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OPPORTUNISTIC INFECTIONS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE TREATED WITH ADVANCED THERAPIES: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Background & aim: Advanced therapies for inflammatory bowel disease (IBD) could potentially lead to a state of immunosuppression with an increased risk of opportunistic infections (OIs). We aimed to update on the incidence of OIs among adult IBD patients in randomized controlled trials (RCTs) of approved biologics and small-molecule drugs (SMDs). Also, we aim to describe OIs definitions utilized in RCTs, to ultimately propose a standardized definition.

Methods: Electronic databases were searched from January 1, 1990, until April 16, 2022. Our primary outcome was incidence rate of overall OIs among IBD patients exposed and unexposed to biologics or SMDs. We also described specific OIs reported in included trials, as well as definitions of OIs within studies when provided.

Results: 90 studies were included. The incidence rate of reported OIs were 0.42 and 0.21 per 100 person-years in patients exposed to advanced therapies and placebo, respectively. This was highest for anti-TNFs (0.83 per 100 person-years) and JAK inhibitors (0.55 per 100 person-years) and lowest for anti-integrins and ozanimod. On meta-analysis, no increased risk of OIs was observed. None of the studies provided a detailed definition of OIs, or a comprehensive list of infections considered as OIs.

Conclusion: Different mechanisms of action may have specific OIs profiles. In the absence of a uniform definition of OIs, these estimates are less reliable. We propose a definition to be used in future studies to help standardized reporting. When using this definition, we saw significant differences in incidence rates of OIs across mechanisms of action.

Keywords: ‘opportunistic infections’; ‘biologic’; ‘small-molecule drugs’

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INTRODUCTION

Inflammatory bowel diseases (IBD) comprise two chronic and often disabling diseases: Crohn's disease (CD) and ulcerative colitis (UC),[1,2] which are frequently associated with an impaired health-related quality of life and complications.[3,4]

The introduction of biologics has dramatically changed the treatment paradigm in moderate-to-severe IBD. However, biologic drugs (i.e. anti-tumour necrosis factor [TNF] agents, vedolizumab, and ustekinumab) have limitations.[5] Recently, drug development has shifted to synthetic small molecule drugs (SMDs), which may have more off target effects. Tofacitinib has been the first Janus kinase (JAK) inhibitor to receive regulatory approval for the treatment of UC.[6] Ozanimod, a sphingosine-1-phosphate receptor modulator, has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with moderate-to-severe UC. Moreover, two selective JAK-1 inhibitors, upadacitinib and filgotinib, have recently received approval for the treatment of UC from the FDA and the EMA, respectively.

Biologics and SMDs are included in the broader term of advanced therapies in IBD, which differs from conventional therapies (i.e., aminosalicylates, immunomodulators, and corticosteroids). Current advanced therapies selectively target immune pathways associated with the pathogenesis of IBD, that could potentially lead to a state of immunosuppression with an increased risk of infections, including opportunistic infections (OIs).[7] OIs are broadly defined as infections caused by microorganisms that generally have limited or no capacity to produce disease in immunocompetent subjects but may appear in the context of an impaired immune system function due to a predisposing condition or its treatment.[8,9]

Patients with IBD receiving advanced therapy should be closely monitored to detect and treat such infections.[10] Several previous systematic reviews and meta-analyses have evaluated the risk of infections and serious infections with the use of advanced therapies in IBD.[11–16] However, the risk and incidence of OIs have been less extensively studied, and most of these studies focused on anti-TNF agents and anti-integrins.[11,17–20] More importantly, there is no clear definition of OI that separates them from other types of infection, which can lead to heterogeneity in reporting of these adverse events in both randomized controlled trials (RCTs) and observational studies.

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Hence, we sought to update the incidence of OI among adult patients with IBD in RCTs of approved biologics and SMDs. In addition, we aimed to describe definitions of OIs in RCTs as well as specific OIs reported within trials, with the goal of proposing a framework for standardized definitions of OI to be used in future studies.

MATERIALS AND METHODS

Our study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO – http://www.crd.york.ac.uk/prospero).[21] We followed the methodology for conducting and reporting a systematic review described in the Cochrane Handbook, the MOOSE proposal, and the PRISMA statement.

Inclusion criteria

We searched for phase 2 and 3 RCTs and associated long-term extension trials involving adult patients with UC or CD. We included induction and maintenance trials. For maintenance trials, we included studies with either a *treat-through* or *randomized responders* designs. All articles irrespective of publication type were considered for inclusion. In the case of multiple studies involving the same population, data from the most recent or most comprehensive one would be included. We focused on biologics and SMDs that are approved by the FDA or the EMA for the treatment of either UC or CD until April 16, 2022. We did not apply language restrictions.

Outcomes

Our primary outcome was to assess the incidence rate of reported OIs among patients with IBD exposed to advanced therapies. Additionally, we estimated the incidence rate of overall OIs among UC patients and CD patients separately, and according to the mechanism of action. Incidence rates were estimated considering the follow-up time of the trials, and then were extrapolated to and described as per 100 person-years. We also describe specific OIs reported in included trials.

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Information sources and search strategy

Published studies were identified using MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from January 1, 1990, until April 16, 2022. Major congresses databases (ECCO, DDW, UEGW) in the period 2019-2021 were also reviewed manually. Search algorithms are listed in supplementary table 1.

Selection process and data extraction

Three authors (PO, JL, IZ) independently reviewed titles/abstracts of studies identified in the search and excluded those that are clearly irrelevant. The full text of the selected articles was analysed to determine whether it contained information on the topic of interest. Their reference lists (and those of relevant systematic reviews and meta-analyses) were hand-searched to identify further relevant publications.

The following information from each study was abstracted into a specially designed data extraction form: citation data, first author's last name, study design, underlying condition (CD, UC), number of patients, study duration, population characteristics, exposure definition (drug, dose, duration), concomitant immunomodulators and/or steroids, and reported outcomes. Additionally, we searched in the methods, supplementary appendixes, and protocols of each of the included studies for any definition of OIs or specific infections and extracted when available. Any differences in data extraction would be settled by consensus, referring to the original article.

Data synthesis and analysis

Controlled studies were selected for meta-analysis. We hypothesized there would be a considerable difference in terms of follow-up time between studies. Hence, outcome measures were described as incidence rate ratios (IRR) with their corresponding 95% confidence interval (CI). R studio software, version 4.0.13 was used for this purpose. Heterogeneity among studies was evaluated by means of Chi Square and I^2 tests. A random-effects

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model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Possible publication bias was assessed by means of the Egger test. Risk of bias was assessed using the Cochrane risk of bias for randomized trials.

We carried out the following sensitivity analyses: firstly, we evaluated the risk of OIs stratified by concomitant use of immunomodulators and systemic steroids; the results were also described as IRR with their corresponding 95% CI. Secondly, the risk of OIs according to type of study (induction, maintenance, or long-term extension studies) was estimated. Since studies were grouped according to similar follow-up duration, the results were described as Risk Ratios (RR) with their corresponding 95% CI.

RESULTS

Literatures search results

Bibliographic search yielded 24186 citations from which 90 studies were finally included for qualitative synthesis as shown in Figure 1. These studies comprised 45 studies conducted on CD patients[22–59] and 45 on UC patients.[60-93]

The main characteristics of included studies are shown in supplementary tables 2 and 3. Most of included studies (80.2%) were RCTs, and the remainder were their long-term extension periods. Overall, 39848 subjects were evaluated in the included studies, of which 18325 were patients with CD and 21523 were patients with UC; 29144 were exposed to any advanced therapy, of which 6336 were exposed to an SMD (tofacitinib, filgotinib, upadacitinib, or ozanimod). Given that currently all 4 SMDs only have FDA or EMA approval for UC treatment, none of the subjects with CD included in this study were exposed to SMDs.

Opportunistic infection incidence rates

Incidence rates of reported OIs in patients with IBD in the included placebo-controlled studies are shown in Table 1. The median time of exposure to advanced therapy was 30 weeks (IQR25-75%, 6-52 weeks). Overall,

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the incidence rate of reported OIs in patients with IBD exposed to advanced therapies was 0.42 per 100 person-years, whereas the incidence rate was 0.21 per 100 person-years in those subjects exposed to placebo. When analysed separately, patients with UC exposed to advanced therapies showed an incidence rate of reported OIs of 0.42 per 100 person-years, whereas patients with CD showed an incidence rate of 0.41 per 100 person-years. Incidence rates of reported OIs differed according to the mechanism of action of advanced therapies, as shown in Table 2.

Overall, 96 types of OIs were described among subjects with IBD exposed to advanced therapies. Supplementary table 4 describes the types of OIs reported in each of the included studies. The most frequent OI identified was candidiasis (oropharyngeal or other location) followed by tuberculosis (figure 2).

Opportunistic infection risk in placebo-controlled studies

Meta-analyses of placebo-controlled studies to analyse the IRR of OI among both UC and CD subjects are shown in figures 3 and 4, respectively. No significant heterogeneity was found in either case; unadjusted IRR of OI in CD and UC subjects were 0.94 (95%CI, 0.41-2.16) and 0.77 (95%CI, 0.46-1.30), respectively. Risk stratification according to the concomitant use of immunomodulators and systemic steroids did not show a significant increase in the IRR of OIs, as shown in supplementary table 5.

We identified minor concerns in terms of risk of bias in 12 studies[30,31,58,61,62,69,70-72,74,75,78] and significant concerns of risk of bias in one study[44] included for meta-analysis (supplementary figure 1).

Sensitivity analyses according to study type are shown in supplementary figures 2, 3, 4, and 5. No significant heterogeneity was identified.

Opportunistic infection definitions across included studies

Of the 90 included trials, none provided a detailed definition of OIs or a comprehensive list of infections considered as OIs. Only the OCTAVE program of tofacitinib in UC mentioned in its protocol that “an external

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independent adjudication committee was utilized to evaluate and adjudicate potential opportunistic infection events based on a consistent set of predefined criteria". However, only definitions of cytomegalovirus (CMV) infections and herpes zoster (HZ) were clearly stated. CMV infection was defined as an OI based on the following criteria:

- Patient with fever, new-onset or increased malaise, leukopenia, neutropenia, or symptoms of end-organ disease (e.g., retinitis, pneumonia, hepatitis, nephritis, etc)

  AND
- Evidence of CMV replication in blood (by PCR, antigen assay or culture) or histological evidence of CMV infection in a tissue specimen.

Whereas HZ was defined as OI based on the following:

- Patient with a maculopapular or vesicular rash in multidermatomal distribution (adjacent or nonadjacent); or any multidermatomal rash accompanied by pain; intraocular disease diagnosed by an ophthalmologist as zoster; or evidence of disseminated disease (encephalitis, pneumonia, diffuse rash, or other).
- For disease other than skin or ocular, demonstration of either varicella zoster virus from lesion or other sample by culture, molecular techniques (PCR), or microscopy.

The Touchstone and the True North programs of ozanimod in UC briefly mentioned in its protocol that "TB, serious bacterial infections, systemic fungal infections, viral infections such as herpes infections (including herpes zoster and disseminated herpes simplex) and protozoan infections will be considered AEs of special interest".

Proposed definition of OIs

We propose a working definition of OIs to be used in future studies in the field of IBD, which is based on the occurrence of certain *marker* infections or presentations (table 3) that highlight the presence of altered host

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immunity in the setting of treatment with advanced therapies. This also takes into consideration the limited available definitions previously used in IBD trials (supplementary tables 2 and 3).

We saw a numerically increase in incidence rates of OIs when estimates were made based on OIs when we used the proposed definition (table 1 and supplementary table 4). When using the proposed definition of OIs, the incidence rate in the overall population exposed to advanced therapies was 0.83 per 100 person-years, whereas in the non-exposed population it was 0.61 per 100 person-years. In CD, the incidence rates of OIs were 0.48 and 0.32 per 100 person-years in subjects exposed and non-exposed to advanced therapies, respectively. In UC, when using the proposed definition, the incidence rate of OIs went up to 1.07 and 0.79 per 100 person-years in subjects exposed and non-exposed to advanced therapies, respectively.

DISCUSSION

We reviewed available data on OIs from RCTs and their long-term extension studies of currently FDA- and/or EMA-approved biologics and SMDs for the treatment of both UC and CD. Evidence regarding the occurrence of OIs in 90 RCTs and their long-term extension studies were synthesized. Although previous systematic reviews have evaluated the risk of OIs in RCTs in the field of IBD in the past,[11,17–20,94] they did not include more recent clinical trials evaluating newer compounds, such as ustekinumab, tofacitinib, ozanimod, upadacitinib, and filgotinib. In the current context of an ever-expanding therapeutic armamentarium in IBD, especially with novel mechanisms of action now available, an update on the incidence of OIs was needed. More importantly, there are no uniform definitions of OI used in RCTs and observational studies in IBD. Previous meta-analyses have already highlighted an increased risk of OIs with the use of advanced therapies, especially with anti-TNF agents.[17,19]

We found that the incidence rate of reported OIs was higher in patients with IBD exposed to advanced therapies versus patients exposed to placebo (0.42 per 100 person-years versus 0.21 per 100 person-years). There were considerable differences in the incidence rates of reported OIs depending on the mechanism of action within advanced therapies. Pooled incidence rate of as-reported OIs of anti-TNF agents' trials was highest (0.83 per 100 person-years), whereas it was lowest in anti-integrins' and ozanimod trials (0.05 and 0

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per 100 person-years, respectively) (table 2). The incidence rates were similar between patients with UC and CD (0.42 and 0.41 per 100 person-years, respectively). However, given that SMDs are only approved for the treatment of UC, this might have influenced the overall incidence of OIs in UC trials.

Importantly, we also found that most clinical trials evaluating advanced therapies in IBD lacked a formal definition of OIs in their methods, available protocols, or supplementary appendix. In the absence of a standardized definition of OIs in clinical trials, we noticed a considerable heterogeneity in the type of infections reported as OIs, which raises concerns regarding the accuracy of estimates in overall OIs in current and previous systematic reviews on the subject.

In a systematic review and meta-analysis of RCTs, Ford and Peyrin-Biroulet found a relative risk (RR) of developing an OI with anti-TNFs of 2.05 (95% CI 1.10-3.85) compared with placebo in patients with IBD.[17] In another systematic review and meta-analysis of RCTs evaluating anti-integrin agents in IBD, Luthra *et al*. found a statistically non-significant increased risk of OIs with the use of non-gut specific (natalizumab) and gut-specific anti-integrin agents (vedolizumab and etrolizumab) [RR = 2.34 (95% CI 0.05-108.72) and RR = 1.55 (95% CI 0.16-14.83), respectively].[18] Bonovas *et al*. evaluated the risk of OIs in RCTs in IBD in a network meta-analysis.[11] They found that exposure to biologics was associated with a statistically significant increased odds of OIs [odds ratio (OR) 1.90, 95% CI 1.21-3.01] with a number needed to harm (NNH) of 194 for one additional OI. They found that this risk was significant for CD (OR 2.39, 95% CI 1.32-4.34), but not for UC (OR 1.32, 95% CI 0.64-2.72).[11] In indirect comparison comparing individual treatments against each other, none reached statistical significance.[11]

Several previous attempts to define infections as OIs have been made in different specific scenarios of immunosuppression. The most distinctive perhaps, is in the context of HIV infection, in which OIs were defined as have been defined as infections that are more frequent or more severe because of HIV-mediated immunosuppression.[95] According to the Medical Dictionary for Regulatory Activities (MedDRA), an OI is an infection by an organism that does not ordinarily cause disease in an individual with an intact immune system but becomes pathogenic in an immunocompromised host. The etiologic agents leading to OIs may be different depending on the cause of the compromised immune function.[96]

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In a comprehensive systematic review that was followed by consensus recommendations on OIs and biologic therapies in immune-mediated inflammatory diseases, Winthrop *et al.* reviewed 368 clinical trials and 195 observational studies.[97] Like in our study, they found most of the studies lacked a formal definition of OIs and significant heterogeneity between studies regarding types of infections considered or reported as OIs. They developed a working definition of OIs as a list of "indicator" infections, markers of an impaired host immunity function in the setting of biologic therapy, to standardize reporting of OIs in future disease-modifying antirheumatic drug trials and observational studies in the field of rheumatology.[97]

However, a specific definition of OIs is needed in the context of clinical trials and observational studies of IBD; there are nuances in the baseline risk of specific infections across IMIDs and the risk of inducing those infections with different advanced therapies depending on the underlying disease.

In the context of a sheer increase in therapeutic options in IBD, knowing the exact efficacy and safety profile of each compound and drug class would impact drug positioning in treatment algorithms.[16,98] The risk of OIs represents an essential aspect of the safety profile of a specific drug or drug class; thus, providing a list of *marker* infections to be reported as OI is paramount. However, OIs are relatively infrequent in clinical trials, and the actual risk of these infections and the overall safety profile of a drug usually unfold after a drug is approved. Hence, adopting a standard definition to be used in clinical trials and in post-marketing and observational studies is also very relevant.

Therefore, we proposed a working definition of OIs, which is based on the occurrence of certain *marker* infections or presentations. Infections that only occur in an immunocompromised host are listed as OIs. Progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection that is caused by the JC virus, is a typical example of such infections.[99,100] The diagnostic criteria of each of these infections are beyond the scope of this paper. However, special consideration should be made to certain infections.

How to define HZ as OIs is particularly relevant, as it may drive changes in the reported overall incidence of OIs with advanced therapies. Clinical trials commonly reported the occurrence of HZ separately from OIs, and some considered them as OIs only when was either multidermatomal, complicated (e.g., intraocular disease), or disseminated (e.g., encephalitis, pneumonia, etc.).[75] Although HZ can occur in healthy individuals, as well as

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in patients with IBD on no advanced therapy, evidence shows that biologics (especially anti-TNF agents and combination with immunomodulators) and newer SMDs are associated with an increased risk of all forms of HZ due to impaired cell-mediated immunity.[12,101-103] Consequently, the occurrence of any form of HZ should be considered as a marker of an alternated immune state and, therefore, an OI. This is line with the definition proposed by Winthrop *et al*. in rheumatologic studies.[97]

Candidiasis was frequently described in our review of the literature. Invasive and disseminated forms of candidiasis are clearly a marker of impaired cell-mediated immunity,[104] and as such, were included in the working definition of OI. Oropharyngeal candidiasis can present in individuals with apparent normal immunity, mainly infants and older adults who wear dentures, and patients with xerostomia or treated inhaled glucocorticoids.[105] However, in the absence of local factors, cellular immune deficiency states are major drivers in this type of infection. What is more, oropharyngeal candidiasis was consistently reported as OI in IBD clinical trials, and consequently we included this presentation of candidiasis in the proposed definition of OIs.

Importantly, we saw significant differences in incidence rates of OIs when estimates were made based on OIs as reported in clinical trials and when we used the proposed definition. This difference was more evident when evaluating incidence rates of OIs according to the mechanism of action, especially for JAK inhibitors and S1P modulators. This difference is likely driven by including any type of HZ as OI. Given that JAK inhibitors and ozanimod are only approved for the treatment of UC, we did not include any trial evaluating SMDs for the treatment of patients with CD. This affected the overall incidence of OI in UC compared to CD when using the proposed definition.

In clinical trials, it is appropriate that these infections should be adjudicated by an external, independent, expert adjudication board. The terminology used to define these should follow the MedDRA, which is a clinically validated international terminology supported by regulatory agencies.[96,106]

This review has multiple strengths. We updated the incidence rate of reported OIs, which is especially relevant given that newer compounds with different mechanisms of action (i.e., ustekinumab, tofacitinib, and ozanimod) have recently became available. A comprehensive search for OIs definitions within studies was made, including grey literature, such as study protocols when available. We also propose for the first time a

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working definition of OIs specifically to IBD to be used in future studies, based on a list of infections and presentations.

However, our study also has limitations. First, we acknowledge that definitions of OI were more likely to be mentioned in the studies' protocols, and we only had access to some of them. Second, we sought to review clinical trials of approved advanced therapies for IBD; thus, more contemporary clinical trials of newer compounds (i.e., anti-p19 IL-23 agents) could have incorporated definitions of OIs not captured by our study. Third, we did not seek to provide case definitions for every infection listed as OI (except for CMV infection and HZ). Fourth, the median follow-up of included studies was relatively short (30 weeks), which might underestimate the incidence rate of OIs. Fifth, we did not evaluate individual patient level data, and the adjudication process within trials was not evaluated. Finally, we included a meta-analysis and no statistically significant differences were seen between advanced therapies and placebo; wide confidence intervals were observed when estimating IRR of OIs and consequently, the results of this meta-analysis, should be cautiously interpreted. This might be explained by the differential follow-up between the intervention and placebo groups and the substantial number of studies with zero events.

In conclusion, advanced therapies in IBD are associated with OIs among patients with IBD, and differences in incidence rates according to drug classes were seen. However, in the absence of a clear definition of OI, these estimates might not be precise. In this context, we propose a more granular definition of OIs to be used in future clinical trials and observational studies to help standardize reporting of these infections. When using a standardized definition, we saw significant differences in incidence rates of OIs across different mechanisms of action, highlighting the need for a uniform reporting of these infections. We plan to validate this definition of OIs in IBD in a Delphi consensus in the near future.

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PAO: consulting fees from Abbvie, Takeda, and Janssen; Honoraria from Takeda and Janssen; support for attending meetings and/or travel from Abbvie, Takeda, Janssen and Ferring. JSL: consulting fees from Abbvie; Honoraria from Janssen. IZ: speaker fees from Abbvie, Janssen, Takeda, Ferring, Pfizer, Biotoscana; consulting fees from Abbvie, Takeda, Bristol Myers Squibb; grants from Takeda, Pfizer. VJ: consulting fees from Abbvie, Alimentiv, Eli Lilly, GlaxoSmithKline, Arena Pharmaceuticals, Genentech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Topivert, and Celltrion; speaker fees from Takeda, Janssen, Shire, Ferring, Abbvie, and Pfizer. MTA: trainer or lecturer fees for Prime CME, Janssen, Focus Medical Communications, Cornerstones Health, Inc and Imedex; consultant fees from Boehringer-Ingelheim, Landos Biopharma, Gilead, Prometheus Biosciences, Takeda, UCB Biopharma SRL, Eli Lilly, Bellatrix Pharmaceuticals, Abbvie, GI Health Foundation and Bristol Myers Squibb. DTR: grants from Takeda, consultant fees for Abbvie, Altrubio, Arena Pharmaceuticals, Bristol-Myers Squibb, Genentech/Roche, Gilead Sciences, Iterative Scopes, Janssen Pharmaceuticals, Lilly, Pfizer, Prometheus Biosciences, Takeda, and Techlab Inc. WR: speaker fees for Abbott Laboratories, Abbvie, Aesca, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, Yakult; consultant fees from Abbott Laboratories, Abbvie, Aesca, Algernon, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, Astra Zeneca, Avaxia, Roland Berger GmbH, Bioclinica, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, DSM, Elan, Eli Lilly, Ernest & Young, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nash Pharmaceuticals, Nestle, Nippon Kayaku, Novartis, Ocera, OMass, Otsuka, Parexel, PDL, Periconsulting, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble,

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Prometheus, Protagonist, Provention, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, Setpointmedical, Sigmoid, Sublimity, Takeda, Therakos, Theravance, Tigenix, UCB, Vifor, Zealand, Zyngenia, and 4SC; advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Astellas, Astra Zeneca, Avaxia, Biogen IDEC, Boehringer-Ingelheim, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, DSM, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestle, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Zealand, Zyngenia, and 4SC. FM: speaker fees from Merck Sharp & Dohme, Abbvie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira and Biogen. JFR: speaker fees from AbbVie, MSD, Takeda, Pfizer, Ferring, and Falk; consultancy fees from Abbvie, MSD, Takeda, Pfizer, Janssen, Mundipharma, and GlaxoSmithKline; and research grants from Takeda and Abbvie. SD: Honoraria from Abbvie, Ferring, Hospira, Johnson and Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz and Boehringer-Ingelheim.

CR: speaker, consultant, and advisory board member for Astellas, Janssen, Gilead, Merck Sharp and Dohme. LPB: Grants from Abbvie, MSD, Takeda, Fresenius Kabi; Consulting fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Inotrem, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics; Honoraria from Abbvie, Galapagos, Janssen, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Pfizer, Sandoz, Biogen, MSD, Arena, Gilead, Hikma, Amgen, Vifor; Support for attending meetings and/or travel from Abbvie, Galapagos, Janssen, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Pfizer, Sandoz, Biogen, MSD, Arena, Gilead, Hikma, Amgen, Vifor; Participation on a Data Safety Monitoring Board or Advisory Board of Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Inotrem, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan,

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AUTHORS' CONTRIBUTIONS:

PAO: Project administration, Data curation, Resources, Methodology, Visualization, Writing original draft, Writing review & editing. JSL: Data curation, Resources, Software, Formal analysis, Methodology, Visualization, Writing original draft, Writing review & editing. IZ: Data curation, Resources, Methodology, Visualization. VJ, MTA, DTR, WR, FM, JFR, SD, CR: Supervision, Writing review & editing. LPB: Conceptualization, Supervision, Writing review & editing.

JSL and PAO contributed equally.

DATA AVAILABILITY STATEMENT:

All data are provided in the Article and in the supplementary appendix.

FIGURE LEGENDS:

Figure 1: Flow diagram of assessment of studies identified in the systematic review.

Figure 2: Distribution of opportunistic infections in included studies.

Figure 3: Meta-analysis of placebo-controlled ulcerative colitis studies.

Figure 4: Meta-analysis of placebo-controlled Crohn's disease studies.

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Table 1. Incidence rates (per 100 person-years) of opportunistic infections among inflammatory bowel disease subjects in included studies

	Exposed to biologics/SMD (as reported)	Exposed to placebo (as reported)	Exposed to biologics/SMD (proposed definition)	Exposed to placebo (proposed definition)
Overall population	0.42	0.21	0.83	0.61
UC population	0.42	0.23	1.07	0.79
CD population	0.41	0.16	0.48	0.32

SMD: small-molecule drug; UC: ulcerative colitis; CD: Crohn's disease

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Table 2. Incidence rates (per 100 person-years) of opportunistic infections among inflammatory bowel disease subjects according to mechanism of action of advanced therapy

	Exposed to biologics/SMD (as reported)	Exposed to biologics/SMD (proposed definition)
Anti-TNF	0.83	0.94
Anti-integrin	0.05	0.1
Anti-IL12/23	0.27	0.27
JAK inhibitor	0.55	2.45
S1P modulator	0	0.48

SMD: small molecule drug; TNF: tumor necrosis factor; IL: interleukin; JAK: Janus kinase; S1P: sphingosine-1-phosphate receptor

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Table 3: Proposed marker infections or presentations of opportunistic infections in inflammatory bowel disease

Infection
Bacterial infections
Invasive listeriosis
Invasive salmonellosis
Legionellosis
Non-tuberculous mycobacterium disease
Tuberculosis
Fungal infections
Acremonium infection
Blastomycosis
Candidiasis (oropharyngeal, oesophagic, or invasive)
Coccidioidomycosis
Cryptococcosis
Fusarium infection
Histoplasmosis
Invasive aspergillosis
Microsporidiosis
Mucormycosis (*Mucor, Rhizopus, Lichtheimia*)
Paracoccidioidomycosis
Pneumocystis jirovecii
Scedosporium infection
Sporotrichosis
Talaromycosis
Viral infections
BK virus-associated nephropathy
CMV disease
EBV-associated PTLD
HBV reactivation
Herpes zoster
Invasive HSV disease
JC virus-associated progressive multifocal leukoencephalopathy
Parasitic infection
Cryptosporidiosis (severe or prolonged disease)
Strongyloidiasis (hyperinfection/disseminated disease)
Toxoplasmosis
Trypanosoma cruzi reactivation

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus

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Figure 1

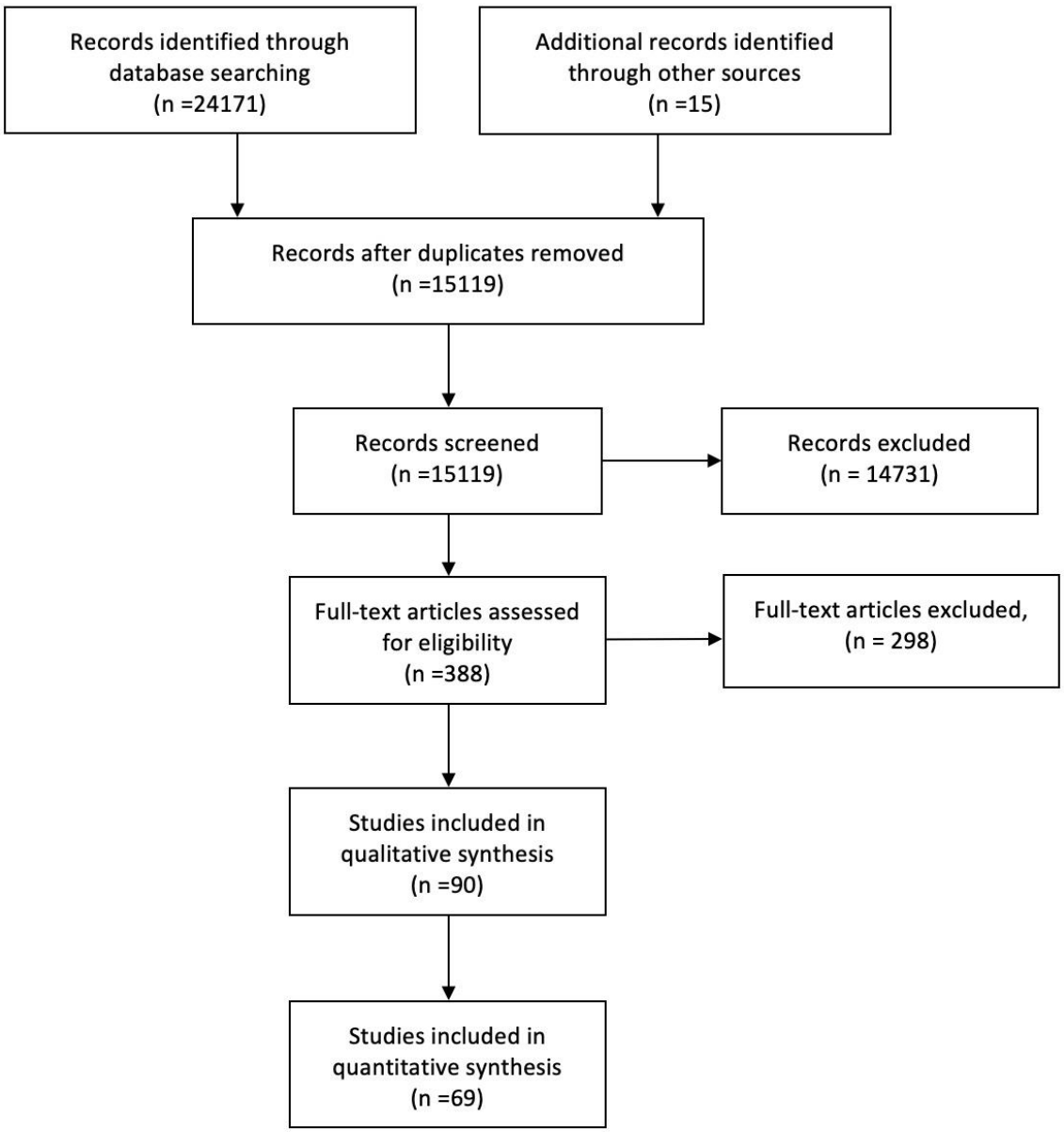

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Figure 2

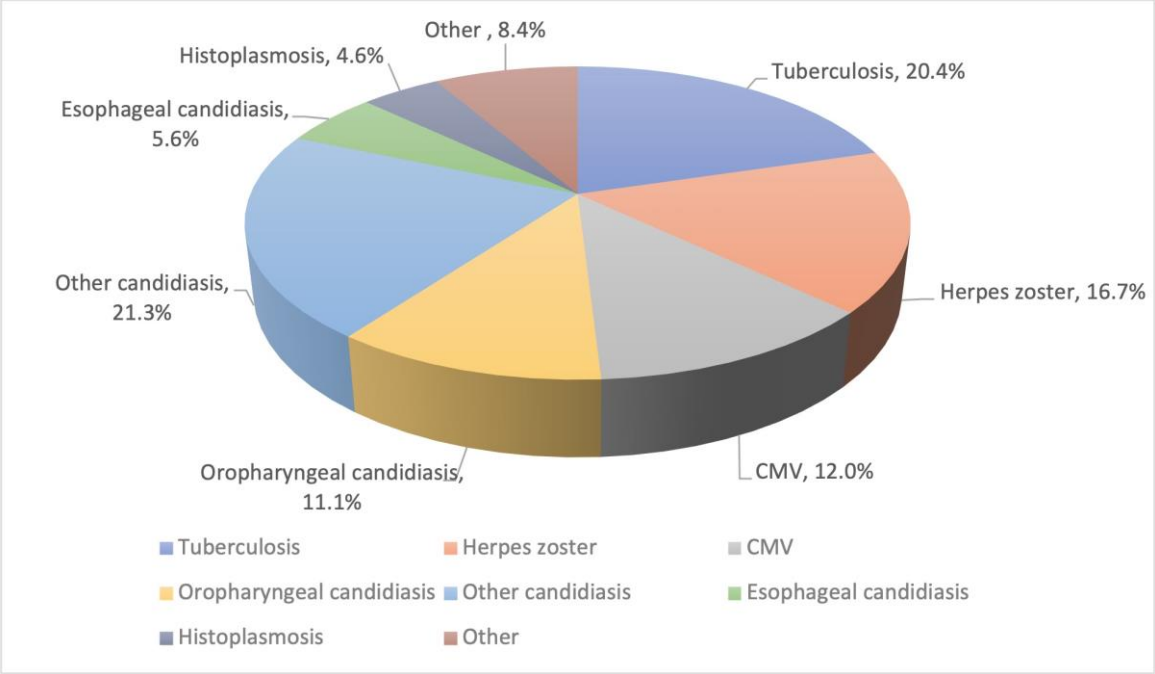

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Figure 3

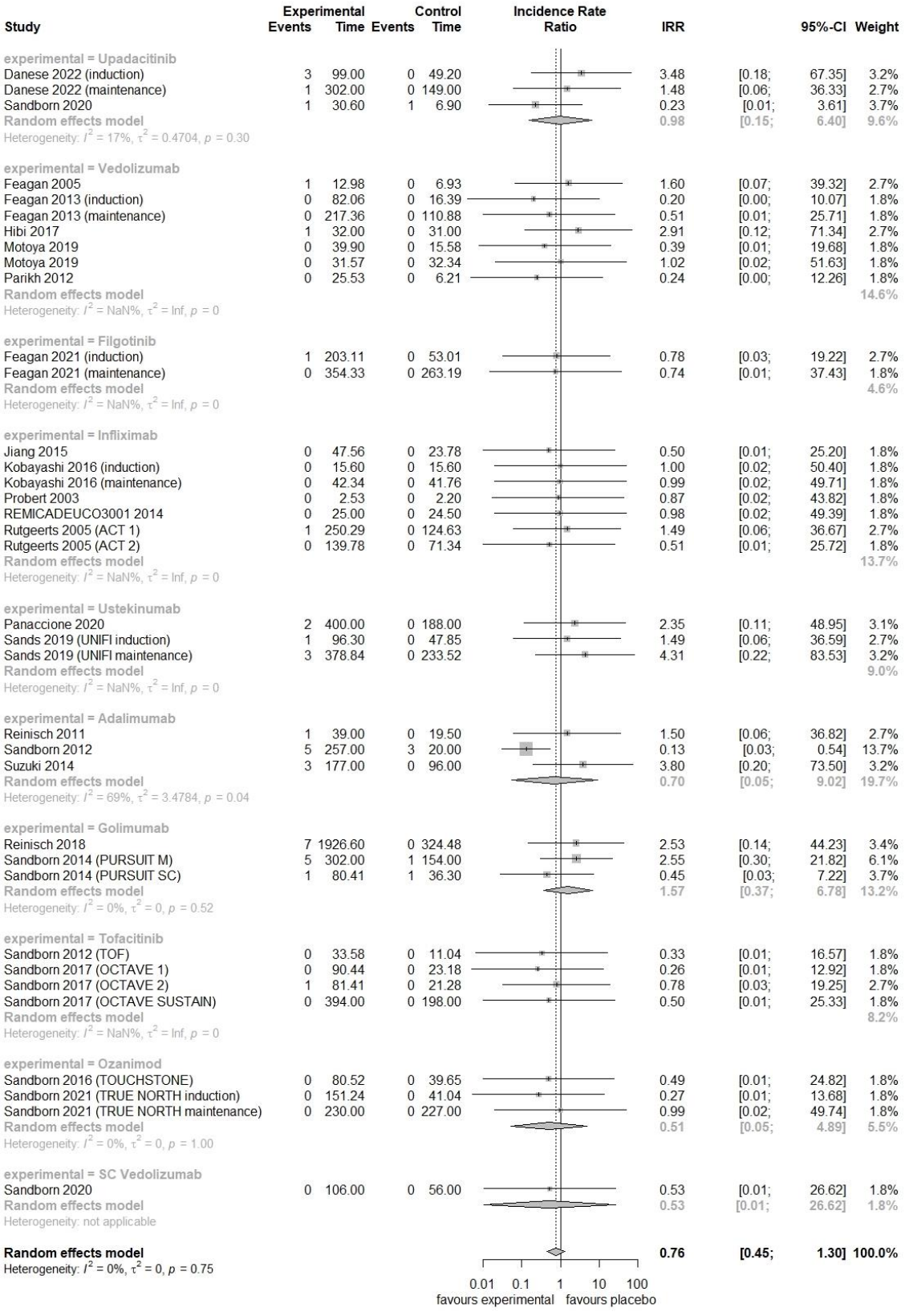

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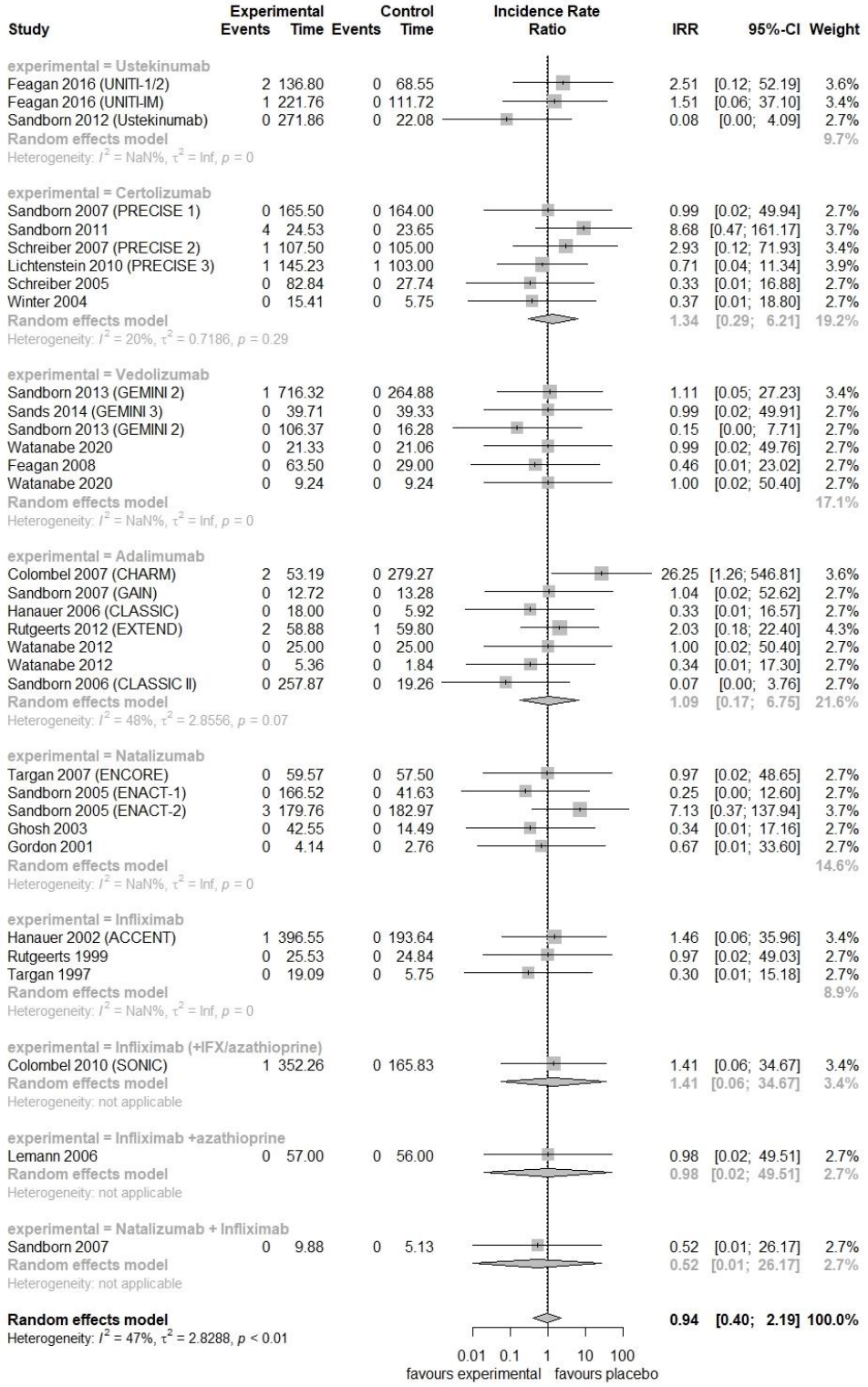
Figure 4



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