TMR

REVIEW

Gastroenterology & Hepatology Research 2022;4(4):19. https://doi.org/10.53388/ghr2022-12-061

Emerging therapies for inflammatory bowel disorder

Mohammad Waqas[1*], Aafreen Ali Nyaz[1], Nikunj Agarwal[1]

[1]Faculty of medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi 0179, Georgia.

[*]**Corresponding to:** Mohammad Waqas, Faculty of medicine, Ivane Javakhishvili Tbilisi State University, 1 Ilia Chavchavadze Avenue, Tbilisi 0179, Georgia. E-mail: mohammad.waqas003@med.tsu.edu.ge.

Author contributions

Waqas, Aafreen, and Nikunj found, went through, and formulated multiple drafts that eventually made us get the final draft. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

The authors would like to acknowledge the supervision and guidance of Srijamya whose help has played a vital role in the timely submission of this document, furthermore the team members have equally put their effort into formulating the tables and adding the relevant information. The authors would also like to thank the university, Ivane Javakhishvili Tbilisi State University, faculty of medicine, for giving us the chance to be able to conduct our research and publish it. There has been no financing or monetary support for the research studies or in preparation of the manuscript.

Abbreviations

IBD, inflammatory bowel disorder; CD, Crohn's disease; UC, ulcerative colitis; TNF, tumor necrosis factor; JAK, janus kinase; STAT, signal transducer and activator of transcription; IL, interleukin; S1P, sphingosine-1-phosphate; PDE, phosphodiesterase; FMT, fecal microbiota transplantation.

Peer review information

Gastroenterology & Hepatology Research thanks all anonymous reviewers for their contribution to the peer review of this paper.

Citation

M Waqas, Aafreen A N, Nikunj A. Emerging therapies for inflammatory bowel disorder. Gastroenterol Hepatol Res. 2022;4(4):19. doi: 10.53388/ghr2022-12-061.

Executive editor: Chen-Xia Lu.

Received: 23 September 2022; **Accepted:** 09 November 2022; **Available online:** 13 December 2022.

Abstract

Inflammatory bowel disorder (IBD) affects over 5.2 million individuals in North America and Europe alone. IBD is a term used to describe a condition of chronic inflammation in the Gastrointestinal tract-primarily the intestines. While the exact etiology is not fully understood, it is generally accepted that the cause of the inflammation may be due to an abnormal immune response to the gut bacteria. IBD is a progressive disease and can cause various gastrointestinal-related complications. This makes it crucial to discover new treatments and to improve the treatments that are already available. The aim of the study is to answer the question, "What are the emerging therapies for IBD"?

In this section, the currently available therapies for IBD are discussed, among which some have already been shown to be effective against IBD whereas some are still in various stages of clinical trials. These therapies include drugs that affect janus kinase - signal transducer and activator of transcription pathway, drugs that impact anti-adhesion molecules, drugs that inhibit anti-interleukin, drugs that modulate sphingosine-1-phosphate receptor, drugs that inhibit phosphodiesterase-4, and finally a technique known as fecal microbial transplant.

Many treatments are available today, and new ones are constantly emerging. Some therapies like phosphodiesterase-4 inhibitors and fecal microbiota transplantation that may be the optimum treatment are still under clinical trials, and more research is required for them to be safe, viable, and beneficial options, whereas others are available for usage by the patient but have adverse complications and side effects such as anti-tumor necrosis factor-α or janus kinase - signal transducer and activator of transcription inhibitors.

Keywords: inflammatory bowel disorder; emerging therapies for inflammatory bowel disorder; therapies for Crohn's disease; therapies for ulcerative colitis

Introduction

Inflammatory bowel disorder (IBD) is a term used to describe a condition of chronic inflammation in the gastrointestinal tract – primarily the intestines. While the exact etiology of the disease is not fully understood, it is generally accepted that the inflammation results due to an abnormal immune response to the gut bacteria with various contributing genetic and environmental factors. IBD presents with symptoms such as abdominal pains, weight loss, rectal bleeding, persistent diarrhea, etc. It has two main subtypes – Crohn's disease (CD) and ulcerative colitis (UC).

IBD is a progressive disease that can lead to many complications, such as anemia, strictures, perforation, and even cancer. These complications increase the risk of hospitalizations and the need for surgery and lead to an overall decrease in quality of life.

IBD affects over 2 million individuals in North America, 3.2 million in Europe, and millions worldwide [1]. The rising incidence of IBD around the world has made it crucial to discover and improve new and existing treatment options for these conditions.

The current treatment protocol for IBD includes the use of biologics to achieve mucosal healing and clinical remission [2]. Over the past two decades, there have been many advancements in IBD therapies. The most popular and common IBD therapy today is anti-tumor

necrosis factor (anti-TNF). The use of anti-TNF in moderate to severe IBD has resulted in a decrease in the need for surgical intervention and improved health outcomes. Anti-TNF therapy has also been effective in treating the extraintestinal manifestations of IBD.

However, despite its success in many patients, it is not a guaranteed treatment option for all patients. Approximately 30% of the patients suffering from IBD fail to respond to anti-TNF therapy, and 40% of those patients that do initially respond to it eventually stop responding. Additionally, anti-TNF agents have also been associated with side effects such as the increased risk of infections and a possible increased risk of malignancy [3].

This has led to the need to discover alternative therapies for IBD. Today, following the developments in understanding the various immunological mechanisms underlying the condition, we have many emerging therapies for IBD that target the various etiopathological mechanism of the disease. We have the use of janus kinase (JAK) signal transducer and activator of transcription (STAT) – JAK-STAT inhibitors, anti-adhesion molecules, anti-interleukin molecules, sphingosine-1-phosphate receptor modulators as well as fecal microbial transplants.

This review aims to consolidate the various existing and emerging therapies for IBD, understand their mechanism of action, and evaluate their efficacy through various clinical trials. The review also aims to compare the benefits and risks of the available IBD therapies.

Body

Although there are many strategies to treat IBD, relapses and failures are common. As a result, there is a constant need for research in this area to find other modalities that may be more effective. The currently available therapies for IBD are discussed in this section. Some of the therapies have already been shown to be effective in the treatment of IBD, while others are still in various phases of clinical trials. An understanding of the mechanisms behind the various available treatment options allows us to further study and come up with the most effective treatment options for this condition.

Anti-TNF

TNF antibody is a pivotal proinflammatory cytokine in the immunopathogenesis of IBD.

Anti TNF like infliximab, adalimumab, and certolizumab pegol have shown clinical efficacy in CD and UC. The lamina propria CD14+ macrophages bound with TNF, showed more response in IBD while TNF therapies acting at the periphery did not induce any cell apoptosis [4].

JAK-STAT inhibitors

One of the main routes of pathogenesis in IBD is that the inflammatory process is mediated by cytokines such as IL-9, IL-12, and IL-23, as well as interferon Gamma.

The cytokines in turn are mediated by the activation of a signaling pathway called the JAK-STAT pathway [2].

The JAK family comprises four intracellular tyrosine kinases – JAK1, JAK2, JAK3, and nonreceptor tyrosine-protein kinase 2 – that activate STATs through autophosphorylation. The binding of cytokines to specific receptors on the JAK proteins activates the transcription process which mediates the inflammation that is characteristic of IBD. Inhibiting the JAK-STAT pathway would prevent the inflammatory process from proceeding hence, making JAK-STAT inhibitors one of the new forms of IBD therapies [3].

Drugs that inhibit the JAK-STAT pathway are many. However, few of them have proven to be efficacious and many are still in clinical trials at various stages. To name few, Tofacitinib, Filgotinib, and Upadacitinib are the main drugs that utilize this mechanism of action.

Tofacitinib is an oral, non-selective JAK-inhibitor agent. Clinical trials have shown that it is effective in treating UC as well as CD resulting in remission in both cases [2, 3, 13].

Filgotinib is also an oral agent that is highly selective towards JAK1. A randomized clinical trial proved its efficacy in treating CD. Its effectiveness in the treatment of UC is still under study and results, as of now, are still being determined. It was seen in the trials that those patients who were treated with this drug showed higher rates of infection post-treatment as compared to the placebo group [2, 3, 13].

Upadacitinib is yet another oral JAK-STAT inhibitor that selectively inhibits JAK1. Trials have shown a certain degree of effectiveness with higher doses of this drug in both UC and CD. However, this drug has not yet been approved for public use [2, 3].

There have been speculations that selective inhibition may have some beneficial effects in terms of efficacy and safety, but further research needs to be done, as at this point, most of it is theoretical [8].

Anti-adhesion agents

Another route of pathogenesis in IBD is inflammation which results from the migration of pro-inflammatory leukocytes into the gut mucosa [3]. This migration process is mediated by interactions between certain molecules on the surface of lymphocytes – called integrins and vascular adhesion molecules present on the endothelial cells in the gut. This interaction results in the movement of the pro-inflammatory cells from the blood vessels into the gut – resulting in inflammation [1].

This mechanism of pathogenesis has been used to develop drugs called anti-adhesion molecules, which prevent the interactions between the integrins and the adhesion molecules – therefore limiting the inflammatory process that is characteristic of IBD. The integrins on lymphocytes pertaining to the gut have two main subtypes – alpha-4 and beta-7 [3, 13].

The drugs in this class include – Natalizumab, Vedolizumab, and Etrolizumab.

Natalizumab is a drug that blocks the alpha-4 subunit of many integrins. Clinical trials have shown that it is effective for both UC and CD. Patients treated with this drug showed remission. However, there was a major adverse effect related to this drug – an elevated risk of a CNS infection called progressive multifocal leukoencephalopathy. This elevated risk was so significant that this drug was removed from the market. It has recently been cautiously reintroduced with its use limited to a very select group of patients [2, 3, 13].

Vedolizumab was the first medication in this class that was approved for the use of UC and CD. It targets both the gut-specific integrin subunits – alpha-4 and beta-7. Many randomized clinical trials have shown it to be effective in treating UC and CD – resulting in remission. It has also been shown to be particularly effective in patients in whom the traditional treatment – anti-TNF agents – failed to produce any effects after a while. It also has a relatively mild adverse effect profile compared to Natalizumab – with no documented cases of progressive multifocal leukoencephalopathy. It is therefore the preferred drug for the treatment of IBD in this class [2, 3, 13].

Etrolizumab selectively targets the beta-7 subunit of integrins. There are several clinical trials that have proved its effectiveness in treating both UC and CD – with patients in remission as compared to the placebo group. However, phase III of the clinical trials is still underway and this drug has not yet been approved for public use [2, 13].

Inhibitors of interleukin (IL)

IL-12 and IL-23 are cytokines that induce the differentiation of naive T-cells into helper T cells – Th1 and Th17 respectively [13]. These helper T cells are central to the inflammatory pathogenesis of IBD. Inhibition of these interleukins can be effective in treating IBD.

Ustekinumab is a drug that inhibits the p40 subunit of both IL-12 as well as IL-23. It has been proven to be effective in treating mild to moderate CD. However, the drug is yet to be extensively studied as its safety profile has not yet been appropriately defined [3, 13].

There are a few more drugs under this class like Brazikumab and Risankizumab, which are still under clinical trials.

Sphingosine-1-phosphate (S1P) receptor modulators

S1P is a signaling lipid found in the circulation and most tissues. S1P's biological functions have been linked to its ability to activate a family

of five G protein-coupled receptors, S1P receptors 1–5, and also serve as an activator of the IL-6/STAT3 pathway in IBD [9]. The binding of sphingosine ligand to this receptor facilitates the migration of lymphocytes from secondary lymphoid organs to blood and tissue which mediates inflammation. By modulating these receptors, this pathway of inflammation in IBD can be blocked [3].

There have been many experiments that have shown promising results both in vivo and invitro for the treatment of IBD and that the S1P inhibitors have many of the same effects of TNF-α that prevent the deleterious activation of neutrophils, macrophages, and mast cells, and neutrophil infiltration into the mucosa [10].

The only notable drug in this class is Ozanimodh. It is an oral agent that acts as a selective agonist to the S1P receptor subtypes 1 and 5. Upon binding, this drug causes the internalization of the S1P receptor and its subsequent degradation – thereby reducing the migration of lymphocytes into the gut [3].

A double-blind placebo-controlled trial showed that Ozanimodh was effective in treating patients with UC. For patients with CD, this drug has shown to have a certain degree of effect. However, results of phase III trials are yet to be released [2].

Phosphodiesterase-4-inhibitors (PDE-4-inhibitors)

PDE-4 inhibitors are one of the enzymes responsible for the breakdown of intracellular cyclic adenosine monophosphate – an important component of the intracellular inflammatory cascade. The PDE-4-inhibitors prevent this breakdown, which results in an increased intracellular concentration of cyclic adenosine monophosphate, thereby downregulation of the immune response [13].

Apremilast is the one drug under this class that is being studied as a treatment option for IBD. In phase II of a double-blind placebo-controlled trial, this drug has shown tentative positive results for the treatment of UC. However, it is not yet known, if this drug is effective or not as phase III trials have not been initiated [2, 13].

Fecal microbiota transplantation (FMT)

One of the primary understating of the pathogenesis behind IBD is the inappropriate response to the gut microbiota. This correlation between the microbial environment of the gut and the immune system has been studied for many years now.

The manipulation of the gut microbial composition has been shown to alter the immune response, which is a very promising option for IBD therapy.

FMT is a technique in which fecal matter from a healthy donor is transplanted into a patient [14]. It is done by gastrointestinal endoscopic administration of frozen stool [5], and it has been found that O splanchnicus is a key component that promotes both metabolic and immune cell protection from UC [6]. A recent meta-analysis that included 53 studies, concluded that there was clinical remission in 36% of UC patients and 50.5% of CD patients who had undergone fecal microbial transplants [13].

Inflammatory bowel disease at times may develop severe complications such as toxic colitis, toxic megacolon, intestinal perforation, fistulas, abdominal abscesses, malignancy, primary sclerosing cholangitis, pouchitis, and other extraintestinal complications are anemia, thromboembolic events or osteoporosis.

The prognosis for IBD depends on different factors, which include the severity of the disease and the age at diagnosis. The disease is life-disrupting, but it doesn't shorten the life expectancy as such.

Results

With the latest IBD therapy treatment it is understood that IBD cannot be completely cured however, one can have a better quality of life.

IBD is a disease exposed to a different type of exposome, the genome, the microbiome, and the immunome may initiate the different type of responses to different receptors, activate different signaling molecules, bind different DNA loci, express and transcribe different genes, translate different proteins, and produce distinct pro-inflammatory products which all ultimately lead to IBD.

Current therapies that are being used include sulfasalazine (Azulfidine, Salazopyrin) and its 5ASA derivatives, glucocorticosteroids, immunomodulators/immunosuppressants in UC and CD. Some of them are being used since the 90s, these have shown symptomatic improvement and have been the mainstay treatment providing a relief factor to patients but has not been able to act as a cure but new therapies like interleukin 10 and 11 inhibitors have shown complete remission in 50% of patient, its dosing strategies still need to be investigated and researched before further use.

TNF-α, like infliximab, showed results in patients at first dose but have adverse effects ranging from mild complications such as headache, nausea, upper respiratory tract infection, fatigue, myalgia, rhinitis, pain, pruritus and dyspnea, where as some patients showed hypersensitivity which made these not a viable option to be considered in these IBD patients.

S1P receptor modulators and agonists, Ozanimod efficacy and safety needs to be researched upon further, as side effects include liver damage, increase in liver aminotransferase levels which makes this drug less appealing than the other emerging therapies.

JAK Inhibitors, tofacitinib for the treatment of moderate to severe active UC has been approved. The long-term safety of tofacitinib remains unclear and the main side effects include herpes zoster virus infection and thrombosis; therefore, more clinical trials are needed. One needs to consider the ratio of risk to benefit when using JAK inhibitors.

PDE-4-inhibitors, apremilast have shown some benefit with the patients of active UC.

However, more investigation is needed in the efficacy and safety justifying the fact that this drug is still in phase 2 and phase 3 trials, no specific data is available to support this as a treatment.

One of the best treatments available is FMT, which showed a clinical remission of almost 36% in CD and 50.5% UC. The main advantage of FMT lies in the complete ecosystem it provides from healthy individuals, including full spectrum of microbial organisms but things that still need research and investigation include the long-term efficacy, which is unknown, and the route of transmission which is most beneficial in FMT is still under investigation, the implementation and management of FMT is unknown. FMT is expected to be a new therapy option for the treatment of IBD, hopefully with more clinical trials it may emerge as the most beneficial treatment ever found.

Discussion

In this article we went through and stated the different therapies that have been available and therapies that have been developed for the one suffering from IBD, these include the likes of IL's. JAK-STAT inhibitors, S1P receptor modulators, PDE-4-inhibitors and FMT, the reader has to consider that the patient suffering from IBD cannot lead a normal life due to the adverse complications associated with it leading to lowered quality of life, some may even be unable to carry out their daily activities without extra assistance. The choice and efficacy of a treatment must also take into consideration the positive impact it has on the patient's quality of life and of those around them, but this does not rule out the fact that most of the therapies come with their own set of adverse side effects that may cause more harm than good for some individuals. During the research it has been made evident that more research is required in this field not only to find and refine the therapies available but to form a holistic treatment regimen, and to answer questions such as the possibility of using multiple therapy modalities and what effect they may have; positive and negative both. The treatment of choice is solely based subjectively on the condition of the patient and what they prefer and prioritize which heavily impacts the choice and course of treatment that may be suitable for them. More research will immensely benefit not only the patients but also the health care providers in making a decision that is in the patient's best interest.

Conclusion

IBD is a serious condition that affects a major population world-wide and causes multiple serious complications prompting the health care professionals to look for new therapies as well as improve on the ones present. Over the decade multiple modes of treatments aimed at the symptoms of IBD have been developed however they come with adverse effects hence, one should consider the risks before they start on a treatment, furthermore, most of the therapies available are aimed at alleviating the adverse symptoms of IBD and granting the patient a better quality of life. A comparison of the different available therapies has been made in Table 1 to get a better and holistic view.

Table 1

Drug class	Agent	Administration	CD	UC
Anti-TNF	Infliximab, Adalimumab, Certolizumab	IV, SC, SC	Clinical remission at week 4, approved in EU and USA	Approved in EU and USA
FMT	Fecal matter	Through endoscopy	50% remission	36% remission
Inhibitors of IL	IL-12 and IL-23, Ustekinumab	SC	Phase III, active	Not involved
JAK-STAT inhibitors	Tofacitinib, Filgotinib, Upadacitinib	Oral, oral, oral	Phase III recruiting, Phase III recruiting, Phase II recruiting	Phase IIb recruiting, Phase III recruiting, Phase llb /III recruiting
S1P	Ozanimodh	Oral	Phase III recruiting	Phase III completed
Anti-adhesion agents	Natalizumab, Vedolizumab, Etrolizumab	IV, IV, IV	Approved in USA, N/A, Phase III recruiting	Phase II completed

References

1. Ananthakrishnan AN, Kaplan GG, Ng SC. Changing Global Epidemiology of Inflammatory Bowel Diseases: Sustaining Health Care Delivery Into the 21st Century. *Clin Gastroenterol Hepatol* 2020;18(6):1252–1260. Available at: http://doi.org/10.1016/j.cgh.2020.01.028
2. Al-Bawardy B, Shivashankar R, Proctor DD. Novel and Emerging Therapies for Inflammatory Bowel Disease. *Front Pharmacol* 2021;12:651415. Available at: http://doi.org/10.3389/fphar.2021.651415
3. Chudy-Onwugaje KO, Christian KE, Farraye FA, Cross RK. A State-of-the-Art Review of New and Emerging Therapies for the Treatment of IBD. *Inflammatory Bowel Dis* 2018;25(5):820–830. Available at: http://doi.org/10.1093/ibd/izy327
4. Atreya R, Zimmer M, Bartsch B, et al. Antibodies Against Tumor Necrosis Factor (TNF) Induce T-Cell Apoptosis in Patients With Inflammatory Bowel Diseases via TNF Receptor 2 and Intestinal CD14+ Macrophages. *Gastroenterology* 2011;141(6):2026–2038. Available at: http://doi.org/10.1053/j.gastro.2011.08.032
5. Hamazaki M, Sawada T, Yamamura T, et al. Fecal microbiota transplantation in the treatment of irritable bowel syndrome: a single-center prospective study in Japan. *BMC Gastroenterol* 2022;22(1):342. Available at: http://doi.org/10.1186/s12876-022-02408-5
6. Lima SF, Gogokhia L, Viladomiu M, et al. Transferable Immunoglobulin A–Coated Odoribacter splanchnicus in Responders to Fecal Microbiota Transplantation for Ulcerative Colitis Limits Colonic Inflammation. *Gastroenterology* 2022;162(1):166–178. Available at: http://doi.org/10.1053/j.gastro.2021.09.061
7. Schoenfeld PS. Advances in IBS 2016: A Review of Current and Emerging Data. *Gastroenterol Hepatol* 2016;12(8):1–11. Available at: https://www.gastroenterologyandhepatology.net/supplements/advances-in-ibs-2016-a-review-of-current-and-emerging-data
8. Harris C, Cummings JRF. JAK1 inhibition and inflammatory bowel disease. *Rheumatology (Oxford)* 2021;60(Supple 2):ii45–51. Available at: http://doi.org/10.1093/rheumatology/keaa896
9. Maines LW, Fitzpatrick LR, French KJ, et al. Suppression of Ulcerative Colitis in Mice by Orally Available Inhibitors of Sphingosine Kinase. *Dig Dis Sci* 2007;53(4):997–1012. Available at: http://doi.org/10.1007/s10620-007-0133-6
10. Saba J, Degagne E. S1pping fire: Sphingosine-1-phosphate signaling as an emerging target in inflammatory bowel disease and colitis-associated cancer. *Clin Exp Gastroenterol* 2014;7:205–214. Available at: http://doi.org/10.2147/CEG.S43453
11. Zundler S, Becker E, Weidinger C, Siegmund B. Anti-Adhesion Therapies in Inflammatory Bowel Disease—Molecular and Clinical Aspects. *Front Immunol* 2017;8:891. Available at: http://doi.org/10.3389/fimmu.2017.00891
12. Ghosh S, Panaccione R. Review: Anti-adhesion molecule therapy for inflammatory bowel disease. *Therap Adv Gastroenterol* 2010;3(4):239–58. Available at: http://doi.org/10.1177/1756283X10373176
13. Weisshof R, El Jurdi K, Zmeter N, et al. Emerging Therapies for Inflammatory Bowel Disease. *Adv Ther* 2018;35:1746–1762. Available at: https://doi.org/10.1007/s12325-018-0795-9
14. Weingarden AR, Vaughn BP. Intestinal microbiota, fecal microbiota transplantation, and inflammatory bowel disease. *Gut Microbes* 2017;8(3):238–252. Available at: http://doi.org/10.1080/19490976.2017.1290757