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Azathioprine combined with either rifaximin (A microecological inhibitor) or infliximab for inflammatory bowel disease: Differential impacts on intestinal barrier function, inflammatory response and stress injury

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Abstract: **Background**: Inflammatory bowel disease (IBD) is an immune-related chronic intestinal inflammatory disease. In recent years, the incidence of IBD has increased significantly and the trend of younger age is obvious. **Objectives**: This prospective cohort study compared the effects of microecological inhibitors (rifaximin, RIF) plus azathioprine (AZA) versus infliximab (IFX) plus AZA in patients with active IBD. **Methods**: A total of 130 patients were randomized into two groups and treated for 12 weeks. Key outcomes included intestinal barrier function [Diamine oxidase (DAO), Fecal calprotectin (FC), Lipopolysaccharide (LPS)], mucosal repair markers [Epidermal growth factor (EGF), Transforming growth factor-β1 (TGF-β1)], inflammatory factors [Interleukin-6 (IL-6) and Tumor necrosis factor-α (TNF-α), C reactive protein (CRP)] and oxidative stress indices [Superoxide dismutase (SOD), Malondialdehyde (MDA)]. **Results**: IFX+AZA rapidly reduced pro-inflammatory cytokines (TNF-α decreased, CRP increased) and mucosal injury markers (DAO increased), but elevated LPS levels ($P<0.05$). In contrast, RIF + AZA enhanced mucosal repair (EGF decreased, TGF-β1 decreased) and antioxidant capacity (SOD decreased, MDA increased), with less liver enzyme elevation. The study suggests IFX + AZA is superior for acute inflammation control via TNF-α inhibition, while RIF + AZA offers long-term benefits in mucosal healing and oxidative balance through microbiota modulation. **Conclusion**: IFX + AZA for rapid induction remission and RIF+AZA for maintenance therapy in IBD

Keywords: Azathioprine; Inflammatory bowel disease; Infliximab; Intestinal barrier function; Microecological inhibitors; Oxidative stress

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INTRODUCTION

As an immune-related condition, inflammatory bowel disease (IBD) is characterized by chronic and recurrent inflammation of the intestinal mucosal layer, with its main forms being ulcerative colitis (UC) and Crohn's disease (CD) (Bruner *et al.*, 2023). In recent decades, the incidence of IBD has climbed substantially, with a growing trend of the disease affecting individuals at a younger age (Ashton & Beattie, 2024). Clinically, the central pathological elements of IBD are confirmed to be a compromised intestinal epithelial barrier and a dysregulated mucosal immune response. These factors eventually cause intestinal mucosal ulceration, bleeding and even carcinogenesis in severe cases (Khan *et al.*, 2023). Infliximab (IFX) was the first biological agent developed to target TNF-α. The dual-target treatment strategy, integrating IFX and azathioprine (AZA), has become a first-line therapy for inducing remission in moderate-to-severe IBD. Its efficacy, with remission rates of 60-70%, is attributed to the neutralization of TNF-α-mediated inflammatory cascades by IFX and the suppression of T-cell proliferation by AZA (Singh *et al.*, 2021; Lowell *et al.*, 2024). However, approximately 30% of IFX-managed patients require modifications to their treatment plans due to secondary treatment failure, such as the generation of anti-drug antibodies. Additionally, long-term IFX use raises the risk of opportunistic infections (e.g., tuberculosis and opportunistic fungi) and lymphoma (Peyrin-Biroulet *et al.*, 2022). Meanwhile, microecological intervention strategies such as non-absorbable antibiotics and targeted microbiota modulators have become a new and promising direction in IBD treatment. These methods work by suppressing pathogenic bacteria's over proliferation in the intestine (e.g., adherent-invasive Escherichia coli) and restoring microbiota-mucosal immune homeostasis (Wallace *et al.*, 2023).

Yet, we have identified two major shortcomings in the existing studies on IBD therapy. On the one hand, systematic analyses comparing microecological inhibitors + AZA versus IFX + AZA remain insufficient, whereas on the other hand, there is a scarcity of literature documenting the differential effects of these two regimens on the repair of intestinal barrier function, the modulation of the

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inflammatory microenvironment and the mechanisms of stress-related injury. As a consequence, the adaptability of these combination regimens (which act on different targets) to the individual differences of patients has not been clarified, making it challenging to implement targeted and precise treatment.

Thus, the present study aims to conduct a systematic comparison of how the "microecological inhibitor + AZA" and "IFX + AZA" regimens affect intestinal barrier function, inflammatory responses and stress-induced injury in IBD patients by means of a prospective cohort study. Findings from this research are expected to shed light on the distinct mechanisms through which the two regimens regulate intestinal barrier repair and mitigate stress injury. In turn, this will offer targeted treatment alternatives for IBD in the future and ultimately drive the shift of IBD management from experience-based to mechanism-oriented therapeutic interventions.

MATERIALS AND METHODS

Sample size justification

The primary outcome for sample size calculation was the post-treatment change in DAO activity (a marker of intestinal mucosal integrity, with decreased levels denoting repair) (Alemany-Fornés *et al.*, 2025). Input parameters were derived from pilot studies: an expected ΔDAO of -15 U/mL in the microecological inhibitor + AZA group and -22 U/mL in the IFX + AZA group, each with a standard deviation of 10 U/mL. A two-independent-sample t-test design was employed with $\alpha = 0.05$ (two-tailed) and 80% power ($\beta = 0.2$). The calculation yielded a minimum requirement of 52 subjects per group. Given a projected 20% attrition rate (e.g., from loss to follow-up or participant withdrawal), the sample size was increased to 65 per group, resulting in a final cohort of 130 patients.

Subject recruitment and grouping

A selection of 130 active IBD patients was conducted at our gastroenterology unit from January 2024 through May 2025. The *inclusion criteria* encompassed: (1) fulfillment of diagnostic criteria for IBD (Gordon *et al.*, 2023) with confirmed active UC (Mayo score 2-3) or CD (Crohn's Disease Activity Index [CDAI] ≥150); (2) age range 18-70 years; (3) no exposure to biological agents (e.g., IFX, adalimumab), immunosuppressants (e.g., AZA, methotrexate), or microecological modulators (e.g., probiotics, prebiotics) within 3 months preceding enrollment; (4) capability and willingness to provide informed consent. *Exclusion criteria* consisted of: (1) clinically significant infectious conditions (active tuberculosis, sepsis, etc.); (2) autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus); (3) severe cardiac, hepatic, or renal dysfunction; (4) current pregnancy or breastfeeding status; (5) medication history involving antibiotics or proton pump inhibitors within 4 weeks; (6) history of alcohol dependence or substance abuse. Random assignment was implemented via random number table methodology, dividing eligible subjects into two intervention groups: one receiving rifaximin (RIF)-based microecological inhibition with AZA (Group A) and the other receiving IFX plus AZA (Group B). The study received ethical approval from our institutional review board (No. WK2024102) and follows Helsinki Declaration guidelines.

Treatment schemes

The administered treatment protocols were standardized as follows: RIF (400 mg, three times a day); IFX (5 mg/kg via intravenous infusion following induction at weeks 0, 2 and 6, then maintained every 8 weeks); AZA (initial dosage 1-2 mg/kg/day, titrated based on complete blood counts to ensure leukocyte levels remained $>3\times10^9$/L). A uniform treatment duration of 12 weeks was applied to all study subjects.

Sample collection and preservation protocols

Each patient provided 3–5 mL of fasting venous blood pre-treatment and post 12 weeks of treatment. The blood samples were left at ambient temperature for 30 minutes, followed by centrifugation. The upper serum layer was transferred to EP tubes and kept in a -80°C freezer for storage until testing. In addition, fresh morning fecal samples were aseptically collected from the surface using sterile EP tubes, with strict avoidance of urine/water contact. All fecal samples were analyzed within 2 hours of collection.

Outcome measures

Quantitative analysis of biomarkers was conducted using enzyme-linked immunosorbent assays (ELISAs). Serum measurements included diamine oxidase (DAO), epidermal growth factor (EGF), transforming growth factor-β1 (TGF-β1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), while fecal assessments encompassed Fecal calprotectin (FC), lipopolysaccharide (LPS), intestinal fatty acid binding protein (i-FABP) and fecal lysozyme (FLE). For fecal analysis, samples were prepared by homogenizing with extraction buffer (1:10 w/v), incubating at 37 °C for 30 minutes and centrifuging to obtain supernatant. Following a 1:1000 dilution, samples were applied to pre-coated plates and incubated for 2 hours at room temperature. Plates were washed before the addition of Horseradish Peroxidase (HRP)-labeled secondary antibodies. Optical density was measured at 450 nm after substrate reaction. All concentrations were determined through standard curve interpolation. Quality control included running low and high controls (coefficient of variation [CV] <10%) and performing weekly instrument calibration.

C reactive protein (CRP) concentration was measured by immunoturbidimetric assay. Samples underwent automated dilution before being added to reaction cuvettes containing CRP-specific latex particles. The resulting turbidity from

antigen-antibody complexes was quantified by light scattering (CRP-M1000, Mindray). Quality control measures incorporated daily instrument calibration and running two-level (low and high) control sera with inter-assay CV maintained below 3%.

Superoxide dismutase (SOD) and malondialdehyde (MDA) levels were measured calorimetrically. For SOD: samples were diluted 1:5 and introduced into a reaction mixture containing xanthine oxidase to generate superoxide anions. The degree of reaction inhibition by SOD was determined by monitoring absorbance at 450 nm. For MDA: samples were mixed with a thiobarbituric acid (TBA) reagent, heated in boiling water and cooled, after which absorbance was read at 532 nm for concentration calculation. Quality control included running standardized SOD and MDA references with each assay batch (Kit purchased from Beijing Biyuntian Biotechnology Co., LTD.).

Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine (Cr) levels were measured on a Beckman Coulter AU5800 automated biochemistry analyzer. After labeling with patient information, samples were placed in sample holders for automatic analysis. The instrument utilized the International Federation of Clinical Chemistry (IFCC) rate method for ALT and AST assays and the Jaffe kinetic method for Cr quantification. Results were automatically generated and recorded by the system. Quality control measures involved running high- and low-concentration control sera (CV <2%), along with daily calibration and wavelength verification.

Finally, the adverse reactions during the treatment process of the two groups of patients were statistically analyzed, such as abnormal liver and kidney functions, rashes, infections, etc.

Statistical analysis

SPSS 30.0 software (IBM, USA) served as the tool for performing statistical analyses. Categorical data, which were formatted as [n(%)], were compared through the chi-square test. Continuous data with a normal distribution, shown in the form of ($\bar{\chi}\pm s$), underwent inter-group comparison via independent samples t-tests and intra-group comparison using paired t-tests. Statistical significance was defined as a P-value of less than 0.05.

RESULTS

Comparability analysis

Variables such as age, gender and disease category of subjects in the two study groups were statistically analyzed. The findings showed that none of the differences between the groups reached statistical significance (P>0.05), demonstrating that the inter-group disparities are small and the groups possess comparability (Table 1).

Intestinal barrier function assessment

The assessment of intestinal barrier function revealed comparable baseline DAO, FC and LPS levels between groups (P>0.05). Post-intervention assessment revealed decreased biomarker levels in both groups, with Group B achieving significantly greater reduction magnitudes for DAO (32.680%) and FC (29.500%) than Group A (P<0.05). In contrast, LPS concentrations were measured to be significantly higher in Group B following treatment completion (P<0.05) (Fig. 1).

Intestinal mucosal repair evaluation

Subsequently, the variation in intestinal mucosal repair capability was monitored across the groups. Likewise, pre-treatment measurements showed no statistical intergroup differences (P>0.05). Following the intervention, i-FABP and FLE concentrations declined in both groups and the reduction was more pronounced in the Group A compared to Group B (P<0.05). Meanwhile, EGF and TGF-β1 rose in both groups, with Group A exhibiting higher concentrations than Group B (P<0.05) (Fig. 2).

Inflammatory response measurement

Regarding inflammation, the pre-treatment test results of the two groups did not exhibit any statistical difference (P>0.05). Post-treatment, IL-6, TNF-α and CRP concentrations declined in both groups and the reduction was more significant in Group B compared to Group A (P<0.05) (Fig. 3).

Stress injury determination

Finally, we measured oxidative stress markers in both cohorts. Post-treatment SOD activity increased across the groups, with significantly greater elevation in Group A versus Group B (P<0.05). MDA levels decreased in both groups, but were lower in Group A (P<0.05) (Fig. 4).

Adverse reactions

Finally, we tallied the adverse reactions during the treatment process of the two groups of patients. The results showed that there was no statistically significant difference in the total incidence of adverse reactions between Group A and Group B (P>0.05). Additionally, ALT, AST and Cr remained stable in Group A (P>0.05), whereas Group B showed a 15.534% increase in ALT after treatment (P<0.05) (Table 2).

DISCUSSION

In this prospective cohort study, we evaluated two combination therapies for IBD: the microecological inhibitor RIF plus AZA versus IFX plus AZA. The findings revealed that both treatment strategies enhanced intestinal barrier function, suppressed inflammation and mitigated oxidative stress-induced damage; however, variations existed in their action mechanisms and effectiveness.

Table 1: Clinical data of groups A and B

Groups	n	Age (years old)	Sex Male / Female	Body mass index (kg/m^2)	Types of IBD UC / CD	Initial onset of illness Yes / no
Group A	65	58.523±8.469	42 (64.615) / 23 (35.385)	23.585±2.589	52 (80.000) / 13 (20.000)	55 (84.615) / 10 (15.385)
Group B	65	57.969±8.157	38 (58.462) / 27 (41.538)	23.403±2.598	55 (84.615) / 10 (15.385)	59 (90.769) / 6 (9.231)
Statistical (t or χ^2)		0.380	0.520	0.399	0.475	1.140
P		0.705	0.471	0.691	0.491	0.286

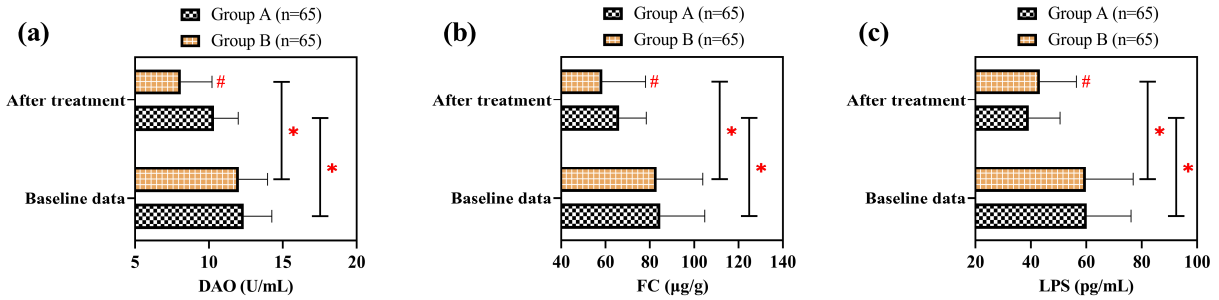

Fig. 1: Comparison of the intestinal barrier function markers before and after treatment in group A and group B. (a) comparison of DAP, (b) comparison of FC, (c) comparison of LPS. Note: * indicates that there is a difference in the comparison results of paired t test within the group (P<0.05), and # indicates that there is a difference in the comparison results of independent sample t test between the groups (P<0.05).

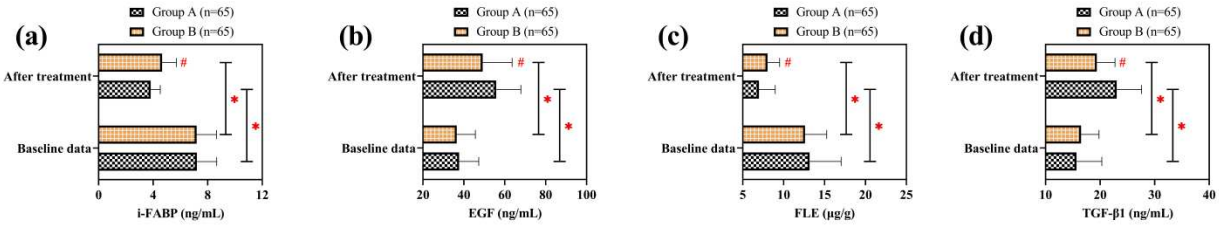

Fig. 2: Comparison of intestinal mucosal repair markers before and after treatment in group A and group B. (a) comparison of i-FABP, (b) comparison of EGF, (c) comparison of FLE, (d) comparison of TGF-β1. Note: *indicates that there is a difference in the comparison results of paired t test within the group (P<0.05) and # indicates that there is a difference in the comparison results of independent sample t test between the groups (P<0.05).

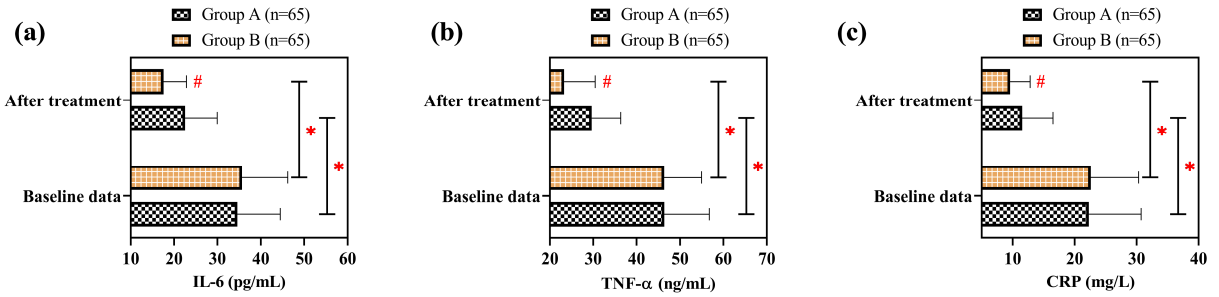

Fig. 3: Comparison of inflammatory factors before and after treatment between group A and group B. (a) comparison of IL-6, (b) comparison of TNF-α, (c) comparison of CRP. Note: *indicates that there is a difference in the comparison results of paired t test within the group (P<0.05) and # indicates that there is a difference in the comparison results of independent sample t test between the groups (P<0.05).

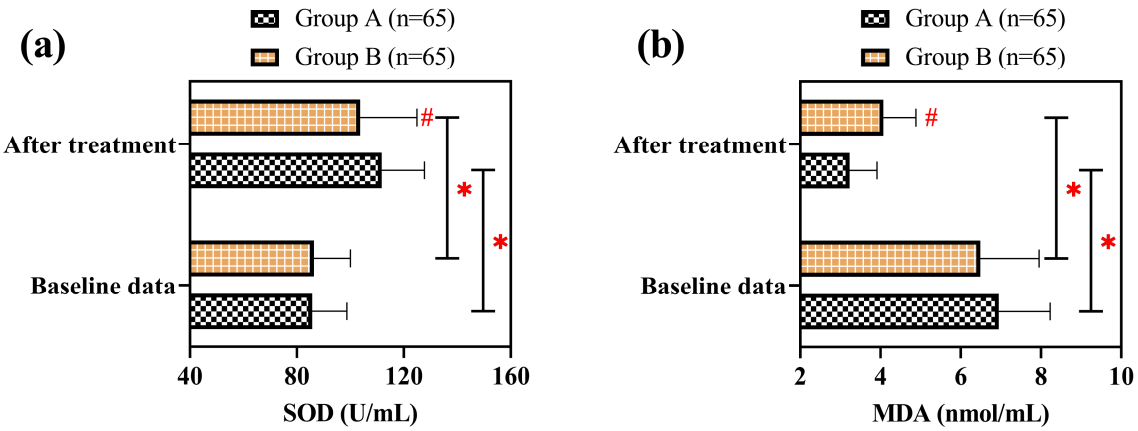

Fig. 4: Comparison of stress injury markers before and after treatment in group A and group B. (a) comparison of SOD, (b) comparison of MDA. Note: * indicates that there is a difference in the comparison results of paired t test within the group (P<0.05) and # indicates that there is a difference in the comparison results of independent sample t test between the groups (P<0.05).

Table 2: Comparison of safety

	Groups	Group A	Group B	Statistical (t or χ^2)	P
ALT (U/L)	Baseline data	32.040±7.372	31.691±7.520	0.267	0.79
	After treatment	31.623±7.890	36.614±6.582*	3.916	<0.001
AST (U/L)	Baseline data	29.451±9.086	29.989±7.419	0.37	0.712
	After treatment	29.932±8.120	29.505±9.179	0.281	0.779
Cr (μmol/L)	Baseline data	85.192±26.313	83.845±24.720	0.301	0.764
	After treatment	84.480±26.473	84.662±25.874	0.04	0.969
Adverse reactions	Rash	3 (4.62)	2 (3.08)		
	Abdominal pain/bloating/diarrhea	7 (10.77)	5 (7.69)		
	Infection	2 (3.08)	2 (3.08)		
	Total	12 (18.46)	9 (13.85)	0.511	0.475

Note: * indicates that there is a difference in the comparison results of paired t test within the group (P<0.05).

Over the 12-week study, the IFX + AZA strategy showed more prominent benefits in quickly lowering pro-inflammatory factors and mucosal injury markers, likely due to direct TNF-α pathway targeting. On the other hand, the microecological inhibitor + AZA strategy performed better in facilitating the repair of intestinal mucosa and combating oxidative stress, implying its potential for long-term repair via microbiota-immune regulation.

To begin with, our results revealed a greater post-treatment decline in DAO and FC concentrations in Group B, implying that biologics like IFX may reduce mucosal damage by quickly inhibiting inflammatory responses. This supports existing evidence that blocking TNF-α, a key inflammatory mediator, facilitates prompt resolution of intestinal inflammation and restoration of epithelial junction integrity (Souza *et al.*, 2023). Nevertheless, after receiving treatment, Group B had higher LPS levels compared to Group A. This finding suggests that IFX + AZA therapy may induce treatment-related dysbiosis or microbial imbalance, as elevated LPS reflects increased translocation of endotoxins due to disruptions in gut microbiota composition. While IFX exerts an indirect impact on intestinal permeability by inhibiting neutrophil chemotaxis, its immunosuppressive effects could promote the overgrowth of gram-negative bacteria, leading to endotoxin leakage. This is consistent with studies indicating that long-term IFX use alters microbial diversity (Carlsen *et al.*, 2024). Conversely, the reduction in LPS levels in Group A underscores the role of RIF in selectively clearing pathogenic bacteria (e.g., E. coli), thereby restoring microbiota balance and reducing endotoxin translocation. This clearance helps decrease the translocation of endotoxins into the blood, indirectly aiding barrier restoration (Hong *et al.*, 2022).

Regarding mucosal healing capacity, Group A demonstrated significantly higher post-treatment EGF and TGF-β1 levels compared to Group B, suggesting that microecological intervention may promote tissue regeneration by modulating mucosa-repairing cytokines. EGF, secreted by intestinal epithelial cells, facilitates cell migration via activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway (Stefani *et al.*, 2021). TGF-β1 enhances the mechanical integrity of the mucosal barrier by promoting collagen synthesis in fibroblasts through Smad-dependent signaling (L. Liu *et al.*, 2023). In Group B, the broad

immunosuppressive effects of biological agents—particularly the constrained expansion of Treg cells—may have compromised the establishment of a sustained anti-inflammatory microenvironment, thereby limiting the continuous secretion of reparative factors (X. Liu *et al.*, 2023). This mechanism may account for the more pronounced decline in mucosal repair markers observed in this group. Furthermore, Group A exhibited a more substantial reduction in i-FABP and FLE, indicating reduced neutrophil infiltration and more complete resolution of inflammation, which establishes a favorable milieu for mucosal recovery (Su *et al.*, 2021).

Later on, our observations revealed that while the inflammatory factor levels dropped in both treatment groups post-intervention, Group B exhibited superior anti-inflammatory efficacy. This outcome is consistent with the ability of the IFX-AZA combination to rapidly interrupt the TNF-α signaling cascade. Notably, though, research by Qiu T and colleagues has indicated that RIF is capable of suppressing the activation of the TLR4/NF-κB pathway, lowering IL-17 secretion and facilitating Treg proliferation (Qiu *et al.*, 2025). This property could serve as a potential underpinning for the long-term anti-inflammatory benefits associated with the RIF + AZA combination. In the meantime, microecological protocols may also maintain immunoregulatory functions by modifying the metabolic by-products of the microbial community, like short-chain fatty acids (Yu *et al.*, 2021). Another consideration is that the inflammatory factor levels in Group B might experience a rebound once treatment is ceased. Nevertheless, since this study failed to conduct further monitoring of the long-term inflammatory alterations in patients from the two groups, no conclusive judgment can be made at present.

Finally, regarding stress injury markers, Group A showed a greater increase in SOD activity and a more marked decrease in MDA, highlighting the advantage of the microecological inhibitor + AZA regimen in reducing oxidative injury. Intestinal dysbiosis has been indicated to correlate with elevated lipid peroxidation products (Wang *et al.*, 2025). RIF lowers ROS production by inhibiting LPS-producing bacteria including E. coli (Yuan *et al.*, 2024). Conversely, while Group B (IFX + AZA) achieved superior short-term inflammatory suppression, extended treatment may adversely influence antioxidant pathways via bile acid metabolic interference (Jian *et al.*, 2022), raising concerns about oxidative rebound after drug withdrawal. Notably, the observed increase in ALT levels following therapy in Group B further suggests higher potential hepatotoxicity associated with long-term IFX and AZA co-administration.

Drawing on the above findings, our results support a "phased precision therapy" approach for IBD. This is directly informed by the differential outcomes: (1) In the acute phase, IFX + AZA (Group B) achieved rapid reduction in pro-inflammatory markers (CRP, TNF-α) and mucosal injury (DAO), making it suitable for patients with high inflammatory burden. (2) For maintenance therapy, RIF + AZA (Group A) demonstrated superior mucosal repair (EGF, TGF-β1) and antioxidant capacity (SOD, MDA), benefiting those with persistent barrier dysfunction or oxidative stress. These findings enable personalization based on individual patient profiles—such as inflammatory status and microbiota balance—rather than a one-size-fits-all strategy. For instance, patients with elevated LPS or low EGF levels post-induction could switch to RIF + AZA for long-term stability. Still, several limitations merit consideration. The single-center design, relatively small sample size (n=130) and restriction to Han Chinese patients may limit how widely these results can be applied. Additionally, the 12-week duration does not allow evaluation of long-term outcomes like mucosal healing or cancer risk. Due to technical constraints, we also could not use multi-omics technologies (e.g., metagenomics or metabolomics) to fully explore microbiome-host interactions. We plan to address these aspects in subsequent studies with broader populations and more advanced analytical methods.

CONCLUSION

In this 12-week study, IFX + AZA facilitated acute-phase inflammatory control, as evidenced by significant reductions in TNF-α, CRP and DAO levels. Conversely, RIF + AZA enhanced mucosal repair (elevated EGF and TGF-β1) and oxidative balance (increased SOD, decreased MDA). The rise in LPS with IFX + AZA suggests potential microbiota disruption, while stable liver enzymes with RIF + AZA indicate better safety. However, long-term efficacy and generalizability require further validation due to the short duration and single-center design.

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Author's contributions
All authors have made substantial contributions to this study. Specifically, Yuanxiang Gong and Peisong Zhang: Responsible for research conceptualization, experimental design, data collection and initial draft writing. Yuanxiang Gong and Peisong Zhang: Participated in methodology development, data analysis and manuscript revision. Renda Han and Jia Guo: Provided resources, supervised the project, and reviewed the final draft. All authors have read and approved the final manuscript.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

The study received ethical approval from the Hubei Provincial Hospital of Traditional Chinese Medicine review board (No. WK2024102) and complies with the Helsinki Declaration.

Conflict of interest

The authors declare no conflicts of interest.

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