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Incidence of Uveitis in Patients With Axial Spondylarthritis Treated With Biologics or Targeted Synthetics: A Systematic Review and Network Meta-Analysis

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Objective. Anterior uveitis is a common extra-articular manifestation of axial spondyloarthritis (AxSpA). We set to evaluate the risk of anterior uveitis (AU) with biologics and synthetic disease-modifying drugs in AxSpA.

Methods. We conducted a systematic review and meta-analysis to identify phase II/III double-blinded randomized controlled trials of anti–tumor necrosis factor (TNF) monoclonal antibodies (mAb), anti–interleukin-17 (anti–IL-17), and Janus kinase inhibitors (JAKi) in AxSpA. Patient-exposure years (PEY) were calculated using the per-protocol approach. Incidence rate (IR) of AU/100 person-years were calculated by treatment group using the random effects approach. Network meta-analysis (NMA) was used to estimate risk of AU in treatment groups, expressed as IR ratios (IRRs). Bias was assessed using the Cochrane Risk of Bias-2 tool.

Results. Forty-four trials were included: 17 anti-TNF mAb (1,004 PEY), 9 etanercept (180 PEY), 13 anti–IL-17 (1,834 PEY), and 6 JAKi (331 PEY). The IR of AU were as follows for anti-TNF mAb: 4.1, 95% confidence interval (CI) 0–8.5; etanercept: 5.4, 95% CI 0–16.0; anti–IL-17: 2.8, 95% CI 1.6–4.1; JAKi: 1.5, 95% CI 0.0–3.0; and placebo: 10.8, 95% CI 7.4–14.1. In NMA, IRRs of treatments compared with placebo were as follows for anti-TNF mAb: 0.32, 95% CI 0.10–1.04; etanercept 0.42, 95% CI 0.08–2.38; anti–IL-17: 0.43, 95% CI 0.19–0.98; and JAKi: 0.32, 95% CI 0.06–1.67. Comparisons between anti-TNF mAb, anti–IL-17, and JAKi did not demonstrate any significant difference in AU risk. Using the surface under the cumulative ranking curve approach to rank AU risk, anti-TNF mAbs were associated with the lowest risk followed by JAKi, anti–IL-17, and etanercept. All treatments were ranked superior to placebo.

Conclusion. Anti-TNF mAbs, JAKi, and anti–IL-17 appear protective against AU events in individuals with AxSpA, with no significant differences in risk of AU between treatments.

INTRODUCTION

Axial spondyloarthritis (AxSpA) is a chronic inflammatory disorder, primarily affecting the axial skeleton. One of the commonly observed extraspinal manifestations in AxSpA is anterior uveitis (AU) characterized by inflammation of the iris and ciliary body. This ocular complication occurs in up to a third of patients with AxSpA,[1,2] with greater prevalence in radiographic AxSpA compared with nonradiographic AxSpA,[3] and can lead to significant morbidity risk.

Targeted immunomodulatory therapies, such as anti–tumor necrosis factor (anti-TNF) agents, and more recently, anti-interleukin 17 (anti–IL-17) and Janus kinase inhibitors (JAKi), have significantly enhanced the treatment landscape in AxSpA. Randomized controlled trials (RCTs) in AxSpA characteristically focus on axial disease activity as their primary endpoint rather than uveitis events. RCTs in other diseases, such as Behcet's, have examined uveitis flares as their primary outcome. These trials have demonstrated the efficacy of anti-TNF monoclonal antibodies (mAb).[4] The same has not been seen with anti–IL-17.[5]

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Phase II RCTs examining JAKi are ongoing and have not yet been published. Observational data examining uveitis in AxSpA have indicated a protective effect with anti-TNF, with superiority of the mAbs compared with etanercept.[6–8] Relatively less protection against uveitis was shown for anti–IL-17 when compared with anti-TNF mAbs.[9] The recently published Assessment of Spondyloarthritis International Society (ASAS)-European Alliance of Associations for Rheumatology guidelines advocate TNF mAb inhibition over other treatment strategies in recurrent AU.[10]

A network meta-analysis (NMA) published in 2021 examining uveitis in patients with AxSpA treated with anti-TNF and anti–IL-17A drugs (secukinumab and ixekizumab) reported lower odds of AU flare with anti-TNF mAb compared with anti–IL-17A.[11] However, this NMA did not include data on JAKi or the anti–IL-17AF drug bimekizumab. These have since been licensed for the treatment of AxSpA. There were also methodological aspects of the previous NMA that could have introduced bias. The primary objective of this study was to determine the anterior uveitis in patients with AxSpA treated with anti-TNF, anti–IL-17, or JAKi and compare the effects of these therapies on AU relative to placebo.

MATERIALS AND METHODS

The study was conducted in accordance with the preferred reporting items for systematic reviews guidelines[11] and registered with the international prospective register of systematic reviews (Prospero 2023 CRD42023408414). No ethical approval was required as per Health research authority (HRA) guidance. Data are available upon reasonable request. All data used in this study are available online within the provided reference list and can be shared upon reasonable request.

Search strategy and information sources. A systematic literature search was performed by two investigators (DN and ASU) using MEDLINE and EMBASE, from the database inception to July 2023. The search was rerun to December 2023 prior to final analysis to identify further studies that could be retrieved for incorporation in the systematic review. The drugs of interest were anti-TNF mAb (infliximab, adalimumab, golimumab, certolizumab) and soluble receptor fusion (etanercept), anti–IL-17A (secukinumab, ixekizumab) and anti–IL-17AF inhibitor (bimekizumab) and JAKi (tofacitinib, upadacitinib, and filgotinib).

Because this was an updated systematic review since the review published in 2021, the search for anti-TNF and anti–IL-17A were run from May 2020. The search terms were [ankylosing spondylitis OR spondylart* OR spondyloa*] AND [infliximab OR certolizumab OR adalimumab OR golimumab OR etanercept OR secukinumab OR ixekizumab]. The search for anti–IL-17AF (bimekizumab) and JAKi were run from inception and included the search terms [ankylosing spondylitis OR spondylart* OR spondyloa*] AND [bimekizumab OR tofacitinib OR baricitinib OR upadacitinib OR filgotinib].

Study selection and data collection. We identified English language publications of phase II and III RCTs. Conference abstracts were excluded. RCTs were included if they met the following criteria: (1) the study included patients diagnosed with AxSpA according to the ASAS[12] or modified New York criteria[13]; (2) the study evaluated either anti-TNF, anti–IL-17, or JAKi; and (3) the study included a placebo comparator or another active treatment arm. Open-labeled controlled studies were only included if they had an initial double-blind period with detailed safety analysis. No restrictions were applied to the length of follow-up. Studies presenting duplicate data were excluded. Titles and abstracts of studies retrieved using the search strategy were screened independently by two investigators, DN and ASU. The full text of the potential studies for inclusion were retrieved and assessed for eligibility. Study quality and risk of bias were assessed using the Cochrane Collaboration's Risk of Bias 2 tool.[14]

Data were extracted independently by two reviewers. Disagreements over study eligibility or risk of bias were resolved through discussion with a third reviewer, KB. Data collated included the source (author, journal, and publication date), study design, sample size, dosage and schedule of the treatment, duration of RCT and/or of the double-blind period, patient characteristics, percentage of patients with a history of AU, and concomitant use of conventional synthetic disease modifying antirheumatic drugs (csDMARDs) and corticosteroids or nonsteroidal antiinflammatory drugs (NSAIDs).

Data synthesis and statistical analysis. Analyses were undertaken using Stata 17 and R (version 4.2.2). The primary outcome of interest was AU events. This included new onset AU and relapses, reported under either the term "uveitis" or "iritis." The distinction between uveitis and iritis can be subtle because both conditions involve inflammation in the anterior part of the uvea, particularly affecting the iris, and these terms are often used interchangeably. For studies not reporting on AU, it was assumed there were no events. These RCTs were not excluded from the analyses because this would have introduced systematic bias. Summary data rather than individual-level data were aggregated for quantitative analyses. Patient exposure years (PEY) were calculated for placebo and treatment arms. A per-protocol (PP) analysis was employed, in which patients could contribute time to both the treatment and placebo arms (ie, initially to the placebo group when receiving placebo, and thereafter to the treatment group when crossed into the treatment arm to receive the study drug).

Crude incidence rates (IRs) of AU were calculated for each RCT. For each treatment, a pooled estimate of IRs was calculated using a random effects approach. NMA was employed using

restricted maximum likelihood models to allow indirect comparisons between the therapies. A fixed continuity correction of 0.1 was applied to each arm of studies that had one or more groups with zero events. Network plots were used to describe treatment comparisons. Pooled estimates of the relative risk of AU between each treatment arm and placebo were compared, expressed as incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Indirect estimates of the IRRs of AU between treatment arms were also compared. A probability of treatment superiority was calculated based on estimated probabilities using the parameters derived from the NMA and reported as a rank according to the surface under the cumulative ranking curve (SUCRA). A SUCRA value of 1 indicates the treatment is certain to be the most effective in the network, whereas a value of 0 indicates it is certain to be the least effective. SUCRA results should be interpreted with caution, especially if there is heterogeneity in the network, or the underlying studies are of poor quality, or data are limited.[15] Publication bias was assessed using funnel plots. Pairwise meta-analysis was performed for direct treatment comparisons only, using the random effects inverse variance method, and compared graphically using forest plots.

Sensitivity analyses. We performed a sensitivity analysis calculating PEY using an intention-to-treat protocol. We also performed sensitivity analyses restricted to (1) RCTs that reported on AU, (2) RCTs with >10% of the trial population with a history of AU, and (3) RCTs with a low-risk bias.

RESULTS

Search results and trial characteristics. We included 33 of the 34 studies from the previous systematic review of anti-TNF and anti–IL-17A,[11] excluding one RCT that did not meet our inclusion criteria (open label trial) (Supplementary Materials 1). Our search of anti-TNF and anti–IL-17A from March 2020 to December 2023 identified 796 articles, of which only 1 RCT met the inclusion criteria. We also included one study identified in a clinicaltrials.gov search that was published prior to March 2020 and had not been included in the previous systemic review. Our search of anti–IL-17AF and JAKi from inception until December 2023 identified 263 articles, of which 9 RCTs met inclusion criteria. In total, 44 studies were eligible for inclusion in our analysis. This comprised 5,910 patients with axSpA treated with a biologic or targeted synthetic and 3,791 treated with placebo.

Forty-three trials included in this meta-analysis compared one treatment arm with placebo (Table 1), and one RCT compared two biologic arms, ixekizumab and adalimumab versus placebo. The median duration of the controlled period was 16 weeks (range: 8–104 weeks, interquartile range: 12–24 weeks). Eleven trials had a crossover period. TNFi was assessed in 17 mAb arms (2,020 patients) and 9 etanercept arms (731 patients). IL-17Ai was assessed in 10 IL-17A arms (2,049 patients) and 3 IL-17AF arms (407 patients). JAKi was assessed in 6 trials (703 patients) (Table 1).

Risk of bias was assessed across different domains according to the Cochrane Collaboration's Risk of Bias 2 tool. Of the included studies, 26 of 44 (59%) had an overall low risk of bias. Trials with recent publication years were least likely to be at high risk of bias across the assessed domains. (Supplementary Table 2).

Characteristics of the patients with AxSpA. The different treatment groups were similar in terms of age, Bath Ankylosing Spondylitis Disease Activity Index at baseline, and use of NSAIDs and corticosteroids. There were disparities in gender distribution, ranging from 43% male to 87% male predominance. Few studies focused on early disease, with only five studies reporting a median symptom duration of fewer than five years. Co-prescription of steroids was generally low, prescribed in <15% of participants in most trials (22 of the 28 trials reported on steroids), whereas the proportion of participants prescribed a concomitant csDMARD ranged from 14% to 49%. Only 28 studies reported on history of AU at baseline; the proportion of patients with a past history of AU ranged from 3% to 46%, with some imbalance between the treatment and placebo groups.

Anterior uveitis (AU). In total, 26 studies reported on uveitis episodes occurring during the trial period in their safety analyses. Uveitis occurred in 9 patients receiving anti-TNF mAbs with 1,004 PEY, 4 on etanercept with 180 PEY, 40 on anti–IL-17 with 1,834 PEY, and 5 on JAK inhibitors with 331 PEY. In the placebo control group, 58 patients had AU with 1,343 PEY. For studies that did not report on uveitis events in both the treatment or placebo arms it was assumed that there were no uveitis events. This included 10 of 17 anti-TNF mAb, 6 of 9 etanercept, 1 of 14 anti–IL-17, and 1 of 7 JAKi arms.

Pooled estimates of IRs of AU per 100 patient-years were 4.1, 95% CI 0–8.5 for anti-TNF mAbs, 5.4, 95% CI 0–16.0 for etanercept, 2.8, 95% CI 1.6–4.1 for anti–IL-17, and 1.5, 95% CI 0.0–3.0 for JAKi. In the pooled placebo group, estimates of IRs were 10.8, 95% CI 7.4–14.1 per 100 person-years. This ranged from an IR of 7.4 in the JAKi placebo group to 14.9 in the anti-TNF mAbs placebo group.

NMA. Network plots depicting treatment comparisons are shown in Figure 1. The NMA included mostly two-armed trials with a placebo arm. There was only one direct comparison, between ixekizumab (IXE) and adalimimab (ADA) from a three-arm trial with placebo. The effect size for all treatments compared with placebo were similar and in the direction of protection, generally with wide 95% CIs: anti-TNF mAbs: IRR 0.32, 95% CI 0.10–1.04; etanercept (ETN): IRR 0.42, 95% CI 0.08–2.38; anti–IL-17: IRR 0.43, 95% CI 0.19–0.98; and JAKi: IRR 0.32, 95% CI

Table 1. Characteristics of the included randomized controlled trials*

Study Name	Year	Study duration, weeks	Intervention name	Intervention dose, mg	Intervention (n)	History of uveitis intervention (n)	Comparator name	Comparator (n)	History of uveitis comparator (n)
Van der Heijde D et al. (16)	2006	24	Adalimumab	40 mg/2 wk	208	68	PBO	107	27
Sieper J et al. (ABILITY-1) (17)	2013	12	Adalimumab	40 mg/2 wk	91	12	PBO	94	10
Huang F et al. (18)	2014	12	Adalimumab	40 mg/2 wk	229	5	PBO	115	5
Haibel H et al. (19)	2008	12	Adalimumab	40 mg/2 wk	22	4	PBO	24	1
Landewé R et al. (RAPIDAxSpA) (20)	2014	24	Certolizumab	200 mg/2 wk	203	NR	PBO	107	NR
Deodhar A et al. (C-AxSpAnd) (21)	2019	52	Certolizumab	400 mg at wk 0, 2, 4, then 200 mg/2 wk	159	28	PBO	158	36
Inman R et al. (GO-RAISE) (22)	2008	24	Golimumab	50 mg/4 wk or 100 mg/4 wk	278	58	PBO	78	25
Deodhar A et al. (GO-ALIVE) (23)	2018	16	Golimumab	2 mg/Kg IV at week 0, 4, 12 then/8 wk	105	NR	PBO	103	2
Sieper J et al. (GO-AHEAD) (24)	2015	16	Golimumab	50 mg/4 wk	98	NR	PBO	100	NR
Bao C et al. (25)	2014	24	Golimumab	50 mg/4 wk	108	NR	PBO	105	NR
Van der Heijde D et al. (ASSERT) (26)	2005	24	Infliximab	5 mg/kg at wk 0, 2, 6, 12 and 18	201	72	PBO	78	25
Barkham N et al. (27)	2009	16	Infliximab	5 mg/kg at wk 0, 2, 6, and 12	20	NR	PBO	20	NR
Inman R et al. (28)	2010	46	Infliximab	3 mg/kg at wk 0, 2, and 6	39	NR	PBO	37	NR
Marzo-Ortega et al. (29)	2005	30	Infliximab	5 mg/kg at wk 0, 2, 6, 12, and 22	28	NR	PBO	14	NR
Sieper J et al. (INFAST) (30)	2014	28	Infliximab	5 mg/kg at wk 0, 2, 6, 12, 18, and 24	106	NR	PBO	52	NR
Braun J et al. (31)	2002	12	Infliximab	5 mg/kg at wk 0, 2, and 6	35	17	PBO	35	15
Gorman JD et al. (32)	2002	16	Etanercept	25 mg twice/wk	20	NR	PBO	20	NR
Davis JC et al. (33)	2003	24	Etanercept	25 mg twice/wk	138	39	PBO	139	43
Brandt J et al. (34)	2003	12	Etanercept	25 mg twice/wk	16	5	PBO	17	3
Calin A et al. (35)	2004	12	Etanercept	25 mg twice/wk	45	NR	PBO	39	NR
Van der Heijde D et al. (36)	2006	12	Etanercept	25 mg twice/wk or 50 mg/wk	305	33	PBO	51	4
Barkham N et al. (37)	2010	12	Etanercept	25 mg twice/wk	20	NR	PBO	20	NR
Dougados M et al. (SPINE) (38)	2011	12	Etanercept	50 mg/wk	39	13	PBO	43	12
Dougados M et al. (39)	2014	12	Etanercept	50 mg/wk	106	8	PBO	109	9
Dougados M et al. (SPARSE) (40)	2014	8	Etanercept	50 mg/wk	42	5	PBO	48	3
Deodhar A et al. COAST-W (41)	2019	16	Ixekizumab	80 mg/2 wk or 80 mg/4 wk	212	NR	PBO	104	NR
Van der Heijde D et al. COAST-V[a] (42)	2018	16	Ixelizumab	80 mg/2 wk or 80 mg/4 wk	164	38	PBO	87	14
	2018	16	Adalimumab	40 mg/2 wk	90	19			
Deodhar A et al. COAST-X (43)	2020	52	Ixekizumab	80 mg/2 wk or 80 mg/4 wk	198	22	PBO	104	12
Baeten D et al. (44)	2013	28	Secukinumab	IV 10 mg/kg/3 wk	24	7	PBO	6	2
Baeten D et al. (MEASURE1) (45)	2015	16	Secukinumab	IV 10 mg/kg at wk 0, 2, 4 then SC 150 or 75 mg/4 wk	249	40	PBO	122	22
Baeten D et al. (MEASURE2) (45)	2015	16	Secukinumab	150 or 75 mg at wk 1, 2, 3, then/4 wk	145	21	PBO	74	13
Pavelka K et al. (MEASURE3) (46)	2017	52	Secukinumab	IV 10 mg/kg at wk 0, 2, 4 followed by SC 300 mg or 150 mg/4 wk	150	NR	PBO	75	NR
Kivitz A et al. (MEASURE4) (47)	2018	104	Secukinumab	150 mg at wk 0, 1, 2, 3, then/4 wk	233	44	PBO	117	27

(Continued)

Table 1. (*Cont'd*)

Study Name	Year	Study duration, weeks	Intervention name	Intervention dose, mg	Intervention (n)	History of uveitis intervention (n)	Comparator name	Comparator (n)	History of uveitis comparator (n)
Deodhar A et al. (PREVENT) (48)	2021	52	Secukinumab	150 mg at wk 0, 1, 2, 3, then/4 wk	369	47	PBO	186	18
Huang F et al. (MEASURE 5) (49)	2020	16	Secukinumab	150 mg at wk 0, 1, 2, 3, then/4 wk	305	NR	PBO	153	NR
Van der Heijde D et al. (BE MOBILE1) (50)	2023	24	Bimekizumab	160 mg/4 wk	128	19	PBO	126	21
Van der Heijde D et al. (BE MOBILE2) (50)	2023	24	Bimekizumab	160 +mg/4 wk	221	33	PBO	111	24
Van der Heijde D et al. (BE AGILE)[b] (51)	2020	48	Bimekizumab	160 mg/4 wk	58	15	PBO	60	15
Deodhar A et al. (52)	2021	16	Tofacitinib	5 mg twice day	133	28	PBO	136	25
Van der Heijde D et al. (53)	2017	16	Tofacitinib	5 mg twice day	52	12	PBO	51	7
Van der Heijde D et al. (SELECT-AXIS 1) (54)	2019	14	Upadacitinib	15 mg once day	93	NR	PBO	94	NR
Deodhar A et al. (SELECT-AXIS 2) (55)	2022	14	Upadacitinib	15 mg once day	156	12	PBO	157	11
Van der Heijde A et al. (SELECT-AXIS 2) (56)	2022	14	Upadacitinib	15 mg once day	211	21	PBO	209	15
Van der Heijde A et al. (TORTUGA) (57)	2018	12	Filgotinib	200 mg once day	58	NR	PBO	58	NR

* AxSpA, axial spondyloarthritis; IV, intravenous; NR, not reported; PBO, placebo; SC, subcutaneous.
[a] COAST-V trial had three arms (ixelizumab, adalimumab, and PBO).
[b] BE AGILE had another four arms of bimekizumab 16 mg, 64 mg, 160 mg, and 320 mg dose. The 160 mg dose was only included in the analysis for consistency with other bimekizumab trials on AxSpA.

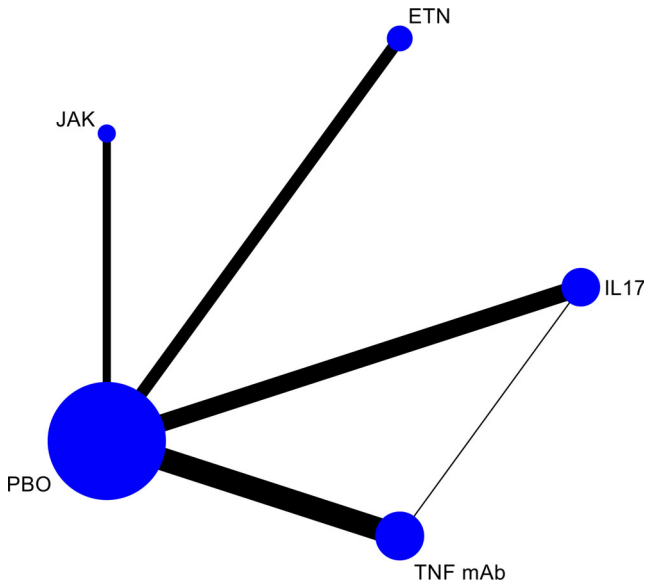

Figure 1. Network plots of NMA showing the number of studies for each treatment (blue node size) and number of treatment comparisons (black line thickness) in the included RCTs. NMA is an extension of pairwise meta-analysis, in which treatments can be compared by indirect comparisons across studies based on a common comparator (ie, placebo). It facilitates the comparison of treatments in a connected network, ie, as TNF mAb and anti–IL-17 were compared with placebo in different RCTs, their risk of uveitis with TNF mAb and anti–IL-17 can be estimated indirectly via their common relationship with placebo. A valid NMA should satisfy the assumption of transitivity, that there are no systematic differences between the studies other than the treatments being compared and demonstrate consistent results with pairwise meta-analysis, representing agreement between direct and indirect comparisons. Anti–IL-17, anti-interleukin 17; ETN, Etanercept; JAK, Janus kinase; mAb, monoclonal antibodies; NMA, network meta-analysis; PBO, placebo; RCT, randomized control trial; TNF, tumor necrosis factor.

0.06–1.67 (Figure 2). The IL-17 class was the only group to demonstrate a statistically significant lower IRR compared to placebo. Indirect comparisons between the treatment arms using NMA did not demonstrate any significant difference in the risk of AU between the different treatments.

Using the SUCRA approach to rank AU risk between treatments, all treatments ranked superior to placebo. The SUCRA rankings were similar between anti-TNF mAbs, JAKi, anti–IL-17, and etanercept with no clear superiority among the drugs (Supplementary Material 3).

Pairwise meta-analysis of treatment groups compared with placebo demonstrated similar effect-size estimates to the NMA (Supplementary Figure 4). The "leave-one-out" analysis, which systematically removes one study at a time and presents the summary effect estimates without that study, did not demonstrate any undue influence of individual studies on pooled estimates (Supplementary Figure 5).

There was little evidence of asymmetry on visual examination of the funnel plot. Egger's test was significant for indicating the presence of small sample effects, potentially due to publication bias. However, pooled effects remained statistically significant when adjusted for small sample effects using the precision-effect test and precision-effect estimate with standard errors (PET-PEESE) approach. Thus, any potential publication bias does not make a substantive difference to the conclusion that treatments are protective compared to placebo (Supplementary Material 6).

Sensitivity analysis. In an intention-to-treat (ITT) analysis, pooled estimates of IRs of AU with anti-TNF mAbs, etanercept, and anti–IL-17 were similar to the PP analyses, whereas the IRs were higher with JAKi (ITT IR: 3.7, 95% CI 0–7.7 versus PP IR 1.5, 95% CI 0.0–3.0). Indirect comparisons between the treatment arms in NMA did not demonstrate any significant differences in risk of AU between the different treatments. The effect size of the IRRs for all treatments compared to placebo remained in the direction of protection but were not statistically significant (Supplementary Figure 7).

Restricting to studies that had a low risk of bias (26 studies) continued to demonstrate similar findings to the main analysis with no difference in risk of AU between treatment arms. When treatment arms were compared with placebo, the direction of the effect for all treatments was toward protection; however, the effect sizes were not statistically significant (Supplementary Figure 8).

Restricting analyses to studies that reported on uveitis events (26 studies) (Supplementary Figure 9) and restricting to studies with >10% of the population reporting a history of AU (21 studies) (Supplementary Figure 10) demonstrated no difference in risk of AU between the treatment arms. The effect size of the IRRs of anti-TNF mAbs, etanercept, anti–IL-17, and JAKi compared to placebo were in the same direction.

DISCUSSION

Using combined data from the AxSpA clinical trial programs for multiple licensed biologic or targeted synthetic DMARDs, we demonstrated the incidence of AU in AxSpA from 1 to 5 per 100 person-years in those on treatment and 11 per 100 person-years in those from the placebo groups in RCTs. Our indirect comparisons between the treatment arms using NMA did not demonstrate any significant difference in risk of AU between different treatment modalities.

When interpreting this NMA, we must consider the rarity of AU events and acknowledge that small differences in event rates could shift the overall findings. Our NMA has demonstrated a statistically significant reduction in AU risk with anti–IL-17 class compared to placebo. The protective effect of IL-17 was confirmed in sensitivity analysis limited to studies enriched with individuals with past uveitis, which supports that this observation may be genuine. Nonetheless, this finding should be interpreted with caution. Although not statistically significant, the point estimates for AU risks with anti-TNF mAbs and JAKi were very similar to that seen

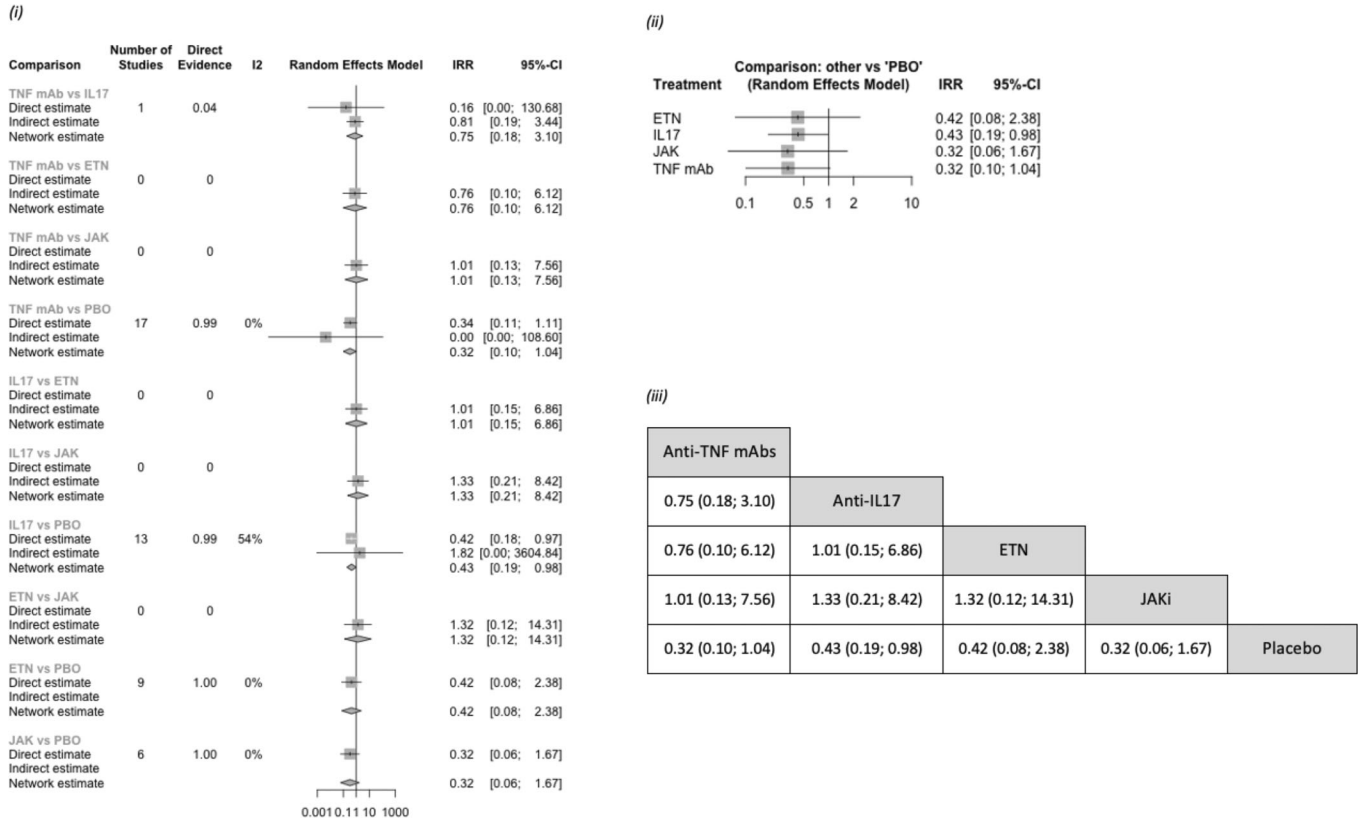

Figure 2. Network meta-analysis, using a PP approach to calculate exposure. (*i*) Forest plot of direct, indirect, and network IRR estimates of comparisons between all treatments. (*ii*) Forest plot of network IRR estimates of comparisons between treatments and placebo. (*iii*) Summary table of network IRR estimates of comparisons between all treatments. The referent group for comparisons is the treatment arm appearing at the end of the row; ie, in the first row of estimates the referent is anti–IL-17, in the second row the referent is ETN, in the third row the referent is JAK, and in the fourth row the referent is placebo. ETN, Etanercept; anti–IL-17, anti-interleukin 17; 95% CI, 95% confidence interval; IRR, incidence rate ratio; JAK, Janus kinase; mAb, monoclonal antibodies; PBO, placebo; PP, per-protocol; TNF, tumor necrosis factor.

with anti–IL-17. The direction of these effects was large and consistent across sensitivity analyses. In the SUCRA ranking, although there was little difference between the drugs, anti-TNF mAbs and JAKi ranked superior to anti–IL-17. Furthermore, the results from the pairwise analysis of direct comparisons with placebo were more consistent with the SUCRA ranking, with anti-TNF mAbs and JAKi demonstrating a statistically significant protection against AU.

All three classes of drug (anti-TNF mAbs, anti–IL-17, and JAKi) have mechanistically plausible reasons to be associated with a lower rate of AU. The protective effects of anti-TNF mAbs have been demonstrated in multiple observational studies.[6,8] We have shown that etanercept does not exhibit the same protective qualities. This has been reported in other rheumatic diseases with RCTs specifically designed to compare anti-TNF mAb with etanercept.[58] Differences in TNF receptor unit inhibition,[59] cytokine modulation of T-cell responses,[60] and pharmacokinetics of the drug are potential explanations. The protective effect of JAKi is less well documented. Phase II studies in idiopathic AU have shown a reduction in the risk of uveitis flare,[61] whilet case report and case series in juvenile idiopathic arthritis (JIA) patients with recalcitrant AU have reported success.[62,63] A phase III clinical trial evaluating baricitinib in JIA AU is ongoing.[64] Mechanistically, it is not surprising that JAKi are efficacious against AU. The JAK pathway plays a key role in inflammatory cell regulation, cytokine production, and proinflammatory signal transduction. Animal studies in experimental AU have established a mechanism of action, with inhibition of pathogenic Th1 cells, reducing interferon-γ and strengthening the development of the Th-17 cell.[65]

RCTs using IL-17A in noninfectious uveitis have been disappointing. Despite an early proof-of-concept study suggesting some beneficial effects with secukinumab in the treatment of uveitis,[66] results from three RCTs in a heterogeneous AU population did not report any difference in efficacy compared with placebo.[5] A phase II clinical trial did find that higher doses and intravenous delivery of secukinumab were associated with higher responder rates and remission of uveitis, suggesting subcutaneous administration may not be sufficient.[67] In animal models, the expression of IL-17 correlates with the onset of uveitis and upregulates TNF-α in retinal cells, contributing to the pathogenesis of the disease.[68] Interestingly, in mice models, blocking IL-17A

did not reduce the pathogenicity of TH17 cells, but instead elevated their expression of granulocyte-macrophage colony-stimulating factor and IL-17F.[69] This may suggest that inhibition of IL-17F in addition to IL-17A could provide additional protection against AU.

The results of this study contrast those of the NMA published by Roche et al,[11] which reported a decreased incidence of AU with anti-TNF mAb compared with anti–IL-17A (odds ratio 0.34, 95% CI 0.12–0.92). There are several likely explanations for why we did not observe similar findings. The first relates to our inclusion of data from recently published bimekizumab studies, which reported a lower incidence of AU relative to placebo (4 vs 11 events, respectively, across combined studies). Long-term safety analyses from bimekizumab phase II trials in AxSpA[70] continue to report a lower IR of AU, whereas safety data from psoriatic arthritis trials have not reported any cases of AU.[29,30] The difference in mechanism of action between the drugs that target IL-17A versus those targeting IL-17AF may provide some explanation for the lower rate of AU in the bimekizumab trials. Second, there are differences in the methodologies used between our study and Roche et al. We used a PP approach to calculate exposure time, which can have advantages when examining safety signals. The PP approach calculates event rate per time exposed to the drug, rather than event rates as a proportion of initiation allocation to study arms. A PP approach helps to ensure no apparent safety signal is missed if one is present. We acknowledge that, in most studies, the placebo arm follow-up is short with patients in the placebo arm switching over the treatment group at week 12, which means that there is an imbalance in exposure time that could lead to bias toward a null result. It is notable that placebo exposure time has gradually reduced in clinical trials as it becomes ethically less acceptable to leave patients on a placebo in an AxSpA RCT. Our sensitivity analyses using an ITT model are consistent with this, with wider CIs for the observed treatment effects.

The PET-PEESE approach, which accounts for small sample effects, increased (instead of reduced) the magnitude of the pooled effect for each treatment against placebo. This finding was likely due to smaller studies being more likely to have zero events in one (or both) arms, and thus a continuity correction being applied, which biases estimates at the study level toward the null. Irrespectively, the PET-PEESE approach indicates that publication bias is unlikely to be a major cause for concern. If anything, the estimates are conservative, and the true effect is potentially larger than reported.

Our systemic review has several strengths. Despite the included RCTs spanning a period of two decades, the trials were relatively homogenous. The "leave one out" analyses did not demonstrate any single influential study that was dominating the pooled estimates. Because we considered AU a safety signal, we employed a PP analysis that increased the duration of time exposed to a treatment and therefore the likelihood for an event to occur. We feel this is a robust method for evaluating safety events and is a strength of this study.

There are a number of important limitations. First, several studies did not report AU. In these cases, we assumed that there were no AU events, which may not have been true, and the incidence of AU could have been underestimated. Comparison between treatment arms and placebo are unlikely to be affected, but this may impact indirect comparison between therapies, particularly as older anti-TNF mAbs and etanercept studies were less likely to report on AU compared with more recent anti–IL-17 and JAKi RCTs. Our sensitivity analysis restricting to studies that reported on AU events demonstrates similar findings. Second, we did not have access to the precise definition of an AU flare, which is reliant on a window of time without any AU diagnosis, particularly in those with known AU disease, and likely varied between studies. Third, over a third of studies did not report on prior history of AU. A prior history of AU is a major risk factor for de novo AU events. It is thus crucial to take into consideration the proportion of patients with AU history in each study and across treatment arms. In individual studies that did report on AU history, there were imbalances between the treatment and placebo groups, whereas across all studies the proportion of patients with an AU history ranged from 3% to nearly half the cohort. Fourth, we present data on over 3,000 person-years of exposure to treatment, though the anti-TNF mAbs and anti–IL-17 are the major contributors to exposure time. We only present 1,300 person-years of exposure to placebo, reflecting the short duration of placebo exposure in most RCTs. Fifth, the proportion of RCTs with zero events in our study is high, with unbalanced exposure time. The choice of a fixed continuity correction increases the variance of the pooled IRR estimate and could have influenced our results. The addition of continuity correction can affect the assessment of heterogeneity, and it becomes more challenging to determine whether the heterogeneity observed is due to true treatment differences or a consequence of the correction. Last, it is crucial to acknowledge the limitations of NMA methodology, and that, in the absence of direct comparisons within clinical trials, interpretation of our results must be made with caution.

In conclusion, for individuals with AxSpA, anti-TNF mAbs, JAKi, and anti–IL-17 appear protective against AU events. Compared with placebo, a statistically significant reduction in AU risk is seen with the anti–IL-17 class. There is no difference in AU risk between the different treatment modalities. Our findings do not support the recommendation for preferential use of anti-TNF mAbs over JAKi or anti–IL-17.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bechman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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