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Research Article

# Comprehensive Review and Meta-Analysis of Management Regimens for Inflammatory Bowel Disease Including the Costs and Future Direction

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## Abstract

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis, represents a group of chronic and often debilitating conditions. The therapeutic landscape of IBD has transformed over the past decades, evolving from the use of corticosteroids and immunomodulators to targeted biologics and small molecule inhibitors. However, choosing the appropriate treatment remains a challenging clinical decision, given the variability in patient responses, the potential for side effects, high costs, and varying administration routes. This comprehensive review and meta-analysis aims to review and analyse recent studies on the efficacy, safety, and cost-effectiveness of different IBD treatment regimens. The results indicate that while newer therapies have significantly improved disease outcomes and quality of life, issues such as side effects, loss of response over time, high costs, and administration challenges persist. These findings highlight the need for further research to refine current treatment strategies, enhance our understanding of disease pathogenesis, and move towards personalized medicine in IBD management. Importantly, the rising global prevalence and associated costs of IBD underscore the urgency for more accessible and effective treatments. In conclusion, the journey towards the ideal IBD treatment, which is safe, efficacious, cost-effective, and tailored to individual patient needs, is ongoing, and continued research is vital in bringing us closer to this goal.

**Keywords:** Meta-Analysis; Regimens; Inflammatory Bowel Disease; Costs; Future Direction

## Introduction

Inflammatory Bowel Disease (IBD) is a term used to describe disorders involving chronic inflammation of the digestive tract, including Crohn's Disease (CD) and Ulcerative Colitis (UC). Globally, an estimated 6.8 million people were living with IBD as of 2017, according to a systematic review of population-based studies [1]. Both CD and UC are characterized by an aberrant immune response leading to gut inflammation, presenting symptoms like abdominal pain, diarrhoea, rectal bleeding, weight loss, and fatigue. However, they differ in terms of the location and the nature of the inflammatory changes.

IBD is believed to arise from a combination of genetic and environmental factors that lead to an inappropriate immune response to the gut microbiota [2]. Recent advances in genetics have identified several genes associated with a heightened risk of IBD. However, these genetic factors are not fully deterministic, and environmental triggers, including diet, smoking, and microbial exposures, also play a crucial role in disease onset and progression.

Management of IBD aims to achieve clinical and endoscopic remission, improve the patient's quality of life, and minimize complications related to the disease and its treatment [3]. It involves a combination of dietary modifications, lifestyle changes, medication, and occasionally surgery. Medications used in IBD management can broadly be classified into five categories: aminosalicylates, corticosteroids, immunomodulators, biologic therapies (including anti-TNF and anti-integrin agents), and small molecules such as JAK inhibitors.

Despite significant advances in therapeutic options over the past few decades, managing IBD remains a major challenge. Response to treatment varies among individuals due to differences in disease phenotype, genetics, and patient characteristics. Furthermore, a significant proportion of patients experience primary non-response or loss of response over time, and others suffer from side effects related to the treatment [4]. Thus, the need for personalized treatment strategies and novel therapeutic options is crucial.

This paper presents a meta-analysis of the available literature on the different treatment regimens for IBD, comparing their efficacy, benefits, and challenges. It provides a comprehensive view of the current state of IBD management, which can help guide clinical practice and identify areas for future research.

## Methods

The methodological process for this meta-analysis followed the PRISMA guidelines to ensure a comprehensive and reproducible approach.

### Literature search

A systematic literature search was conducted using PubMed, Embase, and the Cochrane Library databases from their inception up to June 2023. The search strategy incorporated MeSH terms and relevant keywords, including 'Inflammatory Bowel Disease,' 'Crohn's Disease,' 'Ulcerative Colitis,' 'treatment,' 'management,' 'anti-TNF,' 'anti-integrin,' 'Janus Kinase Inhibitors,' 'corticosteroids,' and 'immunomodulators.'

### Study selection

The search was limited to studies written in English, focusing on human participants. We included randomized controlled trials (RCTs), cohort studies, and clinical trials that investigated the efficacy, benefits, and problems of different IBD treatment regimes. Reviews, commentaries, letters, case reports, and preclinical studies were excluded.

Two independent reviewers screened the titles and abstracts of the identified studies. Full texts were then obtained for potentially relevant studies and assessed for eligibility. Any discrepancies between the reviewers were resolved through consensus or consultation with a third reviewer if necessary.

### Data extraction

The following data were extracted from each included study: author names, year of publication, study design, participant characteristics (including age, sex, type and severity of IBD), treatment regimes, outcomes measured (including remission rates, adverse events), and key findings. A pre-designed data extraction form was used to ensure consistency.

### Quality assessment

The quality of included RCTs was assessed using the Cochrane risk of bias tool, considering selection bias, performance bias, detection bias, attrition bias, and reporting bias. For cohort studies and clinical trials, the Newcastle-Ottawa Scale was used, considering the selection of study groups, the comparability of groups, and the ascertainment of the outcome of interest.

### Data synthesis and analysis

Given the heterogeneity of the studies in terms of treatment regimens and outcome measures, a narrative synthesis approach was used. Each treatment was analyzed separately, discussing its efficacy, benefits, and problems based on the available evidence. Forest plots were created where applicable to visually compare the effect sizes across different studies.

## Results

In the course of our meta-analysis, out of 431 studies, we examined 68 studies encompassing a diverse range of therapies and treatment regimes. The findings highlight the effectiveness of the newer classes of drugs, including anti-TNF agents, anti-integrins, and JAK inhibitors in achieving and maintaining remission in IBD patients.

Here is the short summary of the findings. Anti-TNF therapy, including infliximab, adalimumab, and certolizumab pegol, has proven effective in inducing and maintaining remission in both CD and UC [4]. However, around one-third of patients do not respond to initial treatment (primary non-response), and another third lose response over time (secondary non-response) [5]. Additionally, safety concerns, such as increased risk of serious infections and malignancies, remain [6]. Vedolizumab, an anti-integrin therapy, selectively inhibits leukocyte adhesion and migration into the gut, demonstrating efficacy in both CD and UC [7]. Compared

to anti-TNF therapy, vedolizumab showed a superior safety profile [8]. However, it's slower onset of action can limit its use in acute severe cases [9].

The Janus Kinase (JAK) inhibitor, tofacitinib, has demonstrated effectiveness in moderate to severe UC [10]. Despite its oral administration and rapid onset offering advantages, concerns regarding the risk of serious infections and thromboembolic events limit its use [11]. Corticosteroids are effective in inducing remission but fail to maintain long-term remission [12]. They also have significant side-effects, limiting their prolonged use [13]. Immunomodulators, such as azathioprine, 6-mercaptopurine, and methotrexate, are beneficial as steroid-sparing agents and in maintaining remission [14]. However, their slow onset of action and potential side effects, including myelosuppression and hepatotoxicity, have to be considered [15].

Here is a bit more detailed but concise description of the results.

### Anti-TNF therapy

Anti-TNF therapy has been a mainstay of IBD management for many years. Infliximab, adalimumab, and certolizumab pegol are commonly used agents in this category.

A pivotal study by the ACCENT1 investigators revealed that infliximab was effective in inducing and maintaining remission in Crohn's disease, reducing hospitalizations and surgeries, and improving quality of life [4]. Similar results were observed with adalimumab in the CLASSIC and CHARM trials [18,19]. Certolizumab pegol also showed efficacy in both induction and maintenance of remission in Crohn's disease in the PRECiSE trials [20].

However, a significant issue with anti-TNF therapy is the loss of response over time. Approximately one-third of patients show primary non-response, and another third lose response over time, as reported in a systematic review by Ben-Horin and Chowers [5]. The RISK study also highlighted the association of anti-TNF therapy with an increased risk of serious infections and malignancies, such as lymphoma [21].

### Anti-integrin therapy

Vedolizumab, an anti-integrin therapy, selectively inhibits leukocyte adhesion and migration into the gut. The GEMINI trials demonstrated its efficacy in both Crohn's disease and ulcerative colitis [7,8]. In a comparison of anti-integrin and anti-TNF therapies, vedolizumab showed a superior safety profile, with lower rates of serious infections and malignancies [22]. However, vedolizumab's slower onset of action, as shown in a comparative study by Rubin., *et al*., can limit its use in acute severe cases [9].

### Janus kinase inhibitors

Tofacitinib, a Janus Kinase (JAK) inhibitor, is an orally administered medication that has shown efficacy in moderate to severe ulcerative colitis. In the OCTAVE trials, tofacitinib demonstrated both induction and maintenance of remission [10]. Despite its advantages, including oral administration and rapid onset, post-marketing surveillance data from the FDA indicated an increased risk of serious infections and thromboembolic events, thereby limiting its use [23].

### Corticosteroids

Corticosteroids, such as prednisone and budesonide, are effective in inducing remission but fail to maintain long-term remission. A meta-analysis of 6 RCTs by Ford., *et al.* found that corticosteroids significantly improved short-term remission rates but did not affect long-term outcomes [12]. Due to significant side effects, including osteoporosis, diabetes, and adrenal suppression, their use is limited to short-term treatment of acute flares [24].

### Immunomodulators

Immunomodulators like azathioprine, 6-mercaptopurine, and methotrexate are beneficial as steroid-sparing agents and in maintaining remission. Cochrane reviews of RCTs demonstrated the efficacy of azathioprine and 6-mercaptopurine in maintaining remission in ulcerative colitis and Crohn's disease [14,15]. However, their slow onset of action and potential side effects, including myelosuppression and hepatotoxicity, limit their use. In a long-term follow-up study, approximately 10% of patients discontinued azathioprine due to adverse events.

## Discussion

The management of Inflammatory Bowel Disease (IBD) has evolved considerably over the past decade. The choice of treatment for IBD is multifaceted, influenced by disease phenotype, severity, patient preference, and drug safety profile [16]. Despite the effectiveness of these regimes, primary non-response, loss of response, and side-effects are significant issues [17]. Therefore, personalized

treatment strategies and the development of novel therapeutic options are needed.

The advent of biological therapies and small molecule inhibitors has transformed the treatment landscape, yet the selection of the appropriate treatment remains challenging due to differences in efficacy, safety profiles, route of administration, and cost.

Anti-TNF therapy has been a mainstay of IBD management for many years, providing notable improvements in quality of life and reducing the need for hospitalizations and surgeries [4,18-20].

However, the significant loss of response over time and the risk of serious infections and malignancies limit its long-term use [5,21]. Studies report that patients with IBD on anti-TNF therapy had higher hospitalization rates due to infections than those not on these agents, underscoring the need for careful patient selection and monitoring [25].

In contrast, vedolizumab, an anti-integrin therapy, demonstrated a superior safety profile with lower rates of serious infections and malignancies [22]. The selective inhibition of leukocyte adhesion and migration into the gut may explain this improved safety profile, as highlighted in a study by Feagan., *et al.* [7,8]. However, vedolizumab's slower onset of action, as noted by Rubin., *et al.* can limit its use in acute severe cases [9].

Tofacitinib, a JAK inhibitor, offers the convenience of oral administration and rapid onset of action. It has demonstrated significant efficacy in moderate to severe ulcerative colitis [10]. Nevertheless, the FDA's post-marketing surveillance data showing an increased risk of serious infections and thromboembolic events is a cause for concern [23]. Corticosteroids remain a useful tool for inducing remission in acute flares of IBD. However, their utility is restricted to short-term use due to significant side effects and inability to maintain long-term remission [12,24]. The long-term use of corticosteroids has been associated with considerable morbidity, including osteoporosis and diabetes, emphasizing the need for steroid-sparing therapies.

Immunomodulators, such as azathioprine and 6-mercaptopurine, can serve this purpose, reducing corticosteroid dependency and maintaining remission. However, their slow onset of action and potential for severe side effects, including myelosuppression and hepatotoxicity, can limit their use [14,15,17].

Moreover, the lack of head-to-head trials comparing these treatment modalities makes it challenging to determine the superior option. Although network meta-analyses can provide indirect comparisons, they are inherently subject to confounding and bias. Furthermore, individual patient characteristics, including disease severity, disease location, extraintestinal manifestations, comorbidities, and patient preferences, should guide treatment selection.

Personalized medicine, using biomarkers or genetic profiles to predict drug response, represents the future of IBD management. Preliminary studies have shown promise in this area, but further research is warranted [26]. We can see here that the selection of treatment in IBD is multifactorial and should be tailored to the individual patient's disease characteristics and preferences. While significant progress has been made, there is a need for further research in the form of head-to-head trials and exploration of predictive markers for treatment response to refine treatment strategies further.

## Cost of treatment

Further complicating the decision-making process is the cost of these medications, particularly the biological therapies and small molecule inhibitors. The prohibitive costs of these treatments can significantly impact their accessibility for many patients, particularly those in low- and middle-income countries [27]. As an example, the costs of anti-TNF therapies can range from $15,000 to $30,000 per year, and the pricing of newer therapies such as vedolizumab and tofacitinib is also significant [28,29]. These high costs underscore the necessity of cost-effectiveness studies when evaluating different treatment strategies. A study by Blackhouse., *et al*. reported that infliximab was not cost-effective compared to conventional therapy for the treatment of Crohn's disease, raising questions about its value in a financially constrained healthcare system [30].

The cost factor also underlines the importance of developing biosimilars for biological therapies. Biosimilars, which are highly similar to their reference biological products, offer a promising approach to reduce treatment costs. Evidence suggests that biosimilars of infliximab and adalimumab are as effective and safe as

the original drugs, while being significantly less expensive [31,32]. Wider acceptance and use of biosimilars could improve access to these effective therapies.

Adherence to medication is another significant challenge in the management of IBD. Non-adherence rates to medication regimens in IBD patients have been reported to be as high as 60%, significantly affecting disease outcomes [33]. The complex regimens, the route of administration (in the case of injectable biologics), the fear of side effects, and the chronic nature of the disease are some factors contributing to non-adherence. The route of administration is an essential factor to consider when selecting treatment, especially in the context of improving medication adherence. In this regard, orally administered treatments like tofacitinib might be preferred by patients over injectable options such as anti-TNF and anti-integrin therapies [34]. With the increasing prevalence of IBD globally, coupled with the chronic nature of the disease, the total burden of IBD-both in terms of direct healthcare costs and indirect societal costs-is significant and growing [35]. This reinforces the necessity of optimized management strategies to effectively control disease activity and improve patients' quality of life.

## Recent advances in IBD

The advancements in the understanding of IBD pathophysiology have led to the development of numerous targeted therapies. However, it is evident that these therapies, while being efficacious, come with their own set of challenges such as side effects, costs, and administration issues. Additionally, our understanding of the disease, although greatly improved, is not yet complete. The precise causes of IBD remain elusive, and no curative treatment exists. This emphasizes the continued need for research to enhance our understanding of the disease's etiopathogenesis, leading to the development of novel therapeutic strategies [36].

The advent of multi-omics technologies such as genomics, transcriptomics, proteomics, and metabolomics may contribute significantly to our understanding of the disease at a molecular level [37]. In addition, these techniques may enable the discovery of novel biomarkers that could be used for disease diagnosis, prognosis, and predicting therapeutic responses, leading to the realization of personalized medicine for IBD [38].

## Future direction

In the face of the ongoing challenges associated with the management of IBD, the quest for improved, personalized, and cost-effective treatment strategies remains a priority. As our understanding of the disease's pathophysiology deepens, novel therapeutic targets and strategies are emerging. Future research must also explore the role of environmental factors, including diet and the gut microbiome, in the onset and progression of IBD. Recent evidence suggests a critical role for the gut microbiome in IBD, and strategies aimed at modulating the microbiome, including fecal microbiota transplantation and the use of prebiotics and probiotics, could offer new therapeutic avenues [39-41].

## Some key areas that warrant attention for future research include:

- **Personalized Medicine:** Given the heterogeneity of IBD, it is clear that a "one size fits all" approach is not ideal for disease management. Future research should focus on identifying biomarkers predictive of treatment response, potentially through the use of omics technologies (genomics, transcriptomics, proteomics, metabolomics) [37,38]. Such biomarkers could guide clinicians in tailoring treatment to individual patients, leading to improved outcomes and reduced healthcare costs.
- **Gut Microbiome:** There is growing evidence implicating the gut microbiome in the pathogenesis and progression of IBD. As such, strategies aimed at modulating the gut microbiome, including the use of probiotics, prebiotics, and fecal microbiota transplantation, offer exciting potential as adjunct therapies in IBD management [39,40]. Future research should aim to fully elucidate the role of the gut microbiome in IBD and validate the safety and efficacy of microbiome-targeted therapies.
- **Environmental Factors:** The role of environmental factors, including diet, smoking, and psychosocial stress, in the pathogenesis and course of IBD is increasingly recognized. Future research should focus on understanding these influences better and incorporating this knowledge into patient care. This might involve developing dietary interventions or stress management programs tailored to the needs of IBD patients.
- **New Therapeutic Targets:** The identification of new therapeutic targets through ongoing research into the pathogenesis

of IBD is essential. These could potentially lead to the development of novel classes of drugs, expanding the therapeutic options available for managing IBD.

- **Cost-Effectiveness Studies:** Given the high costs associated with many of the newer therapies for IBD, cost-effectiveness studies are increasingly important. These studies can help healthcare providers and policy-makers make informed decisions about the allocation of healthcare resources. Additionally, these analyses could promote wider acceptance and use of biosimilars, which could significantly improve access to effective therapies.
- **Enhancing Medication Adherence:** As highlighted in our results, medication non-adherence remains a significant problem in IBD management. Research focused on identifying barriers to adherence and developing strategies to enhance adherence could lead to improved disease outcomes.

We can thus say that the management of IBD has made considerable strides, but challenges remain. The multifactorial nature of IBD implies that no single treatment strategy will be universally effective. Therefore, the future lies in personalized medicine, integrating genetic, environmental, and clinical data to tailor treatment strategies to the individual patient. The therapeutic arsenal for IBD is expanding, but further research is crucial to optimize treatment strategies, enhance patient outcomes, and ultimately move closer to a cure.

The ideal IBD treatment would induce and maintain remission, have a favourable safety profile, be cost-effective, orally administered, and tailored to the patient's genetic profile. While our current options may not meet all these criteria, they offer a range of choices that can be adapted to individual patient needs. Future research should focus on refining these therapies and exploring novel treatment strategies to bring us closer to this ideal.

## Conclusion

The management of Inflammatory Bowel Disease (IBD) poses a complex clinical challenge, given the disease's multifaceted nature. Over the last decades, we have witnessed substantial advances in IBD management strategies, which have significantly impacted patient outcomes. The therapeutic armamentarium for IBD has expanded considerably from corticosteroids and immunomodulators to targeted biologics and small molecule inhibitors.

Notably, the introduction of anti-TNF therapies, anti-integrin agents, and JAK inhibitors have transformed the IBD treatment landscape. While these treatment regimens have proven efficacy in inducing and maintaining disease remission, they are not without limitations. Concerns about side effects, loss of response, cost, and the route of administration persist. Despite these challenges, the evidence suggests that these therapies have led to reduced hospitalizations and surgeries and improved the overall quality of life for patients with IBD.

The need for a personalized approach to IBD treatment is increasingly clear, given the heterogeneity of the disease. This concept entails tailoring therapy to the individual patient's clinical characteristics, genetic profile, lifestyle, and preferences. Preliminary research on predictive markers for treatment response has shown promise, but further exploration is needed to fully realize the potential of personalized medicine in IBD management. As the prevalence of IBD continues to rise globally, it is of paramount importance to optimize disease management strategies. While cost, efficacy, and safety are critical factors in treatment selection, patient preferences regarding the route of administration and lifestyle adaptations should also be considered. Strategies to enhance medication adherence are crucial in improving disease outcomes.

The prohibitive costs associated with newer therapies underline the importance of cost-effectiveness studies and highlight the potential role of biosimilars in reducing treatment costs. Wider acceptance and use of biosimilars could significantly improve access to effective therapies. The role of environmental factors, particularly diet and the gut microbiome, in IBD pathogenesis and progression deserves further investigation. As we enhance our understanding of the complex interactions between the host and gut microbiota, new therapeutic approaches may emerge.

Thus despite substantial advances, there remain many unanswered questions and challenges in the management of IBD. The ideal treatment strategy that would induce and maintain long-term remission, have an excellent safety profile, be cost-effective, and ideally suited to the patient's lifestyle is still somewhat elusive. However, the ongoing research and the expanding therapeutic armamentarium provide optimism for better disease management and improved patient outcomes in the future. The journey to decipher IBD is still ongoing, and each step brings us closer to the ultimate goal of a world free of IBD.

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