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Association Between Biologics and Janus Kinase Inhibitors With Inflammatory Bowel Disease as Paradoxical Reactions: A Real-World Assessment

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ABSTRACT

Background and Objective: With limited evidence connecting paradoxical inflammatory bowel disease (paradoxical IBD) to the newest biologics and Janus kinase inhibitors, our study aims to investigate the occurrence of paradoxical IBD induced by these agents in treating other immune-mediated inflammatory diseases (IMIDs). We aim to identify associated risk signals, the primary affected population, and the risk profile changes over time.

Methods: We performed disproportionality analysis to evaluate paradoxical IBD risk signals using data from the FDA Adverse Event Reporting System. Stratification analyses according to IBD subtype, age, gender, and agents' indications were performed. Weibull shape parameter (WSP) test was conducted to assess paradoxical IBD risk changes over time. Linkage disequilibrium score regression and Mendelian Randomization were employed to evaluate genetic correlations and causality between these agents' indications (i.e., non-IBD IMIDs) and IBD.

Results: This study included 3296 patients reporting 3407 occurrences of paradoxical IBD following using these agents as primary suspects. Among TNF blockers, consistent positive signals for paradoxical IBD were noted: Adalimumab (n = 1983, ROR [95%CI] = 1.55 [1.47–1.63]), Infliximab (n = 545, ROR [95%CI] = 2.12 [1.95–2.32]), Certolizumab Pegol (n = 342, ROR [95%CI] = 1.9 [1.71–2.12]), and Golimumab (n = 154, ROR [95%CI] = 1.64 [1.4–1.93]). Ustekinumab, an IL-12 and IL-23 antagonist, also showed a strong positive signal (n = 155, ROR [95%CI] = 2.03 [1.73–2.39]). Conversely, Upadacitinib, Tofacitinib (Janus kinase inhibitors), and Risankizumab (IL-23 antagonist) exhibited insignificant associations with paradoxical IBD. Crohn's disease (CD) is the mainly developing form. WSP analysis identified two temporal patterns of paradoxical IBD: early failure and random failure types. Significant genetic correlations between three IMIDs and IBD were uncovered, with psoriasis specifically found to causally elevate CD risk.

Conclusions: This study identifies paradoxical IBD as a consistent positive signal across multiple IMID agents, predominantly manifesting as CD, potentially aiding in timely detection and therapeutic decision-making.

Zhi-Qing Zhan and Jia-Xin Li contributed equally to this work.

Summary

- Summarise the established knowledge on this subject
  - Previous studies have predominantly focused on paradoxical adverse events (PAEs) in dermatology or rheumatology, with very limited evidence regarding paradoxical inflammatory bowel disease (paradoxical IBD).
- What are the significant and/or new findings of this study?
  - Consistent positive signals for paradoxical IBD were observed among four TNF blockers and the IL-12 and IL-23 antagonist Ustekinumab, but not among Janus kinase inhibitors or the IL-23 antagonist Risankizumab.
  - Crohn's disease was the prevailing form of paradoxical IBD, irrespective of the type of biological agent used.
  - There were two distinct different temporal patterns of paradoxical IBD caused by biologics: early failure type and random failure type.

1 | Introduction

Recently, the advent of biological agents has revolutionized treatment for systemic immune-mediated diseases such as rheumatoid arthritis (RA), psoriasis, and inflammatory bowel diseases (IBD) [1]. However, in addition to known adverse effects, rare and unexpected side effects termed as paradoxical effects have emerged. Paradoxical adverse events (PAEs) are defined as the onset of a pathological condition during biological therapy that typically responds to this drug class. The implicated agents must have demonstrated prior efficacy in treating the induced condition [1, 2]. PAEs, rare and unobserved during these agents' developmental stages, were later identified in isolated cases or case series [1]. Typical instances include the emergence of de novo psoriasis during anti-tumor necrosis factor (TNF)-α therapy for conditions like RA or IBD, or psoriasis exacerbation during its own or psoriatic arthritis treatment with an anti-TNFα agent. In contrast, IBD onset or worsening in patients undergoing anti-IL-17A therapy are not deemed paradoxical as these conditions are known to be unresponsive to such agents [3]. PAEs can lead to significant impairment, making early detection and management of these drug class effects crucial, particularly in conditions like IBD, where alternative therapeutic options are relatively scarce. However, previous studies have predominantly focused on PAEs in dermatology or rheumatology [3–5], with very limited evidence regarding IBD as a paradoxical effect (i.e., paradoxical IBD). Most existing evidence stems from case reports [6, 7], leaving a significant gap in comprehensive, systematic investigations of paradoxical IBD in real-world setting.

Consequently, this study aims to address the following questions: (1) which biological agents or Janus kinase inhibitors are more likely to induce paradoxical IBD; (2) whether a paradoxical IBD occurs at all or preferentially in a certain patient population; and (3) how does the risk of paradoxical IBD evolve over time? We performed a pharmacovigilance study based on adverse event (AE) data from FDA Adverse Event Reporting System (FAERS) to explore potential paradoxical IBD induced by six biologics and two Janus Kinase inhibitors across various populations. Furthermore, prior research suggests genetic predisposition as a risk factor for paradoxical IBD [8]. Studies have associated IBD with other immune-mediated inflammatory diseases (IMIDs), some of which share similar genetic characteristics with IBD [8, 9]. In this context, paradoxical IBD may represent the 'unmasking' of an underlying inflammatory disease process in susceptible individuals. To delve deeper, we used linkage disequilibrium score regression (LDSC) and Mendelian Randomization (MR) [10] to investigate genome-wide genetic correlations and causality between these agents' indications (excluding IBD) and IBD. Finally, considering our current limited knowledge of PAEs and the expected rise in cases like paradoxical IBD due to increased biological use, we further propose suggestions for future management of PAEs. The study design is outlined in Figure 1.

2 | Methods

2.1 | Data Sources of Pharmacovigilance Analysis

FAERS is a public post-marketing pharmacovigilance database compiling global data on millions of AEs for approved drugs and biologics. It enables the detection of unexpected AE patterns potentially overlooked in clinical trials due to participant limitations [11]. This study investigates eight commonly used biologics and Janus kinase inhibitors, including Adalimumab, Certolizumab Pegol, Infliximab, Golimumab, Ustekinumab, Upadacitinib, Risankizumab, and Tofacitinib, which are indicated for both IBD and other IMIDs. These agents represent diverse classes of IMIDs therapies—TNF blockers, IL-12 and IL-23 antagonists, and Janus kinase inhibitors—enable a thorough assessment of the risk for paradoxical IBD among various therapeutic categories. We extracted AE reports related to these agents from the FAERS Dashboard, using both generic and trade names as search terms, covering data from its inception on January 1, 2004, to Q4 2023. Only those medications identified as primary suspect agents were considered for analysis. Adverse reactions in the FAERS database are categorized using Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) codes [11]. During the retrieval process, we restricted the indications in the adverse reaction reports to those excluding IBD for each agent, and confined the PT to IBD and its subtypes, including Crohn's disease (CD) and ulcerative colitis (UC). Given that the data were anonymized, this study did not require ethical committee approval. The FDA's prescribing information for each agent is summarized in Supporting Information S1: Table S1.

2.2 | Statistical Analysis of Pharmacovigilance Analysis

Disproportionality analysis is a data mining algorithm that identifies adverse drug reactions in large pharmacovigilance databases by comparing the observed frequency and the background frequency of drug-related AEs [11]. In this study, we used the Reporting Odds Ratio (ROR), a proven method for disproportionality analysis, to identify potential paradoxical IBD. When the lower limit of the 95% confidence interval (CI) for the

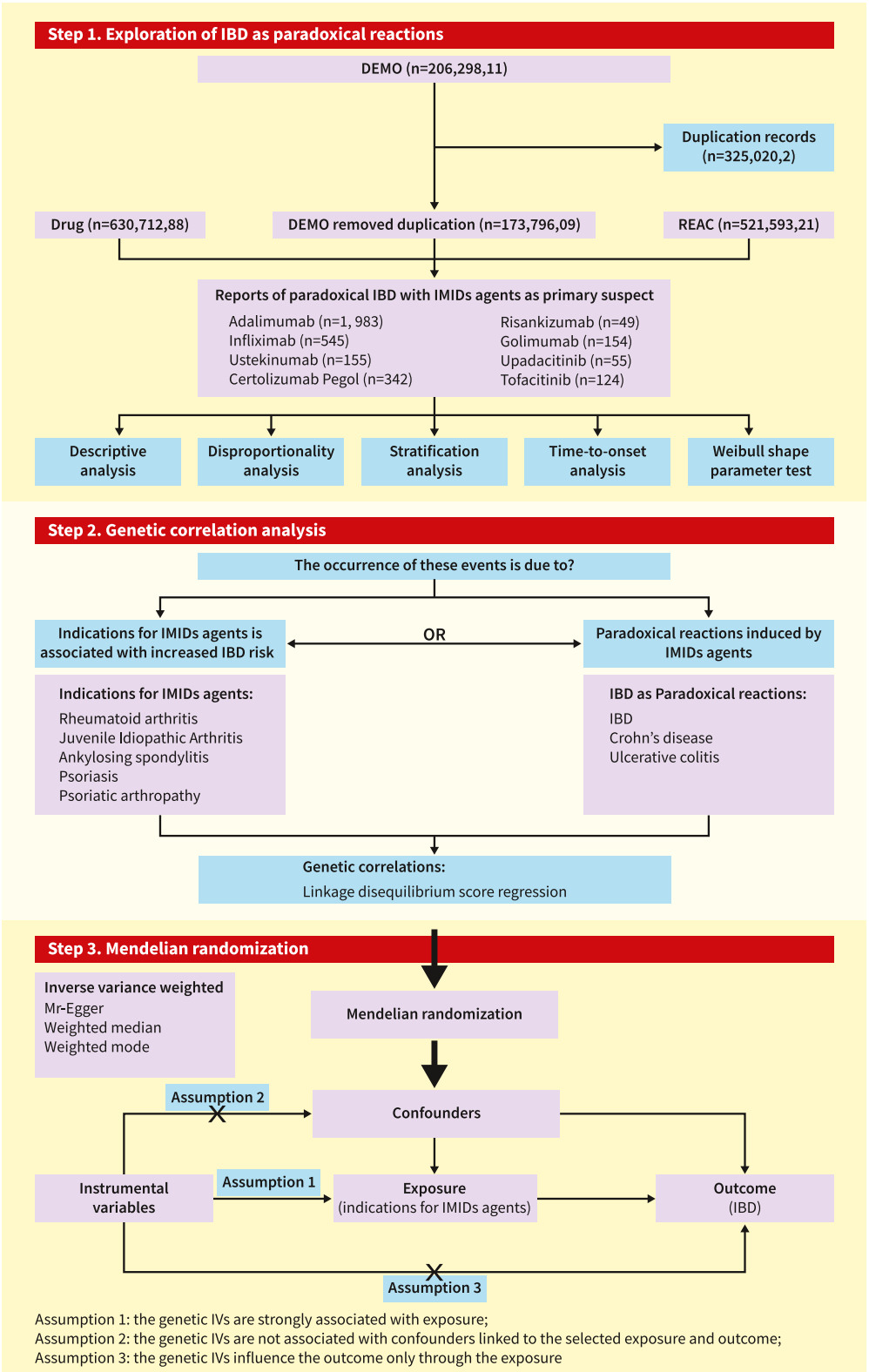

FIGURE 1 | Study design. DEMO, demographic and administrative information; DRUG, detailed drug-related data; IBD, inflammatory bowel disease; IMIDs, immune-mediated inflammatory diseases; IVs, instrumental variables; REAC, the preferred terminology for adverse events. **n* signifies the count of reports, with each patient potentially contributing ≥ 1 records.

ROR value is > 1.0 with at least 3 target AE reports [11], it suggests a potential high risk of the drug causing the AE, indicating a positive signal for paradoxical IBD. The ROR can also compare agents' adverse reaction risks, with a higher ROR indicating a higher paradoxical IBD risk. Stratification analyses encompassed two primary aspects: Initially, we performed population stratification by examining IBD subgroups (CD and UC), age groups (0–18, 18–65, ≥ 65), and gender, with the indications limited to all

non-IBD indications and the PT restricted to IBD and its subtypes. Subsequently, we conducted indication stratification, evaluating the paradoxical IBD risk of these agents within specific IMIDs (excluding IBD). The Weibull shape parameter (WSP) test was conducted to anticipate changes in AEs over time [12]. The median time to AE onset was calculated using the formula: Time-to-onset = event time—start time [13]. The WSP test results reveal three hazard models: wear-out failure (increasing AE risk over time, $\beta > 1$, 95% CI > 1), early failure (decreasing AE risk over time, $\beta < 1$, 95% CI < 1), and random failure (constant AE risk over time, 95% CI of β includes 1) [12]. Time to onset analysis and the WSP test were also conducted with stratified analyses by age, gender, and IBD subtypes to enhance more personalized surveillance. The WSP tests were performed using Minitab v20.0.

2.3 | MR Analysis and Genetic Correlation Analysis

Supporting Information S1: Table S2 presents the GWAS data used for MR analysis and genetic correlation analysis. MR analysis uses genetic variants associated with the exposure as instrumental variables (IVs) to investigate the potential causality of risk factors related to the outcome [14]. IV selection follows these assumptions: (1) IVs have a strong association with exposures; (2) IVs are not connected to confounding factors; and (3) IVs are not directly related to outcomes [15]. To fulfill the first assumption, we selected SNPs associated with each trait at a genome-wide significance threshold of $p < 5 \times 10^{-8}$. We retained only SNPs with a large physical distance (≥ 10,000 kb) and a low likelihood of linkage disequilibrium ($R^2 < 0.001$) [16]. Our study explored the causal links between five non-IBD indications of the previously mentioned agents and IBD/CD/UC using four methods: inverse variance weighted (IVW), weighted median, MR-Egger, and weighted mode [17–19]. The IVW method is considered the most reliable for estimating causal effects when all selected SNPs are valid IVs [18]. We used the false discovery rate (FDR) for multiple testing correction, considering FDR q-values < 0.05 as significant. The MR analysis was executed using R (version 4.1.3) with the 'Two-Sample MR' package.

We further employed LDSC to assess genome-wide genetic correlations for 15 pairwise traits between IBD/CD/UC and these five indications: Rheumatoid Arthritis (RA), Psoriatic Arthropathies, Psoriasis, Juvenile Idiopathic Arthritis (JIA), and Ankylosing Spondylitis (AS). LDSC analyzes the relationship between test statistics and linkage disequilibrium to measure polygenic signal or bias contributions. It allows genetic correlation assessment based on GWAS summary statistics, unaffected by sample overlap [10]. The analysis was conducted using the 'ldscr' R package.

3 | Results

3.1 | Descriptive Analysis of Paradoxical IBD in IMIDS Agent Users

Figure 1 depicts the detailed data processing, while Supporting Information S1: Table S3 presents the clinical characteristics of paradoxical IBD in users of these agents. A total of 3407 paradoxical IBD reports concerning six biologics and two Janus Kinase inhibitors were collected, including: Adalimumab (n = 1983), Infliximab (n = 545), Certolizumab Pegol (n = 342), Ustekinumab (n = 155), Golimumab (n = 154), Tofacitinib (n = 124), Upadacitinib (n = 55), Risankizumab (n = 49). The ranking of paradoxical IBD proportion compared to all PTs for each agent is as follows: Infliximab (1.058%), Certolizumab Pegol (0.725%), Ustekinumab (0.576%), Golimumab (0.555%), Adalimumab (0.553%), Upadacitinib (0.190%), Tofacitinib (0.184%), and Risankizumab (0.157%). Patients were stratified into four age groups (< 18, 18–65, 65–85, > 85), with most patients falling in the 18–65 age group, followed by the 65–85 age group. Across all agents, females accounted for a higher proportion of paradoxical IBD than males, particularly with Tofacitinib (82%), Certolizumab Pegol (69.9%), and Adalimumab (61.8%).

3.2 | Disproportionality Analysis for Paradoxical IBD

Figure 2 presents the signal outcomes for paradoxical IBD following the use of each agent. Consistent positive signals for paradoxical IBD were observed among the following TNF blockers: Adalimumab (n = 1983, ROR [95%CI] = 1.55 [1.47–1.63]), Infliximab (n = 545, ROR [95%CI] = 2.12 [1.95–2.32]), Certolizumab Pegol (n = 342, ROR [95%CI] = 1.9 [1.71–2.12]), and Golimumab (n = 154, ROR [95%CI] = 1.64 [1.4–1.93]). A strong positive signal was also detected in the IL-12 and IL-23 antagonist, Ustekinumab (n = 155, ROR [95%CI] = 2.03 [1.73–2.39]). However, the Janus kinase inhibitors Upadacitinib and Tofacitinib, and the IL-23 antagonist Risankizumab, demonstrated an insignificant association with paradoxical IBD. Notably, among the biologics displaying positive signals for paradoxical IBD, CD is the mainly developing form, but not UC. In the five biological agents with positive signals for paradoxical IBD, stratified analysis by two IBD subtypes as PTs showed significant positive signals for both CD and UC. This discrepancy was particularly pronounced in TNF blockers, exemplified by Adalimumab: CD (n = 1328, ROR [95%CI] = 1.82 [1.7–1.94]) versus UC (n = 557, ROR [95%CI] = 1.42 [1.29–1.56]). A similar trend was observed in the IL-12 and IL-23 antagonist, Ustekinumab: CD (n = 114, ROR [95%CI] = 2.52 [2.09–3.03]) versus UC (n = 33, ROR [95%CI] = 1.44 [1.02–2.03]).

Figure 2 presents the results of gender- and age-based stratification analyses. Gender-specific stratified analyses indicated that among the five biologics identified with positive signals for paradoxical IBD, both subgroups persistently showed strong positive signals for paradoxical IBD. Furthermore, the number of paradoxical IBD cases in females was higher than in males across these biologics. For Certolizumab Pegol and Golimumab, males showed higher signal strength for paradoxical IBD compared with females. Similarly, we found that paradoxical IBD predominantly occurred in the 18–65-year-old demographics, regardless of the type of biologic. In summary, these results illustrate the signal differences for paradoxical IBD across various age and gender groups. Supporting Information S1: Table S4 presents the paradoxical IBD risk associated with each agent in specific IMIDs (excluding IBD). Notably, Adalimumab exhibited

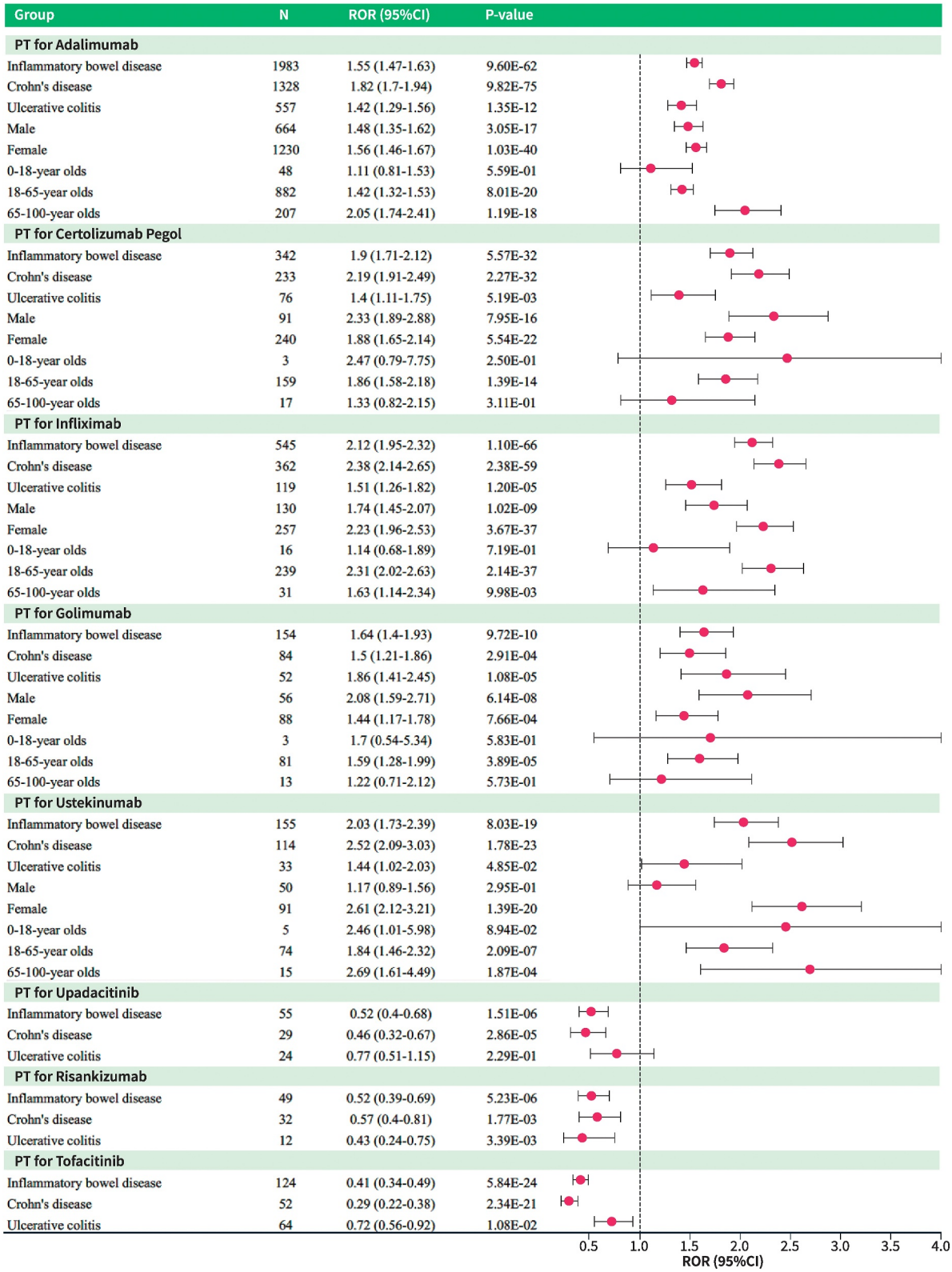

FIGURE 2 | Signal outcomes for paradoxical inflammatory bowel disease following the use of eight agents. *N signifies the count of reports, with each patient potentially contributing ≥ 1 records.

the strongest positive signal for paradoxical IBD when treating JIA (n = 57, ROR [95%CI] = 1.81 [1.33–2.47]). Additionally, Infliximab demonstrated positive signals for paradoxical IBD across various non-IBD indications, with the strongest signals observed in plaque psoriasis (n = 58, ROR [95%CI] = 2.29 [1.76–2.97]) and RA (n = 181, ROR [95%CI] = 1.97 [1.70–2.30]). Furthermore, Certolizumab Pegol showed a strong positive signal in RA (n = 166, ROR [95%CI] = 2.25 [1.92–2.63]), and Ustekinumab exhibited a notable signal in psoriatic arthritis (n = 32, ROR [95%CI] = 2.18 [1.54–3.11]).

3.3 | Time to Onset Analysis and WSP Test

Table 1 presents the results of the WSP test and the time to onset of paradoxical IBD following different agents. The median onset times for paradoxical IBD induced by these eight agents ranged from 128 days for Tofacitinib to 368 days for Certolizumab Pegol. In the WSP analysis evaluation, we noted that the 95% CIs were < 1 for Adalimumab, Infliximab, Golimumab, and Tofacitinib, indicating an early failure type (a reduction risk in paradoxical IBD risk over time). Conversely, for Certolizumab Pegol, Ustekinumab, Upadacitinib, and Risankizumab, the calculations showed a 95% CI of β that includes 1, corresponding to a random failure type (a consistent paradoxical IBD risk over time). Due to the constraint of insufficient sample sizes reporting onset times, stratified analyses could only be performed for Adalimumab. In the WSP analysis evaluation across various subgroups, Adalimumab consistently demonstrated an early failure type. The median time to onset of Adalimumab-induced paradoxical IBD was observed to be later in CD [Median (IQR) = 354 (82.25–769)] compared to UC [Median (IQR) = 231 (66.25–741.25)], and later in males [Median (IQR) = 309 (88–858)] compared to females [Median (IQR) = 285 (74.50–730.50)].

3.4 | Results of Genetic Correlations and MR Analysis

Figure 3 illustrates the genetic correlations and causality between the five IMIDs, serving as indications for the aforementioned agents, and IBD along with its subtypes. Supporting Information S1: Table S5 presents the results of MR Analysis. After adjusting for multiple testing, we discerned pervasive genome-wide significant genetic correlations, notably between AS with IBD (rg = 0.536, FDR = 1.45×10^{-8}), JIA with IBD (rg = 0.334, FDR = 3.61×10^{-5}), and psoriasis with IBD (rg = 0.268, FDR = 1.45×10^{-8}). These significant genetic correlations remained robust even after subgroup analyses for IBD subtypes. MR analysis revealed that only psoriasis was causally linked with an elevated risk of IBD (OR = 1.18, 95% CI = 1.06–1.31, FDR = 0.013). Intriguingly, a subtype-specific

TABLE 1 | Results of time-to-onset analysis and Weibull distribution.

				Weibull distribution		
Agents	**Types of agents**	**Subgroup**	**Time-to-onset (days) Median (IQR)**	**Scale parameter α (95% CI)**	**Shape parameter β (95% CI)**	**Failure type**
Adalimumab	TNF blocker	IBD	308 (82.25–749.25)	494.12 (405.21–583.03)	0.75 (0.68–0.83)	Early failure
		UC	231 (66.25–741.25)	460.52 (294.73–626.31)	0.69 (0.56–0.81)	Early failure
		CD	354 (82.25–769)	505.47 (398.46–612.48)	0.77 (0.67–0.86)	Early failure
		Male	309 (88–858)	506.90 (353.94–659.86)	0.79 (0.65–0.93)	Early failure
		Female	285 (74.50–730.50)	482.71 (373.21–592.22)	0.73 (0.64–0.82)	Early failure
		18–65-year olds	285 (80–935)	491.80 (382.30–601.30)	0.76 (0.66–0.86)	Early failure
Infliximab	TNF blocker	IBD[a]	310 (78.75–1022.25)	640.41 (369.82–910.99)	0.64 (0.51–0.77)	Early failure
Certolizumab Pegol	TNF blocker	IBD[a]	368 (81.75–555.00)	433.82 (278.47–589.17)	0.83 (0.65–1.02)	Random failure
Golimumab	TNF blocker	IBD[a]	143 (26–762)	318.16 (119.52–516.81)	0.61 (0.43–0.79)	Early failure
Ustekinumab	IL-12 and IL-23 antagonist	IBD[a]	331 (33.5–520.5)	350.55 (112.86–588.24)	0.79 (0.47–1.11)	Random failure
Upadacitinib	Janus kinase inhibitor	IBD[a]	261 (130–282)	360.06 (75.59–644.52)	1.18 (0.41–1.95)	Random failure
Risankizumab	IL-23 antagonist	IBD[a]	130 (22.5–240)	152.14 (2.78–301.5)	0.8 (0.32–1.28)	Random failure
Tofacitinib	Janus kinase inhibitor	IBD[a]	128 (43–527.5)	378.8 (53.17–704.43)	0.65 (0.39–0.91)	Early failure

Abbreviations: CI, confidence interval; IQR, interquartile range.
[a]Results for certain subgroup were not presented due to insufficient sample sizes reporting onset times, precluding the conduct of statistical analysis.

Exposure	Outcome	OR (95% CI)	FDR for MR	Genetic correlation (SE)	FDR for LDSC
Rheumatoid arthritis	IBD	1.03 (0.95-1.11)	0.638	0.10 (0.05)	7.77E-02
Rheumatoid arthritis	CD	0.95 (0.86-1.06)	0.638	0.09 (0.06)	1.38E-01
Rheumatoid arthritis	UC	1.09 (0.99-1.21)	0.294	0.08 (0.05)	1.38E-01
Ankylosing spondylitis	IBD	1.03 (0.99-1.06)	0.294	0.54 (0.09)	1.45E-08
Ankylosing spondylitis	CD	1.01 (0.97-1.05)	0.770	0.49 (0.09)	2.32E-07
Ankylosing spondylitis	UC	1.05 (1-1.09)	0.203	0.43 (0.09)	9.36E-06
Juvenile idiopathic arthritis	IBD	1.05 (0.93-1.19)	0.638	0.33 (0.08)	3.61E-05
Juvenile idiopathic arthritis	CD	1.01 (0.82-1.24)	0.961	0.22 (0.08)	6.17E-03
Juvenile idiopathic arthritis	UC	1.11 (0.98-1.25)	0.294	0.42 (0.09)	2.74E-05
Psoriasis	IBD	1.18 (1.06-1.31)	0.013	0.27 (0.04)	1.45E-08
Psoriasis	CD	1.27 (1.12-1.44)	0.003	0.26 (0.05)	2.05E-07
Psoriasis	UC	1.08 (0.98-1.2)	0.294	0.22 (0.05)	3.03E-05
Psoriatic arthropathies	IBD	0.92 (0.73-1.16)	0.638	-0.38 (0.23)	1.36E-01
Psoriatic arthropathies	CD	0.89 (0.64-1.25)	0.638	-0.62 (0.33)	7.77E-02
Psoriatic arthropathies	UC	0.95 (0.79-1.14)	0.639	-0.24 (0.28)	4.04E-01

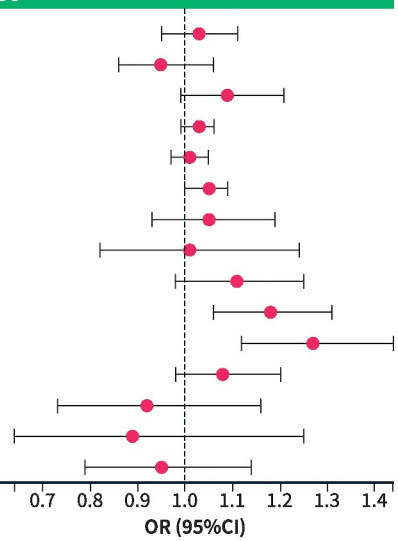

FIGURE 3 | Genetic correlations and causality between five immune-mediated inflammatory diseases, often used as indications for IBD agents, and inflammatory bowel disease with its subtypes. CD, Crohn's disease; CI, confidence interval; FDR, false discovery rate; IBD, inflammatory bowel disease; LDSC, linkage disequilibrium score regression; OR, odds ratio; UC, ulcerative colitis.

analysis revealed psoriasis to be causally linked with CD (OR = 1.27, 95% CI = 1.12–1.44, FDR = 0.003) but not with UC. No significant causal relationships were detected in the other pairwise comparisons.

4 | Discussion

Biologic-induced IBD is the second most common paradoxical reaction in rheumatic patients (845 of 12,731 cases) [20]. Predicting its occurrence is challenging due to the absence of reliable biomarkers and defined phenotypic or clinical traits [4]. The scarcity of research, primarily case reports [21–25], limits our understanding of paradoxical IBD related to biologics and Janus kinase inhibitors in the real world. This study is the first to identify paradoxical IBD signals induced by six biological agents and two Janus kinase inhibitors through disproportionality analysis, exploring clinical characteristics such as age, gender specificity, and onset time. We further unveiled significant genetic correlations between AS with IBD, JIA with IBD, and psoriasis with IBD. MR analysis showed that only Psoriasis causally increased IBD risk (remains significant in CD subanalysis, but not UC), with no causal relationships in other pairs. These insights clarify the intricate link between paradoxical IBD occurrence and biological therapies, aiding in early diagnosis and optimal management.

Prior research primarily reported on TNF blocker-induced IBD [26–30], with Uskudar et al. noting a fourfold relative risk increase of new-onset IBD in AS patients on anti-TNF treatment versus other drugs [31]. A nationwide study reported 16 IBD cases post-anti-TNF-α initiation for inflammatory rheumatic diseases, mainly AS or related SpA, with all patients showing improved intestinal conditions after anti-TNF-α discontinuation or monoclonal antibody drug switch [32]. Our study confirmed these findings, consistently identifying paradoxical IBD as a positive signal across four TNF blockers, with the most cases in Adalimumab (n = 1983) and the strongest signal strength in Infliximab (ROR [95%CI] = 2.12 [1.95–2.32]). We also, for the first time, identified a positive paradoxical IBD signal in the IL-12 and IL-23 antagonist Ustekinumab. However, we found no significant association between the use of two Janus kinase inhibitors, namely Upadacitinib and Tofacitinib, as well as the IL-23 antagonist Risankizumab, and the subsequent induction of paradoxical IBD. The exact causal mechanism of paradoxical IBD remains unclear and is subject to ongoing debate. Several hypotheses have been proposed to explain PAEs, including cytokine imbalance, differential immunological properties of monoclonal antibodies and TNF-α soluble receptor, unopposed type I interferon production, and a shift toward a Th1/Th2 profile [1, 7, 8]. Of these, cytokine disequilibrium is probably the most plausible explanation. Biological agents alter the cytokine environment, potentially initiating or redirecting pathological pathways leading to PAE. Using TNF blockers as an example, these agents can not only reach inflamed but also healthy tissue. In the latter, they bind to target proteins such as TNF-α, disrupt the cytokine balance (e.g., the interferon to TNF-α ratio), activate dendritic cells, and potentially induce PAEs [4]. For paradoxical IBD, another plausible explanation could be that the disease is influenced by dysregulation of the immune response to microbial antigens in the intestinal lumen. Heightened T cell reactivity to these antigens or a failure of regulatory T cells to control normal responses might trigger disease onset [33]. The normal mucosal immune system in the intestine inhibits T cells responsive to bacterial flora from inducing harmful immune reactions. Oh et al. noted that TNF-α blockade by neutralizing antibodies can inhibit these regulatory T cells [34].

It's noteworthy that our findings revealed CD as the prevailing form of paradoxical IBD, irrespective of the type of biological agent used. This is consistent with previous research indicating that under anti-TNF-α therapy, CD constitutes 94% of observed IBD cases, with UC being less common at 6% [32]. Evidence suggests that a genetic predisposition favoring paradoxical effect

development may have a significant influence [35]. In other words, genetic variants more prevalent in CD than UC could predispose CD to PAEs. For instance, NOD2/CARD15 gene variants have been identified as genetic risk factors for CD, which might be associated with the paradoxical CD but not UC [36]. In light of the previously discussed pathophysiological hypotheses, the subtype differentiation might be explained as follows: Biological agents may disrupt cytokine balance in patients with predisposing genetic factors such as NOD2/CARD15 gene mutations, creating a conducive environment for CD development [32]. This could lead to a higher prevalence of paradoxical CD. Interestingly, our MR analysis also revealed a causal association between genetically predicted psoriasis and CD but not with UC. This suggests that the genetic variations predisposing individuals to psoriasis may also enhance their susceptibility to CD. Despite observing significant genetic correlations in pairs including AS with IBD, and JIA with IBD, the MR analysis did not indicate causal relationships between these disease pairs. In short, these findings suggest that differences among paradoxical IBD subtypes may be linked to genetic predisposition. However, further investigations are warranted to validate these hypotheses.

Another significant finding of our study is the higher number of paradoxical IBD reports in females compared to males across all agents, with females reporting approximately twice as many cases for Adalimumab, Certolizumab Pegol, and Infliximab as compared to males. In light of our analysis on the proportion of indications, this disparity can be interpreted in the context of biologics primarily indicated for RA as follows: given the higher incidence of RA in females [37–39], they are more frequently administered these biologics, which consequently leads to a higher number of reported paradoxical IBD cases. However, in the case of biologics primarily indicated for AS (a condition with a higher prevalence in males) such as Infliximab and Golimumab [40–43], we still observed a significantly higher number of paradoxical IBD reports in females. This suggests that the gender disparity in paradoxical IBD is not solely attributable to the gender prevalence of the indications for biological agents, indicating the presence of other contributing factors. Nevertheless, due to the limited reports, the gender-specificity of paradoxical effects hasn't been previously documented. Our findings hint that paradoxical IBD may be more common in females. More research is needed to confirm the actual incidence and identify the high-risk patients. Stratified analyses by indication also revealed varying paradoxical IBD risks among agents across specific indications. Notably, Infliximab and Ustekinumab displayed positive signals for paradoxical IBD in all non-IBD indications. Adalimumab in the treatment of JIA, Certolizumab Pegol in RA, and Golimumab in AS exhibited stronger signals for paradoxical IBD compared with their effects in other non-IBD indications. These observations highlight the necessity for intensified monitoring of patients, particularly those in high-risk subgroups, and could warrant a reevaluation of treatment protocols to mitigate potential harm. Future research endeavors should concentrate on unraveling the underlying mechanisms and crafting predictive biomarkers to facilitate safer therapeutic approaches in IMIDs.

PAEs induced by biological therapy exhibit distinct kinetics compared to typical adverse drug reactions [4]. Previous studies revealed that the time to onset of paradoxical IBD under anti-TNF-α therapy varies greatly [7, 21]. Uskudar's research reported an average period of 15.14 ± 8.5 months (median 12 months) for new-onset IBD in patients treated with anti-TNF agents [31]. Braun's study noted a mean onset or flare of IBD after 242 days (range 57–545 days) [44]. Our study further reveals that the median onset times for paradoxical IBD triggered by eight different agents span from 128 days for Tofacitinib to 368 days for Certolizumab Pegol. In addition, we performed a WSP test to evaluate whether the incidence of paradoxical IBD will increase or decrease over time. Our results revealed distinct Weibull distribution patterns among various agents. Paradoxical IBD induced by Adalimumab, Infliximab, Golimumab, and Tofacitinib showed an early failure type feature, indicating a gradually decreasing risk. While those induced by Certolizumab Pegol, Ustekinumab, Upadacitinib, and Risankizumab presented a random failure type feature, suggesting a consistent risk over time. These findings could equip clinicians with valuable cues for the early identification and prompt intervention of paradoxical IBD. Moreover, they underscore the need for intensified surveillance and long-term multidisciplinary follow-up, particularly for biologics with longer median induction times or those exhibiting random failure type features.

Several limitations should be considered when interpreting our study findings. Firstly, the FAERS database, being a spontaneous reporting system, may introduce reporting bias, underreporting, and duplicate entries, potentially impacting the accuracy and generalizability of our results. Secondly, incomplete information on dosage, complications, and other details within the database hinders a comprehensive understanding of paradoxical IBD. Consequently, our study cannot assess the correlation between biological agent dosage and paradoxical IBD, nor thoroughly evaluate other potential risk factors. However, there is currently no well-recognized method to mitigate the influence of these factors on disproportionality analysis [45]. Lastly, it is important to note that disproportionality analysis in pharmacovigilance studies is difficult to make a causal inference [46]. Future research should delve deeper into paradoxical IBD, especially the pathophysiological hypotheses and patient-specific genetic risk factors, which are crucial for guiding therapeutic decisions.

4.1 | Suggestions for Future PAEs Management

Given the complexity of chronic immune-mediated diseases, involving multiple immunological pathways, the occurrence of paradoxical IBD is not inherently surprising. Moreover, with the anticipated increased use of biologics and Janus Kinase inhibitors in the near future, the incidence of paradoxical IBD is expected to rise. In this sense, the emergence of paradoxical reactions induced by these agents, including paradoxical IBD, warrants attention. The detection of positive signals for paradoxical IBD across these agents in this study further underscores this concern. Therefore, we propose the following suggestions for future PAE management (Figure 4):

1. It's crucial that PAEs, including paradoxical IBD, be thoroughly recorded in biological registers, incorporating patient demographics, indications, time to onset, time to

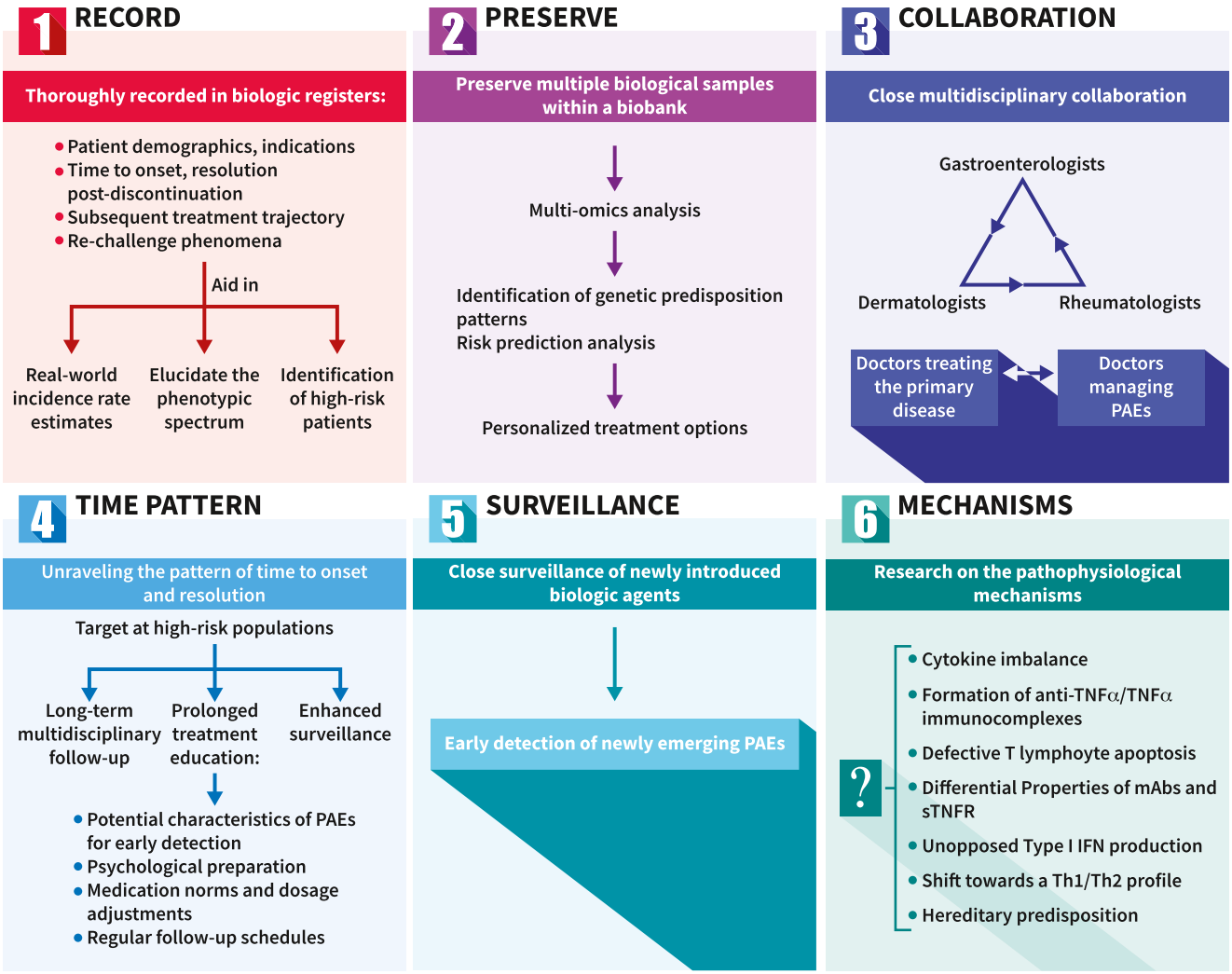

FIGURE 4 | Six key recommendations for better management of paradoxical adverse events in the future.

resolution post-discontinuation, subsequent treatment trajectory, and any re-challenge phenomena observed. This not only refines real-world incidence rate estimates but also, importantly, aids in clarifying the phenotypic spectrum of biologic-induced PAEs, facilitating the identification of high-risk patients.

2. It is recommended to preserve multiple biological samples from affected patients in a biobank. This approach will enable the elucidation of potential genetic predisposition patterns via cluster analysis. Moreover, omics analyses based on diverse sample types (e.g., serum, skin, and intestinal mucosal samples) can enhance risk prediction analysis. These endeavors will establish the foundation for the future implementation of personalized treatment strategies tailored to mitigate PAEs.

3. Given the likelihood that the original indications for biological agents and the paradoxical effects they induce may not occur within the same organ or system (e.g., dermatology and gastroenterology and rheumatology), it is crucial to maintain close collaboration between physicians treating the primary disease and those managing PAEs.

4. Future research should elucidate the pattern of time to onset and resolution of biologic-induced PAEs, thereby facilitating enhanced surveillance and long-term multidisciplinary follow-up for high-risk populations. Additionally, patients should be provided with appropriate education regarding this prolonged treatment, which includes educating them on potential characteristics of PAEs for early detection, psychological preparation, medication norms, regular follow-up schedules, and potential dosage adjustments.

5. Close surveillance of newly introduced biological drugs is of paramount importance to promptly detect emerging or previously undescribed PAEs.

5 | Conclusions

This study elucidates the occurrence pattern of paradoxical IBD, identifying it as a positive signal across multiple IMID agents, with CD being the predominant form. These findings broaden our understanding of this novel issue and might serve as a

valuable resource for clinicians to timely detect paradoxical IBD and make appropriate therapeutic decisions.

Author Contributions

Zhi-Qing Zhan: conceptualization, equal, methodology, equal, formal analysis, equal, data curation, equal, writing–original draft, leading. **Jia-Xin Li:** data curation, supporting, writing–original draft, supporting. **Ying-Xuan Chen:** funding acquisition, leading, writing–review and editing, supporting. **Jing-Yuan Fang:** funding acquisition, supporting, writing–review and editing, supporting. All authors read and approved the final manuscript.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data can be obtained upon a reasonable request to Zhi-QingZhan@sjtu.edu.cn.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.