Oral Biologics Therapy For Inflammation Bowel Disease : A Review

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Abstract: Crohn's disease and ulcerative colitis are two types of the chronic gastrointestinal condition known as "inflammatory bowel disease." Chronic exacerbation and remission phases characterise it, which has a significant impact on quality of life. Although its cause is uncertain, an overactive immune response in the gut wall is what drives it. Overproduction of adhesion molecules and proinflammatory cytokines is a result of the activated immunological response. Monoclonal antibodies used in biological therapies are made in a lab to inhibit particular bodily proteins from producing inflammation. These biologics have fundamentally altered how inflammatory bowel disease is treated. Anti-tumor necrosis factor (TNF), anti-integrins, and anti-interleukin (IL) 12/23 are the three types of biologics. When compared to placebo, all biologics had a greater clinical response and mucosal healing. The most effective drug is infliximab, although it can produce antibodies that prevent it from working, which results in a loss of response in these cases, golimumab works well. If used as a first-line treatment, certolizumab is more efficient. Vedolizumab is effective if corticosteroid and immunomodulator therapy has failed. Biological therapy should replace steroid therapy because it includes the entire body and has serious side effects. However, further research is required before biological therapy may be used as the first line of treatment for inflammatory bowel disease.

Keywords: Inflammation Bowel Disease, Infliximab, Adalimumab, Golimumab, Certolizumab, Vedolizumab, Ustekinumab

INTRODUCTION

Drugs made from chemicals differ from biologics in several areas that have an impact on their manufacture, administration, cost, and clinical efficacy. Here are the most significant variations and what they mean. It's like the difference between a lightning bug and a bolt of lightning: the difference between the almost right word and the right word is incredibly significant. The three little letters are important, as Mark Twain once said, and this is also true of the distinctions between drugs that are developed chemically and physiologically. However, the three letters this time are DNA. From natural protein sutures to fibrinogen coagulant factors, protein-based biologies and devices are utilised to treat everything from wrinkles to rattlesnake stings. Prophylactic medications, in vivo diagnostic devices, and therapeutic goods are all examples of biotechnological applications in healthcare. Biotechnology offers molecular diagnostic tests and imaging agents for identifying a variety of health issues, from high LDL cholesterol to drug-resistant HIV strains. This field's advancements are fast deconstructing Western medicine. Biotechnological medicine begins with the identification of a genetic variation and relies on therapies that manipulate it as opposed to beginning with a sickness and looking for its cause. By expanding on the idea, it has the potential to forecast health condition and take appropriate action — the fundamental idea of prevention around which managed care was based. However, none of this is cheap, which raises serious questions about how to spend resources and choose patients wisely. Therefore, in order to purchase and use biologic drugs efficiently, one must have an understanding of their mysterious activity and structure, the uniqueness of their action, and how they differ from conventional therapeutic agents. Although the creation of human growth hormone, insulin, and agents that stimulate the production of red blood cells was not a recent development, the targets have grown exponentially as a result of advances in genetic knowledge and our growing understanding of disease mechanisms and subcellular Drugs made from chemicals differ from biologics in several areas that have an impact on their manufacture, administration, cost, and clinical efficacy. Here are the most significant variations and what they mean[1].

Crohn's disease (CD) and ulcerative colitis are two conditions that collectively make up the chronic relapsing and remitting intestinal illnesses known as inflammatory bowel disease (IBD)[2]. Despite some similarities between CD and UC, there are unique clinical and pathological characteristics that set the two illnesses apart[3,4]. IBD has an uncertain etiopathogenesis, however it is assumed that interactions between immune dysfunction and genetic factors, environmental exposure, and gut flora play a significant role in these complicated diseases[5]. IBD treatment is mostly determined by the disease's location and severity. As a result, many classification schemes have been employed. By location, behaviour, and age at diagnosis, the Montreal classification classifies CD, while classifying UC is based on
the severity of the recurrence and the extent of the disease[6,7]. CD activity determines illness severity, which is divided into three categories: light (CDAI score), moderate to severe (CDAI 220 to 450), and severe fulminant (CDAI >450). A CDAI score of less than 150 denotes remission from the disease[8]. According to the Truelove-Witts Index, the third European Crohn's and Colitis Organisation (ECCO) recommendations for UC divide the severity of the disease into three categories: mild, moderate, and severe. Less than 4 stools per day, no bleeding, and no mucosal abnormalities at endoscopy are considered signs of remission in UC. IBD has traditionally been treated with mesalamine, steroids, and immunomodulators. Following the introduction of antitumor necrosis factor (anti-TNF) medicines, therapy has significantly changed in recent years. The increased risk of tuberculosis (TB) with anti-TNF medicines is still a concern despite their effectiveness. The purpose of this review is to talk about how biologics and TB interact with one another in individuals with IBD [9].

Inflammation Bowel Disease Management:
There are now a number of medical therapy options for IBD, and they differ based on the illness site, disease activity (mild/moderate/severe), and disease status (e.g. IBD is typically treated with corticosteroids, immunomodulators, and 5-aminosalicylic acid (5 ASA/aminosalicylates/mesalamine) In UC, aminosalicylates are mostly used topically or orally to sustain remission and to induce remission in moderate disease[10]. In order to bring about remission in cases of moderate to severe disease, corticosteroids are the cornerstone of treatment for IBD flares. For mild illness to promote remission, oral beclomethasone dipropionate is an alternative to traditional steroids[11]. As helpful adjunct therapies, immunomodulators including azathioprine, mercaptopurine, and methotrexate are safer and better tolerated than long-term steroid therapy. For the maintenance of remission in UC and CD, mercaptopurine or azathioprine monotherapy is also employed[12]. Intravenous corticosteroids are advised for acute, severe UC. Intravenous cyclosporin and/or surgery are common choices for people who don't react to intravenous steroids. Biologics are advised as an effective treatment for patients with moderate to severe IBD who are not receptive to conventional medication or with substantial small bowel involvement in CD[13]. Today, the goals of treatment for IBD include preserving mucosal healing, sustaining steroid-free remission, and generating clinical remission, 20% of individuals treated with corticosteroids do not achieve remission, and more than 20% develop steroid dependence[14]. The mainstay of treatment for these patients is biologics. Biologics are now crucial in treating difficult CD and severe acute UC[15]. The traditional "step-up" method puts the emphasis on starting therapy with drugs that carry a lower risk of serious adverse effects. In this method, patients who are steroid-dependent or steroid-refractory are the only ones who are given immunomodulators and biologics[16,17]. Biologics and immunomodulators are used as the first-line therapy in the "top-down" method after diagnosis. This strategy seems to be founded on the possible disease-modifying effects of early biologic intervention[18]. An additional choice is a "accelerated step-up" strategy, which combines traditional step-up therapy with the early or immediate administration of immunomodulators[19]. Four anti-TNF medications (infliximab, adalimumab, golimumab, and certolizumab) as well as two adhesion molecule antagonists are now approved biologic therapies for IBD (natalizumab and vedolizumab). Additionally, the U.S. Food and Drug Administration (USFDA) recently approved the oral Janus kinase (JAK) inhibitor tofacitinib for the treatment of UC[20]. Ustekinumab has also been licenced for the treatment of CD. The emergence of primary nonresponse (i.e., lack of response to induction treatment) and subsequent nonresponse is a major problem with anti-TNF medications (i.e., initial response during induction treatment followed by loss of response during maintenance treatment)[21,22]. The "top-down" strategy may not be successful in achieving remission in about 40% of IBD patients[23]. In addition, when immunomodulators are used together, there is a risk of major adverse effects including opportunistic infections like TB[20,21] and the potential for the development of neoplasia like lymphoma or non-malignant skin cancer[24].

Biological Therapy For Inflammation Bowel Disease:
Anti-integrins belong to the second category of biological treatments. Lymphocyte recruitment and migration into the intestinal mucosa cause the inflammation [25]. Leukocytes are adhered to by endothelial cells via integrins, endothelial adhesion molecules, and chemokine receptors such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and mucosal addressin cell adhesion molecule-1 (MAdCAM-1)[26]. Leukocyte migration to the site of inflammation is impeded by anti-integrin drugs because they bind to integrins and inhibit them[27]. Transmembrane receptors called integrins are found on inflammatory cells and aid in cell adhesion, signalling, and migration. Anti-IL 12/23 is the third and newest class, and it inhibits the common p40 subunit[28]. The following medicines are covered in this article.

Anti-Tumor Necrosis Factor-Antibodies

Infliximab
A chimeric monoclonal antibody called infliximab has a strong affinity for binding to alpha-TNF on macrophages and T cells, which results in cell lysis [29]. 112 participants were enrolled in a study by Hyams et al. to assess the effectiveness of infliximab in youngsters. The patients received infliximab 5mg/kg at weeks 0 and 2, and six. In order to receive additional infusions at either eight-week or twelve-week intervals, the patients who had responded to this medication through week ten were separated into two equal groups at random. Clinical response was 88.9% and clinical
remission was 58.9% at week 10. Clinical remission was at 55.8% and clinical response was at 63.5% for the patients taking infliximab every eight weeks at week 54. In addition, 33.3% and 23.5 percent, respectively, of the patients who received infliximab every 12 weeks showed a clinical response[30]. Clinical response and remission are seen to occur less frequently every 12 weeks than every 8 weeks. The effectiveness of this medication in children was 88% at week 10. To combat the immunogenicity of infliximab, Pampilicheal et al. conducted a retrospective research. As is well known, infliximab's immunogenicity and ensuing failure of therapy are caused by antibodies to the drug. However, his research indicates that a rise in infliximab antibody concentration is to blame for treatment failure. Low levels of infliximab antibodies do not have an impact on the medication's effectiveness. Then he began treating 22 patients with infliximab and monitored them for 17.5 months. Only 15 of the 22 patients continued receiving treatment. This demonstrates that infliximab had a favourable effect on 75% of patients. In order to determine if immunomodulatory can overcome the infliximab therapeutic failure caused by anti-infliximab antibodies and enhance the clinical response of infliximab, Ben-Horin et al. did a retrospective investigation. He administered immunomodulatory to five individuals who had infliximab-related antibodies. Three individuals received azathioprine/6-mercaptopurine, whereas two patients received methotrexate. Before and after immunomodulatory were administered, blood levels of infliximab antibodies were assessed. Following immunomodulators, the concentration of infliximab antibodies was reduced, and clinical response was reinstated in all patients. This demonstrates how patients' responses to infliximab can be restored by the addition of immunomodulators. The study by Ben-Horin et al. is the least strong of all studies when compared because of the limited number of patients [31].

Adalimumab

A recombinant human monoclonal antibody called adalimumab binds to tumour necrosis factor-alpha and displaces it from the TNF receptor. Cells with surface TNF and complement are also lysed by it. Adalimumab was tested for safety and effectiveness in a study by Colombel et al. on 1,094 patients with moderately to highly active ulcerative colitis[32]. He carried out the ULTRA (Ulcerative Colitis Long-Term Remission and Maintenance in Adalimumab 1, 2, and 3 placebo-controlled investigations. In ULTRA 1 and 2, 600 patients were enrolled. After four years of follow-up, 199 patients were still receiving adalimumab therapy. At week 208, the rates of remission per partial Mayo score were 24.7%. In ULTRA 3, 588 patients were signed up. Three years later, 360 patients were still receiving adalimumab treatment. After three years, the remission rate for each partial Mayo score was 63.6%. For four years, adalimumab medication for inflammatory bowel disease is well tolerated. Adalimumab keeps the mucosal healing, remission, and quality of life intact. Adalimumab's effectiveness and clinical response in relation to antibodies against it (AAA) and trough levels are discussed by Paul et al. (TRA). He recruited 1,941 individuals with inflammatory bowel disease for 14 systematic review studies. 13 of those studies revealed a link between high TRA and positive clinical outcomes [33]. The effectiveness of adalimumab and TRA, however, is unaffected by immunosuppressive therapy. However, combined therapy lengthened the period for dose escalation. Only one study found no link between a high TRA and a positive clinical outcome. Additionally, he carried out seven meta-analysis investigations. AAA and clinical response were found to be negatively correlated in six investigations with 536 participants. Positive AAA carries a greater chance of clinical response loss, and if the TRA is high, the clinical response is also good. Adalimumab's effectiveness and maintenance of clinical remission in moderate to severe ulcerative colitis were studied by Sandborn et al. There were 494 patients in the trial. Adalimumab was administered to the patients in doses of 160 mg at first, 80 mg at week 2, and thereafter 40 mg every other week or a placebo. Following up took place at weeks eight and 52. Clinical remission rates were 16.5% with adalimumab and 9.3% with a placebo at week eight. The rates of clinical remission at week 52 were 8.5% with placebo and 17.3% with adalimumab. Sandborn et al. examined the efficacy of adalimumab and the maintenance of clinical remission in patients with moderate to severe ulcerative colitis. The trial included 494 patients. Patients received doses of adalimumab in the amounts of 160 mg at first, 80 mg at week 2, and then 40 mg every other week or a placebo. There was follow-up at weeks 8 and 52. At week eight, clinical remission rates with adalimumab were 16.5% and 9.3%, respectively. At week 52, the rates of clinical remission with placebo were 8.5% and those with adalimumab were 17.3%. The patients were therefore included in ULTRA 1, 2, and 3 to address this. In Paul's study, the analysis was stronger and included more cases when it was restricted to adults. Additionally, Sandborn's study is a subgroup analysis and only includes a small number of patients[34].

Golimumab

A retrospective analysis with 115 patients was carried out for 9.8 months by Martineau et al. to report the efficacy and safety of golimumab. The clinical response was 55.8% after 3.8 months. This study demonstrates that golimumab is helpful for the patients following the failure of infliximab and adalimumab therapy. Gibson et al. presented a study in which the efficacy and safety of administering golimumab subcutaneously for two years of maintenance therapy were evaluated in patients with mild to severe ulcerative colitis [35]. Patients who had a 52-week course of either a placebo, golimumab 50 mg, or golimumab 100 mg once every four weeks were eligible for evaluation in the 54-week period. The majority of patients were able to continue modest disease activity during the 104th week, or about 86% of them. Similar to what was reported in the 54th week, this mediation was safe. Without any new safety signals, the two-year usage of golimumab in maintenance therapy was helpful. In patients who have finished golimumab
induction therapy, Sandborn et al. conducted double-blind trials. The participants started maintenance treatment, which consisted of 50 mg, 100 mg, and placebo every four weeks until week 52. In the patients who got 50 mg, 100 mg, or a placebo at week 54, the clinical response was 47%, 49.7%, and 31.3%, respectively. At weeks 30 and 54, the patients who received golimumab 100mg had greater clinical remission and healing than the ones who got a placebo. The safety profile of golimumab is presented in this study. These studies demonstrate golimumab's effectiveness and safety. With no new safety profile, this medication can be taken in maintenance therapy for more than two years. The study by Martinneau et al. has the fewest populations and no endoscopic data, making it the weakest.

Certolizumab Pegol:
A humanised fab fragment known as certolizumab pegol has been pegylated. Although it has a strong affinity for alpha-tumor necrosis factor, it has little effect on the death of T cells or monocytes. To assess the effectiveness of certolizumab, Schreiber et al. conducted a randomised, doubleblind, placebo-control experiment on 668 individuals. At weeks 0–2, 2–4, the patients received 400 mg of certolizumab subcutaneously. Six weeks into the induction therapy, 428 of the 668 patients showed positive responses and began the maintenance therapy. The exclusion criteria resulted in the exclusion of three patients. Certolizumab 400 mg was administered every four weeks to 215 patients on maintenance therapy while 210 individuals received a placebo. Clinical remission was 51.4% in patients who received a placebo and 69.9% in those who received certolizumab for their condition. According to this study, patients who got maintenance therapy fared better than those who received a placebo in terms of clinical remission and responsiveness to medical therapy. Certolizumab's effectiveness and safety were described in a research by Moon et al. Infliximab, adalimumab, and natalizumab were the three biologic medicines that made up the majority of his 358 patients who had previously failed them. Certolizumab was the second biological agent in 112 patients, and the third biological agent in 189 patients. The outcomes demonstrated certolizumab's clinical advantages for patients who had previously undergone unsuccessful biological treatments. This outcome is supported by numerous additional early findings. This medication may be more efficient when taken as a first- or second-line medication. A retrospective chart study for certolizumab pegol dose and clinical response was done by Stein et al. He enlisted 87 individuals, the majority of whom had biological therapy fail. Only 27 patients out of 87 had a good clinical response, or 31.%. 31 individuals were then re-induced, and only five of them (16.1%) showed a good clinical response. This study demonstrates that certolizumab was less effective as a second- or third-line treatment, which may be related to immunogenicity or a lack of response mechanisms. If used as the first-line treatment, this medication may be more efficient. The Stein et al. study is weak in the study comparison since it is a small-scale retrospective study with only 100 individuals. The study's findings are unreliable because it was based on various populations and academics who were referred.

Anti Integrin
Natalizumab:
Natalizumab is a human monoclonal antibody that fights the cell adhesion protein 4-integrin. The medication is frequently prescribed to patients with chronic inflammatory diseases such inflammatory bowel disease. The medication works by preventing inflammatory cells from spreading across the cell layers. 248 participants participated in a trial to evaluate the effectiveness of natalizumab. Four groups were created from the patients. Two doses of placebo were given to the first group, one dosage of natalizumab (3 mg) was given to the second group, and two doses of natalizumab (3 mg) were given to the third group and two doses of 6 mg of natalizumab were given to the fourth group. The dosages were separated by four weeks. Two natalizumab infusions were administered to the groups that experienced a rise in remission rates. Remission rates were 44% and responses were 71%, respectively. In individuals with Crohn's disease, this trial demonstrates the short-term efficacy and safety of natalizumab. In a different trial, 10 patients who received an infusion of natalizumab 3 mg were used to examine the medication's effectiveness. Five out of ten patients shown a good clinical response by week two. One more patient displayed a positive clinical response at week four. Therefore, it was determined that this medication is secure, well-tolerated, and enhances quality of life. Two controlled trials were carried out by Sandborn et al. to evaluate the natalizumab induction and maintenance therapy. 905 participants were enlisted, and they either received a placebo or natalizumab 300 mg. In week 10, the Crohn's activity dropped by 70 points. The medication failed to have a positive clinical outcome. The outcomes were nearly identical to those of the patients who received a placebo. Natalizumab was administered to 339 of the 905 patients who responded to the drug every four weeks until week 56. The individuals who used natalizumab for a long time saw positive results. The second natalizumab trial, which was published in 2002, is the weakest because it included just 10 patients.

Vedolizumab:
Vedolizumab is a monoclonal antibody used to treat IBD cases that have not responded to other treatments. For a very long time, there was no medication available for ulcerative colitis or Crohn's disease patients when corticosteroids or previous immune modulators failed. The development of medications like vedolizumab has made it possible to treat these conditions. When using numerous TNF antagonists, patients' response rates tend to decline, making it challenging...
to maintain remission with older medicines like TNF antagonists. Vedolizumab is a gut-selective anti-inflammatory drug since it is an integrin inhibitor, more particularly, an α4β7 integrin inhibitor [44]. Because of the drug’s focus, it is particularly effective in treating inflammatory bowel illness. However, with the advent of this new class of drugs, concerns have been raised about their effectiveness and their capacity to treat patients in real clinical settings. Vedolizumab is working well, according to three distinct research trials that were conducted to evaluate its effectiveness. At 14 weeks of treatment, one-third of 294 inflammatory bowel disease patients in a vedolizumab cohort study were in steroid-free clinical remission. In a different randomised controlled trial, it was discovered that after 10 weeks of treatment, 26.6% of the study population was in remission, as opposed to 12.1% in the placebo group. In a third followup study involving 172 patients, it was discovered that the remission rates for Crohn's disease and 2020 were 48.9% and 23.9%, respectively, for the Vedolizumab group compared to the placebo group. 53.5% and 29.5% of UC at the 14th week, respectively [45]. These studies’ findings clearly demonstrate that vedolizumab therapy has a positive effect on remission after 10 weeks of treatment. It is challenging to predict how effectively the therapy will work for patients with varying degrees of illness severity. Since the trials only included individuals who had disease severity levels greater than a particular threshold, no groups had been stratified based on disease severity. Since the trials only included patients who were above particular severity criteria, they did not stratify groups based on disease severity [46].

### Ustekinumab

A monoclonal antibody against the p40 component of IL 12/23 is called ustekinumab. Retrospective observational research was conducted by Wils et al. on 122 active Crohn's disease patients who had a subcutaneous injection of ustekinumab. Three months later, these patients were checked on. 43 of the patients did not respond to this medicine, whereas 79 of the patients showed a positive clinical response [47]. It was noticed that this medication is helpful in treating active Crohn's disease and symptom reduction. Ustekinumab has a greater therapy response in Crohn's disease than a placebo, according to Sandborn et al. They enrolled participants in two trials, one with 741 participants and the other with 628 participants. Patients in each experiment were given 130 mg of ustekinumab as an injection. 6 mg/kg, or a placebo. They evaluated the patients after six weeks and discovered that ustekinumab has a higher rate of response than a placebo [48]. Then, 397 patients received a maintenance dose of 90 mg administered subcutaneously every eight or 12 weeks. At week 44, patients receiving ustekinumab had a remission rate of 53.1% compared to 48.8% for patients receiving placebo, and it was noted that remission rates were greater in the ustekinumab therapy group than in the placebo group. Sandborn et al. maintained the efficacy and safety monitoring of this medication for a second year. Only patients receiving ustekinumab therapy were recruited; patients receiving placebo were excluded. Only 621 of the 718 patients finished week 92. In some individuals, the dosage was changed from receiving ustekinumab injections every eight weeks to receiving them every 12 weeks till week 44. After that, the dosage was continued until week 92. Patients receiving ustekinumab 90 mg every 12 weeks had effectiveness rates of 72.6%, 74.4%, and 53.3% at week 92 of the randomization, respectively. Ustekinumab 90 mg once every eight weeks, with dose changes for the patients. Ustekinumab every 12 and eight weeks produced identical efficacy findings, but in patients who received dose modifications, it was less effective. The patients using ustekinumab and those taking a placebo experienced the same safety events. According to these research, this medication is safe and exhibits a positive clinical response [49].

![Figure1: Classification of drugs used in IBD](image)

### CONCLUSION

In order to demonstrate the effectiveness and safety of biological therapy in inflammatory bowel disease, this review article summarises a number of studies. Biological therapy has been employed to treat inflammatory bowel disease in recent years. Antibodies known as biologics are made in labs to prevent particular bodily proteins from triggering inflammation. All of the biologics exhibit secure clinical outcomes. Clinical remission and mucosal healing rates in
patients receiving infliximab, adalimumab, golimumab, certolizumab, and vedolizumab therapy. Ustekinumab and natalizumab have demonstrated superior outcomes than placebo. The drug with the best efficacy is infliximab, which is effective in about three-fourths of patients. Due to antibodies being produced against infliximab and adalimumab, golimumab is successful in these patients. Immunomodulators are added to infliximab to assist offset the decrease of responsiveness caused by antibodies made against it. First-line agents such as certolizumab are more efficient. If administered for a brief period of time, natalizumab does not produce a favourable clinical response. When something is kept up for a long time, favourable results become apparent. Vedolizumab is useful for treating conditions where corticosteroids and immunomodulators have failed. Given that biologics have a beneficial effect on the management of inflammatory bowel disease, it is crucial to understand their efficacy. They are extremely selective in their mode of action and can counteract the use of corticosteroids, which affect the entire body and have serious negative side effects. Current literature on mucosal immunity still leaves many questions unanswered. In the treatment of inflammatory bowel disease, mucosal repair is the main goal, and biologics effectively promote mucosal healing. The biologics used to treat inflammatory bowel disease are effective, but additional clinical research is required before we can employ biologic therapy as the first-line drug to treat IBDs.

REFERENCES


18) Rogler, G. (2013). Top-down or step-up treatment in Crohn’s disease?. *Digestive diseases (Basel, Switzerland)*, 31(1), 83–90. [https://doi.org/10.1159/000347190](https://doi.org/10.1159/000347190)


21) U.S. Food and Drug Administration (USFDA). FDA approves new treatment for moderately to severely active ulcerative colitis [Internet]. Silver Spring: USFDA; c2018 [cited 2018 May 30]. Available from: [https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609225.htm](https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609225.htm)


