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Inflammatory Bowel Disease Risk in Patients With Axial Spondyloarthritis Treated With Biologic Agents Determined Using the BSRBR-AS and a MetaAnalysis

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ABSTRACT. ***Objective.*** To determine, among patients with axial spondyloarthritis (axSpA), whether the risk of inflammatory bowel disease (IBD) varies between patients treated with biologic therapies and those treated with other therapies and, specifically, whether the risk is higher in patients treated with etanercept (ETN).

Methods. The British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) was used to determine the incidence of IBD during follow-up and to calculate the incidence rate difference (IRD) per 1000 person-years (PY), between biologic treatment and other treatment groups. We then conducted a systematic review, involving observational studies and randomized controlled trials (RCTs), to perform a metaanalysis to quantify the difference in incidence of IBD between treatment groups.

Results. According to the BSRBR-AS, among people with axSpA, exposure to biologic therapy was associated with an increased incidence of IBD compared to those who were not exposed to biologic therapy (IRD 11.9, 95% CI 4.3-19.6). This finding was replicated across observational studies but was not seen in placebo-controlled RCTs (IRD 2.2, 95% CI −4.1 to 8.5). Data from the BSRBR-AS do not suggest that excess incidence of IBD is associated with exposure to ETN compared to other anti–tumor necrosis factor (TNF) therapies (IRD −6.5, 95% CI −21.3 to 8.5). RCTs and their extensions suggest a small—yet not statistically significant—absolute increased incidence associated with ETN of between 2.1 and 5.8 per 1000 PY compared to other anti-TNF therapies.

Conclusion. There was an excess risk of IBD among persons treated with biologics in observational studies. Only evidence from RCTs suggested that ETN was associated with an increased risk compared to other anti-TNF therapies, albeit with considerable uncertainty.

Key Indexing Terms: axial spondyloarthritis, biologics, etanercept, inflammatory bowel disease, metaanalysis, tumor necrosis factor

Inflammatory bowel disease (IBD) is one of the extramusculoskeletal manifestations (EMMs), formerly called extraarticular manifestations, associated with axial spondyloarthritis (axSpA). In a metaanalysis of 69 studies involving 30,410 patients with radiographic axSpA, Stolwijk et al[1] reported a pooled prevalence of 6.8% (95% CI 6.1-7.7%). A further metaanalysis of studies comparing prevalence in radiographic versus nonradiographic axSpA reported a prevalence of IBD that was marginally lower in the former (−1.4%, 95% CI −2.9 to 0.1%).[1,2]

The prevalence of IBD in the British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS), which comprises 2 cohorts of patients with axSpA starting their first biologic therapy and those naïve to such therapy, has been reported as 10.2%.[3] The same report found that being HLA-B27 negative was the only clinical factor associated with the diagnosis of IBD. Among the cohort who were commencing anti–tumor necrosis factor (TNF) therapy, patients with IBD were much less likely to have been prescribed etanercept (ETN; ie, a soluble fusion protein) in comparison to the monoclonal antibodies in this cohort (ie, adalimumab [ADA], certolizumab pegol [CZP], and golimumab [GOL]; odds ratio [OR] 0.4, 95% CI 0.2-0.6). A large study from Denmark of approximately 80,000 patients with an autoimmune disease other than IBD, for which anti-TNF therapy is an indication, compared incident IBD according to therapy.[4] Patients who had been treated with ETN had a significantly elevated risk of Crohn disease (hazard ratio [HR] 2.0, 95% CI 1.4-2.8) and ulcerative colitis (HR 2.0, 95% CI 1.5-2.8), an excess that was not observed with other anti-TNF agents.

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The aim of the current study was to use the BSRBR-AS to determine whether the incidence of IBD varies between patients treated with biologic therapy and those treated with other therapies; specifically, we aimed to determine whether the incidence is higher in patients treated with ETN. We then combined the results with a metaanalysis of other studies identified by means of a systematic review to quantify any excess risk and uncertainty.

METHODS

BSRBR-AS. The UK-wide BSRBR-AS is a registry that recruited patients meeting Assessment of SpondyloArthritis international Society criteria for axSpA from 83 secondary care centers across Great Britain, between December 2012 and December 2017, and with follow-up until June 2018. Details of the study have previously been published.[5] All patients were naïve to biologic therapy at the time of recruitment; those who were about to commence an eligible biologic therapy were recruited to a biologic cohort, whereas those remaining on conventional therapy were recruited to a nonbiologic cohort. Different biologic therapies became eligible for recruitment at different times during the conduct of the study. Patients were followed up yearly, with additional follow-ups at 3 and 6 months after recruitment for the biologic cohort. At recruitment and at each study follow-up, clinical information on IBD events was collected by trained research nurses: specifically, whether a diagnosis had been made and whether treatment had been prescribed. For the current analysis, participants were eligible provided that (1) information had been recorded in relation to IBD status; (2) they did not have a diagnosis of, or treatment for, IBD either at the time of, or up to 2 months after, recruitment; and (3) they had at least 1 follow-up. As the study involved analysis of risk of IBD associated with individual drugs, among those in the biologic cohort, participants who received multiple biologic drugs were not included.

Clinical information recorded on BSRBR-AS participants included disease duration (ie, time from symptom onset), HLA-B27 status, presence of extraarticular manifestations (ie, uveitis, psoriasis, enthesitis, peripheral joint disease, and dactylitis), and inflammation (ie, C-reactive protein, erythrocyte sedimentation rate, and BMI). Additionally, disease severity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which is scored from 0 (best) to 10 (worst),[6] and the burden of comorbidities by means of a simple count of the presence of 14 clinical conditions.

Both subcohorts—biologic and nonbiologic—were followed up, and the number of incident IBD events were recorded. An exposure time interval, expressed in person-years (PY), was calculated as the time difference between 2 months after the start date of therapy, in the biologic cohort, or 2 months after the recruitment date, in the nonbiologic cohort, and either an IBD event or the date of last follow-up, whichever came first. Only a single case of IBD occurred in the 2-month time window from study entry or start of the biologic drug, not counted in the follow-up. The incidence rate (IR) of IBD events, expressed as cases per 1000 PY, was calculated for both cohorts and by individual biologic drug used. CIs were calculated using the Byar method.[7] Incidence rate ratios (IRRs), and incidence rate differences (IRDs) per 1000 PY, were used to compare treatment cohorts.

Since observational studies are prone to confounding by indication, we conducted a propensity analysis, which takes into account the factors associated with receiving biologic therapy. Univariable logistic regression was performed to establish whether there was an association between baseline variables (ie, clinical and patient-reported variables) and membership in the biologic cohort. Forward stepwise regression was used and identified a group of variables associated with treatment (model entry at $P \leq 0.10$ and removal at $P > 0.15$). The probability of receiving biologic treatment (ie, the propensity score) was determined from the model. Discriminatory ability of the model was assessed by a receiver-operating characteristic curve, sensitivity, specificity, and percentage of correct classified participants. Cox proportional hazard models were used to determine whether there was an association between treatment and incident IBD.[8] First, a model tested the crude association, then the model was adjusted for the quintiles of the propensity score. Schoenfeld residual tests were performed to check whether the hazards were proportional in these models.

All analyses were performed in Stata (version 15; StataCorp LLC) and OpenEpi (https://www.openepi.com/) using the December 2018 (ie, final data) download of the BSRBR-AS. The study received ethical approval from the UK National Research Ethics Service Committee North-East – County Durham and Tees Valley (Research Ethics Committee reference 11/NE/0374), and all participants provided written informed consent.

Metaanalysis. To quantify the risk of developing IBD in patients with axSpA while under treatment with biologic agents, a systematic literature review (SLR) was conducted. A search of articles published up to the second week of July 2021 in PubMed, Embase, the Cochrane Library, and Web of Science was performed, using key terms and MeSH descriptors for axSpA, anti-TNF monoclonal antibody, and IBD. Additionally, a list of relevant randomized controlled trials (RCTs) that are not currently published—and are, therefore, not searchable within the above databases—were identified through www.ClinicalTrials.gov. After an initial search, the resultant list of publications was checked for eligibility using a 3-stage approach, which involved screening manuscript titles, abstracts, and full texts. Screening of titles and abstracts was performed by 2 researchers (O. Rotariu and RB), and discrepancies were discussed with a third author (LED), who acted as an adjudicator. Screening of full texts was performed by the same 2 researchers, with cross-checking of a random 10% of full texts by LED. Any discrepancies were discussed and resolved by group consensus. Published reviews, metaanalyses, and conference abstracts identified by the search were used to identify additional studies. Screening of titles and abstracts was not applied to RCTs, with these proceeding immediately to the full-text stage.

To be considered for inclusion, the published study had to meet the following criteria: it included a population with ≥ 1 group of adult patients, aged ≥ 17 years, who were clinically diagnosed with radiographic or nonradiographic axSpA or who met recognized international criteria; some patients diagnosed with axSpA were treated with a biologic agent; information on the number, proportion, and rate of new-onset IBD cases was presented, which allowed an effect measure to be extracted or calculated; for RCTs, the observation arm was placebo-controlled, and any open-label extensions (OLEs) or extended treatment periods (ETPs) described a constant observation period without any break between the RCT and extension phases; and for observational studies, there was ≥ 1 comparator arm. After the final list of included studies had been identified, their reference lists were manually searched for additional relevant studies.

Eligible studies were categorized into 3 types: RCTs, OLEs or ETPs, and observational studies with comparator arm (OSCAs). Data extraction was performed using a predefined form, undertaken by 1 researcher (RB) and cross-checked by a second researcher (O. Rotariu), with any discrepancies discussed until a consensus was reached. Where there was no mention of IBD in a paper, it was excluded from the primary analysis. In situations where there were IBD cases recorded but there was uncertainty as to whether they were new-onset IBD or flares of existing IBD, these studies were excluded from the primary analysis. We then conducted 2 separate sensitivity analyses in which these cases were (1) all considered to be new onset, and (2) all considered to be flares. In situations where there was no mention of IBD in the paper but other EMMs were recorded, we included these studies in the sensitivity analyses in relation to RCTs and OLEs, assuming that no cases of IBD were recorded. The quality of certainty of the evidence of the included studies was addressed using version 2 of the Cochrane risk-of-bias tool for RCTs and the ROBINS-I tool (Risk of Bias in Non-randomized Studies - of Interventions) for OLEs, ETPs, and OSCAs.[9,10]

For RCTs and OLE or ETP studies, IRs of IBD were calculated—expressed as the number of cases per 1000 PY—for each relevant study arm. In the event that exposure time was missing for noncompleters, this

was estimated assuming that the participants who did not complete the study were exposed for half of the total study duration. The comparison of the rates of developing IBD among different groups is expressed as both an IRR and an IRD. For OSCAs, ORs were calculated to compare the patients treated with biologics with those not treated with biologics. Mantel-Haenszel estimators with fixed effects were used to estimate a pooled effect size.[7] Additional comparisons were made in relation to ETN vs placebo, vs other anti-TNF agents, and vs interleukin 17 (IL-17) agents, according to study type and available data.

RESULTS

Registry data. There were 1851 eligible patients in the BSRBR-AS; 69.2% were male, and the median age was 47.0 (IQR 36.0-59.0) years. Out of these patients, 42.8% (n = 793) were commencing biologic therapy. Patients in the biologic cohort were, on average, younger with shorter axSpA duration, higher inflammatory markers, and poorer disease activity scores (BASDAI; Table 1). A lower proportion of the biologic cohort

Table 1. Characteristics of eligible patients in BSRBR-AS.

	Treated With Biologics, n = 793	Not Treated With Biologics, n = 1058
Demographic factors		
Age, yrs, median (IQR)	43.1 (33.8-53.4)	50.6 (38.9-62.2)
Gender		
Female	238 (30.0)	333 (31.5)
Male	555 (70.0)	725 (68.5)
Clinical factors		
HLA-B27		
Negative	99 (19.9)	126 (16.4)
Positive	398 (80.1)	642 (83.6)
Uveitis		
Not present	611 (77.1)	792 (74.9)
Present	182 (22.9)	266 (25.1)
Psoriasis		
Not present	705 (88.9)	970 (91.7)
Present	88 (11.1)	88 (8.3)
Enthesitis		
Not present	706 (89.0)	967 (91.4)
Present	87 (11.0)	91 (8.6)
Peripheral joint disease		
Not present	635 (80.1)	898 (84.9)
Present	158 (19.9)	160 (15.1)
Dactylitis		
Not present	757 (95.5)	1022 (96.6)
Present	36 (4.5)	36 (3.4)
Symptom duration		
Patients	793 (100)	1058 (100)
Years, median (IQR)	12.0 (5.0-23.0)	20.0 (10.0-33.0)
Disease activity: BASDAI		
Patients	653 (82.3)	856 (80.1)
BASDAI score[a], median (IQR)	6.4 (4.9-7.5)	3.2 (1.7-5.2)
Inflammation: CRP		
Patients	670 (84.4)	782 (73.9)
CRP, mg/dL, median (IQR)	0.7 (0.2-2.2)	0.5 (0.1-1.7)
Inflammation: ESR		
Patients	366 (46.2)	334 (31.6)
ESR, mm/h, median (IQR)	12.5 (5.0-27.0)	8.5 (5.0-19.0)
BMI		
Patients	654 (82.5)	914 (86.4)
BMI, kg/m^2, median (IQR)	27.0 (24.0-31.0)	26.7 (23.9-30.2)
Comorbidities[b]		
Patients	787 (99.2)	1054 (99.6)
No. of comorbidities, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-1.0)

Data are in n (%) unless otherwise indicated. [a] Disease activity scores on the BASDAI range from 0 (best) to 10 (worst). [b] List of comorbidities, including those related to cardiovascular, respiratory, gastrointestinal, renal, and neurological conditions, are as follows: myocardial infarction, angina, heart failure, stroke, hypertension, diabetes, asthma, bronchitis, liver disease, renal disease, tuberculosis, demyelination, depression, and cancer. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BSRBR-AS: British Society for Rheumatology Biologics Register in Ankylosing Spondylitis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

were HLA-B27 positive (80.1% vs 83.6%); more patients in the cohort reported psoriasis, enthesitis, and peripheral joint disease; and fewer reported uveitis. There was little difference between the biologic and nonbiologic cohorts in terms of gender, BMI, number of comorbidities, or proportion with dactylitis. Among the 793 patients commencing biologic therapy, the majority were prescribed adalimumab (n = 454, 57.3%) or ETN (n = 253, 31.9%), with smaller numbers prescribed CZP (n = 63, 7.9%), secukinumab (SEC; n = 9, 1.1%), and GOL (n = 13, 1.6%), and 1 patient (0.1%) was prescribed infliximab (IFX).

Participants were followed up for up to 60 months, and within that time 35 incident cases of IBD were recorded. There were significantly more cases in the biologic cohort (22 cases; 17.0 cases per 1000 PY) compared to the nonbiologic cohort (13 cases; 5.1 cases per 1000 PY), giving an IRR of 3.3 (95% CI 1.7-6.6) and an IRD of 11.9 per 1000 PY (95% CI 4.3-19.6; Table 2). Within the biologic cohort, 6 IBD cases were recorded among those treated with ETN (13.9 cases per 1000 PY) and 16 were recorded among those treated with ADA (20.4 cases per 1000 PY). There was no significant difference in the IR of IBD between patients treated with ETN compared to those treated with nonbiologics (8.8 cases per 1000 PY, 95% CI –2.7 to 20.3), nor between patients treated with ETN compared to those treated with any other anti-TNF agent (IRD –6.5, 95% CI –21.3 to 8.5).

Multivariable regression analysis determined that 3 factors were independently associated with receiving biologic therapy: BASDAI score, symptom duration, and age. The model showed good predictive power (Supplementary Table S1, available with the online version of this article). The percentage of patients treated with biologics increased from 8.3% to 80.1% across quintiles (Supplementary Table S2). The Cox proportional hazard model showed a significant association between treatment with biologics and incident IBD (HR 2.5, 95% CI 1.2-5.1; Supplementary Table S3). Adjusting for the quintiles of the propensity score did not change the strength of the association, and the quintiles of the propensity score were not significant factors in the model (HR 1.00 for a unit increase in quintile, $P = 0.99$).

SLR and metaanalysis. A total of 6035 research articles and 213 RCTs were initially identified through the keyword search, of which 994 and 4, respectively, were removed because of duplication (Supplementary Figure S1, available with the online version of this article). Of the remaining research articles, 3978 were rejected at the title screening stage, 712 were removed during abstract screening, and 308 were removed after review of the full manuscripts. Of the 209 unique clinical trials initially identified via ClinicalTrials.gov, 19 trials were eligible, but the corresponding articles were already identified and included. All other trials (n = 190) were eventually rejected. Within the final 43 included studies, 22 were RCTs,[11-32] 19 were OLEs or ETPs of trials,[12,18,23,24,29-31,33-44] and 2 were OSCAs.[45,46] The results from the BSRBR-AS study were added to the OSCAs for pooled analysis. Half of the RCTs had a high risk of bias, and there were some concerns of bias with the others (Supplementary Figures S2 and S3). All OLEs, ETPs, and OSCAs had a serious risk of bias (Supplementary Table S4, available with the online version of this article).

Among the RCTs, a total number of 3845 participants were exposed to biologic therapy across a follow-up of 1240.7 PY, as compared to 1895 participants exposed to a placebo across a follow-up of 582.6 PY (Table 3). In total, 7 new-onset IBD events were recorded in the biologic group, and 2 were recorded in the placebo group (IR 5.6 per 1000 PY, 95% CI 2.3-11.6 vs IR 3.4 per 1000 PY, 95% CI 0.4-12.4; IRD 2.2, 95% CI –4.1 to 8.5; Table 4). Within the biologic-treated group, 2 of the incident IBD cases were noted among patients being treated with ETN (IR 8.1, 95% CI 0.9-29.4), 1 was noted among patients being treated with CZP (IR 9.5, 95% CI 0.1-52.7), 2 were noted among patients being treated with SEC (IR 5.0, 95% CI 0.6-17.9), and 2 were noted among patients being treated with ixekizumab (IR

Table 2. BSRBR-AS: incidence of IBD following use of biologic or nonbiologic therapy.

Cohort or Treatment	New-Onset IBD Cases, n	Exposure Time, PY	Incidence Rate per 1000 PY (95% CI)	Incidence Rate Ratio (95% CI)	Incidence Rate Difference (95% CI)
Cohorts					
Nonbiologic cohort, n = 1058	13	2547.6[a]	5.1 (2.7 to 8.7)	–	–
Biologic cohort[b], n = 793	22	1291.7	17.0 (10.7 to 25.8)	3.3 (1.7 to 6.6)	11.9 (4.3 to 19.6)
Biologic treatments					
ETN	6	431.3	13.9 (5.1 to 30.3)	–	–
Adalimumab	16	784.2	20.4 (11.7 to 33.1)	–	–
Certolizumab pegol	0	58.2	–	–	–
Golimumab	0	14.7	–	–	–
Infliximab	0	0.1	–	–	–
Secukinumab	0	3.2	–	–	–
Comparisons					
ETN vs nonbiologics	–	–	–	2.7 (1.0 to 7.2)	8.8 (–2.7 to 20.3)
ETN vs other anti-TNF	–	–	–	0.7 (0.3 to 1.8)	–6.5 (–21.3 to 8.5)

[a] Includes 272.2 PY, which is the contribution from the 793 biologic-treated patients before commencing therapy. [b] This cohort was treated with single-biologic therapies. Anti-TNF: anti–tumor necrosis factor; BSRBR-AS: British Society for Rheumatology Biologics Register in Ankylosing Spondylitis; ETN: etanercept; IBD: inflammatory bowel disease; PY: person-year.

Table 3. Metaanalysis of randomized controlled trials: incidence rate of IBD by type of treatment.

Reference, First Author, Year	Study Duration, Weeks	Patients Exposed, n	IBD Cases, n	Follow-up, PY	Incidence Rate per 1000 PY (95% CI)
Patients treated with placebo					
Braun, 2002[11]	12	35	0	8.1	0.0
Gorman, 2002[12]	16	20	0	5.7	0.0
Davis, 2003[13]	24	139	1	58.3	17.2 (0.2-95.4)
Brandt, 2003[14]	6	16	0	1.8	0.0
Calin, 2004[15]	12	39	0	8.7	0.0
van der Heijde, 2005[16]	24	78	0	34.8	0.0
van der Heijde, 2006[17]	24	107	0	33.0	0.0
Haibel, 2008[18]	12	24	0	5.5	0.0
Dougados, 2014[19]	8	48	0	6.2	0.0
Dougados, 2014[20]	12	109	0	24.8	0.0
Baeten, 2015[21]	16	122	0	36.5	0.0
Baeten, 2015[21]	16	74	0	21.8	0.0
Landewe, 2014[22]	24	107	1	37.7	26.5 (0.4-147.6)
Pavelka, 2020[23]	16	76	0	23.0	0.0
Kivitz, 2018[24]	16	117	0	35.7	0.0
Deodhar, 2018[25]	16	103	0	31.1	0.0
Deodhar, 2019[26]	16	104	0	30.3	0.0
van der Heijde, 2018[27]	16	87	0	26.6	0.0
van der Heijde, 2006[28]	12	51	0	11.0	0.0
Huang, 2020[29]	16	153	0	46.5	0.0
van der Heijde, 2020[30]	12	60	0	13.8	0.0
Deodhar, 2021[31]	20	186	0	69.4	0.0
Rusman, 2021[32]	16	40	0	12.3	0.0
Pooled analysis: placebo	–	1895	2	582.6	3.4 (0.4-12.4)
Patients treated with etanercept					
Gorman, 2002[12]	16	20	0	6.1	0.0
Davis, 2003[13]	24	138	1	59.2	16.9 (0.2-9)
Brandt, 2003[14]	6	14	1	6.7	149.3 (2.0-830.4)
Calin, 2004[15]	12	45	0	9.6	0.0
Dougados, 2014[19]	16	86	0	17.8	0.0
Dougados, 2014[20]	24	208	0	70.3	0.0
van der Heijde, 2006[28]	12	305	0	64.1	0.0
Rusman, 2021[32]	16	40	0	12.0	0.0
Pooled analysis: etanercept	–	856	2	245.8	8.1 (0.9-29.4)
Patients treated with other anti-TNF therapy					
Infliximab					
Braun, 2002[11]	12	34	0	7.8	0.0
van der Heijde, 2005[16]	24	201	0	92.1	0.0
Total exposed	–	235	0	99.9	0.0
Adalimumab					
van der Heijde, 2006[17]	24	280	0	108.0	0.0
Haibel, 2008[18]	12	22	0	5.1	0.0
van der Heijde, 2018[27]	16	90	0	27.4	0.0
Total exposed	–	392	0	140.5	0.0
Golimumab					
Deodhar, 2018[25]	28	204	0	79.3	0.0
Total exposed	–	204	0	79.3	0.0
Certolizumab pegol					
Landewe, 2014[22]	24	274	1	105.6	9.5 (0.1-52.7)
Total exposed	–	274	1	105.6	9.5 (0.1-52.7)
Pooled analysis: other anti-TNF	–	1105	1	425.3	2.4 (0.03-13.1)
Patients treated with IL-17 inhibitors					
Secukinumab					
Baeten, 2015[21]	16	249	0	77.2	0.0
Baeten, 2015[21]	16	145	1	43.7	22.9 (0.3-127.3)
Pavelka, 2020[23]	16	150	0	47.3	0.0
Kivitz, 2018[24]	16	233	0	71.7	0.0
Huang, 2020[29]	16	304	0	94.0	0.0
Deodhar, 2021[31]	20	184	1	69.2	14.4 (0.2-80.4)
Total exposed	–	1265	2	403.1	5.0 (0.6-17.9)

Table 3. Continued.

Reference, First Author, Year	Study Duration, Weeks	Patients Exposed, n	IBD Cases, n	Follow-up, PY	Incidence Rate per 1000 PY (95% CI)
Ixekizumab					
Deodhar, 2019[26]	16	212	2	61.7	32.4 (3.6-117.0)
van der Heijde, 2018[27]	16	164	0	49.4	0.0
Total exposed	–	376	2	111.1	18.0 (2.0-65.0)
Bimekizumab					
van der Heijde, 2020[30]	12	243	0	55.4	0.0
Total exposed	–	243	0	55.4	0.0
Pooled analysis: IL-17 inhibitors	–	1884	4	569.6	7.0 (1.9-18.0)
Pooled analysis: all biologics	–	3845	7	1240.7	5.6 (2.3-11.6)

Anti-TNF: anti–tumor necrosis factor; IBD: inflammatory bowel disease; IL-17: interleukin 17; PY: person-year.

Table 4. Metaanalysis: comparison between treatment groups.

Randomized Controlled Trials	Incidence Rate Ratio (95% CI)	Incidence Rate Difference per 1000 PY (95% CI)
Biologic vs placebo	1.6 (0.3 to 7.9)	2.2 (–4.1 to 8.5)
ETN vs placebo	2.4 (0.3 to 16.8)	4.7 (–7.5 to 16.9)
ETN vs other anti-TNF	3.5 (0.3 to 38.2)	5.8 (–6.4 to 18.0)
ETN vs IL-17	1.2 (0.2 to 6.3)	1.1 (–12.1 to 14.3)
IL-17 vs non-ETN anti-TNF	3.0 (0.3 to 26.7)	4.7 (–3.6 to 13.0)
Open-label extensions or extended treatment periods		
ETN vs other anti-TNF	3.5 (0.6 to 19.1)	2.1 (–1.0 to 5.2)
ETN vs IL-17	0.8 (0.3 to 2.4)	–0.7 (–4.0 to 2.6)
IL-17 vs non-ETN anti-TNF	4.3 (1.01 to 18.6)	2.8 (0.8 to 4.7)

Anti-TNF: anti–tumor necrosis factor; ETN: etanercept; IL-17: interleukin 17; PY: person-year.

18.0, 95% CI 2.0-65.0; Table 3). No new cases were observed among those treated with IFX, ADA, GOL, or bimekizumab. Compared to those being treated with another anti-TNF agent and those treated with an IL-17 inhibitor, the ETN group experienced an overall higher IR of IBD, although this was not statistically significant (ETN vs another anti-TNF: IRD 5.8, 95% CI –6.4 to 18.0; ETN vs IL-17 inhibitor: IRD 1.1, 95% CI –12.1 to 14.3; Table 4). There was an excess, again not statistically significant, comparing IL-17 with non-ETN anti-TNF therapy (IRD 4.7, –3.6 to 13.0). Within the OLEs and ETPs, a total of 5072 participants were exposed to a biologic agent for a total of 9313.4 PY; there were 26 incident cases of IBD (IR 2.8 per 1000 PY, 95% CI 1.8-4.1; Table 5). Overall, those treated with ETN experienced an increased incidence of IBD compared to those treated with another anti-TNF agent, as did those treated with IL-17 compared to those treated with a non-ETN anti-TNF agent. The latter difference was statistically significant (IRD 2.1, 95% CI –1.0 to 5.2; IRD 2.8, 95% CI 0.8-4.7; Table 4).

Across the 2 observational studies identified through the SLR plus the above data from the BSRBR-AS, a total of 4024 participants were exposed to a biologic agent, and 5154 were not exposed (Table 6). Over the estimated follow-up period (143-260 weeks), 168 incident cases of IBD were observed in the biologic group, and 100 cases were observed within the nonbiologic group (OR 2.2, 95% CI 1.7-2.8). Those treated with ETN demonstrated increased odds of developing IBD compared to the nonbiologic group (OR 2.4, 95% CI 1.1-5.7), but there was no difference in comparison to other anti-TNF agents (OR 0.9, 95% CI 0.4-2.1).

When we conducted sensitivity analyses taking into account uncertainties of IBD reporting, there were no substantial changes to the estimates obtained or the interpretation of the data (data not shown).

DISCUSSION

The BSRBR-AS demonstrates that, among patients with axSpA, those treated with biologic therapies are more likely to develop IBD (an excess of 11.9 per 1000 PY), and this conclusion is confirmed in the metaanalysis of observational studies. ETN did not carry a higher risk than other anti-TNF therapies. In RCTs, there was only a small (2.2 per 1000 PY) difference in IBD incidence between biologic therapy and placebo groups, whereas among patients treated with anti-TNF, there was a small excess incidence associated with ETN noted in both RCTs and OLEs (5.8 per 1000 PY and 2.1 per 1000 PY, respectively). IL-17 therapy also showed small excess risks compared to anti-TNF therapies other than ETN (4.7 per 1000 PY and 2.8 per 1000 PY, respectively).

The findings of this study need to be considered in the context of some methodological issues. First, the quality of certainty

Table 5. Metaanalysis (RCT extension studies): incidence rates of IBD per 1000 PY using data from open-label extensions and extended treatment period safety trials.

Reference, First Author, Year	Study Duration, Weeks	Patients Exposed, n	IBD Cases, n	Follow-up, PY	Incidence Rate per 1000 PY (95% CI)
Patients treated with etanercept					
Gorman, 2002[12]	43	37	0	64.8	0.0
Davis, 2008[33]	192	257	2	650.0	3.1 (0.4-11.1)
Martín-Mola, 2010[34]	264	81	2	287.0	7.0 (0.8-25.2)
Dougados, 2017[35]	104	205	0	374.0	0.0
Pooled analysis: etanercept	–	580	4	1375.8	2.9 (0.8-7.4)
Patients treated with other anti-TNF therapy					
Infliximab					
Braun, 2008[36]	254	69	0	235.6	0.0
Braun, 2008[37]	102	276	0	411.0	0.0
Total		345	0	646.6	0.0
Golimumab					
Reveille, 2019[38]	52	204	0	203.2	0.0
Total	–	204	0	203.2	0.0
Adalimumab					
Haibel, 2008[18]	52	46	0	37.4	0.0
van der Heijde, 2009[39]	104	311	1	534.0	1.8 (0.02-10.4)
Total	–	357	1	571.4	1.8 (0.02-9.7)
Certolizumab pegol					
van der Heijde, 2017[40]	204	315	1	981.0	1.02 (0.01-5.7)
Total	–	315	1	981.0	1.02 (0.01-5.7)
Pooled analysis: other anti-TNF therapy	–	1221	2	2402.2	0.83 (0.1-3.0)
Patients treated with IL-17 inhibitor therapy					
Secukinumab					
Pavelka, 2020[23]	156	223	0	602.0	0.00
Kivitz, 2018[24]	104	346	0	602.5	0.0
Huang, 2020[29]	52	453	0	457.2	0.0
Deodhar, 2021[31]	104	543	5	757.9	6.6 (2.1-15.4)
Marzo-Ortega, 2020[41]	260	211	5	842.9	5.9 (1.9-13.8)
Baraliakos, 2019[42]	260	360	6	1425.0	4.2 (1.5-9.2)
Total	–	2136	16	4687.5	3.4 (2.0-5.5)
Ixekizumab					
Dougados, 2020[43]	52	641	2	510.2	3.9 (0.4-14.2)
Deodhar, 2020[44]	52	198	1	143.5	7.0 (0.1-38.8)
Total	–	839	3	653.7	4.6 (0.9-13.4)
Bimekizumab					
van der Heijde, 2020[30]	36	296	1	194.2	5.2 (0.1-28.7)
Total exposed	–	296	1	194.2	5.2 (0.1-28.7)
Pooled analysis: IL-17 therapy	–	3271	20	5535.4	3.6 (2.2-5.6)
Pooled analysis: all biologics	–	5072	26	9313.4	2.8 (1.8-4.1)

Anti-TNF: anti–tumor necrosis factor; IBD: inflammatory bowel disease; IL-17: interleukin 17; PY: person-year; RCT: randomized controlled trial.

of the evidence revealed moderate to high levels of bias for all eligible studies. Second, the evidence came from very different study designs, which leads to distinct patterns of exposure and length of follow-up across RCTs, OLEs, and ETPs. Therefore, incidence could reasonably be hypothesized to be related to duration of exposure and the time period for which subjects remained under observation. Therefore, a direct comparison of the results obtained from these different study designs should be treated with caution; further below, we consider methodological issues that may give rise to different results between RCTs and observational studies. Third, there were issues in the reporting of IBD within published studies, such that it was sometimes unclear whether events were new onset or flares; in studies where IBD was not mentioned, it was unclear as to whether no cases had been noted or IBD was not an event of interest. It was of note, therefore, that the results were robust to assumptions made, strengthening the conclusions made by the current study. Finally, although a metaanalysis was undertaken for observational studies, the current study is by far the biggest contributor of data in relation to risk related to ETN and, therefore, strongly influences the result.

Why might results vary between RCTs and observational studies? From a design point of view, RCTs should provide the highest-quality evidence, in that treatment is randomly allocated. However, their relatively short periods of follow-up, even with OLEs, and their generally more restrictive eligibility criteria

Table 6. Comparison of treatment groups among observational studies.

	Biologic-Treated Patients, n	Nonbiologic-Treated Patients, n	Biologic-Treated IBD, n	Nonbiologic-Treated IBD, n	OR (95% CI)	Weight, %
Any biologic treatment vs no biologic treatment						
Walsh, 2018[45]	3077	3830	139	84	2.1 (1.6-2.8)	84.7
Üsküdar Cansu, 2019[46]	154	266	7	3	4.2 (1.1-16.4)	2.5
BSRBR-AS	793	1058	22	13	2.3 (1.2-4.6)	12.8
Pooled OR	–	–	–	–	2.2 (1.7-2.8)	100
Etanercept vs no biologic treatment						
Üsküdar Cansu, 2019[46]	52	266	3	3	5.4 (1.1-27.4)	15.9
BSRBR-AS	253	1058	6	13	2.0 (0.7-5.2)	84.1
Pooled OR	–	–	–	–	2.4 (1.1-5.7)	100
Etanercept vs other anti-TNF therapy						
Üsküdar Cansu, 2019[46]	52	102	3	4	1.5 (0.3-7.0)	20.2
BSRBR-AS	253	531	6	16	0.8 (0.3-2.0)	79.8
Pooled OR	–	–	–	–	0.9 (0.4-2.1)	100

Anti-TNF: anti–tumor necrosis factor; BSRBR-AS: British Society for Rheumatology Biologics Register in Ankylosing Spondylitis; IBD: inflammatory bowel disease; OR: odds ratio.

for entry may work against finding a difference in incidence of IBD even if such a difference existed. We also acknowledge that the estimated combined effects from observational studies were unadjusted; this was necessary given that individual studies adjusted for different variables. The analysis and interpretation of observational studies is susceptible to confounding by indication. In a study of approximately 21,000 patients with axSpA registered in a health insurance fund in Germany, a history of IBD was associated with higher disease activity and a greater likelihood of treatment with biologic agents—as well as conventional disease-modifying antirheumatic drugs—but lifestyle factors were similar.[47] One reasonable hypothesis, in the absence of bias and confounding, is that factors associated with prescription of biologic therapy are also associated with the risk of developing IBD. However, our propensity analysis showed that the HR for developing IBD was almost identical in unadjusted and adjusted models. As noted previously in the BSRBR-AS,[3] prior diagnosis of IBD was associated with significantly lower odds of being prescribed ETN (OR 0.3, 95% CI 0.2-0.6). In the current dataset, the only factor significantly associated with treatment with ETN was a lack of a previous history of uveitis (data not shown); therefore, a propensity analysis could not be undertaken for this. A further methodological issue to consider is the possibility of surveillance bias, namely that those who are under more intensive clinical follow-up (ie, patients treated with biologic therapy in the registry) have more opportunities for other diagnoses to be made.

Within the trials, although the combined effect measures did not show statistical differences between groups, it is of note that there was a higher IR of IBD in the group treated with biologic agents compared to those not treated with biologic agents. Also, there was a small excess risk of IBD in those treated with ETN compared to other anti-TNF therapies. ETN is not effective for the treatment of IBD, and a possible paradoxical effect of its use being associated with increased IBD onset has been postulated[48]: 438 cases were noted to have been reported to the US Food and Drug Administration Adverse Event Reporting System in a study from 2016,[49] while a further 53 cases of IBD onset after treatment with anti-TNF therapy were reported in the literature.[50] Most of the cases in the latter study were a result of treatment of juvenile idiopathic arthritis with ETN. The current study quantifies the possible excess incidence of IBD associated with the use of ETN in patients with axSpA at around 2 per 1000 PY of follow-up, based on OLEs or ETPs of trials, and around 6 per 1000 PY based on RCTs. However, it is reassuring to note that the use of ETN in routine practice does not appear to be associated with an excess risk. This suggests that patients at higher risk of developing IBD are less likely to be prescribed ETN by rheumatologists.

In summary, the relatively infrequent new onset of IBD in patients with axSpA means that even with a nationwide registry and a SLR, there still remains considerable uncertainty in the quantification of risk associated with biologic therapy, specifically ETN. However, 2 specific patterns are clear. A large excess risk evident in observational studies was not replicated in RCTs. Trials and their extensions do suggest a small absolute increased risk associated with ETN compared to other anti-TNF therapies, and with IL-17 compared to anti-TNF therapies other than ETN, although with considerable uncertainty.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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