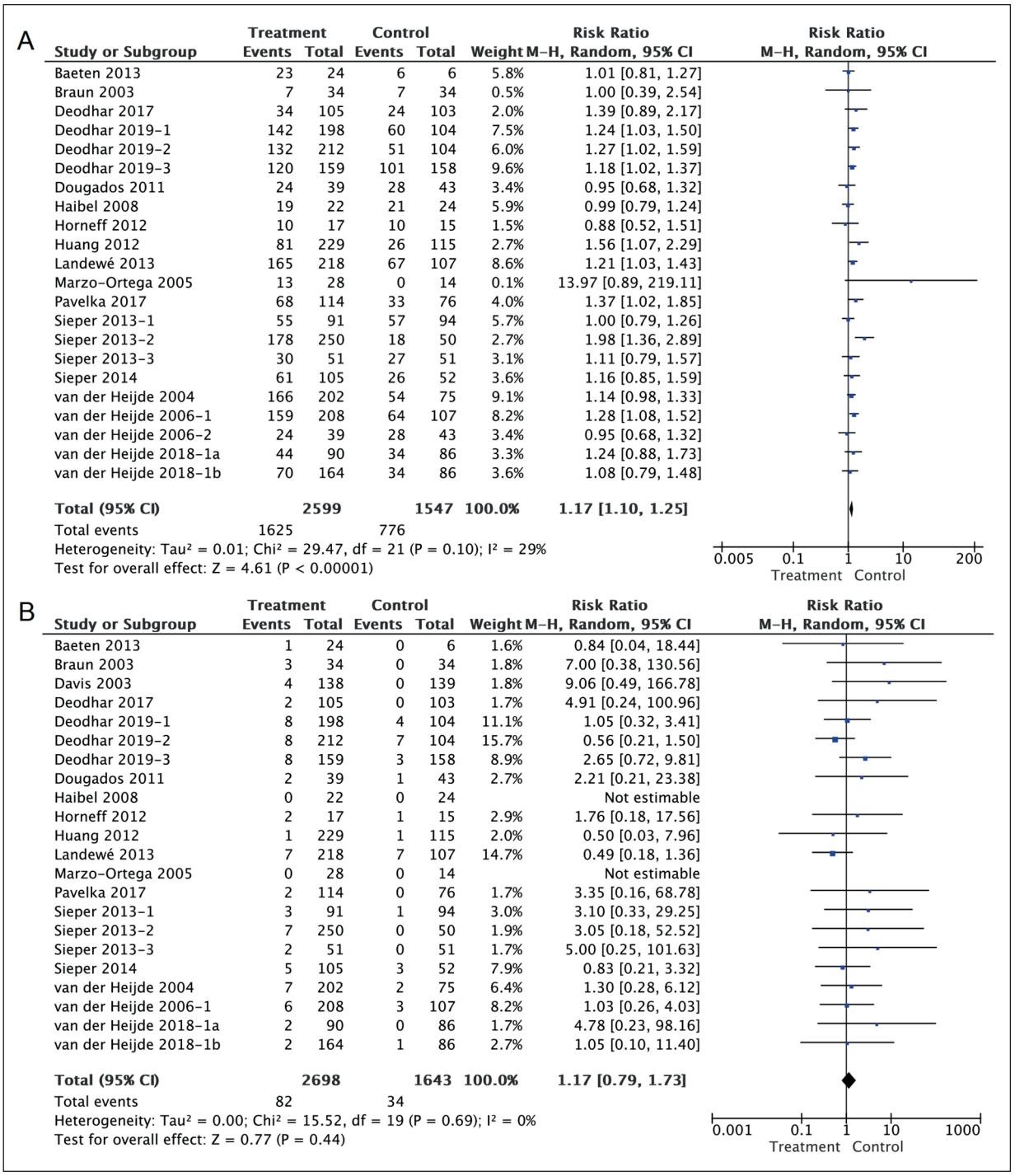

Figure 4. Forest plots estimated for the risk of AEs and serious AEs in biological treatment *vs.* placebo. (**A**) AEs and (**B**) serious AEs. AEs, adverse events.

in the risk of severe infection and severe adverse reactions between patients treated with biological agents and those treated with placebo. We could reasonably believe that biological agents are generally safe in the field of axSpA therapy. It also provides further evidence for the application of biological therapy in axSpA patients.

We should note that this study is based on high-quality RCTs with strict inclusion criteria. However, due to the strict standards of each trial,

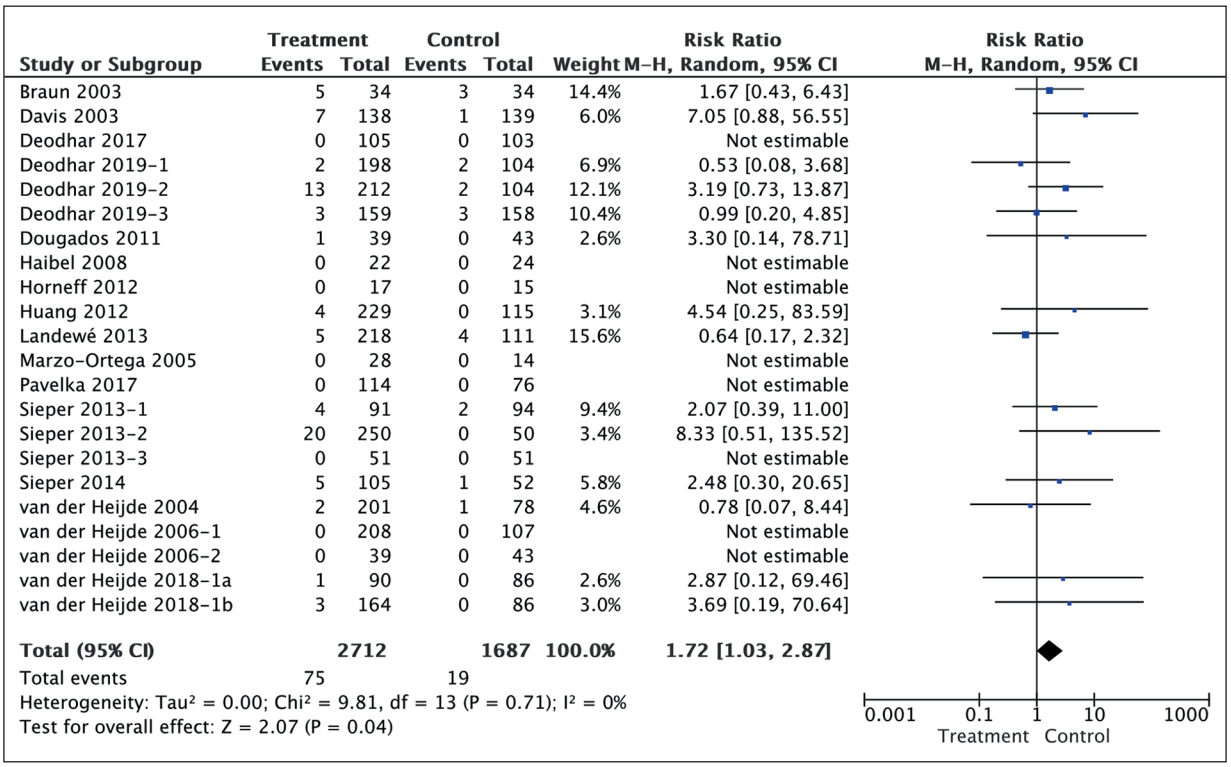

Figure 5. Forest plots estimated for the risk of discontinuation due to AEs in biological treatment *vs.* placebo. AEs, adverse events.

the follow-up times of the included studies were generally short. Some special chronic infections or side effects may not have been reported. These special AEs, such as meningeal inflammation or secondary amyloidosis, were reported in some longer-term cohort studies[42,43]. In addition, malignancies, another common indicator used to evaluate safety, were not reported in this study because of the short follow-up times and insufficient data provided in the included studies. During the short

Table II. Subgroup analysis based on TNFis and interleukin antagonists..

Outcome	Analysis number	RR (95% CI)	p	Heterogeneity test		
				Q	p	I^2 (%)
Infection						
TNFis	13	1.32 (1.14-1.53)	< 0.01	8.28	0.76	0
Interleukin antagonists	5	1.60 (1.19-2.15)	< 0.01	5.00	0.29	20
Serious infection						
TNFis	6	1.49 (0.42-5.36)	0.54	2.22	0.82	0
Interleukin antagonists	2	2.07 (0.23-18.61)	0.52	0.05	0.82	0
AEs						
TNFis	15	1.15 (1.07-1.23)	< 0.01	16.42	0.29	15
Interleukin antagonists	7	1.24 (1.08-1.43)	< 0.01	1.74	0.07	49
Serious AEs						
TNFis	13	1.31 (0.80-2.14)	0.28	11.16	0.52	0
Interleukin antagonists	7	0.95 (0.50-1.82)	0.88	3.73	0.71	0
Discontinuation due to AEs						
TNFis	10	1.57 (0.87-2.83)	0.14	5.82	0.76	0
Interleukin antagonists	4	2.26 (0.73-7.04)	0.16	3.52	0.32	15

Notes: TNFis, tumour necrosis factor inhibitors. RR, risk ratio. 95% CI, 95% confidence interval. AEs, adverse events. *p*-value for overall effect.

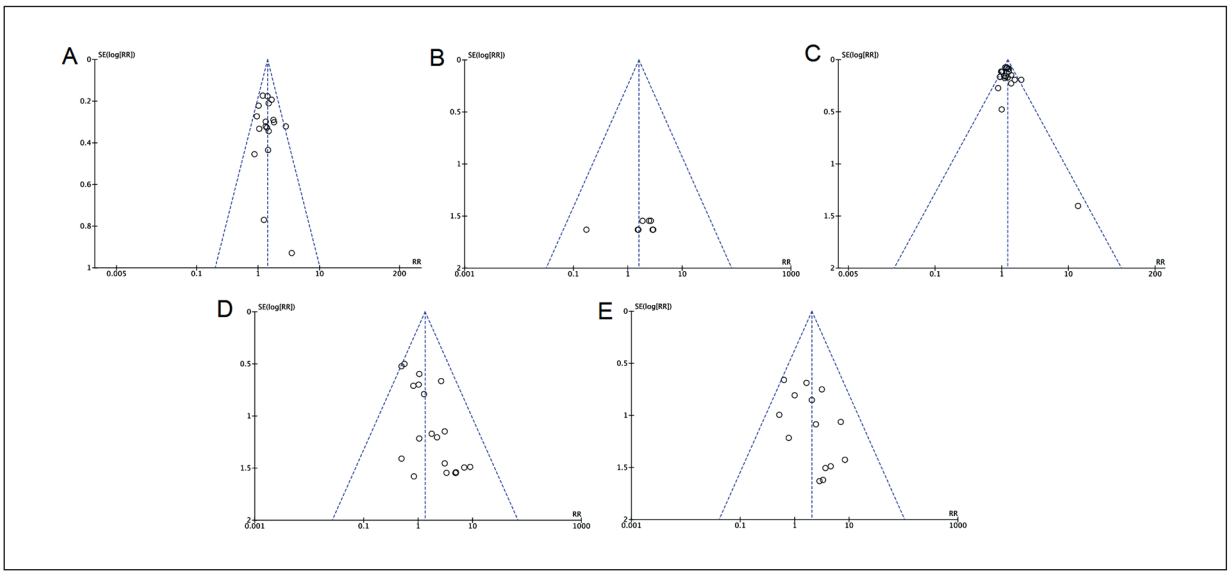

Figure 6. Funnel plots of safety-related indicators in biological treatment versus placebo. (A) to (E) for AEs, serious AEs, infection, serious infection, and discontinuation due to AEs, respectively. AEs, adverse events.

RCT period, it is difficult to determine the relationship between malignant tumours and the use of biological agents. Moreover, the evaluation of the incidence of malignant tumours during RCTs lacks persuasion. A systematic review of RCTs published in 2016, including 15,539 participants, assessed the effect of anti-TNF agents on the occurrence of cancer (any type) in patients with rheumatoid arthritis, psoriatic arthritis or AS[44]. The results indicated that using anti-TNF agents does not significantly affect cancer risk among the above three diseases. This result should be interpreted cautiously because the follow-up time ranged from 2-36 months (9.2 months per patient, on average). The evaluation of tumour incidence using biologics is more suitable for open-label studies or long-term cohort studies, and these studies in patients with axSpA are still lacking.

Other novel biologics for the management of axSpA, such as tofacitinib, filgotinib, and upadacitinib, have been under investigation or trials[45-47]. The current results on the efficiency and safety of biological agents are encouraging, and more research is expected. It is believed that there will be more safe and effective biologics for the treatment of axSpA in the future.

There are some limitations to this study. The RCTs included different races, and people from different regions had different drug tolerances, which might have led to bias. In addition, there were certain differences in the definition of security-related indicators in the included trials, which may lead to bias in the assessment of the risk of security-related events. Moreover, our study only included literature published in English, which may lead to language bias.

Conclusions

This meta-analysis is the first comprehensive assessment of the safety of various biological agents in axSpA patients. There was a significant difference in the risk of infection, AEs, and withdrawal due to AEs between axSpA patients treated with biologics and those treated with placebo, while there was no significant difference in the risk of serious infection and serious AEs. The use of biological agents in axSpA is generally safe and tolerable.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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