Short running head: IBD in axSpA patients

Full title of manuscript: The risk of inflammatory bowel disease in patients with axial spondyloarthritis treated with biologic agents: BSRBR-AS and meta-analysis

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ABSTRACT

Objectives: To determine, amongst patients with axial spondyloarthritis (axSpA), whether the risk of inflammatory bowel disease (IBD) varies between patients treated with biologic and other therapies, and whether specifically the risk is higher in patients treated with etanercept.

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) between biologic treatment and other treatment groups. We thereafter conducted a systematic review (involving observational studies and randomised controlled trials) to perform a meta-analysis to quantify the difference in incidence of IBD between treatment groups.

Results: In BSRBR-AS, among people with axSpA, exposure to biologic therapy was associated with an increased incidence of IBD compared to non-exposed patients (IRD 11.9 95% CI (4.3, 19.6)). This finding was replicated across observational studies but not seen in placebo controlled RCTs IRD 2.2 95% CI (-4.1, 8.5). Data from BSRBR-AS do not suggest that excess incidence of IBD is associated with exposure to etanercept compared to other anti-TNFα therapies (IRD -6.5/1,000 pys 95% CI (-21.3, 8.5)). Trials and their extensions suggest a small (and not statistically significant) absolute increased incidence associated with etanercept of between 2.1 and 5.8 per 1,000 pys compared to other anti-TNFα therapies.

Conclusions: There was an excess risk of IBD amongst persons treated with biologics in observational studies. Only evidence from trials suggested that etanercept was associated with an increased risk compared to other anti-TNFα therapies, albeit with considerable uncertainty.

INTRODUCTION

Inflammatory bowel disease (IBD) is one of the extra-musculoskeletal manifestations (EMM), formerly called extra-articular manifestations, associated with axial spondyloarthritis (axSpA). In a meta-analysis 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% to 7.7%). A further meta-analysis of studies comparing prevalence in radiographic versus non-radiographic axSpA reported a prevalence of IBD which was marginally lower in the former -1.4% 95% CI (-2.9%, 0.1%) (1, 2).

The prevalence of IBD in the British Society for Rheumatology Biologics Register (BSRBR-AS), which comprises two cohorts of axSpA patients 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. Amongst the cohort who were commencing anti-TNFα therapy, patients with IBD were much less likely to have been prescribed etanercept (a soluble fusion protein) in comparison to the monoclonal antibodies in this cohort (adalimumab, certolizumab pegol and golimumab) (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-TNFα therapy is an indication, compared incident IBD according to therapy (4). Patients who had been treated with etanercept had a significantly elevated risk of Crohn's Disease (CD) (Hazard Ratio (HR) 2.0 95% CI (1.4, 2.8)) and Ulcerative Colitis (UC) (HR 2.0 95% CI (1.5, 2.8)), an excess which was not observed with other anti-TNFα agents.

The aim of the current study was to use BSRBR-AS to determine whether the incidence of IBD varies between patients treated with biologic therapy and those treated with other therapies, and specifically to determine whether the incidence is higher in patients treated with etanercept. We will

then combine the results with a meta-analysis 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 which recruited patients meeting ASAS criteria for axSpA from 83 secondary care centres 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" while those remaining on conventional therapy were recruited to a "non-biologic cohort". Different biologic therapies became eligible for recruitment at different times in 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 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 a) information had been recorded in relation to IBD status, b) they did not have a diagnosis of (or treatment for) IBD either at the time of (or up to two months after) recruitment and c) they had at least one follow-up. As the study involved analysis of risk of IBD associated with individual drugs, amongst those in the biologic cohort, participants who received multiple biologic drugs were not included.

Clinical information recorded on BSRBR:AS participants included disease duration (time from symptom onset), HLA-B27 status, presence of extra-articular manifestations (uveitis, psoriasis, enthesitis, peripheral joint disease, dactylitis), inflammation (c-reactive protein (CRP) or erythrocyte

sedimentation rate (ESR)), and body mass index (BMI). Additionally, disease severity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI: scored 0 (best) to 10 (worst)) (6) and the burden of comorbidities via a simple count of the presence of fourteen clinical conditions.

Both sub-cohorts (biologic/non-biologic) were followed-up and the number of incident IBD events recorded. An exposure time interval (expressed in person-years (pys)) was calculated as the time difference between two-months after the start-date of therapy (in the biologic cohort) or two months after recruitment date (non-biologic cohort), and either an IBD event or the date of last follow-up, whichever came first[1]. The incidence rate (IR) of IBD events, expressed as cases/1,000 pys, was calculated for both cohorts and by individual biologic drug used. Confidence intervals were calculated using Byar's method (7). Incidence rate ratios (IRR) and incidence rate difference (IRD) were used to compare between treatment cohorts.

Since observational studies are prone to confounding by indication, we conducted a propensity analysis which takes account of factors associated with receiving biologic therapy. Univariable logistic regression was performed to establish if there was an association between baseline variables (clinical and patient reported) and membership of the biologic cohort. Forward stepwise regression was used and identified a group of variables associated with treatment (model entry at $p \leq 0.1$ and removal at $p > 0.15$). The probability of receiving biologic treatment (propensity score) was determined from the model. Discriminatory ability of the model was assessed by a receiver operating characteristic (ROC) curve, sensitivity, specificity and percent of correct classified participants. Cox proportional hazard models were used to determine if there is an association between treatment and incident IBD (8). Firstly a model tested the crude association, then the model was adjusted for quintile of propensity

[1] Only a single case of IBD occurred in the two-month time window from study entry/start of biologic drug, not counted in follow-up.

score. Schoenfeld residual tests were performed to check if the hazard were proportional in these models (9).

All analyses were performed in STATA (StataCorp LP version 15) and OpenEpi (10) using the December 2018 (final data) download of the BSRBR-AS. The study received ethical approval from the United Kingdom National Research Ethics Service (NRES) Committee North-East – County Durham and Tees Valley (REC ref 11/NE/0374) and all participants provided written informed consent.

Meta-analysis

To quantify the risk of developing IBD in axSpA patients while under treatment with biologic agents, a systematic literature review was conducted. A search of articles published up to the second week of July 2021 in PubMed, EMBASE, Cochrane Library and Web of Science was performed, using key terms and MeSH descriptors for axial spondyloarthritis, anti TNFα/ monoclonal antibody and inflammatory bowel disease. Additionally, a list of relevant Randomized Controlled Trials (RCTs), not currently published (and so 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 three-stage approach which involved screening manuscript titles, abstracts and full texts. Screening of titles and abstracts was performed by two researchers (ORo, RB) and discrepancies discussed, with a third author (LED) who acted as an adjudicator. Screening of full texts was performed by ORo and RB with cross-checking of a random 10% by LED. Any discrepancies were discussed and resolved by group consensus. Published reviews, meta-analyses and conference abstracts identified by the search were used to identify additional studies. Title and abstract screening were 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 at least one group of adult patients (aged at least 17 years) clinically diagnosed with radiographic or non-radiographic axSpA (or meeting recognised international criteria); some patients diagnosed with axSpA were treated with a biologic agent; information on number/proportion/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 extension (OLE) / extended treatment periods (ETPs) described a constant observation period without any break between RCT and extension phases; for observational studies, there was at least one comparator arm. After the final list of included studies had been identified, the reference list of these were manually searched for additional relevant studies.

Eligible studies were categorized into three types; RCTs, OLEs/ETPs, and observational studies with comparator arm (OSCA). Data extraction was performed using a pre-defined form, undertaken by one researcher (RB) and cross-checked by a second (ORo) with any discrepancies discussed until a consensus was reached. Where there was no mention of IBD in the paper, these were excluded from primary analysis. In situations where there were IBD cases recorded but there was uncertainty as to whether they were new onset or flares of existing IBD, for the primary analysis these studies were excluded. We then conducted two separate sensitivity analyses in which these were all considered firstly to be new onset and secondly were all considered to be flares. In situations in which 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/OLEs, assuming that no cases of IBD were recorded. The quality of certainty of evidence of the included studies was addressed using the ROB2 tool for RCTs and the ROBINS-I tool for OLEs/ETPs/OSCA, respectively (11, 12).

For RCT and OLE/ETP studies; incidence rates of IBD were calculated (expressed as the number of cases per 1,000 pys) for each relevant study arm. In the event that exposure time was missing for non-completers, 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 rate of developing IBD amongst different groups is expressed both as an IRR and IRD. For OSCA, ORs were calculated comparing the biologic-treated patients with non-biologic treated patients. Mantel–Haenszel estimators with fixed effects were used to estimate a pooled effect size (7). Additional comparisons were made in relation to etanercept (vs. placebo, vs. other anti-TNF alpha agents, and vs. IL-17 agents according to study type and available data).

RESULTS

Registry data

There were 1,851 eligible patients in BSRBR-AS (69.0% male, median age 47.0 years (interquartile range (IQR) 36.0, 59.0)), of whom 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 were HLA B27 positive (80.1% v 83.6%), more reported psoriasis, enthesitis and peripheral joint disease, but fewer reported uveitis. There was little difference between the biologic and non-biologic cohorts in terms of gender, body mass index, number of comorbidities or proportion with dactylitis. Amongst those commencing a biologic therapy, the majority were prescribed adalimumab (n=454, 57.3%) or etanercept (n=253, 31.9%), with smaller numbers prescribed certolizumab pegol (n=63, 7.9%), secukinumab (n=9, 1.1%) and golimumab (n=13, 1.7%), and one patient (0.1%) were prescribed infliximab.

Participants were followed up for up to 60 months and within that time 35 incident cases of IBD were recorded. There was a significant excess in the biologic cohort (22 cases; 17.0 cases per 1,000 pys) compared to the non-biologic cohort (13 cases; 5.1 cases per 1,000 pys) giving an IRR of 3.3 95% CI (1.7, 6.6) and IRD 11.9 per 1,000 pys 95% CI (4.3, 19.6) (Table 2). Within the biologic cohort, 6 IBD cases were recorded amongst those treated with etanercept (13.9 cases per 1,000 pys) and 16 amongst those treated with adalimumab (20.4 cases per 1,000 pys). There was no significant difference in the incidence rate of IBD between patients treated with etanercept compared to non-biologic treatment, 8.8 cases per 1,000 pys 95% CI (-2.7, 20.3), nor between patients treated with etanercept compared to any other anti-TNFα agent (IRD -6.5 95% CI (-21.3, 8.5)).

Multivariable regression analysis determined three factors independently associated with receiving biologic therapy: BASDAI, symptom duration and age and the model showed a good predictive power (Table S1). The percentage of patients treated with biologics increased from 8.3% to 80.1% across quintiles (Supplementary Table S2). The Cox proportional hazard 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 quintile of propensity score did not change the strength of association, and the quintile of the propensity score was not a significant factor in the model (HR:1.002 for a unit increase in quintile, p = 0.991).

Systematic literature review and meta-analysis

A total of 6,035 research articles and 213 RCTs were initially identified through the key-word search, of which 994 and 4 respectively were removed due to duplication (Supplementary Figure S1). Of the remaining research articles, 3,978 were rejected at the title screening stage, 712 during abstract screen and 308 on reviewing 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 (13-34), 19 were OLEs or ETPs of trials (14, 20, 25-26, 31-33, 35-46) and 2 were OSCAs (47, 48). The results from the BSRBR-AS study were added to the OSCAs for pooled analysis. Half of the RCTs had a "high risk" and there was "some concerns" with the others (Supplementary Figure S2 and Figure S3). All OLE/ETPs and OSCAs had a "serious" risk of bias and that was also the case for OSCA (Supplementary Table S4).

Amongst the RCTs a total number of 3,845 participants were exposed to biologic therapy across 1,240.7 pys follow-up compared to 1,895 participants exposed to a placebo (across 582.6 pys follow-up) (Table 3). Seven new-onset IBD events were recorded in the biologic group and 2 in the placebo group (IR 5.6 per 1,000 pys 95% CI (2.3, 11.6) vs IR 3.4 per 1,000 pys 95% CI (0.4, 12.4); IRD = 2.2 95% CI (-4.1, 8.5)) (Table 4). Within the biologic group, two of the incident IBD cases were noted amongst those being treated with etanercept (IR 8.1 95% CI (0.9, 29.4)), one within certolizumab pegol patients (IR 9.5 95% CI (0.1, 52.7)), two secukinumab (IR 5.0 95% CI (0.6, 17.9)) and two ixekizumab (IR 18.0 95% CI (2.0, 65.0)) (Table 3). No new cases were observed amongst those treated with infliximab, adalimumab, golimumab or bimekizumab. Compared to those being treated with another anti-TNFα agent and those treated with an IL-17 inhibitor, the etanercept group experienced an overall higher incidence rate of IBD, although this was not statistically significant (ETA vs another anti-TNFα: IRD 5.8 95% CI (-6.4; 18.0); ETA vs IL-17 inhibitor: IRD 1.1 95% CI (-12.1; 14.3)) (Table 4). There was an excess, again not statistically significant, comparing IL-17 with non-ETA anti-TNFα therapy (IRD 4.7 (-3.6; 13.0)). Within the OLEs / ETPs, a total of 5,072 participants were exposed to a biologic agent for a total of 9,313.4 pys; there were twenty-six incident cases of IBD (IR 2.8 per 1,000 pys 95% CI (1.8, 4.1)) (Table 5). Overall, those treated with etanercept experienced an increased incidence of IBD (compared to those treated with another anti-TNFα agent), as did those treated with IL-17 (compared to those treated with a non-ETA anti-TNFα agent) with the latter difference being statistically significant (IRD 2.1 95% CI (-1.0; 5.2); IRD 2.8 95% CI (0.8, 4.7)) (Table 4).

Across the 2 observational studies identified via literature review plus the above data from BSRBR:AS, a total of 4,024 participants were exposed to a biologic agent and 5,154 not exposed (Table 6). Over the estimated follow-up period (143 weeks – 260 weeks), 168 incident cases of IBD were observed in the biologic group and 100 within the non-biologic group (OR 2.2 95% CI (1.7, 2.8)). Those treated with etanercept demonstrated increased odds of developing IBD compared to the non-biologic group (OR 2.4 95% CI (1.1, 5.7)) but there was no difference in comparison to other anti-TNFα 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, amongst patients with axSpA, those treated with biologic therapies are more likely to develop IBD (an excess of 11.9 per 1,000 pys), and this conclusion is confirmed in the meta-analysis of observational studies. Etanercept did not carry a higher risk than other anti-TNFα therapies. In RCTs there was only a small (2.2 / 1,000 pys) difference in IBD incidence between biologic therapy and placebo groups while amongst patients treated with anti-TNFα there was small excess incidence associated with etanercept noted in both RCTs and OLEs (5.8 / 1,000 pys and 2.1 / 1,000 pys respectively). IL-17 therapy also showed small excess risks compared to anti-TNFα therapies other than etanercept (4.7 / 1,000 pys and 2.8 / 1,000 pys respectively).

The findings of this study need to be considered in the context of some methodological issues. Firstly the quality of certainty of evidence revealed moderate to high levels of bias for all eligible studies.

Secondly the evidence has come from very different study designs – which leads to distinct patterns of exposure and length of follow-up across RCTs, OLEs, ETPs and incidence could reasonably be hypothesised to be related to duration of exposure and the time period for which subjects remained under surveillance. Therefore, a direct comparison of the results obtained from these different study design should be treated with caution; we consider further below, methodological issues which may give rise to different results between randomised and observational studies. Thirdly, there were issues in the reporting of IBD within published studies such that it was sometimes unclear whether events were new onset or flares or indeed if IBD was not mentioned, whether no cases had been noted or it 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 meta-analysis was undertaken for observational studies, the current study is by far the biggest contributor of data in relation to risk related to etanercept and therefore strongly influences the result.

Why might results vary between trials 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 for entry, may work against finding a difference in incidence of IBD even if such existed. We also acknowledge that the estimated combined effects from observational studies are 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 approx. 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 anti-rheumatic drugs (DMARDs)) but lifestyle factors were similar (49). 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 hazard ratio for developing IBD was almost identical in unadjusted and adjusted models. As noted previously in the BSRBR-AS, prior diagnosis of IBD was

associated with significantly lower odds of being prescribed etanercept (OR 0.3 95% CI 0.2, 0.6). In the current dataset the only factor significantly (or importantly) associated with treatment with etanercept was a lack of a previous history of uveitis (data not shown) and 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 (biologic therapy patients 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 incidence rate of IBD in the group treated with biologic agents compared to those without. Also, there was a small excess risk of IBD in those treated with etanercept compared to other anti TNFα therapies. Etanercept 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 (50): 438 cases were noted to have been reported to the FDA Adverse Event Reporting System in a study from 2016 (51) while a further 53 cases were reported in the literature of IBD onset after treatment with anti TNFα therapy (52). Most of the cases in the latter study were as a result of treatment of juvenile inflammatory arthritis (JIA) with etanercept. The current study quantifies the possible excess incidence of IBD associated with the use of etanercept in patients with axSpA at around 2 per 1,000 person years of follow-up (based on open label extension/ extended treatment periods of trials) and around 6 per 1,000 person years based on RCTs, but it is reassuring to note that the use of etanercept 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 etanercept by rheumatologists.

In summary, the relatively infrequent new-onset of IBD in patients with axSpA means that even with a nationwide registry and a systematic literature review there still remains considerable uncertainty in the quantification of risk associated with biologic therapy and specifically etanercept. However two specific patterns are clear. A large excess risk evident in observational studies is not replicated in RCTs.

Trials and their extensions do suggest a small absolute increased risk associated with etanercept compared to other anti-TNFα therapies (and with IL-17 compared to anti-TNFα therapies other than etanercept), although with considerable uncertainty.

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Table 1. Characteristics of eligible BSRBR-AS patients

		Biologic treated		Non-biologic treated	
Baseline characteristics		**N**	**% or Median (IQR)**	**N**	**% or Median (IQR)**
Demographic factors					
Age	Years	793	43.1 (33.8, 53.4)	1,058	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	1,022	96.6
	Present	36	4.5	36	3.4
Symptom duration	Years	793	12.0 (5.0, 23.0)	1,058	20.0 (10.0, 33.0)
Disease activity (BASDAI)	Scored 0 (best) – 10 (worst)	653	6.4 (4.9, 7.5)	856	3.2 (1.7, 5.2)
Inflammation (CRP)	mg/dL	670	0.7 (0.2, 2.2)	782	0.5 (0.1, 1.7)
Inflammation (ESR)	mm/hr	366	12.5 (5.0, 27.0)	334	8.5 (5.0, 19.0)
Body mass index (BMI)	kg/m^2	654	27.0 (24.0, 31.0)	914	26.7 (23.9, 30.2)
Number of comorbidities*	Count	787	0.0 (0.0, 1.0)	1054	0.0 (0.0, 1.0)

* List of comorbidities (related to cardiovascular, respiratory, gastrointestinal, renal, neurological conditions and cancer): myocardial infarction, angina, heart failure, stroke, hypertension, diabetes, asthma, bronchitis, liver disease, renal disease, tuberculosis, demyelination, depression and cancer.

Table 2. BSRBR-AS: Incidence of IBD following use of biologic / non-biologic therapy

Cohort/Treatment	New onset IBD cases (N)	Exposure time (person-years)	Incidence rate per 1000 person-years (95% CI)	Incidence rate ratio (95% CI)	Incidence rate difference (95% CI)
Cohort					
Non-biologic cohort*	13	2,547.6†	5.1 (2.7, 8.7)		
Biologic cohort**	22	1,291.7	17.0 (10.7, 25.8)	3.3 (1.7, 6.6)	11.9 (4.3, 19.6)
Biologic treatment					
Etanercept	6	431.3	13.9 (5.1, 30.3)		
Adalimumab	16	784.2	20.4 (11.7, 33.1)		
Certolizumab pegol	0	58.2	0		
Golimumab	0	14.7	0		
Infliximab	0	0.1	0		
Secukinumab	0	3.2	0		
Comparisons					
Etanercept vs. non-biologic treatment				2.7 (1.03, 7.2)	8.8 (-2.7, 20.3)
Etanercept vs. other anti TNFα therapy				0.7 (0.3, 1.8)	-6.5 (-21.3, 8.5)

* N = 1,058

** N = 793 treated with single biologic therapies

† includes 272.2 pyrs that is the contribution from the 793 biologic patients before commencing therapy

Table 3. Meta-analysis of randomised controlled trials: Incidence rate of IBD by type of treatment

References	Study duration (weeks)	Patients exposed (N)	Number of IBD cases / Person-years follow-up	Incidence Rate per 1000 person-years (95% CI)
Patients treated with placebo				
Braun, 2002 (13)	12	35	0 / 8.1	0.0
Gorman, 2002 (14)	16	20	0 / 5.7	0.0
Davis, 2003 (15)	24	139	1 / 58.3	17.15 (0.2, 95.4)
Brandt, 2003 (16)	6	16	0 / 1.8	0.0
Calin, 2004 (17)	12	39	0 / 8.7	0.0
van der Heijde, 2005 (18)	24	78	0 / 34.8	0.0
van der Heijde, 2006 (19)	24	107	0 / 33.0	0.0
Haibel, 2008 (20)	12	24	0 / 5.5	0.0
Dougados, 2014 (21)	8	48	0 / 6.2	0.0
Dougados, 2014 (22)	12	109	0 / 24.8	0.0
Baeten, 2015 (23)	16	122	0 / 36.5	0.0
Baeten, 2015 (23)	16	74	0 / 21.8	0.0
Landewe, 2014 (24)	24	107	1 / 37.7	26.5 (0.4, 147.6)
Pavelka, 2020 (25)	16	76	0 / 23.0	0.0
Kivitz 2018 (26)	16	117	0 / 35.7	0.0
Deodhar, 2018 (27)	16	103	0 / 31.1	0.0
Deodhar, 2019 (28)	16	104	0 / 30.3	0.0
van der Heijde, 2018 (29)	16	87	0 / 26.6	0.0
van der Heijde, 2006 (30)	12	51	0 / 11.0	0.0
Huang, 2020 (31)	16	153	0 / 46.5	0.0

van der Heijde, 2020 (32)	12	60	0 / 13.8	0.0
Deodhar, 2021 (33)	20	186	0 / 69.4	0.0
Rusman, 2021 (34)	16	40	0 / 12.3	0.0
Pooled analysis (placebo)		**1,895**	**2 / 582.6**	**3.4 (0.4, 12.4)**
Patients treated with etanercept				
Gorman, 2002 (14)	16	20	0 / 6.1	0.0
Davis, 2003 (15)	24	138	1 / 59.2	16.9 (0.2, 9)
Brandt, 2003 (16)	6	14	1 / 6.7	149.3 (2.0, 830.4)
Calin, 2004 (17)	12	45	0 / 9.6	0.0
Dougados, 2014 (21)	16	86	0 / 17.8	0.0
Dougados, 2014 (22)	24	208	0 / 70.3	0.0
van der Heijde, 2006 (30)	12	305	0/64.1	0.0
Rusman, 2021 (34)	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 TNFα therapy				
Infliximab				
Braun, 2002 (13)	12	34	0 / 7.8	0.0
van der Heijde, 2005 (18)	24	201	0 / 92.1	0.0
Total exposed		235	0 / 99.9	0.0
Adalimumab				
van der Heijde, 2006 (19)	24	280	0 / 108.0	0.0
Haibel, 2008 (20)	12	22	0 / 5.1	0.0
van der Heijde, 2018 (29)	16	90	0 / 27.4	0.0
Total exposed		392	0 / 140.5	0.0
Golimumab				

Deodhar, 2018 (27)	28	204	0 / 79.3	0.0
Total exposed		204	0 / 79.3	0.0
Certolizumab pegol				
Landewe, 2014 (24)	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-TNFα therapy)		**1,105**	**1 / 425.3**	**2.4 (0.03, 13.1)**
Patients treated with IL-17 inhibitors				
Secukinumab				
Baeten, 2015 (23)	16	249	0 / 77.2	0.0
Baeten, 2015 (23)	16	145	1 / 43.7	22.9 (0.3. 127.3)
Pavelka, 2020 (25)	16	150	0 / 47.3	0.0
Kivitz 2018 (26)	16	233	0 / 71.7	0.0
Huang, 2020 (31)	16	304	0 / 94.0	0.0
Deodhar, 2021 (33)	20	184	1 / 69.2	14.4 (0.2, 80.4)
Total exposed		1,265	2 / 403.1	5.0 (0.6, 17.9)
Ixekizumab				
Deodhar, 2019 (28)	16	212	2 / 61.7	32.4 (3.6, 117.0)
van der Heijde, 2018 (29)	16	164	0 / 49.4	0.0
Total exposed		376	2 / 111.1	18.0 (2.0, 65.0)
Bimekizumab				
van der Heijde, 2020 (32)	12	243	0 / 55.4	0.0
Total exposed		243	0 / 55.4	0.0
Pooled analysis (IL-17 inhibitors)		**1,884**	**4 / 569.6**	**7.0 (1.9, 18.0)**
Pooled analysis (all biologics)		**3,845**	**7 / 1240.7**	**5.6 (2.3, 11.6)**

Table 4. Meta-analysis: Comparison between treatment groups

Randomised Controlled Trials	**Incidence Rate Ratio (95% CI)**	**Incidence Rate Difference per 1000 person-years (95% CI)**
Biologic / Placebo	1.6 (0.3, 7.9)	2.2 (-4.1, 8.5)
ETA / Placebo	2.4 (0.3, 16.8)	4.7 (-7.5, 16.9)
ETA / other TNFα therapy	3.5 (0.3, 38.2)	5.8 (-6.4, 18.0)
ETA / IL-17 therapy	1.2 (0.2, 6.3)	1.1 (-12.1, 14.3)
IL-17 / non-ETA TNFα therapy	3.0 (0.3, 26.7)	4.7 (-3.6, 13.0)
Open Label Extensions/Extended Treatment Periods		
ETA / other TNFα therapy	3.5 (0.6, 19.1)	2.1 (-1.0, 5.2)
ETA / IL-17 therapy	0.8 (0.3, 2.4)	-0.7 (-4.0, 2.6)
IL-17 / non-ETA TNFα therapy	4.3 (1.01, 18.6)	2.8 (0.8, 4.7)

Table 5. Meta-analysis (RCT extension studies): Incidence Rates of IBD per 1000 person-years using data from Open Label Extensions and Extended Treatment Periods (safety) trials

Reference	Study duration (weeks)	Patients exposed (N)	Number of IBD cases / Person-years follow-up	Incidence Rate per 1000 person-years (95% CI)
Patients treated with etanercept				
Gorman, 2002 (14)	43	37	0 / 64.8	0.0
Davis, 2008 (35)	192	257	2 / 650.0	3.1 (0.4, 11.1)
Martín-Mola, 2010 (36)	264	81	2 / 287.0	7.0 (0.8, 25.2)
Dougados, 2017 (37)	104	205	0 / 374.0	0.0
Pooled analysis (etanercept)		**580**	**4 / 1,375.8**	**2.9 (0.8, 7.4)**
Patients treated with other TNFα therapy				
Infliximab				
Braun, 2008 (38)	254	69	0 / 235.6	0.0
Braun, 2008 (39)	102	276	0 / 411.0	0.0
Total	102	345	0 / 646.6	0.0
Golimumab				
Reveille, 2019 (40)	52	204	0 / 203.2	0.0
Total		204	0 / 203.2	0.0
Adalimumab				
Haibel, 2008 (20)	52	46	0 / 37.4	0.0
van der Heijde, 2009 (41)	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 (42)	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 inhibitors)		**1221**	**2 / 2,402.2**	**0.83 (0.1, 3.0)**
Patients treated with IL-17 therapy				
Secukinumab				
Pavelka, 2020 (25)	156	223	0 / 602.0	0.00
Kivitz, 2018 (26)	104	346	0 / 602.5	0.0
Huang, 2020 (31)	52	453	0 / 457.2	0.0
Deodhar, 2021 (33)	104	543	5 / 757.9	6.6 (2.1, 15.4)
Marzo-Ortega 2020 (43)	260	211	5 / 842.9	5.9 (1.9, 13.8)
Baraliakos, 2019 (44)	260	360	6 / 1,425.0	4.2 (1.5, 9.2)
Total		2136	16 / 4,687.5	3.4 (2.0, 5.5)
Ixekizumab				
Dougados, 2020 (45)	52	641	2 / 510.2	3.9 (0.4, 14.2)
Deodhar, 2020 (46)	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 (32)	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 inhibitors)		**3,271**	**20 / 5,535.4**	**3.6 (2.2, 5.6)**
Pooled analysis (all biologics)		**5,072**	**26 / 9,313.4**	**2.8 (1.8, 4.1)**

Table 6. Comparison of treatment groups amongst observational studies

Reference / Study	Patients (N): Biologic/Non-biologic treated	IBD (N): Biologic/Non-biologic treated	Odds Ratio (95% CI)	Weight %
Any biologic treatment vs. No biologic treatment				
Walsh, 2018 (47)	3,077 / 3,830	139 / 84	2.1 (1.6, 2.8)	84.7
Uskudar Cansu, 2019 (48)	154 / 266	7 / 3	4.2 (1.1, 16.4)	2.5
BSRBR-AS	793 / 1,058	22 / 13	2.3 (1.2, 4.6)	12.8
Pooled Odds Ratio			**2.2 (1.7, 2.8)**	**100**
Etanercept vs. No biologic treatment				
Uskudar Cansu, 2019 (48)	52 / 266	3 / 3	5.4 (1.1, 27.4)	15.9
BSRBR-AS	253 / 1,058	6 / 13	2.0 (0.7, 5.2)	84.1
Pooled Odds Ratio			**2.4 (1.1, 5.7)**	**100**
Etanercept vs. Other anti-TNF alpha				
Uskudar Cansu, 2019 (48)	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 Odds Ratio			**0.9 (0.4, 2.1)**	**100**

Supplementary Tables and Figures

Table S1. Multivariable regression model

Variable	OR (95% CI)
BASDAI (0 to 10)	1.67 (1.57. 1.77)
Symptom duration (years)	0.979 (0.968, 0.991)
Age (years)	0.976 (0.965, 0.987)

N = 1,506; Log likelihood = -774.49; Area under ROC curve = 0.819; Sensitivity = 70.4%; Specificity = 78.2%; Positive predictive value = 71.2%; Negative predictive value = 77.6%; Correct classified = 74.8%.

Table S2. Characteristics[*] of eligible BSRBR-AS patients within propensity quintiles[**]

	Quintile				
	1	2	3	4	5
Biologic treated[†]	25 (8.3%)	59 (19.6%)	136 (45.2%)	191 (63.5%)	241 (80.1%)
Non-biologic treated [††]	277 (91.7%)	242 (80.4%)	165 (54.8%)	110 (36.5%)	60 (19.9%)
Demographic factors					
Age (years)					
All	60.5	46.9	51.2	45.9	36.4
Bio	55.7	46.9	52.2	45.9	36.4
Non-bio	60.8	47.0	49.2	45.2	38.2
Difference (Bio vs Non-bio)(%)[‡]	8.8%	0.2%	5.9%	1.5%	4.8%
Gender-male					
All	79.5%	66.5%	66.8	65.8%	60.5%
Bio	72.%	84.6%	74.3	69.6%	61.4%
Non-bio	80.1%	62.0%	60.6	59.1%	56.7%
Difference (Bio vs Non-bio)(%)[‡]	10.7%	30.8%	20.3%	16.3%	8.0%
Clinical factors					
HLA-B27 – positive					
All	85.6%	87.0%	82.0	76.7%	76.8%
Bio	66.7%	90.9%	81.8	80.7%	75.7%
Non-bio	87.2%	86.1%	82.2	70.9%	81.1%
Difference (Bio vs Non-bio)(%)[‡]	26.6%	5.4%	0.5%	12.9%	6.9%
Uveitis – present					
All	27.2%	30.2%	26.3%	22.3%	17.6%
Bio	32.0%	28.8%	29.4%	24.1%	19.9%
Non-bio	26.7%	30.6%	23.6%	19.1%	8.3%
Difference (Bio vs Non-bio)(%)[‡]	18.1%	6.1%	21.9%	23.1%	82.3%
Psoriasis – present					
All	9.6%	10.3%	8.0%	10.3%	12.0%
Bio	12.0%	13.6%	7.4%	12.6%	10.8%
Non-bio	9.4%	9.5%	8.5%	6.4%	16.7%
Difference (Bio vs Non-bio)(%)[‡]	24.3%	35.5%	13.8%	65.3%	42.9%
Enthesitis - present					
All	5.6%	11.0%	7.6%	11.0%	14.3%
Bio	12.0%	13.6%	7.4%	8.4%	16.2%
Non-bio	5.1%	10.3%	7.9%	15.5%	6.7%
Difference (Bio vs Non-bio)(%)[‡]	80.7%	27.6%	6.5%	59.4%	83.0%
Peripheral joint disease - present					

All	11.6%	17.6%	17.6%	19.6%	22.6%
Bio	8.0%	23.7%	17.7%	21.5%	23.7%
Non-bio	11.9%	16.1%	17.6%	16.4%	18.2%
Difference (Bio vs Non-bio)(%)‡	39.2%	38.2%	0.6%	26.9%	26.3%
Dactylitis - present					
All	2.7%	4.7%	3.0%	4.0%	5.3%
Bio	0.0%	3.4%	2.2%	4.7%	6.2%
Non-bio	2.9%	5.0%	3.6%	2.7%	1.7%
Difference (Bio vs Non-bio)(%)‡	200.0%	38.1%	48.3%	54.1%	113.9%
Symptom duration (years)					
All	30	19	20	14	8
Bio	28	20	20.5	14	7
Non-bio	30	19	19	13	9.5
Difference (Bio vs Non-bio)(%)‡	6.9%	5.1%	7.6%	7.4%	30.3%
BASDAI (0 to 10)					
All	1.4	2.8	4.9	6.2	7.8
Bio	1.4	2.9	5.0	6.3	7.8
Non-bio	1.4	2.8	4.7	6.0	7.6
Difference (Bio vs Non-bio)(%)‡	0.0%	3.5%	6.2%	4.9%	2.6%
Inflammation (CRP) (mg/dL)					
All	0.6	0.4	0.6	0.7	0.6
Bio	2.1	0.5	0.8	0.7	0.6
Non-bio	0.5	0.4	0.5	0.7	0.9
Difference (Bio vs Non-bio)(%)‡	123.1%	22.2%	46.2%	0.0%	40.0%
Inflammation (ESR) (mm/hr)					
All	8.5	10	12	12	13
Bio	27.0	8	15	12	14
Non-bio	8.0	10	10	10	11
Difference (Bio vs Non-bio)(%)‡	108.6%	22.2%	40.0%	18.2%	24.0%
Body mass index (BMI) (kg/m^2)					
All	26.6	26.4	27.3	27.5	27.1
Bio	27.3	26.6	27.4	27.1	27.0
Non-bio	26.4	26.3	27.2	27.8	27.8
Difference (Bio vs Non-bio)(%)‡	3.4%	1.1%	0.7%	2.6%	2.9%
Number of comorbidities (count)					
All	0	0	0	0	0
Bio	0	1	0	0	0
Non-bio	0	0	0	0	0
Difference (Bio vs Non-bio)(%)‡	Indefinite	200	Indefinite	Indefinite	Indefinite

*Characteristics of the patients in each quintile: % for discrete variables and median for continuous variables, respectively.

** The propensity score represents the probability of starting biologic treatment.

‡ Percentage difference between biologic and non-biologic patients: $\frac{|V_{bio}-V_{non-bio}|}{\frac{V_{bio}+V_{non-bio}}{2}} \times 100\%$, where $V_{bio}$and $V_{non-bio}$ are values in the two cohorts.

† N= 652; †† N = 854.

Table S3. Cox proportional hazard models to test the association between treatment with biologic drugs and development of incident IBD[*]

Variable	Hazard ratio	95% CI	P-value
Unadjusted model			
Biologic treatment (No -reference)	2.5	1.2, 5.1	0.018
Model adjusted for quintile of propensity score			
Biologic treatment (No -reference)	2.4	0.99, 6.0	0.052
Quintiles of propensity score	1.002	0.7, 1.4	0.991

[*] N = 1,506 (652 biologics sub-cohort, 854 non-biologics sub-cohort); 17 IBD cases in the biologics sub-cohort 12 in the non-biologics one; total time at risk : 2889.5 pys; Schoenfeld residual test – (χ^2 = 2.92, df = 2, p = 0.2326).

Table S4. Risk of bias for included OLE/ETPs and OSCA

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Bias
OPEN LABEL STUDIES								
Gorman, 2002 (14)	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Davis, 2008 (35)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Martín-Mola, 2010 (36)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Dougados, 2017 (37)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Braun, 2008 (38)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Braun, 2008 (39)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Reveille, 2019 (40)	Serious	Moderate	Low	Low	Low	Moderate	Moderate	Serious
Haibel, 2008 (20)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
van der Heijde, 2009 (41)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
van der Heijde, 2017 (42)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Pavelka, 2020 (25)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Kivitz, 2018 (26)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Huang, 2020 (31)	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious
Deodhar, 2021 (33)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Marzo-Ortega, 2020 (43)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
Baraliakos, 2019 (44)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious

Dougados, 2020 (45)	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Deodhar, 2020 (46)	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious
van der Heijde, 2020 (32)	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious
OBSERVATIONAL COHORT STUDIES								
Walsh, 2018 (47)	Serious	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Serious
Uskudar Cansu, 2019 (48)	Serious	Moderate	Low	Moderate	Moderate	Moderate	Low	Serious
BSRBR-AS	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	Serious

Figure S1. Flowchart of identification of studies

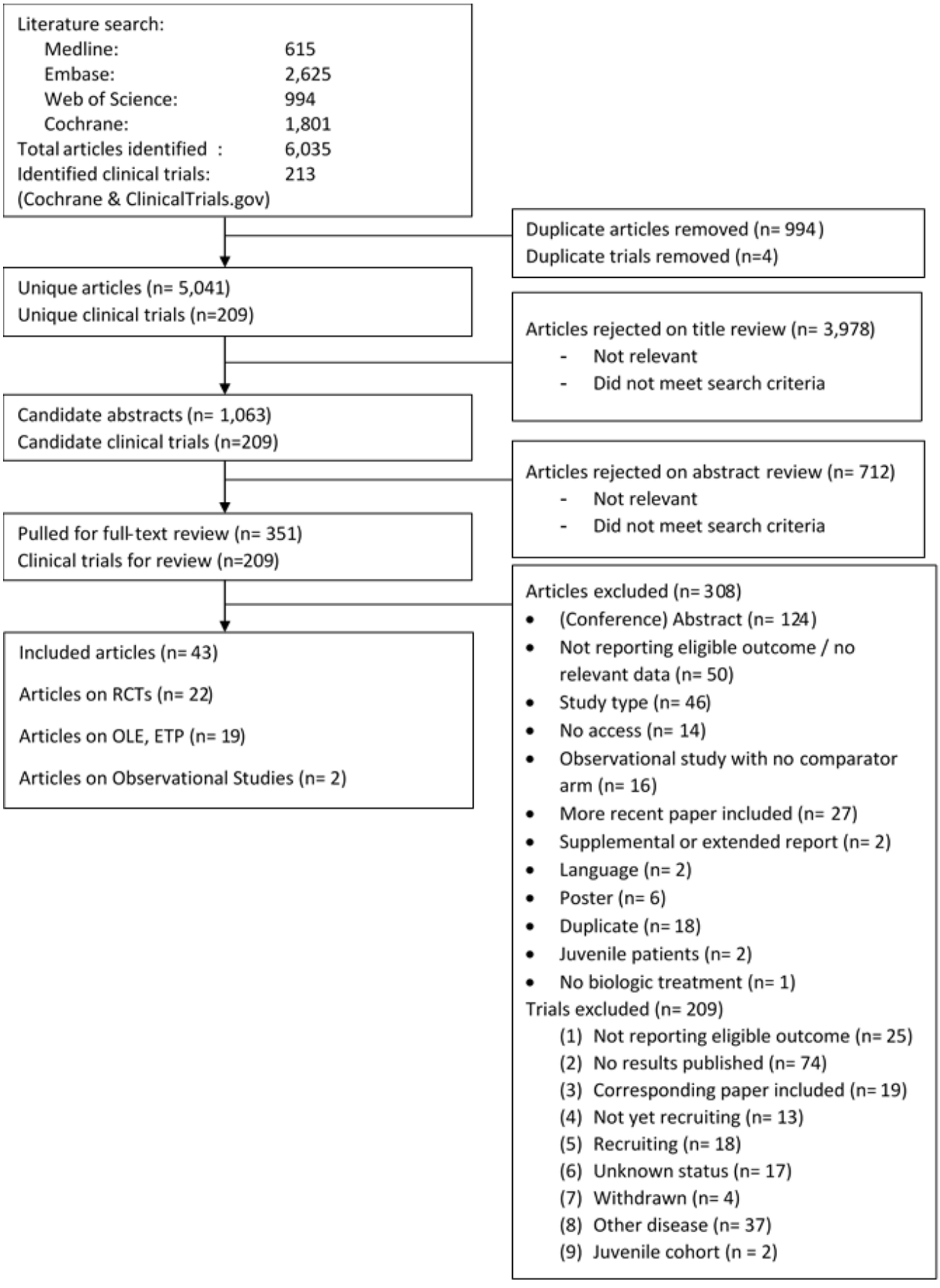

Figure S2. Overall risk of bias for included RCTs

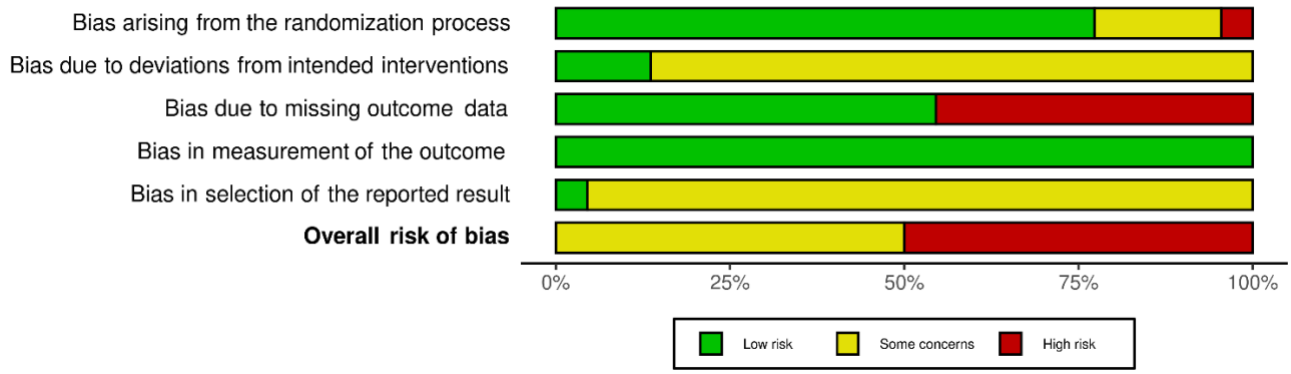

Figure S3: Risk of bias for RCTs