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Research article

Adverse events of biologic or small molecule therapies in clinical trials for inflammatory bowel disease: A systematic review and meta-analysis

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ABSTRACT

Background: Biologic or small-molecule therapies are highly effective for the treatment of inflammatory bowel disease (IBD), and approval by the FDA has significantly increased both their clinical use and the development of novel regimens. However, the identification and management of their associated toxicities poses challenges for clinicians and researchers.
Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) published from January 1, 2000, to October 15, 2022, and in the databases. A random-effects model with logit transformation was applied to the analysis heterogeneity between studies was evaluated using the I^2 statistic with incidence and 95 % confidence interval (CI) for any adverse events (AEs), and serious AEs (SAEs).
Results: In Crohn's disease (CD), the total AE incidence was 67.0 % (95 % CI, 66.2%–67.8 %; I^2 = 97.2 %) for any AEs and 7.3 % (6.9–7.7; 97.2) for serious AEs. In ulcerative colitis (UC), the overall incidence of any and serious AEs was 63.6 % (63.0–64.3; 98.1) and 5.7 % (5.4–6.0; 88.9), respectively. The most common AEs were infections (21.5 [20.3–22.8], 32.6 [31.0–34.2], 25.9 [24.5–27.2], and 13.7 [10.7–16.7]) in CD patients that were treated with TNF antagonists, anti-integrins, anti-IL agents, and JAK inhibitors, respectively, and in UC patients also were infections (22.8 [21.7–24.0], 27.4 [25.9–28.9], and 18.4 [16.7–20.2]), respectively, as well as increases in lactic dehydrogenase levels (23.1 [20.8–25.4]) with JAK inhibitors.
Conclusion: This study offers a comprehensive summary of toxic side effects of IBD treatments and a useful reference for both patients and clinicians.

1. Introduction

Biologic or small-molecule therapies have recently attracted attention. These therapies have achieved significant success in the treatment of inflammatory bowel disease (IBD), and they are rapidly being used clinically, as well as hundreds of ongoing trials exploring further indications [1–5]. Biologics are monoclonal antibodies (mAbs) that target complex molecules of tumor-associated antigens, typically over 150 kDa, while small-molecule drugs have molecular weights of less than 500 Da [6]. Treatment of IBD

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mainly involves the blocking of immune cell migration and/or communication [2]. The effectiveness and toxicity of biologic treatment is strongly influenced by immunogenicity resulting from the generation of antibodies against the durg [7], and immunogenicity depends on both the origin and structure of the therapies [7]. It is thus important that gastroenterologists and researchers familiarize themselves with common clinical options.

IBD treatments are classified into biologic and small-molecule therapies [2]. Biologics include tumor necrosis factor (TNF) antagonists, as well as mAbs against cytokines, integrins, and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1). Small-molecule drugs include inhibitors of Janus kinase (JAK) and phosphodiesterase-4 (PDE4), as well as modulators of the 1-phosphosphingosin (S1P) receptor, amongst others [2]. Since their introduction in 1997, many of these treatments have been approved by the Food and Drug Administration of the USA and the European Medicines Agency, including infliximab (Avakine®), adalimumab (Humira®), certolizumab pegol (Cimzia®), ustekinumab (Stelara®), vedolizumab (Entyvio®), tofacitinib (Tofacinix®), and ozanimod (Zeposia®) [8–10]. The first five of these drugs are used for the treating both Crohn's disease (CD) and ulcerative colitis (UC) and the last two are used only for treating UC(8–10). Unfortunately, long-term treatment with biomolecules can induce immunogenicity through the production of anti-drug antibodies [7], which can reduce the response of the patient to the drug [11,12]. This can be partially mitigated by the concurrent use of immunosuppressants, although this may increased risks of malignancy and infection [13]. Immunosuppression is also associated with various side effects [1,7] including development of hypersensitivity, kidney complications, autoimmune reactions (such as demyelination and drug-induced lupus), and infections [14–18].

It is essential to understand the toxicological properties of biologics. To date, few comprehensive analyses of the clinical toxicity of biologics have been conducted, while the available results indicate that the use of biologics is associated with increased risks of infection and malignancies [19–21]. We thus consider it necessary to study the adverse events (AEs) of these drugs and to use standardized methods for summarizing the AEs and toxicities associated with different biologic agents. This will provide clinicians with suitable information for assessing the risks associated with different treatments.

Concurrent increases in the numbers of IBD patients and treatment options represent a significant challenge in the management of these diseases. However, further data analysis will help select the most effective clinical treatment. Here, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) describing AEs potentially associated with biologic or small-molecule therapies, investigate the incidence and profiles of AEs, as well as both any and serious AEs associated with biologic or small-molecule therapy. The differences in AEs related to specific drug targets and IBD types were also investigated to provide a reference for both patients and clinicians. We also investigated AEs related to infection caused by biological inhibitors.

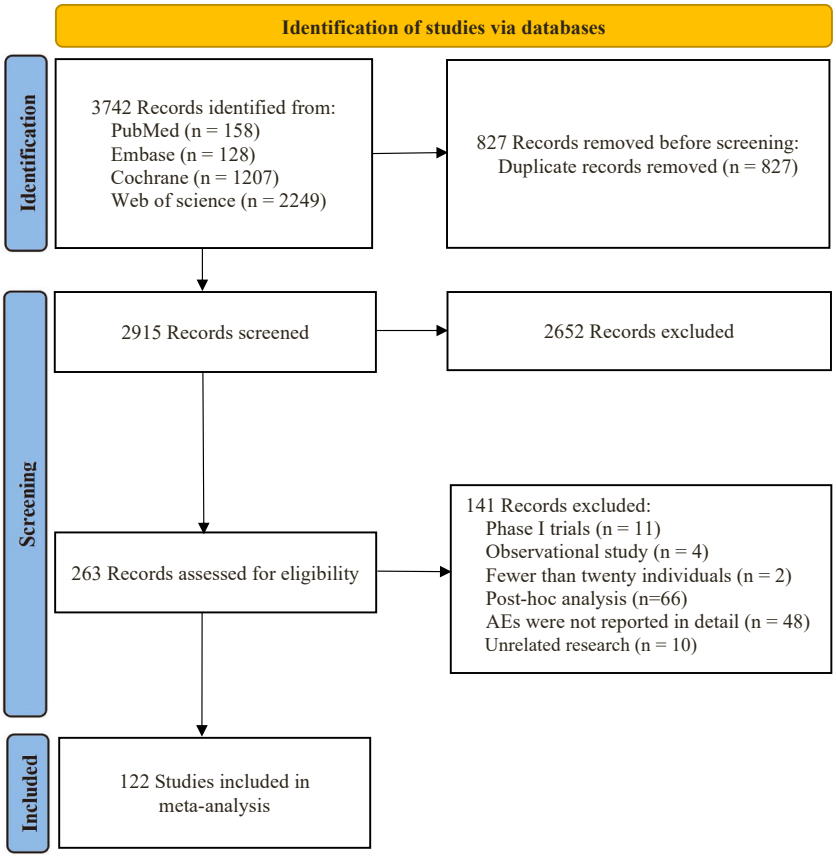

Fig. 1. Study selection process.

2. Method

2.1. Search strategy and study selection

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Program (PRISMA) guidelines and analyzed published RCTs on biologic or small molecule therapies for patients with IBD that reported AEs [22]. The key search terms were "biologic", "small molecule therapies", "IBD", and "clinical trials" which were used to search the PubMed, Cochrane, Embase, and Web of Science databases (eTable 1 in Supplementary Materials) from January 1, 2000, to October 15, 2022. The reference sections of identified articles and reviews were also checked manually for the identification of further relevant publications. The search strategies are outlined in Fig. 1.

The inclusion criteria for articles were [1]: prospective clinical trials on IBD treatment published before October 15, 2022 [2]; subjects that were treated with biologic or small-molecule therapy [3]; clinical trials that reported the incidence of AEs with tabulated data; and [4] publications in English (see eTable 2)(see Fig. 2). The exclusion criteria were [1]: full-text research not available or published [2]; Phase I trials [3]; earlier publications lacking complete data on AEs in the participants [4]; total patient numbers less than 20 [5]; reviews, systematic reviews, meta-analyses, and cost-effectiveness analyses.

2.2. Data extraction

An electronic search was conducted by two independent reviewers with discussion with another senior investigator to review differences to resolve disagreements by consensus. Data tables were prepared for the inclusion of information (eTable 2 in supplementary materials). Summaries of the information on AEs, including the numbers of AEs relative to the numbers of patients, were extracted from the selected articles together with the names of the authors, publication year, the name and phase of the clinical trial, the drugs used for treatment, the numbers of patients treated. Adverse events included any AEs (Common Terminology Criteria for Adverse Events [CTCAE]), serious AEs, deaths, and AEs resulting in discontinuation of treatment. The AE terms were coded according to the Medical Dictionary of Regulatory Activity (MedDRA).

2.3. Statistical analysis

The AE incidence was determined as the number of AEs divided by the total number of patients. The overall incidence of any AEs was pooled as was the incidence of serious AEs. Subgroup analysis was also undertaken to further analyze the influence of IBD type and drug targets. The overall and profile incidence of AEs resulting in discontinuation of treatment, death, or infection, as well as drug types, were also analyzed. The incidence values and 95 % confidence intervals (CIs) were analyzed using a random-effects model with Logit transformation and models were fitted by the restrictive maximum likelihood estimation method.

Differences in the AE incidence between IBD type and treatment drugs were also analyzed. The normality of the data was tested and t-tests were used to analyze differences between data when the *P*-values of the normality test of variance were greater than 0.05; the non-parametric Kruskal-Wallis test was used otherwise. *P*-values <0.05 were considered to indicate a significant difference in the AE incidence between two groups.

Study heterogeneity was determined using the I^2 statistic between studies [23]. The presence of publication bias was assessed by funnel plot, Egger's, and Begg's tests [24]. The results of these three estimates may overstate the aggregate evidence in the meta-analyses [25,26]. Publication bias was further determined using the trim-and-fill method for drawing modified funnel plots, with asymmetry in the plot indicating bias [27]. Risk of bias in the studies was assessed using the Cochrane bias risk tool [28]. STATA version 17, SPSS version 25.0, and the "metafor" and "metan" packages in R version 4.2.1 were used for data analysis.

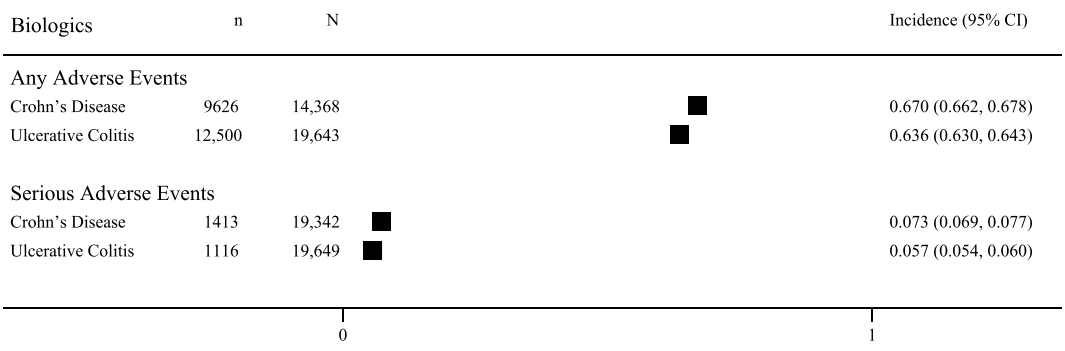

Fig. 2. Overall incidence of AEs in Biologic regimens for patients with IBD.

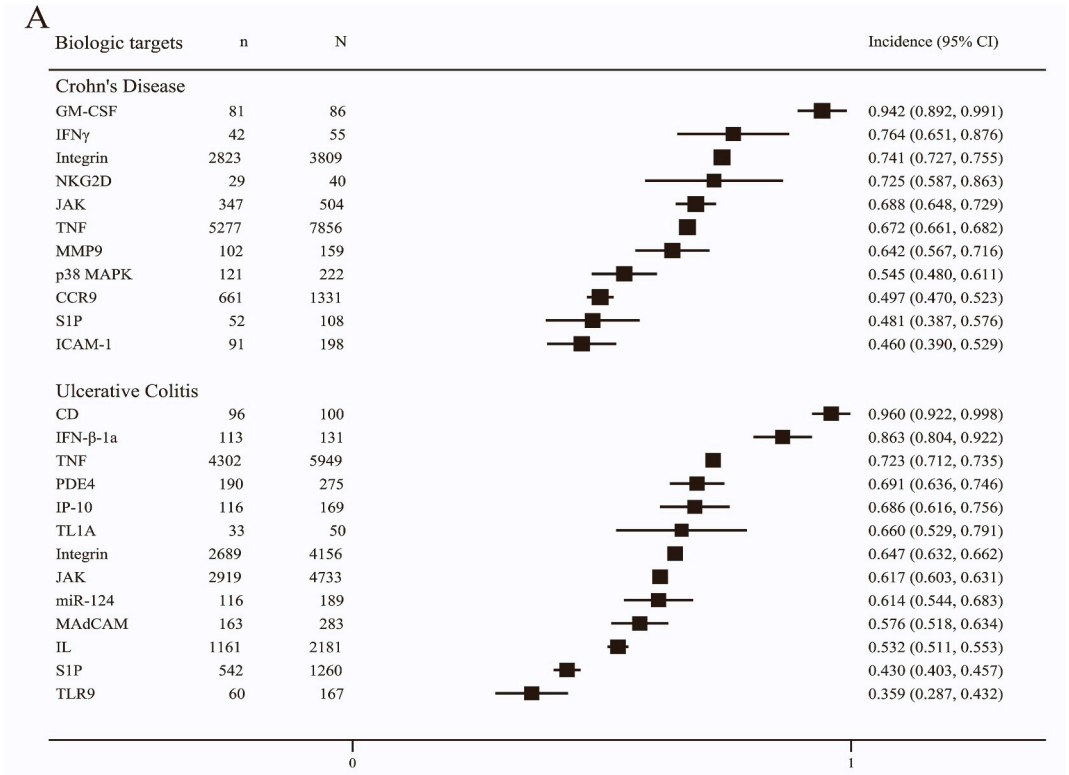

Fig. 3. Overall incidence of any (A) and serious (B) AEs in Biologic regimens for patients with IBD.

3. Results

3.1. Characteristics of subjects in included trials

The initial literature search identified review identified 3742 records. After intensive screening, these were reduced to 122 eligible studies including 39 429 patients (CD, 19 729; UC, 19 700) (Fig. 1; eTable 1 of Supplementary Materials). Overall, 122 clinical trials comprising 39 429 patients were included for the profile of AEs, and out of which 119 trials comprising 24 677 patients (CD, 12 977; UC, 11 700) were used in the overall AE incidence, 3 trials did not report the overall incidence of AE in the article or clinical trial website. In patients with CD, the biologic or small molecule therapies used included tumor necrosis factor (TNF) antagonists (n = 7856), anti-interleukin (anti-IL) agents (n = 5016), anti-integrins (n = 3809), Janus kinase inhibitors (anti-JAK) (n = 504), and others (n = 2544). In patients with UC, the biologic or small molecule therapies used included TNF antagonists (n = 6006), JAK inhibitors (n = 4733), anti-integrins (n = 4156), anti-IL agents (n = 2181) and others (n = 2624) (eTable 2 of Supplementary Materials). Most of the RCTs included in the review were found to have a low risk of bias (eTable 3 of supplementary materials)..

3.2. Overall incidence of adverse events

In analyzing the overall AE incidence, we looked at 119 studies reporting any and serious AEs. The incidence of any AEs was 67.0 % (95 % CI, 66.2%–67.8 %; $I^2 = 97.2$ %) and that of serious AEs was 7.3 % (6.9%–7.7 %; 97.2 %), respectively (Fig. 1). We compiled an overview of the overall AE rate for each biological therapy type based on the drug targets. In patients with CD, the drugs causing any AE most commonly targeted granulocyte-macrophage colony-stimulating factor (GM-CSF) (94.2 % [95 % CI, 89.2%–99.1 %]; 77.1 %), interferon γ (IFNγ) (76.4 % [65.1%–87.6 %]; 0 %), integrin (74.1 % [72.7%–75.5 %]; 98.0 %), natural killer group 2 member D (NKG2D) (72.5 % [58.7%–86.3 %]; 70.9 %), and JAK (68.8 % [64.8%–72.9 %]; 68.8 %). In terms of serious AEs, the most common targets were intercellular adhesion molecule 1 (ICAM-1) (20.3 % [16.4%–24.1 %]; 89.7 %), NKG2D (20.0 % [7.6%–32.4 %]; 70.9 %), sphingosine 1-phosphate (S1P) (12.8 % [2.3%–23.3 %]; 46.9 %), integrin (11.7 % [10.7%–12.8 %]; 4.8 %), and JAK (9.7 % [7.1%–12.3 %]; 47.8 %) (Fig. 3). In patients with UC, the most common targets observed for any AE were a cluster of differentiation (CD) (96.0 % [92.2%–99.8 %]; 89.0 %), IFN-β-1a (86.3 % [80.4%–92.2 %]; 47.6 %), TNF (72.3 % [71.2%–73.5 %]; 98.7 %), phosphodiesterase 4 (PDE4) (69.1 % [63.6%–74.6 %]; 87.9 %), and inducible protein-10 (IP-10) (68.6 % [61.6%–75.6 %]; 92.6 %), while those for serious AEs were CD (17.0 % [9.6%–24.4 %]; 0 %), integrin (8.5 % [7.6%–9.3 %]; 60.0 %), inflammatory microRNA-124 (miR-124) (7.4 % [3.7%–11.1 %]; 0 %), MAdCAM (6.0 % [3.2%–8.8 %]; NA), and human tumor necrosis factor-related ligand 1A (TL1A) (6.0 % [−0.6%-12.6 %]; NA) (Fig. 3).

Over 200 types of AE were found over the 122 trials. To reflect the clinically most relevant AEs, we included those that represented over 5 % of any AEs. In patients with CD, the most common AEs in the "any AE" category resulting from TNF antagonist treatment were infections (21.5 % [95 % CI, 20.3%–22.8 %]), increased white blood cell (WBC) counts (19.5 % [14.0%–25.0 %]), and diarrhea (16.1

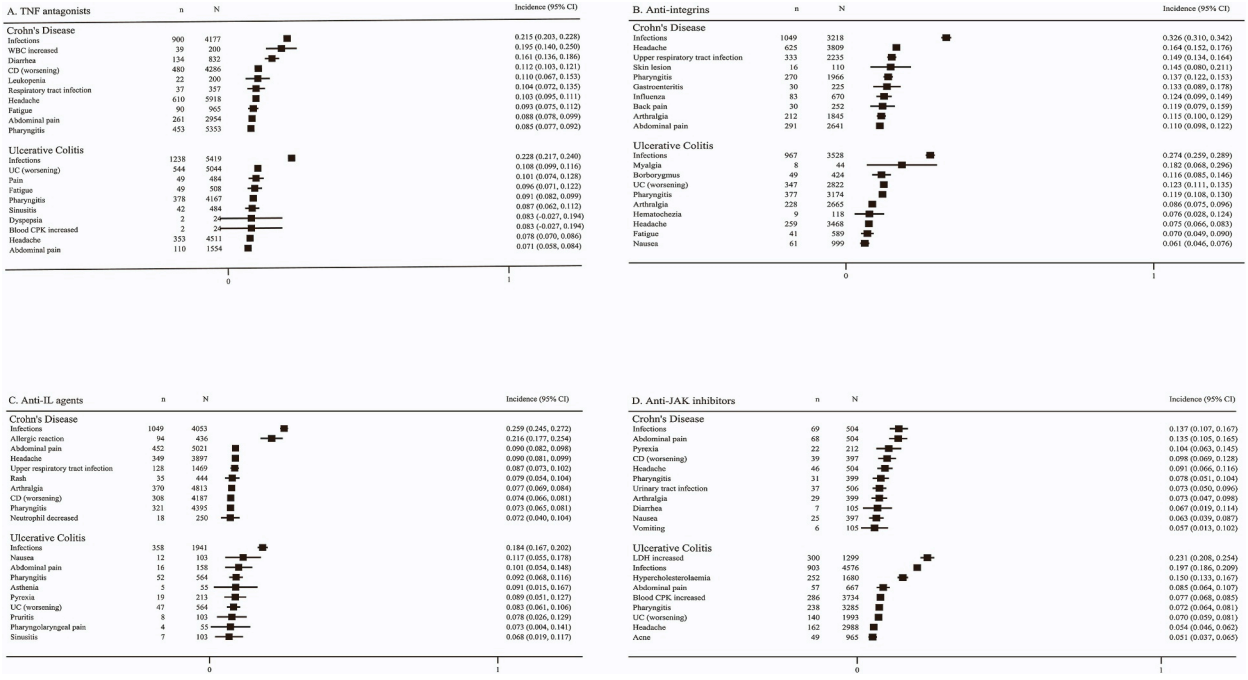

Fig. 4. Incidence of any adverse events in TNF antagonists (A), Anti-integrins (B), Anti-IL agents (C), and JAK inhibitors (D) for patients with IBD.

% [13.6%–18.6 %]), while AEs resulting from anti-integrin treatment were infections (32.6 % [31.0%–34.2 %]), headache (16.4 % [15.2%–17.6 %]), and upper respiratory tract infections (14.9 % [13.4%–16.4 %]). The most common any AEs caused by anti-IL agents were infections (25.9 % [24.5%–27.2 %]), allergic reactions (21.6 % [17.7%–25.4 %]), and abdominal pain (9.0 % [8.2%–9.8 %]) while the most common any AEs by JAK inhibitors were infections (13.7 % [10.7%–16.7 %]), abdominal pain (13.5 % [10.5%–16.5 %]), and pyrexia (10.4 % [6.3%–14.5 %]) (Fig. 4 and eFigs. 1–4 of Supplementary Materials). The most common any AEs caused by S1P, ICAM1, GM-CSF, IFNγ, transforming growth factor β (TGFβ), matrix metalloproteinase-9 (MMP9), p38 mitogen-activated protein kinase (p38 MAPK), NKG2D, and CC chemokine receptor-9 (CCR9) inhibitors were CD worsening (22.2 % [14.4%–30.1 %]), infections (44.4 % [37.5%–51.4 %]), chest discomfort (36.0 % [25.9%–30.1 %]), nausea (19.0 % [7.2%–30.9 %]), infections (19.4 % [12.4%–26.3 %]), abdominal pain (8.2 % [3.9%–12.4 %]), increased levels of alanine amiotransferase (ALT) increased (18.0 % [13.0%–21.3 %]), gastrointestinal disorders and others (42.5 % [27.2%–57.8 %]), and abdominal pain (10.2 % [8.6%–11.8 %]), respectively (eFig. 5 of Supplementary Materials). In patients with UC, the most common any AEs resulting from TNF antagonists were infections (22.8 % [21.7%–24.0 %]), UC worsening (10.8 % [9.9%–11.6 %]), and pain (10.1 % [7.4%–12.8 %]); those resulting from anti-integrin treatment were infections (27.4 % [25.9%–28.9 %]), myalgia (18.2 % [6.8%–29.6 %]), and borborygmus (11.6 % [8.5%–14.6 %]); the most common any AEs caused by anti-IL agents were infections (18.4 % [16.7%–20.2 %]), nausea (11.7 % [5.5%–17.8 %]), and abdominal pain (10.1 % [5.4%–14.8 %]) while the most common any AEs caused by JAK inhibitors were increased lactic dehydrogenase (LDH) levels (23.1 % [20.8%–25.4 %]), infections (19.7 % [18.6%–20.9 %]), and hypercholesterolemia (15.0 % [13.3%–16.7 %]) (Fig. 4 and eFigs. 1–4 of Supplementary Materials). Furthermore, the most common any AEs resulting from treatment targeting CD, S1P, Toll-like receptor 9 (TLR9), TL1A, PDE4, miR-124, MAdCAM, IP-10, and IFN inhibitors were nausea (21.4 % [12.7%–30.2 %]), infections (12.9 % [10.9%–14.8 %]), UC worsening (12.0 % [7.1%–16.9 %]), borborygmus (28.0 % [15.6%–40.4 %]), headache (20.4 % [15.6%–25.1 %]), headache (21.2 % [24.6%–37.8 %]), infections (26.8 % [16.1%–25.6 %]), infections (21.9 % [15.7%–28.1 %]), and headache (53.4 % [44.9%–62.0 %]), respectively (eFig. 6 of Supplementary Materials).

We included serious AEs that occurred in over 1 % of the overall incidence of serious AE. In patients with CD, the most common serious AEs results from TNF antagonists were malnutrition (8.0 % [−20.6%-18.6 %]), CD worsening (5.2 % [4.0%–6.4 %]), and abdominal pain (3.7 % [2.5%–5.0 %]); the most common resulting from anti-integrin drugs were abdominal adhesions (8.3 % [−7.3%-24.0 %]), CD worsening (4.1 % [1.9%–6.3 %]), and serious infection (2.7 % [2.1%–3.3 %]); those caused by anti-IL agents were abdominal pain (6.1 % [4.1%–8.0 %]), CD worsening (3.7 % [2.5%–5.0 %]), and abdominal abscess (3.6 % [2.1%–5.2 %]) and those resulting from JAK inhibitors were serious infection (3.7 % [0.1%–7.3 %]), abdominal abscess (1.4 % [0%–2.7 %]), and perianal abscess (1.0 % [0%–2.0 %]) (Fig. 4 and eFigs. 1–4 of Supplementary Materials). The most common serious AEs caused by S1P, ICAM1, GM-CSF, IFNγ, TGFβ, and MMP9 inhibitors were CD worsening (10.2 % [4.5%–15.9 %]), rash (9.6 % [5.5%–13.7 %]), CD worsening (7.0 % [1.6%–12.4 %]), CD worsening (7.1 % [−0.6%–14.9 %]), abdominal pain (1.6 % [−0.6%–3.8 %]), and CD worsening (3.1 % [0.4%–5.9 %]), respectively (eFig. 5 of Supplementary Materials). In patients with UC, the most common serious AEs caused by TNF

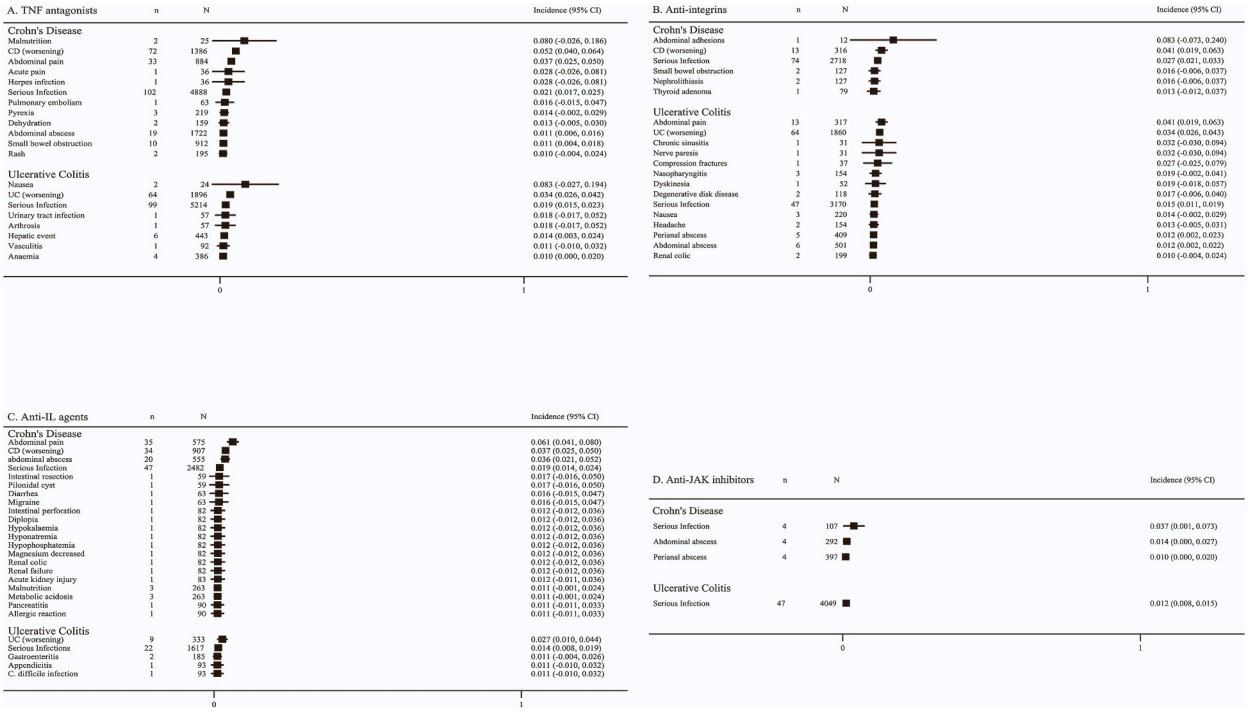

Fig. 5. Incidence of serious adverse events in TNF antagonists (A), Anti-integrins (B), Anti-IL agents (C), and JAK inhibitors (D) for patients with IBD.

antagonists were nausea (8.3 % [−2.7%-19.4 %]), UC worsening (3.4 % [2.6%–4.2 %]), and serious infection (1.9 % [1.5%–2.3 %]); those caused by anti-integrins were abdominal pain (4.1 % [1.9%–6.3 %]), UC worsening (3.4 % [2.6%–4.3 %]), and chronic sinusitis (3.2 % [−3.0%–9.4 %]); those resulting from anti-IL agents were UC worsening (2.7 % [1.0%–4.4 %]), serious infections (1.4 % [0.8%–1.9 %]), and gastroenteritis (1.1 % [0.4%–2.6 %]); those resulting from JAK inhibitors were serious infection (1.2 % [0.8%–1.5 %]) (Fig. 5 and eFigs. 1–4 of Supplementary Materials). The most common serious AEs caused by CD, S1P, TLR9, TL1A, PDE4, miR-124, MAdCAM, and IP-10 inhibitors were UC worsening (6.3 % [−5.6%–18.1 %]), abdominal pain (2.0 % [−0.7%–4.7 %]), UC worsening (2.4 % [0.1%–4.7 %]), UC worsening (4.0 % [−1.4%–9.4 %]), renal colic (1.8 % [−0.2%–3.9 %]), headache (4.2 % [1.4%–7.1 %]), UC worsening (2.8 % [0.9%–4.8 %]), and vomiting (1.2 % [−0.4%–2.8 %]), respectively (eFig. 6 of supplementary materials).

3.3. Overall incidence of infection

Over the 122 studies, 112 (91.8 %) reported the overall incidence and profiles of infection involving 33 777 patients with IBD. The overall incidence of infection was 19.7 % (15.6%–23.8 %; 96.4 %) and that of serious infections was 1.6 % (1.2%–2.0 %; 69.3 %), respectively (Fig. 6). Infections occurred most commonly in drugs targeting ICAM-1 (44.4 % [37.5%–51.4 %]; NA), GM-CSF (44.4 % [37.5%–51.4 %]; NA), and IFN (42.7 % [34.3%–51.2 %]; NA) while serious infections were most apparent with drugs targeting CD (4.8 % [0.2%–9.3 %]; 0 %), integrin (2.1 % [1.7%–2.4 %]; 96.0 %), and TNF (2.0 % [1.7%–2.3 %]; 96.9 %) (Fig. 6). The most common infection sites and pathogens associated with TNF antagonists were the upper respiratory tract (5.6 % [5.0%–6.2 %]) and herpes virus (1.9 % [1.3%–2.6 %]), respectively, while those related to anti-integrin treatment were lower respiratory tract (5.6 % [3.2%–8.0 %]) and Epstein-Barr virus (EBV) (2.9 % [1.9%–4.0 %]) infections, respectively. Infection sites and pathogens resulting from anti-JAK inhibitors were urinary tract (5.8 % [3.5%–8.1 %]) and candidiasis (3.7 % [0.1%–7.3 %]), respectively (Fig. 7) while the most

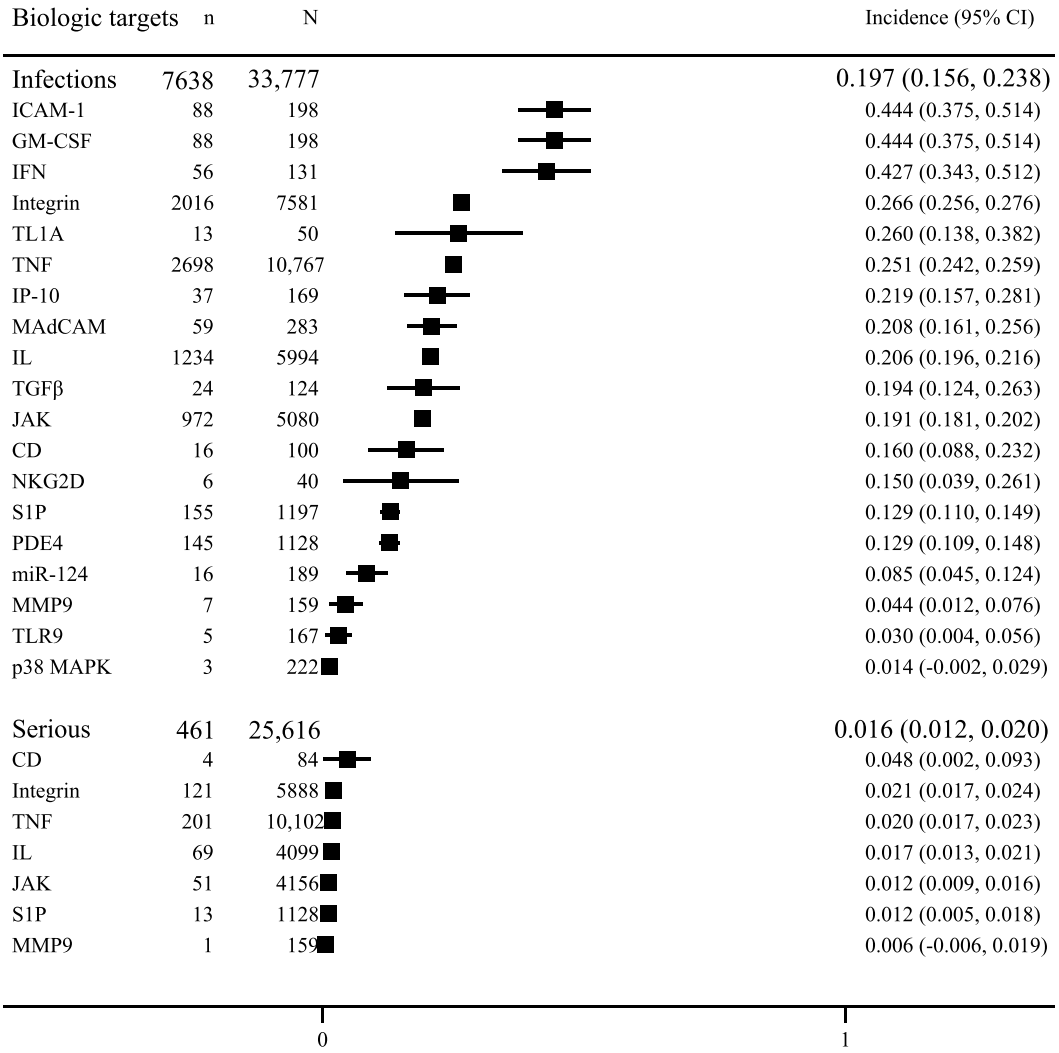

Fig. 6. Overall incidence of infections and serious infections in patients with IBD.

Fig. 7. Incidence of infections in TNF antagonists (A), Anti-integrins (B), Anti-IL agents (C), and JAK inhibitors (D) for patients with IBD.

common infection sites associated with S1P, CD, TGF-β, p38 MAPK, MMP9, ICAM-1, GM-CSF, TLR9, PDE4, and IFN inhibitors were the urinary tract (5.3 % [1.9%–8.6 %]), gastrointestinal tract (6.3 % [−5.6%-18.1 %]), urinary tract (8.1 % [3.3%–12.9 %]), upper respiratory tract (1.4 % [−0.2%-2.9 %]), urinary tract (2.5 % [0.1%–4.9 %]), upper respiratory tract (13.6 % [8.9%–18.4 %]), upper respiratory tract (7.0 % [1.6%–12.4 %]), upper respiratory tract (3.0 % [0.4%–5.6 %]), upper respiratory tract (4.9 % [1.6%–8.2 %]), and upper respiratory tract (42.7 % [34.3%–51.2 %]), respectively. The most common pathogens associated with S1P and CD inhibitors were herpes virus (0.8 % [0.2%–1.3 %]) and candidiasis (1.2 % [−1.1%-3.5 %]), respectively (eFig. 7 of supplementary materials).

3.4. AEs associated with treatment discontinuation and death

Over the 122 studies, 116 (95.1 %) reported treatment-related AEs that led to treatment discontinuation of treatment. Of 37 997 patients, there were 1986 (CD, 1122; UC, 864) discontinued treatment due to AEs, an overall incidence of 5.2 % (5.0%–5.5 %). Forty-four AEs were included in the present study, while 1770 were not described in detail in the included studies. The most common reasons for discontinuing treatment were CD worsening (n = 59 [3.0 %]), UC worsening (52 [2.6 %]), abdominal abscess (14 [0.7 %]), perianal abscess (10 [0.5 %]), and intestinal perforation (6 [0.3 %]) (eTable 5 of Supplementary Materials).

In all, 117 (95.9 %) reported treatment-related deaths. A total of 34 deaths (CD, 19; UC, 15) occurred out of the 38 053 patients, an overall incidence of 0.08 % (0.06%–0.12 %). Twenty-eight AE types were reported and six were not described in detail. The most common causes of treatment-related death were acute respiratory failure (6 [18.0 %]), cardiac arrest (5 [15.0 %]), acute coronary syndrome (4 [12.0 %]), sepsis (3 [9.0 %]), and pulmonary embolism (2 [6.0 %]) (eTable 6 of Supplementary Materials).

3.5. Difference analysis and study heterogeneity

Statistical analysis showed no significant differences in AE incidence in relation to IBD types, target agents in CD, and target agents in UC ($p = 0.764$, 0.830, and 0.395, respectively), serious AEs ($p = 0.473$, 0.777, and 0.860, respectively), treatment-related AEs leading to discontinuation ($p = 0.636$, 0.186, and 0.145, respectively), and treatment-related deaths ($p = 0.796$, 0.819, and 0.381, respectively). However, the any AE incidence differed significantly in both CD and UC patients treated with anti-JAK inhibitors ($p = 0.021$) (eTable 4 of Supplementary Materials).

A meta-regression model was used to quantify the heterogeneity between the included studies and sources of heterogeneity, such as IBD type and drug targets, were analyzed. Significant sources of heterogeneity were defined by $p < 0.05$(eTable 7 of Supplementary Materials). Neither the classical nor revised funnel plots showed any obvious asymmetry, suggesting that there was no significant publication bias (the presence of asymmetry in the revised funnel plot analyzed by the scissor-supplement method would be an indication of publication bias). The absence of publication bias was confirmed by Egger's ($p > 0.05$) and Begg's ($p > 0.05$) tests (eFigs. 8–13 of Supplementary Materials).

4. Discussion

With a large number of biologic and small-molecule drugs have proved highly effective for treating IBD(29), clinicians and patients must pay attention to possible treatment-related AEs and safety issues associated with these novel therapies. Clinical trials play major roles in the identification of these problems and the relatively high incidence of AEs associated with these therapies requires thorough investigation to ensure the safety of the drugs. To address this, we conducted an overview and analysis of the incidence of such AEs to assess these issues, which will provide a reference for the management and treatment of IBD in clinical practice.

We conducted a meta-analysis of 122 studies including 39 429 patients (CD, 19 729; UC, 19 700) involving 55 biologic or small-molecule therapies and 19 categories of drug targets to evaluate the incidence and profiles of AEs associated with IBD treatment. Overall, the AE incidence in the RCTs ranged from 4 % to 96 % over the different interventions. This current systematic review is, to the best of our knowledge, the largest and most complete on the topic. Many findings have emerged from the analysis that have important implications for therapeutic decision-making. First, the pooled data demonstrated that the overall rates of AEs, SAEs, discontinuation, and death mostly showed no significant differences between the various IBD types and biologic treatment. Although JAK inhibitors are highly effective and lead to rapid improvement of symptoms, they are used as second-line therapy due to the high AE incidence in IBD patients [29]. Second, infection was the predominant AE not only for anti-TNF antagonists but also for integrins, anti-IL agents, and JAK inhibitors in both CD and UC. Previous studies have focused on the relationship between serious infection and biologic therapies in IBD patients but the conclusions were inconsistent. While Peyrin-Biroulet et al. found that TNF antagonists were not associated with an increased risk of serious infection [30], Lichtenstein et al. observed an increased risk of infection in patients treated with IFX (31). We further summarized information on the infection sites and associated pathogens, finding that infections most commonly occurred in the respiratory and urinary tracts. In terms of pathogens, Shah ED et al. reported that anti-TNF agents were linked with greater risks of opportunistic infections [32]. While treatment with JAK inhibitors raises the risk of herpes zoster infections in patients with immune-related disorders [33]. Our findings are consistent with previous meta-analyses, the herpes virus was most often associated with infections resulting from treatment with TNF antibodies and integrins, while the most common pathogens associated with anti-IL agents and anti-JAKs were EBV and candida. This suggests that all biologic therapies have the potential to suppress intrinsic systemic immunity. In clinical practice, clinicians and patients should be aware of such infection-related manifestations to allow early treatment and adjustment of management strategies. Third, apart from infections, worsening of both CD or UC was found to be prevalent and was frequently associated with discontinuation of treatment. Abdominal or perianal abscesses were also strongly associated with treatment-related discontinuation. It has been reported that patients with inadequate disease control may be more prone to disease-related complications [34], which could indicate the need for the development of more effective therapeutic options in the future [35]. Last but not least, treatment-related deaths were found to be relatively rare, affecting only 34 of 37 997 patients. The causes of mortality were mostly acute respiratory failure and cardiac events. Thrombosis is known to be a rare complication of IBD and was included with cerebrovascular events in our study. The reason for this is the activation of the coagulation cascade by inflammatory factors associated with IBD which can lead to the development of thrombosis [36]. Studies have shown an incidence of 1.3–7% of thromboembolic events associated with IBD (37), representing the third leading cause of death (10 %) in these patients [38], clinicians should be aware of this increased risk and take appropriate measures for prevention in treatment accordingly. Taken together, these findings may provide useful reminders to clinicians when treating IBD patients with biologics.

The side effects found by previous meta-analyses were similar to those observed in the present study. The most frequent AE associated with vedolizumab was upper respiratory tract infection including nasopharyngitis and *Clostridium difficile* infection [39]. There are two reasons for this result. On the one hand, the respiratory, urinary, and gastrointestinal tracts were the most common sites of infections, as they are connected to the external environment. On the other hand, opportunistic infections usually have a negligible effect on the health of immunocompetent individuals but can be more severe in immunosuppressed populations. In addition, we found that headaches were a frequent AE associated with integrin, anti-IL, and JAK inhibitor treatment. However, the underlying molecular mechanisms of headaches remain unknown [40]. Another study reported that inflammatory factors played a role in neuropathic pain mediated by the production of prostaglandin E2 (PGE2) and pro-inflammatory cytokines such as TNF-α and interleukins (IL-1β, IL-6) [41], which are involved in pain generation [41]. Clinical observation after a clinical trial found that tofacitinib-related AEs were skin reactions and headaches [42]. Hence, we speculate that biologic agents reduce the role of certain inflammatory factors in the intestinal mucosa, although these factors also play physiological roles in other sites. Overall, the precise molecular mechanism of potential treatment-related AEs requires further exploration which could offer net benefit in making treatment decisions to improve patient prognosis and quality of life.

Our work has multiple merits. First, previous reports have focused on specific AEs such as infections, opportunistic infections, serious infections, and psychiatric manifestations, and they analyzed limited numbers of publications often only summarizing the occurrence of single side effects [34,43–45]. Here, we summarized the most common of any AEs (>5 %) and more than 1 % of serious AEs associated with CD and UC. Second, previous studies have tended not to focus on the drug targets when assessing AEs associated with IBD treatment with biologic or small-molecule therapies [46]. Our research focused on the analysis of AEs, serious AEs, and infections in relation to different drug targets. Third, we summarized the causes of AEs, serious AEs, treatment-related discontinuations, and deaths in detail. Compared with previous studies, conducted a more comprehensive description of the AEs associated with biologic treatments in CD and UC. In general, this meta-analysis and systematic review is the first to comprehensively report the common AEs and detail causes of discontinuation and death with subgroup analyses for biologic therapies based on IBD type and drug agents. Importantly, although the toxicity profiles of different targets have distinct characteristics, we provide the basis for clinicians to select biological agents according to the characteristics of different patients.

Several shortcomings are inevitable in our study. Firstly, RCTs might underestimate the incidence rate of AEs due to restricted

sample sizes and shorter follow-up periods. we also did not explore the incidence of tumors to the limitations in the study duration. However, the initial period allows a greater opportunity to identify the presence of opportunistic or serious infections. Large-scale real-world studies based on large populations are required for the characterization of the safety profiles of novel therapies in the future. Second, we analyzed only AEs with an incidence of more than 5 % and serious AEs with an incidence of over 1 %, thus ignoring rare AEs. Furthermore, the list of infection sites and opportunistic infections in IBD clinical trials was not comprehensive, and the definitions of opportunistic infections used in RCTs were not uniform. Thus, the results should be interpreted with caution. In addition, we did not analyze infusion-related reactions, as we included a large number of drugs. It is known that injection reactions are closely related to the injection mode, species homology, and the structure and size of the drug molecule. Further, we included some biologics and small molecules that are not currently approved for IBD, for example, NKG2D and ICAM-1 in CD, and anti-CD agents and IP-10 in UC patients [47–50], which not only have poor efficacy but also have a high incidence of AEs or serious AEs. The study also evaluated the safety data of induction and maintenance together, which may have reduced the incidence of some AEs. Finally, the results may also be affected by any bias or mistake made by the researchers in the original studies, and the results applied only to the group of patients eligible for the included trial. Large, real-world studies need to be conducted to verify our results. Nevertheless, the precise attributable risk associated with each target drug is difficult to distinguish and although this meta-analysis offers a detailed evaluation of the AEs between CD and UC across multiple therapies, the key drivers of toxicities associated with biologic and small-molecule therapies require further exploration in the future.

5. Conclusions

This meta-analysis summarized the incidence of common treatment-related AEs associated with the use of biologic and small-molecule therapies for IBD, together with analyzing the causes of treatment discontinuation and treatment-associated death. As the use of biologics increases, the drivers of their associated toxicities require further investigation. However, toxicities related to the drug targets themselves were found to vary. This allows the selection of specific biologic therapies and management strategies for specific patient groups according to the drug and target type, target expression and distribution, and IBD type. This comprehensive overview of AEs associated with biologic and small-molecule therapies offers a reference for clinicians and may guide clinical practice.

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Ethics approval and consent to participate

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, it does not require the approval of the independent ethics committee.

Availability of data and materials

All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25357.

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