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Review Article

Emerging Therapies And Advances In The Management Of Crohn's Disease

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ABSTRACT

Crohn's disease (CD) is defined as the chronic inflammation of gastrointestinal tract characterized by a relapsing-remitting course and significant morbidity. Traditional therapies, including corticosteroids, immunomodulators (e.g., azathioprine, methotrexate), and anti-TNF agents (e.g., infliximab, adalimumab), have been pivotal in inducing and maintaining remission. However, a subset of patients experiencing refractory disease or adverse effects necessitating alternative treatment approaches. Recent years have witnessed a transformation in CD management with the introduction of biologics targeting diverse inflammatory pathways. Agents like Vedolizumab and Natalizumab, which block adhesion molecules α4-integrin and α4β7 integrin, respectively, demonstrate efficacy in gut-selective immunosuppression. IL-23 inhibitors like Risankizumab and Ustekinumab offer an alternative approach by targeting cytokines implicated in Th17 cell differentiation, showing promise in inducing and sustaining remission in moderate to severe CD. Small molecule therapies have emerged as a prominent advancement, particularly Janus kinase inhibitors (JAKi) such as Filgotinib and Upadacitinib. By inhibiting intracellular signaling cascades downstream of cytokine receptors, JAKi modulate immune responses and exhibit efficacy in steroid-refractory and biologic-naive patients. Beyond pharmacological innovations, novel therapeutic strategies are expanding the treatment paradigm. Sphingosine 1-phosphate receptor modulators (S1PR) like Ozanimod harness sphingosine signaling to regulate lymphocyte trafficking, offering oral alternatives with favorable safety profiles. Non-pharmacological interventions such as fecal microbiota transplantation (FMT) and stem cell transplantation represent innovative approaches in managing refractory disease and perianal manifestations, leveraging insight from immune modulation and gut microbiome. This comprehensive review synthesizes current evidence and ongoing research to highlight the evolving landscape of CD management. While these

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advancements offer unprecedented therapeutic options, challenges persist in optimizing treatment efficacy, safety, and long-term outcomes. Future directions should include precision medicine initiatives, biomarker discovery, and therapeutic combinations aimed at achieving sustained remission and improving quality of life in individuals with CD.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing disorder that primarily affects gastrointestinal tract (GIT), leading to significant healthcare costs and morbidity. [1] It consists of Ulcerative colitis (UC) and Crohn's disease (CD). Crohn's disease involves chronic inflammation, periods of flare-up and remission, and progressive symptoms that can affect any part of GIT. During the initial 90 days post-diagnosis, some patients may develop stricturing or fistulizing complications. [2] Crohn's disease is most prevalent in Northern Europe, New Zealand and North America, with peak incidences between the ages of 15-30 and 40-60. It is more commonly seen in urban areas and has a higher incidence among Northern Europeans and individuals of Jewish descent (3.2 per 1000 people), [3] although, recent studies have reported increased number of cases in rapidly industrializing areas of Africa, Asia and Australasia. [4] In previous two decades, the likelihood of developing inflammatory, structuring, and penetrating complications are 12%, 18%, and 70%, respectively. These complications often necessitate multiple surgeries and can lead to disability, affecting patients' physical and mental well-being. However, recent trends indicate a decrease in surgery rates for CD, which may be attributed to the timely and effective use of medical therapies. [5] Significant progress has been made in IBD treatment, with anti–tumor necrosis factor (anti-TNF) agents becoming a cornerstone of CD management. These may lead to better health outcomes and reduced surgical procedures needs, and they are also effective in treating perianal and extra-intestinal symptoms of IBD.[1] Despite advancements in biologics (biological drugs) for CD, the remission rates after one year of therapy with individual agents remain at 30–50%. This rate declines with second-line therapies, and eventually, 80% patients require surgery. Early treatments, such as anti-TNFs, have broad mechanisms to control the unusual immune response in CD. With a deeper understanding of etiopathogenesis, newer treatments targeting specific pathways are currently developed. Additionally, several non-pharmacological approaches are available or being explored to complement pharmacotherapy. [6]

NOVEL DRUGS FOR CROHNS DISEASE

1. ANTI-ADHESION MOLECULES

Adhesion molecules on endothelium and leukocyte integrins interact to draw leukocytes to vascular endothelium of inflammatory tissues. Intestinal inflammation can be decreased by inhibiting these interactions, thereby restricting the inflammatory cell migration to intestinal lining. [7]

Natalizumab

- Natalizumab, a recombinant monoclonal antibody originally approved in the U.S. in 2004 for multiple sclerosis, is the first anti-adhesion agent approved for treating moderate to severe CD. It works by blocking the binding of α4β7 and α4β1 integrins on T cells to vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). This action prevents T cells from migrating into tissues, thereby reducing inflammation in CD. [1]
- In ENCORE trial, which involved 509 patients with moderate to severe CD and higher CRP levels, Natalizumab showed effectiveness in inducing and maintaining remission compared to a placebo. Participants received 300 mg of IV Natalizumab or a placebo at 0, 4, and 8 weeks. The primary

outcome measured was the sustained response from week 8 through week 12. The Natalizumab group demonstrated a significantly higher response rate (48% vs. 32%; P < 0.001) and a greater proportion achieved sustained remission (26% vs. 16%; P = 0.002) compared to the placebo group. [8]

- The use of natalizumab has been significantly limited due to its link with progressive multifocal leukoencephalopathy (PML), a serious central nervous system infection. PML occurs when the John Cunningham virus (JCV) becomes active again, and this is thought to happen because natalizumab blocks α4β1 integrins from binding to VCAM-1. This inhibition reduces T cell migration, which is crucial to protect against CNS viral activity. [9]
- In a study involving natalizumab-treated patients, the PML incidence was 2.1 cases per 1000 patients, with nearly 22% of those affected succumbing to the disease. The study also found that individuals at the highest risk of PML had an incidence rate of 11.1 cases per 1000 patients. Factors that increased the PML risk included prior immunosuppressant therapy, positive anti-JCV antibodies and extended natalizumab treatment duration. [10]
- According to available data, risk of PML may be lower in patients without anti-JCV antibodies who receive natalizumab for no longer than 8 months. [11]
- Minor adverse events with natalizumab use include infusion reactions, headaches, nausea, and drug antibodies development. [8]

Vedolizumab

- Being a monoclonal antibody, vedolizumab is approved for treating CD, acts by interacting with only α4β7 integrin (no interaction with α4β1 integrins) on T cells, preventing their binding to MAdCAM-1 on endothelial cells. This specificity limits lymphocyte infiltration, thereby improving chronic gut inflammation without affecting CNS immune cell infiltration. This distinction provides an advantage over natalizumab, which has been linked to PML. [1]
- The GEMINI 2 and 3 trials investigated vedolizumab's efficacy in CD. These studies demonstrated less favorable outcomes for clinical remission (CR) at week 6 compared to UC cohorts. GEMINI 3 did not collect mucosal healing data. It was suggested that vedolizumab might require longer treatment periods in CD compared to UC to effectively induce and maintain remission. By week 10, vedolizumab was shown to be more effective than placebo in inducing remission, and GEMINI 2 demonstrated its superiority over placebo in achieving CR and avoiding steroid use at week 52. A meta-analysis also confirmed vedolizumab's effectiveness in both inducing and maintaining CR in CD, although it was found to be less effective than adalimumab in maintaining remission. [12][13]
- Several studies, including those of Shelton, Amiot and Baumgart, with extented follow-up periods have demonstrated that vedolizumab effectively induces and maintains remission by week 14 in both anti-TNFα-naïve and anti-TNFα-treated patients. [14]

Etrolizumab

- A monoclonal antibody such as Etrolizumab binds specifically to β7 subunit of the αEβ7 and α4β7 integrins (heterodimeric), thereby restricting their interactions with E-cadherin and MAdCAM-1, resulting in prevention of inflammatory cells migration to the intestines and modulating their impact on intestinal epithelium. [15]
- The BERGAMOT trial (Phase III) randomly assigned 300 patients with moderate-to-severe CD who received either placebo (105 mg

every 4 weeks) or SC etrolizumab (210 mg at 0, 2, 4, 8, and 12 weeks) in a ratio of 1:2:2. Both doses resulted in higher CR rates by Week 6 and endoscopic remission (ER) by Week 14 when compared with a placebo (105 mg: 21%, 210 mg: 17.4%, placebo: 3.4%). ADRs were similar among the treatment groups and placebo, with common side effects including fatigue, headache, abdominal pain and nasopharyngitis. Notably, zero instances of PML were reported. These findings suggest rapid efficacy and a favorable safety profile. [16]

- Recent research on CD patients indicates that etrolizumab reduces the activation of proinflammatory genes and the expression of cytotoxic intraepithelial lymphocytes (IEL). [17]

Abrilumab

- Abrilumab is a monoclonal antibody which specifically targets α4β7 integrin, a validated target in IBD treatment. Many trials have assessed abrilumab for treating moderate-to-severe CD in individuals who did not respond adequately to immunosuppressive agents, corticosteroids, or anti-TNF agents. [15]
- In a study involving CD patients, abrilumab did not meet its primary endpoints for response on week 8 and remission on week 12. However, beneficial effects on remission and response rates were observed with the medication. [18]

2. IL-23 ANTAGONISTS

- Polymorphism of IL-23 receptor gene can result in CD development.Moreover, Agents that block IL-23, such as ustekinumab, also affect IL-12 because of their shared p40 subunit. This dual blockade can potentially interfere with IL-12's beneficial functions in infection prevention and anti-tumor immunity. Therefore, by targeting p19 subunit (specific to IL-23) can provide therapeutic benefits by specifically inhibiting IL-23 while sparing IL-12. This targeted approach promises to maintain comparable safety profiles while potentially reducing the infections risk and preserving anti-tumor responses. Currently, four such agents focusing on p19 subunit are currently in development, highlighting the ongoing advancements in this therapeutic area. [19]

Risankizumab

- Risankizumab's efficacy in moderately severe CD was evaluated in randomized phase III trials (ADVANCE and MOTIVATE). [20] These trials demonstrated significantly higher complete remission rates within 12 weeks. Patients who had not initially achieve remission benefited from subsequent open-label IV risankizumab. Maintenance therapy data from FORTIFY study further supports its effectiveness in sustaining remission. [21]

Brazikumab

- Brazikumab was evaluated in an open-label phase IIa clinical trial involving patients with moderate to severe CD. This placebo-controlled, double-blind, 12-week trial involved individuals receiving IV Brazikumab 700mg per placebo, on first day and day 29 followed by 100-week open-label phase where patients received SC brazikumab 210 mg every 4 weeks and a 36-week follow-up period after treatment. The trial showed that Brazikumab was safe over the 100-week period, especially in patients who could not tolerate or did not respond to one or more anti-TNFα treatments. [22]

Guselkumab

- Guselkumab, a human IgG1 monoclonal antibody approved for treating psoriasis in the US, Japan, Canada, and the EU. The Phase II and III trials, GALAXI 1, GALAXI 2, and GALAXI 3 are specifically focused on CD patients and are aimed to evaluate various

aspects including biomarkers, pharmacokinetics, safety and efficacy. GALAXI 1, for instance, assessed the safety and efficacy of guselkumab in moderate-to-severe CD patients who had either not responded adequately to immunosuppressants or corticosteroids. Patients treated with guselkumab demonstrated superior response rates, clinical biomarker improvements, and endoscopic enhancements, when compared with a placebo. [15][23][24]

Mirikizumab

- A RCT (Phase II trial) involved testing of mirikizumab on patients with active CD. Participants received either 200 mg, 600 mg, or 1,000 mg of IV mirikizumab or a placebo. By Week 12, ER and CR rates were found to be higher in 600 mg group (37.5% response, 15.6% remission) and the 1,000 mg group (43.8% response, 20.3% remission) compared to the placebo group (10.9% response, 1.6% remission). [25]

Ustekinumab

- Ustekinumab, a monoclonal antibody targeting the p40 subunit of IL-12 and IL-23, is approved for moderate-to-severe CD. In UNITI-1, UNITI-2, and IM-UNITI trials, ustekinumab showed superior efficacy compared to placebo, benefiting patients regardless of prior anti-TNF exposure. UNITI-1 focused on patients with severe, long-standing CD who had not responded to anti-TNF agents, while UNITI-2 included mostly treatment-naïve patients. Both trials, along with IM-UNITI, demonstrated reductions in CRP and FCP levels at weeks 8 and 44. Serious adverse effects were reported in 9.9% to 15% of patients, with thirteen experiencing serious infections. [26]

3. JAK INHIBITORS

- Inflammatory cytokines activate the JAK-STAT signaling pathway that plays a key role in immune responses and inflammation. JAK inhibitors are small-molecule drugs that block Janus kinases, disrupting the signaling that leads to the production and release of pro-inflammatory cytokines.

Filgotinib

- Filgotinib, an oral small molecule that inhibits JAK1 phosphorylation is approved for rheumatoid arthritis in 2020 (Europe) and also has been studied for CD in FITZROY study. [15]
- The FITZROY (Phase II) study, a placebo-controlled, double-blind, randomized trial, demonstrated encouraging results for filgotinib in moderately-to-severely active CD. At Week 10, clinical remission (CR) was observed in 47% of patients on 200 mg filgotinib, compared to 23% on placebo (p=0.008). Although endoscopic outcomes have not shown significant differences, better results may emerge during the maintenance phase. [27]

Upadacitinib

- In the Phase II CELEST study on upadacitinib for moderate-to-severe CD involving 220 patients, higher doses (24 mg) showed significantly improved ER rates compared to placebo, but there were no significant differences in CR rates by Week 16. Three herpes zoster reactivation cases were reported, with no treatment discontinuations, and no thromboembolic events occurred. Two cases of intestinal perforations were observed in active luminal CD areas, raising questions about the medication's role versus disease progression. Larger, longer studies are needed to clarify these findings. [28]

4. SPHINGOSINE 1-PHOSPHATE RECEPTOR MODULATORS (S1P)

- Ozanimod binds to S1P5 and S1P1 receptors, causing their internalization and reducing the B and T lymphocytes migration to the

bloodstream as well as inflamed intestinal tissues. This mechanism helps to prevent the spread of inflammation. [19]

- In the STEPSTONE program, an open-label Phase II trial, patients with active CD received ozanimod 1 mg daily. At Weeks 12 and 52, colonoscopies showed that 43.3% and 26.7% of patients achieved ≥25% and ≥50% reductions in the Simple Endoscopic Score for Crohn's Disease (SESCD), respectively, especially in those with less active baseline endoscopic disease. By Week 12, CR, defined as a Crohn's Disease Activity Index (CDAI) decrease of ≥100 and a CDAI <150, was achieved in 66% and 46% of patients, respectively. Common side effects included abnormal liver function, nasopharyngitis, arthralgia, hypertension and rash. Rare side effects such as macular edema or bradycardia may occur due to nonselective agonism of S1P3 receptors. [29][30]

NON PHARMACOLOGICAL TREATMENT

1. **FAECAL MICROBIOTA TRANSPLANT**

- Research into faecal microbiota transplant (FMT) has expanded beyond treating C. difficile infections to exploring its potential in managing IBD. Studies over the last two decades highlights the critical role of gut microbiota in IBD pathogenesis. Patients with IBD exhibit distinct faecal bacterial profiles, marked by higher levels of pathogenic bacteria like Escherichia coli, Campylobacter spp., and Mycobacterium avium, and lower levels of beneficial flora such as Bacteroides and Firmicutes. Additionally, IBD patients often decreased bacterial diversity and increased mucosal invasion, phenomena rarely seen in healthy individuals. [31]
- A systematic review of 18 studies assessing FMT as primary therapy for IBD showed promising outcomes. Among 122 FMT-treated patients, the overall remission rate was 45%. Subgroup analysis indicated high response in CD compared to UC, with 61% achieving CR in CD versus 22% in UC. [32]
- In a specific CD study, a pilot RCT assigned 24 patients in steroid-induced remission to receive either FMT or placebo via colonoscopy. The FMT group showed a significant reduction in the Crohn's Disease Endoscopic Index of Severity (CDEIS) at Week 6 compared to placebo (p=0.03). Although placebo group had higher CD flare rates, alpha diversity initially improved in the FMT group but normalized by Week 14, suggesting a temporary effect. Previous research suggested potential waning efficacy over time, though ongoing FMT therapies continue to show clinical promise. [33][34]

2. **STEM CELL TRANSPLANTATION (SCT)**

Luminal disease

- SCT, once recognized for its coincidental benefit in reducing CD activity during treatment for other conditions, is now actively studied as a targeted therapy for CD itself. This approach involves intense immunoablative conditioning followed by the infusion of either matched donor stem cells (allogeneic) or the patient's own previously harvested cells (autologous). Allogeneic transplants aim to reset immune system genetically, while autologous transplants aim to replace aberrant immune responses with healthy stem cells, both with the goal of achieving complete inflammation healing and possibly resetting responses to previous ineffective treatments. [19]
- The ASTIC trial, a significant randomized controlled study, assessed autologous SCT in CD patients resistant to multiple immunosuppressive agents. While the primary goal of sustained remission without treatment at one year was not met, more SCT

recipients discontinued active treatment and showed notable improvements in clinical and endoscopic disease activity compared to standard care. A subsequent analysis revealed that a significant proportion achieved steroid-free clinical remission and complete endoscopic healing at early follow-up periods. However, serious adverse events, including one fatal case, prompted caution and early termination of the trial. [35][36]

- Following ASTIC, the ASTIClite study aimed to refine SCT protocols for safety and efficacy, but it also faced challenges and was discontinued. Consequently, SCT remains a last-resort option for severe, refractory CD cases, where potential benefits must be carefully balanced against substantial risks. Ongoing research aims to optimize SCT approaches to enhance safety and efficacy for this complex condition. [37]

Perianal disease

- Perianal disease in CD poses significant challenges due to its often poor response to conventional therapies, driving the search for innovative treatments. Mesenchymal stem cells (MSCs), derived from adipose tissue, have been explored since 2003 for their potential in treating perianal CD. These cells are pluripotent, capable of differentiating into various tissue types, and exhibit immunomodulatory properties. They home to inflammation sites, site of release anti-inflammatory cytokines, and enhance regulatory T cells, which can help mitigate inflammation.
- Darvadstrocel (MSC therapy) has shown promising results in treating perianal Crohn's disease (CD) in a Phase III trial. By Week 24, significantly more patients treated with darvadstrocel achieved fistula healing compared to placebo (50% versus 34%; p=0.024), with sustained benefits observed over one year (56.3% versus 38.6%; p=0.01). These findings led to darvadstrocel's approval in Europe, and ongoing studies like ADMIRECD II in the United States and real-world data from the INSPIRE registry continue to assess its effectiveness and safety. Cost remains a significant hurdle for wider adoption of this therapy. [38][39][40]

3. REGULATORY T CELL-BASED THERAPIES

- Inflammatory bowel disease arises from immune system dysregulation, marked by excessive inflammation and insufficient regulatory mechanisms. Regulatory T cells are crucial in maintaining immune balance by suppressing harmful immune responses, including those in the gut. Animal studies show that regulatory T cells can mitigate intestinal inflammation, suggesting their potential therapeutic role in IBD. [19]
- Efforts like the TRIBUTE trial in the UK are exploring the use of retinoic acid receptor-α-treated regulatory T cells, which may enhance their ability to migrate to inflamed gut tissues, potentially improving treatment outcomes for CD patients. [41]

4. DIET

- Diet plays a significant role in both the development and management of inflammatory bowel disease (IBD), with growing scientific interest and medical acknowledgment. Dietary interventions, such as exclusive enteral nutrition (EEN), which involves a liquid formula diet, have shown superiority over corticosteroids in inducing remission, particularly in pediatric CD. Despite challenges in adherence among adults, EEN is well-established in preoperative care to reduce surgical risks and is supported for early use after CD diagnosis. [19]

- The Crohn's disease exclusion diet (CDED) combined with partial enteral nutrition (PEN) has also been studied, showing comparable rates of corticosteroid-free remission to EEN in pediatric populations. CDED emphasizes lean proteins, starches, and fibers while excluding foods thought to disrupt gut microbiota and intestinal barrier function, potentially linking reduced short-chain fatty acid (SCFA) levels to IBD pathogenesis. [42]

NOVEL SURGICAL INTERVENTION

- It's recognized by ECCO guidelines that a stapled ileocolic side-to-side anastomosis is preferred over hand-sewn end-to-end techniques in Crohn's Disease (CD) surgery due to lower postoperative complications. Recent efforts to reduce postoperative recurrence (POR) in CD focus on optimizing surgery timing and mesentery management during anastomosis, though challenges like safely managing inflamed tissue and achieving effective hemostasis hinder extensive mesenteric resection adoption.
- Evidence from a retrospective study of 64 patients suggests that extensive mesenteric resection significantly reduces subsequent surgery needs compared to conventional methods, with minimal reoperations noted in the extensive resection group over two years. [43]
- The Kono-S technique, a large lumen, hand-sewn antimesenteric functional end-to-end anastomosis, has demonstrated effectiveness in reducing POR, supported by studies showing low recurrence rates at five and ten years. [44] [45]
- Early laparoscopic ileocolic resection, as highlighted by the LIR!C trial, has shown comparable efficacy to infliximab for treating active ileocaecal CD resistant to conventional therapies, with potential benefits including reduced subsequent surgery rates and improved long-term treatment outcomes. [46] [47]

CONCLUSION

Each therapeutic approach is evaluated for efficacy, safety, and patient suitability, reflecting the complex interplay between genetic predisposition, environmental factors, and abnormal regulation of immune system in IBD etiopathogenesis. While biologic agents have revolutionized treatment paradigms, concerns regarding long-term safety, immunogenicity, and treatment resistance persist. Non-pharmacological strategies, though promising, require further validation through rigorous clinical trials to establish the efficacy and proper utilization in clinical practice. The incorporation of personalized medicine approaches, informed by advances in biomarker research and genetic profiling, holds promise for tailoring treatment regimens to individual patient profiles.

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