Comparative Role of Anti-TNF Agents versus IL-12/23 Inhibitors in Inflammatory Bowel Disease: An Updated Review

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ABSTRACT

Treatments for Crohn's Disease (CD) and Ulcerative Colitis (UC), two conditions that fall under the umbrella of Inflammatory Bowel Disease (IBD), must be both safe and effective. This review compares the effectiveness and safety of anti-TNF agents and IL-12/23 inhibitors, specifically in the context of IBD management. Randomized controlled trials (RCTs), observational studies, and meta-analyses involving adult IBD patients were all included in the review. Anti-TNF agents (infliximab and adalimumab) were shown to significantly improve clinical remission rates and reduce complications, particularly with early intervention. However, these agents were associated with adverse effects such as infections and autoimmune reactions. IL-12/23 inhibitors, particularly risankizumab, showed superior efficacy in achieving and maintaining remission with a better safety profile. The findings prove that IL-12/23 inhibitors might be more effective for patients who are unresponsive to anti-TNF therapies. In conclusion, both anti-TNF agents and IL-12/23 inhibitors effectively manage IBD, with IL-12/23 inhibitors offering a favorable safety profile. Early intervention and personalized treatment strategies are significant for optimizing patient outcomes. It will take additional research to validate these results and improve treatment strategies.

***Keywords**: Anti-TNF Drugs, Crohn's Disease, IL-12/23 Inhibitors, Inflammatory Bowel Disease, Ulcerative Colitis*

ABSTRAK

Penyakit Radang Usus (IBD), yang mencakup Penyakit Crohn (CD) dan Kolitis Ulseratif (UC), membutuhkan perawatan yang efektif dan aman. Review article ini membandingkan efikasi dan keamanan agen anti-TNF dan inhibitor IL-12/23, khususnya dalam konteks pengelolaan IBD. Review article ini mencakup uji coba terkontrol secara acak (RCT), studi observasional, dan meta-analisis yang melibatkan pasien dewasa dengan IBD. Agen anti-TNF (infliximab dan adalimumab) terbukti secara signifikan meningkatkan tingkat remisi klinis dan mengurangi komplikasi, terutama dengan intervensi dini. Namun, agen ini dikaitkan dengan efek samping seperti infeksi dan reaksi autoimun. Inhibitor IL-12/23, khususnya risankizumab, menunjukkan efikasi superior dalam mencapai

dan mempertahankan remisi dengan profil keamanan yang lebih baik. Temuan ini menunjukkan bahwa inhibitor IL-12/23 mungkin lebih efektif untuk pasien yang tidak merespons terapi anti-TNF. Kesimpulannya, baik agen anti-TNF maupun inhibitor IL-12/23 efektif dalam mengelola IBD, dengan inhibitor IL-12/23 menawarkan profil keamanan yang lebih baik. Strategi perawatan yang dipersonalisasi dan intervensi dini sangat penting untuk mengoptimalkan hasil pasien. Investigasi yang lebih menerangkan diperlukan untuk memastikan temuan ini dan menyempurnakan pendekatan terapeutik.

Kata Kunci: *Agen Anti-TNF, Kolitis Ulseratif, Inhibitor IL-12/23, Penyakit Radang Usus, Penyakit Crohn*

INTRODUCTION

Inflammatory Bowel Disease (IBD) leads to a substantial clinical obstacle due to the intricate chronic nature of the immune disequilibrium that underpins its pathology. IBD is primarily composed of two diseases: Crohn's Disease (CD) and ulcerative colitis (UC), both of which are characterized by gastrointestinal tract inflammation that persists over time. Aminosalicylates, corticosteroids, and immunosuppressive agents, which are traditional treatments for IBD, have long been used to manage symptoms by suppressing immune activity.[1] However, these conventional therapies often fail to provide sustained remission and are associated with significant side effects,[1,2] underscoring the requirement for additional effective and safer therapeutic choices.

Research on the pathogenesis of IBD has revealed the critical role of inflammatory cytokines and their signaling pathways. Among these, TNF-α (tumor necrosis factor-alpha) has been a prominent target, with anti-TNF agents demonstrating considerable efficacy in reducing inflammation and inducing remission in patients with IBD.[2,3] Despite their effectiveness, anti-TNF therapies are not without drawbacks. Patients often experience adverse effects, including an increased risk of infections, demyelinating diseases, and autoimmune reactions,[1-3] which limit their long-term use and necessitates the exploration of alternative treatment strategies.

The IL-23 pathway has come to light as a significant factor in the inflammatory processes associated with IBD, specifically because active Th17 cells are connected to the etiology of both UC and CD.[3] Genetic studies have identified variations in the IL-23 receptor among IBD patients, indicating a predisposition that could be targeted therapeutically.[3,4] IL-12 and IL-23 pathways targeted by the advent of biologics, such as ustekinumab, offer a novel approach by potentially addressing the underlying immune dysregulation more effectively than traditional therapies.[4,5] These biologics have shown promise in clinical trials,[3-5] giving people who do not respond well to anti-TNF medications.

Given the evolving landscape of IBD treatment, it is crucial to assess the effectiveness and safety of these newer therapies in comparison with established treatments. This review aims to compare the therapeutic outcomes of anti-TNF agents along with IL-12/23 inhibitors, focusing on the early usage of TNF antagonists with the therapeutic potential of Risankizumab, an IL-23 inhibitor. We seek to provide insights that will aid clinicians in optimizing treatment strategies, ultimately improving patient outcomes through personalized and effective therapeutic approaches.

UNDERSTANDING THE THERAPEUTIC LANDSCAPE OF IBD

Clinical Outcomes of Anti-TNF Agents

Table 1 provides a detailed outline of the studies assessing the effects of anti-TNF agents on Inflammatory Bowel Disease (IBD) outcomes. The key findings highlight the effectiveness of anti-TNF agents in achieving clinical remission and reducing complications in patients with Crohn's Disease.

Haens et al. (2018) conducted a randomized control trial to determine if maintaining infliximab levels above 3 mg/mL would lead to increased rates of clinical remission in patients with Crohn's Disease.[6] The study found that increasing the infliximab dosage resulted in patients achieving corticosteroid-free clinical remission. Colombel et al. (2015) performed a randomized control trial and post hoc analysis to evaluate the correlation between initial variables and treatment outcomes.[7] The study found that mixed therapy with infliximab and azathioprine was superior in achieving various composite remission metrics compared to azathioprine or infliximab monotherapy. This combination therapy also reduced symptom remission in patients with Inflammatory Bowel Disease (IBD) patients. Schreiber et al. (2013) investigated the influence of disease duration on clinical outcomes and safety in Crohn's Disease patients using adalimumab.[8]

The study demonstrated that adalimumab significantly improved clinical remission rates, particularly in patients with a shorter disease duration. This subgroup had the highest remission rate and fewer adverse events. Safroneeva et al. (2015) carried out a cohort study examining the impact of prior administration of TNF antagonists on illness consequences in Crohn's Disease.[9] The study concluded that initiating TNF-antagonist treatment promptly reduces the occurrence of bowel strictures, the need for surgery, and associated complications compared to starting these medications more than two years after diagnosis.

Clinical Outcomes of IL-12/23 Inhibitors

Table 2 summarizes studies assessing the effects of IL-12/23 inhibitors on IBD outcomes. These studies consistently show the superior efficacy of IL-12/23 inhibitors, particularly risankizumab, in inducing and maintaining clinical remission in patients with moderately to severely active Crohn's Disease.

Feagan et al. (2017) conducted a randomized, double-blind, placebo-controlled trial to assess the effectiveness and safety of risankizumab in patients with moderately to severely active Crohn's Disease.[3]

Table 1. Summary of Studies Assessing the Effects of Anti-TNF Agents on Inflammatory Bowel Disease (IBD) Outcomes

Author (year)	Study Design	Sample Size	Aim	Intervention	Results
Haens et al., 2018[6]	Randomized control trial	122	To explore if implementing therapeutic drug monitoring to uphold blood levels of infliximab above 3 mg/mL would lead to increased rates of clinical in patients diagnosed with CD.	Infliximab	The findings indicate that increasing the infliximab dosage resulted in a patient achieving corticosteroid-free clinical remission.
Colombel et al., 2015[7]	Randomized control trial	188	To assess the correlation between initial variables and treatment with the attainment of various composite remission indicators.	Infliximab	Combination therapy demonstrated superior efficacy in attaining diverse composite remission metrics compared to azathioprine or infliximab monotherapy while also reducing symptom remission in patients with IBD.
Schreiber et al., 2013[8]	Randomized control trial	777	To investigate the influence of disease duration on clinical outcomes and safety in CD patients using adalimumab	Adalimumab for less than two years	After one year, adalimumab showed a significant improvement in clinical remission rates among patients with moderately to highly active CD. The subgroup with the shortest disease duration experienced the highest remission rates and fewer adverse event occurrences.
Safroneeva et al., 2015[9]	Cohort Study	540	To examine the correlation between early administration of IM and/or TNF antagonists and a decreased number of illness consequences in comparison to late treatment in CD	TNF antagonist treatment	Commencing treatment for CD promptly with TNF-antagonists decreases the occurrence of bowel strictures, the necessity for surgery, and associated problems in comparison to initiating these medications more than two years after diagnosis.

Note: CD = Crohn's Disease; IBD = Inflammatory Bowel Disease; TNF = Tumor Necrosis Factor; IM = Immunomodulators.

Table 2. Summary of Studies Assessing the Effects of IL-12/23 Inhibitors on Inflammatory Bowel Disease (IBD) Outcomes

Author (Year)	Study Design	Sample Size	Aim	Intervention	Results
Feagan et al., 2017[3]	Randomized, Double-blind, Placebo-controlled	121	Examine risankizumab, a humanized monoclonal antibody that targets interleukin-23, for safety and effectiveness in individuals with moderately to severely active CD.	Risankizumab	Risankizumab had better efficacy than placebo, leading to clinical remission of the patients with active CD. Targeted silencing of interleukin-23 by suppressing p19 seems to be a promising therapeutic strategy for CD.
Ferrante et al., 2022[5]	Randomized, Double-blind, Placebo-controlled	542	Assess the effectiveness and safety of prolonged intravenous initiation of Risankizumab in CD.	Risankizumab	Risankizumab subcutaneously was a stable and successful method of maintaining remission in patients with CD. This gives a new therapeutic alternative to patients over many categories.
Feagan et al., 2018[4]	Extension Study	108	Assess the efficacy and safety of prolonged intravenous initiation of Risankizumab in CD.	Risankizumab	In the case of prolonged intravenous administration of Risankizumab, clinical response rates were substantially increased, and remission was achieved at week 26.

Note: CD = Crohn's Disease; IBD = Inflammatory Bowel Disease

The study found that risankizumab had better efficacy than placebo, leading to clinical remission of the active Crohn's Disease patients.[3] This targeted silencing of interleukin-23 by suppressing p19 appears to be a promising therapeutic strategy for Crohn's Disease. Ferrante et al. (2022) performed a randomized, double-blind, placebo-controlled trial to assess the efficacy of prolonged intravenous risankizumab in Crohn's Disease.[5] The study proved that risankizumab administered subcutaneously was effective in maintaining remission in patients with Crohn's Disease, providing a new therapeutic alternative for these patients. Feagan et al. (2018) conducted an extension study further to evaluate the efficacy and safety of prolonged intravenous risankizumab.[4] The study demonstrated that prolonged intravenous administration of risankizumab significantly increased clinical response rates and achieved remission at week 26, reinforcing the potential everlasting benefits of risankizumab in Crohn's Disease treatment.[4]

BALANCING EFFICACY AND SAFETY IN IBD THERAPIES

Anti-TNF agents, including infliximab and adalimumab, have shown significant efficacy in achieving clinical remission and reducing complications in Crohn's Disease.[10] For instance, Haens et al. (2018) showed that maintaining higher blood levels of infliximab led to increased rates of corticosteroid-free clinical remission, emphasizing the importance of dose optimization.[6] Similarly, Colombel et al. (2015) found that combination therapy with infliximab and azathioprine was more effective in achieving diverse composite remission metrics compared to monotherapy, suggesting that a multifaceted approach can enhance therapeutic efficacy.[7] Early intervention with anti-TNF agents appears crucial, as Schreiber et al. (2013) reported higher remission rates and fewer adverse events in patients with a shorter disease duration when given adalimumab.[8] Safroneeva et al. (2015) further corroborated this by demonstrating that early administration of TNF antagonists reduced the occurrence of bowel strictures and the requirement for surgery,[9] highlighting the potential for these agents to alter the disease course if introduced promptly. Despite these positive outcomes, the safety profile of anti-TNF agents remains unclear. The higher incidence of adverse events,[10,11] including demyelinating syndrome and autoimmune reactions, necessitates careful monitoring and patient selection to mitigate the risks. These adverse effects can significantly affect patient quality of life and long-term treatment adherence, underscoring the need for alternative therapeutic options.[1,3,10]

IL-12/23 inhibitors, particularly risankizumab, have emerged as a promising alternative with a more favorable safety profile and superior effectiveness in specific contexts.[11-14] Feagan et al. (2017) and Ferrante et al. (2022) demonstrated that risankizumab led to better clinical remission rates than placebo, providing strong evidence for its efficacy in inducing and maintaining remission.[3,5] The extension study by Feagan et al. (2018) reinforced these findings, showing sustained therapeutic benefits with prolonged intravenous administration.[4] Risankizumab's ability to target the IL-23 pathway selectively is a significant advancement in treating Crohn's Disease.[12-14] By inhibiting the p19 subunit of IL-23, risankizumab effectively reduces inflammation and disease activity, offering a targeted approach that minimizes systemic immunosuppression.[4,5,12] This targeted action not only enhances efficacy but also reduces the likelihood of adverse events, making it a safer long-term option compared to anti-TNF agents.

CLINICAL DECISION-MAKING IN IBD TREATMENT

Current evidence strongly supports the integration of IL-12/23 inhibitors into the therapeutic arsenal for Crohn's Disease.[4,5,10] The reviewed studies consistently show that these inhibitors, particularly risankizumab, offer superior clinical remission rates and a more favorable safety profile than traditional anti-TNF agents. This suggests a shift towards more targeted therapies that can provide effective disease control with fewer side effects.[15,16] The importance of early intervention is a recurrent theme across studies. Patients receiving early treatment with either anti-TNF agents or IL-12/23 inhibitors tend to have better clinical outcomes, highlighting the need for prompt diagnosis and therapy initiation. This is particularly relevant in clinical practice, in which delays in treatment initiation can lead to disease progression and increased complications.[15]

LIMITATIONS AND FUTURE DIRECTIONS IN IBD MANAGEMENT

Moreover, the heterogeneity among the included studies, such as variations in patient populations,

treatment regimens, and outcome measures, underscores the need for personalized treatment approaches. Tailoring therapy based on individual patient profiles, including genetic, environmental, and disease-specific factors, can optimize outcomes and reduce the risk of adverse events. Biomarker-driven approaches to predict treatment responses and guide therapeutic decisions are active research areas that hold promise for improving personalized care in IBD. Although this review provides robust evidence supporting the effectiveness and safety of IL-12/23 inhibitors, several limitations must be acknowledged. Heterogeneity in study designs, patient populations, and treatment protocols poses challenges to the generalizability of the findings. Additionally, reliance on electronic databases and the exclusion of non-English language studies may introduce selection bias.

Future research should focus on large-scale, long-term studies with diverse patient populations to confirm these findings and to establish standardized protocols for using IL-12/23 inhibitors in clinical practice. Investigating biomarkers that predict treatment response is crucial for refining personalized treatment strategies and enhancing patient outcomes. Moreover, comparative studies between different IL-12/23 inhibitors and other emerging biologics will provide further insight into the optimal management of Crohn's Disease

CONCLUSION

In conclusion, this review highlights the potential of IL-12/23 inhibitors, particularly risankizumab, as superior therapeutic options for managing Crohn's Disease. These inhibitors offer significant clinical benefits with a more favorable safety profile than anti-TNF agents. Early intervention and personalized treatment approaches targeting the IL-23 pathway hold promise for optimizing patient outcomes in IBD. Ongoing research and refinement of therapeutic strategies are essential to advance the management of Crohn's Disease, ensuring better long-term outcomes for patients.

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