Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

Recent Treatment for Management of Inflammatory Bowl Disease

Jyoti Jha[1], Vandana Sahani[2] and Shivanand Patil[3]

[1]Research Scholar, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun, INDIA.

[2]Associate Professor, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun, INDIA.

[3]Professor, Shree Dev Bhoomi Institute of Education Science and Technology, Dehradun, INDIA.

[1]Corresponding Author: jhajyoti1806@gmail.com

www.jrasb.com || Vol. 3 No. 6 (2024): December Issue

Received: 26-11-2024	**Revised:** 30-11-2024	**Accepted:** 13-12-2024

ABSTRACT

Due to the development of biologics and small molecule medicines (SMDs), there has been a substantial shift in the approach that is taken to treat inflammatory bowel disease (IBD). This shift has been brought about by the introduction of these treatments. It is important to note that these treatments will not be effective to each and every patient, and it is quite likely that a "ceiling effect" will take place when biologic monotherapy is delivered. Taking into consideration this predicament, it is evident that there is a requirement that has not yet been fulfilled for the purpose of maximising the utilisation of biologics and being able to anticipate therapeutic responses. For the purpose of treating patients who are experiencing either an initial lack of response or a subsequent loss of response to traditional biologics and SMDs, there is an urgent requirement for the development of novel medications that have innovative action mechanisms. It has been suggested that a unique method might be utilised in order to improve the efficacy of treatment for inflammatory bowel disease (IBD). This is due to the fact that the combination of several biologics or SMDs has the capability to reduce inflammation in a variety of different ways. According to the evidence that is currently available for inflammatory bowel disease (IBD), individuals who have refractory IBD and who have not responded to several biologic treatments or who have extraintestinal symptoms may benefit from dual targeted therapy. Equally as crucial is the identification of the proportion of patients suffering from inflammatory bowel disease (IBD) who are responding favourably to biological combination therapy in order to maintain remission of the condition. The objective of this review is to present a synopsis of the newly developed biologics and SMDs, as well as the current state of bio-logics and SMDs. This is done with the intention of highlighting the progress that has been achieved towards the development of personalised treatment for inflammatory bowel disease (IBD).

Keywords- IBD, Disease, Ulcer, Medication.

I. INTRODUCTION

There is a category of autoimmune disorders that are referred to as inflammatory bowel diseases, or IBDs for short. These diseases are marked by persistent inflammation that is not communicable and mostly affects the lining of the gastrointestinal system [1,2,3]. According to [4,5], the immunological dysregulation and inflammatory dysfunction that are the outcomes of this illness that is notably persistent, progressive, and recurring have a substantial influence on the quality of life of patients. There are four types of inflammatory bowel disease that are the most common: Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis (IC), and unclassified colitis (IBD-U). These diseases have substantial histological and clinical characteristics, despite the fact that they affect different parts of the digestive system when they manifest themselves. Unlike CD, which can affect any region of the gastrointestinal tract, from the mouth to the anus, in a pattern that is discontinuous, UC mostly affects the mucosa of the colon in a pattern that is continuous [1,6,7]. CD can also affect any section of the gastrointestinal tract including the anus. Both CD and UC are capable of being subdivided into a selection of different categories. The region of the colon that is affected is what leads to the classification of ulcerative colitis into its several subtypes. Proctitis, which is

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

confined to the digestive system, proctosigmoiditis, which extends into the sigmoid, distal ulcerative colitis, which extends beyond the sigmoid, and pancolitis, which spans the entire colon, including the cecum, are the subtypes that fall under this category. Among the phenotypes that are used to categorise CD, the most common ones are penetrating, inflammatory, and structuring presentations [1]. On the other hand, we have inflammatory presentations. Since 2005, the Montreal classification has been utilised as a standard framework for the diagnosis of inflammatory bowel disease (IBD). This framework is founded on clinical, molecular, and serological criteria [8,9,10]. Because there is currently no known treatment for inflammatory bowel disease (IBD), patients are forced to rely on symptomatic therapy that focus on reducing inflammation and boosting the repair of the gut [11,12,13].

These therapies are designed to alleviate symptoms of the condition. Due to the fact that these medications frequently cause adverse effects and have the potential to result in clinical failure or loss of response [12,14,15,16,17,18], it is of the utmost importance that meticulous monitoring and the investigation of treatment methods that are more effective be carried out. Diarrhoea, abdominal pain, bleeding from the rectal region, and a diminished appetite are some of the clinical indications of symptoms [11,19]. However, this list is not exhaustive. There are approximately 25–40% of individuals who are diagnosed with inflammatory bowel disease (IBD), which is considered a systemic disease since it can develop in other parts of the body. Moreover, the gastrointestinal system is the principal location where its effects manifest themselves, which is an additional point to consider. There are a number of symptoms that are usually linked with the EIM [4,6,11,19,20]. Some of these symptoms include fever, weariness, arthritis associated with inflammatory bowel disease (IBD), anaemia, oral aphthous ulcers, pyoderma gangrenosum, fever, nephrolithiasis, osteoporosis, anterior uveitis, and erythema nodosum. On a patient-by-patient basis, the EIM can be dramatically different. Due to the fact that individuals with inflammatory bowel disease (IBD) may exhibit a wide variety of symptoms, the process of diagnosing this disorder is not only challenging but also time-consuming. It is for this reason that it is of the utmost importance to have a comprehensive understanding of these symptoms in order to uncover fresh and helpful biomarkers as well as alternative treatment alternatives [21,22].

As a result of the fact that it was discovered for the first time in the 20th century, the incidence and prevalence of inflammatory bowel disease (IBD) have significantly increased over the course of the past several decades, particularly in industrialised nations such as those in North America and Europe (Figure 1). Indeed, the illness is more prevalent among white people, who have the highest incidence rate of the condition. On the other hand, inflammatory bowel disease (IBD) has become more widespread in countries that have just recently undergone industrialisation, particularly in Latin America, Africa, and Asia, as well as among immigrant populations that migrate to these countries [3,11,19,23,24]. This is especially true in nations that have recently undergone internationalisation. For every year, there are roughly 400,000 new cases of inflammatory bowel disease (IBD) that are diagnosed. According to the Global Burden of Disease (GBD) figures for 2019, [25] it is estimated that approximately 5 million people are considered to be affected by this ailment. There are a number of factors that can influence the prevalence of inflammatory bowel disease (IBD), including ones such as age and gender. An indication of this would be the fact that the prevalence of diseases that manifest themselves for the first time in children is increasing and accounts for twenty-five percent of all cases [12,23,26,27].

In continental Europe, there were 15 instances recorded for every 100,000 person-years, as indicated by the outcomes of the research conducted by EpiCom and Epi-IBD [28]. Although Western countries appear to be enjoying a stability of the condition, the prevalence of inflammatory bowel disease (IBD) continues to rise. This is despite the fact that the disorder is becoming more prevalent. Given that inflammatory bowel disease (IBD) often manifests itself in early adulthood, has a low mortality rate, and there is currently no therapy for it [29], the fact that this trend is occurring should not come as a surprise to anyone. Because inflammatory bowel disease (IBD) is becoming more common, it is of the utmost need to have a more in-depth understanding of the molecular basis of the disease in order to develop individualised treatments and diagnostic tools. This is because IBD is becoming becoming more widespread.

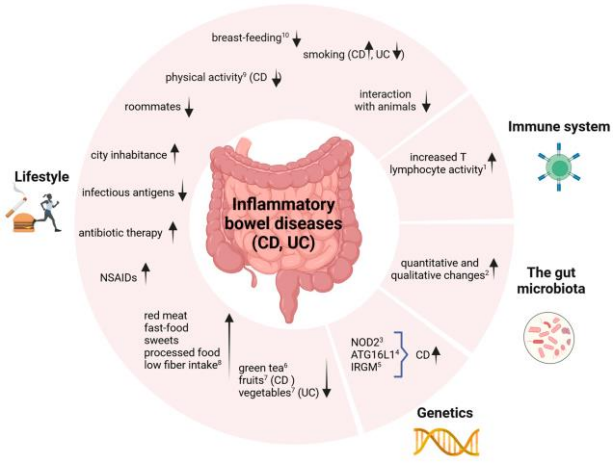


Fig: 1 Inflammatory bowel disease (IBD) is characterised by a unique set of signs and symptoms that can be identified at its onset. ATG16L1, autophagy-related-16-like-1, CD, IRGM, NOD2, nucleotide oligomerisation binding domain 2, NSAIDs, ulcerative

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

colitis, and UC are all abbreviations for abbreviations that signal "higher risk" or "lower risk," respectively. To put it another way, the letters ATG16L1 and CD are some of the abbreviations that represent these abbreviations. Antibodies are to blame for an excessively robust humoral immune response, which is brought about by an elevation of Th2 and Th1 activity, respectively, in UC and CD. This is done in order to combat the inflammatory response. Because antibodies are the ones accountable for the immunological reaction, this is the situation that has arisen. The occurrence of inflammation can be attributed to the fact that pro-inflammatory cytokines, which encompass tumour necrosis factor-alpha (TNFα), interleukin-6 (IL6), and interleukin-12 (IL12), are more prevalent than anti-inflammatory cytokines. Patients who had UC had a considerably larger ratio of strains belonging to the Enterobacteriaceae family to those belonging to the Bacteroides family. At the third position, there is the autosomal recessive gene that is known as NOD2 (nucleotide oligomerisation binding domain 2).

This gene is responsible for the inheritance pattern. To be more explicit, it is accountable for the coding of the immune response that is not particular to bacterial antigens. (4) An peculiar immune response to microorganisms that are located within biological cells is caused by the ATG16L1 (autophagy-related-16-like-1) gene, which is comparable to NOD2. This gene is responsible for the immunological response. An aberrant immunological response to bacteria that are present within cells is caused by IRGM, which is also known as immunity-related GTPase M. Another name for this gene is NOD2, which is also responsible for this defective immune response.

The anti-inflammatory benefits of green tea polyphenols were also seen, and it was demonstrated that these effects were comparable to the effects that sulfasalazine had on someone who suffered from colitis. Those who suffer from inflammatory bowel disease (IBD) usually have a difficult time maintaining the health of their intestinal barrier. This may be at least partially attributed to flavonoids, which are compounds that are found in plants. Due to the fact that this is the case, it is probable that the bacteria that live in the intestinal tract will create fewer short-chain fatty acids.

II. CROHN'S DISEASE

There are a number of potential complications that can develop in the mucosa as a result of Crohn's disease, which is one of the most widespread inflammatory illnesses that can be found anywhere in the world. These complications include structures, fistulas, ulcers, and granulomas. The terminal ileum region is the most common location where gastrointestinal CD manifests itself; nonetheless, the condition can cause harm to any part of the body, including the mouth and the rectum. This is despite the fact that the terminal ileum occurs most frequently. The clinical signs of chronic diarrhoea include a multitude of symptoms, such as weight loss, abdominal pain, malnutrition, diarrhoea (including bloody diarrhoea), and diarrhoea. Furthermore, diarrhoea is one of the symptoms.[10] Symptoms that are not associated with the gastrointestinal tract are quite uncommon. Some examples of these abnormalities include skin diseases and arthritic problems. In spite of this, symptoms of metastatic Crohn's disease can be discovered on the skin, muscles, or bones, and these symptoms can be used to diagnosis people who have a hidden intestinal condition [11].

The fact that the risk of getting coronary artery disease is five times higher for first-degree relatives of patients who are affected by the condition [12,13] is evidence that the disease may have a genetic foundation. Another piece of evidence suggests that the disease may be inherited. In individuals who suffer from chronic obstructive pulmonary disease (CD), it is possible that the persistent inflammation of the intestinal tract can be attributed to the localised production of specific cytokines. These cytokines include interleukin-12 (IL-12), interleukin-17 (IL-17), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-ά) [14,15].

Antigen-presenting cells (APC) and macrophages are responsible for the synthesis of interleukin-12 (IL-12) and interleukin-18 (IL-18), which are responsible for the polarised differentiation of Th1 lymphocytes. The subsequent consequence of this is an escalation in the release of proinflammatory cytokines, which include tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN^3). Furthermore, antigen-presenting cells are responsible for the release of a greater variety of inflammatory cytokines, including IL-1, IL-6, IL-8, IL-12, and IL-18, which ultimately leads to an unending cycle of inflammation [16]. This is because Th1 cytokines are responsible for the release of these cell types.

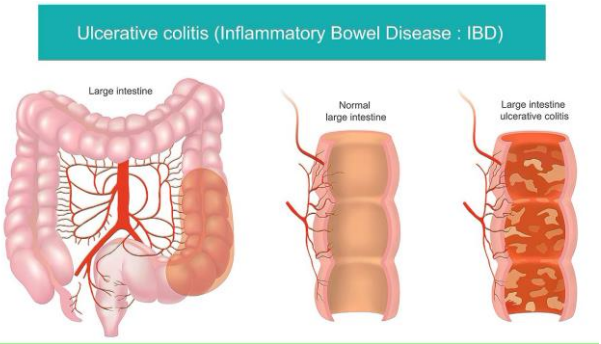


Fig: 1 IBD Normal vs Ulcer causing intestine

III. ULCERATIVE COLITIS

Subsurface ulcerations, granules, and a vascular pattern are the most obvious characteristics that distinguish ulcerative colitis from other types of

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

inflammatory bowel disease. Ulcerative colitis is a type of inflammatory bowel disease. The inflammation that occurs in UC is restricted to the mucosal layer of the colon, in contrast to the transmural inflammation that can occur in CD, which can spread throughout the entire gastrointestinal tract [17,18].

In contrast, the inflammation that occurs in UC is only found in the colon. The reliability of the Montreal classification, which is a system that is frequently used to identify inflammatory bowel disease phenotypes including UC [88], is not well documented. There is a lack of data on the methodology behind the categorisation. This is due to the fact that there is a remarkable diversity in the clinical manifestations of UC. Different clinical manifestations are associated with UC, some of which include petechial haemorrhage, granulation tissue, petechial mucus discharge, and other symptoms. UC is distinguished by a multitude of clinical manifestations. While the disease is in remission, the mucosa may appear normal. This is the opposite of what you would expect. There is a possibility that the condition may cause the intestines to grow, which may lead to the development of deep ulcers and, in the most severe instances, intestinal perforation [19,20]. Deep ulcers are another complication that can be brought on by the disease in the most severe situations.

The emission of an excessive amount of interleukin-13, which is responsible for both chronic inflammation and an elevated risk of UC [21], will be the defining characteristic of this illness. Individuals who have been diagnosed with UC have been reported to exhibit a Th2-response, which may be identified by the elevated secretion of IL-4, IL-5, and IL-9 [22]. In addition to the involvement of Th1 that has been observed, this is also present. According to the findings of a number of studies, the Th9 cells that are created by effectors are the ones responsible for the synthesis of IL-9 as well as the PU.1 transcription factor, which is the factor that is responsible for regulating cellular communication. Both of these factors work together to control the production of a large number of tight-junction proteins and to limit the proliferation of intestinal epithelial cells.

In animal and human models of UC, these elements, when taken as a whole, facilitate the movement of particular bacterial species, which in turn leads to the activation of the immune system and the production of inflammation of the mucosa. In clinical as well as experimental settings, this is consistent with the findings. As is the case with CD, there is an increase in the expression of cytokines that are linked with Th17 in UC. This expression is also increased in CD.

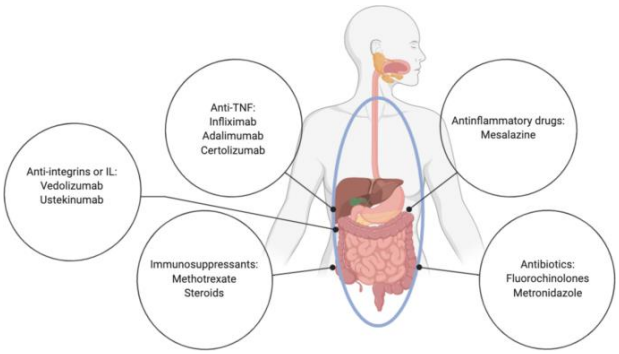


Fig: 2 Drugs Used for IBD

IV. DRUGS CURRENTLY IN USE IN PATIENTS WITH IBD

The present focus in the treatment of inflammatory bowel disease (IBD) is on achieving transmural repair in order to prevent additional structural damage and on maintaining clinical remission. This is with the goal of preventing further structural damage.[10] As a consequence of this, it is recommended that patients who suffer from moderate to severe inflammatory bowel disease (IBD) use biologics and/or combination medications. [11] Existing small molecule and biological treatments for inflammatory bowel disease (IBD) include the following: agents that inhibit tumour necrosis factor (TNF) [infliximab, adalimumab, certolizumab, golimumab]; agents that prevent adhesions [vedolizumab, natalizumab]; agents which concentrate on interleukin (IL)-12/23 [ustekinumab, UST]; and agents that inhibit Janus kinase (tofacitinib). It is regrettable that the number of individuals for whom the biological monotherapies that are currently accessible are efficacious has reached a point where they are no longer effective. By way of illustration, it is estimated that only thirty to fifty percent of those who are now having symptoms are able to attain mucosal or clinical remission following the administration of biological beginning treatment. Furthermore, studies have shown that the percentage of patients who are able to achieve long-term remission without the use of corticosteroids is less than thirty percent [13–16]. Novel pharmaceutical research is advancing at a rapid pace in order to address the needs of patients who do not respond to conventional biologics and SMDs, have lost their responsiveness to these treatments, or are intolerant to them. This is being done in order to satisfy the requirements of patients who are unable to tolerate existing treatments.It is [17].

V. BUDESONIDE

Mechanism of Action

Causing remission during the active phase of Crohn's disease and maintaining remission after therapy has been completed are two of the ways that Budesonide

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

is used in the treatment of mild to severe instances of the disease. Budesonide is also used to treat Crohn's disease.of the third kind For adult patients, it is recommended that they take 9 milligrammes of budesonide orally once day for a period of eight weeks in order to induce remission into their illness. This is done in order to get the desired medical outcome. In the case that you experience recurrent bouts of active illness, you may be required to take an additional dose of 9 milligrammes of budesonide for a period of eight weeks. The recommended dosage for children and adolescents who weigh more than twenty-five kilogrammes and are between the ages of eight and seventeen is nine milligrammes of budesonide to be taken orally once daily for a period of eight weeks, followed by six milligrammes of budesonide to be taken orally once daily for a period of two weeks. When symptoms have been managed (Chrohn's Disease Activity Index [CDAI] less than 150), the recommended dosage for adults to maintain clinical remission is six milligrammes of budesonide administered orally once daily for up to three months. This dosage is recommended after an eight-week course of treatment during the active phase of the disease. The aforementioned dosage is recommended for adults. In the event that the patient's symptoms have not become more severe, the physician ought to make an effort to wean the patient off of the medication completely after three months have passed. However, it has not been established that there are any significant therapeutic benefits associated with continuing treatment with 6 mg of budesonide for more than three months in a continuous manner.

Due to the fact that it promotes the repair of the mucosal tissue that is situated in the distal lesions, the medication budesonide is implemented as a secondary treatment for ulcerative colitis.It is [4]: Each dose of the budesonide rectal foam formulation that is being evaluated contains two milligrammes of the medication. this formulation is being studied. It is only possible to administer it in this manner; there is no other way to do it. Patients with active distal ulcerative colitis that is mild to severe and affects the rectum and sigmoid colon but does not extend more than forty cm beyond the anal edge are advised to take Budesonide. Budesonide is delivered to patients. The drug Budesonide is administered to these patients in order to induce regression. A metric dose of budesonide should be administered twice day for a period of fourteen days when the medication is administered intravenously. Once it has been completed, deliver one metric dosage intravenously once every day for a total of twenty-eight days. Rectal foam is combustible, thus the patient must avoid any source of fire, including smoking, while the medicine is being provided to them and for a small length of time afterward. This includes making sure the patient does not smoke. This includes the immediate environment in which the patient is located. The more current budesonide capsule, which causes the medication to be disseminated throughout the colon, has the potential to be effective in generating remission in patients with active ulcerative colitis that varies from mild to severe and do not react to oral mesalamine. This is because the capsule causes the medication to be dispersed throughout the colon. [5] Suppositories containing budesonide are utilised throughout the entirety of the therapy process for acute ulcerative proctitis.[6]

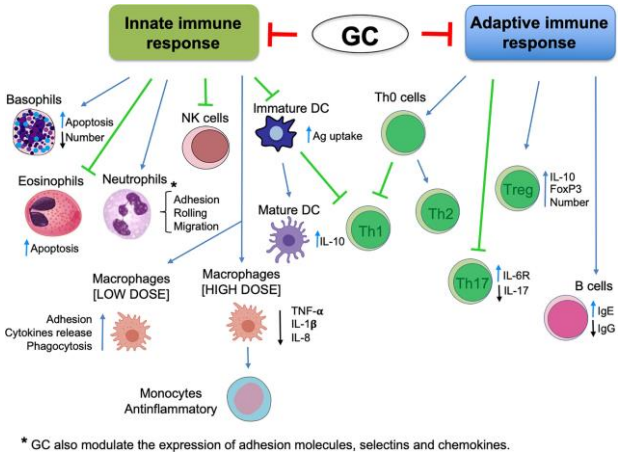


Fig: 3 MOA of Budesonide

Adverse Drug Reaction

Budesonide, a potent glucocorticoid that is administered topically, has been shown to reduce inflammation and improve sickness symptoms while causing less dysfunction in the hypothalamic-pituitary-adrenal axis when compared to oral prednisone at dosages that are therapeutically equivalent. Budesonide has the ability to enter the systemic circulation and begin its effects when administered at higher doses.

Contraindication

The use of budesonide is not recommended for anyone who has ever experienced an adverse reaction to budesonide or any of its constituent medicines. Anyone who has a strong sensitivity to milk proteins should not take Budesonide in its powder form for inhalation. This is because Budesonide is a respiratory medication.

Thiopurines

On the other hand, thiopurines have been utilised for the treatment of inflammatory bowel disease (IBD) for a considerable amount of time [20,21], despite the fact that neither the FDA nor the EMA have permitted their usage for this kind of treatment.12 However, adverse pharmacological reactions can occur in as many as 28 percent of patients who are taking thiopurine, and approximately one third of those patients cease taking the medication as a result of these reactions. [22] [23] When it comes to the treatment of inflammatory bowel disease (IBD), TDM has the potential to improve clinical efficacy and reduce drug-associated toxicity. This is accomplished by optimising the usage of thiopurines.32: The fact that the enzymes that are involved in the metabolism of thiopurines have

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

varied activity and that the active metabolites that they create might vary from patient to patient is suggested to explain, at least in part, why thiopurines have such a wider range of effects on different individuals.[24] [25]

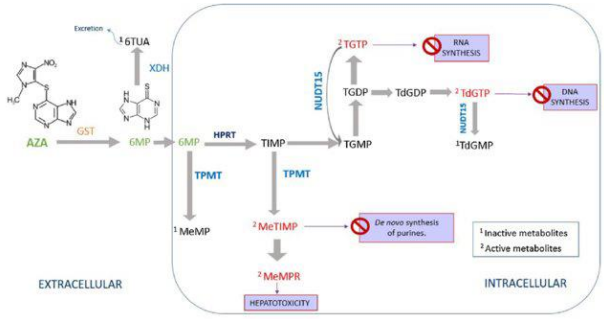


Fig: 4 The TPMT and NUDT15 enzymes are responsible for mediating the AZA thiopurine metabolic pathway. Azathioprine, GST, 6-MP, 6-mercaptopurine, XDH, 6TUA, HPRT, thioinosine monophosphate, TPMT, methylthioinosin, MeTIMP, and other chemicals are included in this assortment of substances.

Adverse Drug Reaction

The flu-like symptoms (malaise, fever, myalgia) and gastrointestinal disturbances (nausea, vomiting, abdominal pain) are the most common but least serious adverse effects of thiopurines. As a result, many patients cease using the medication because of these symptoms.

Contraindication

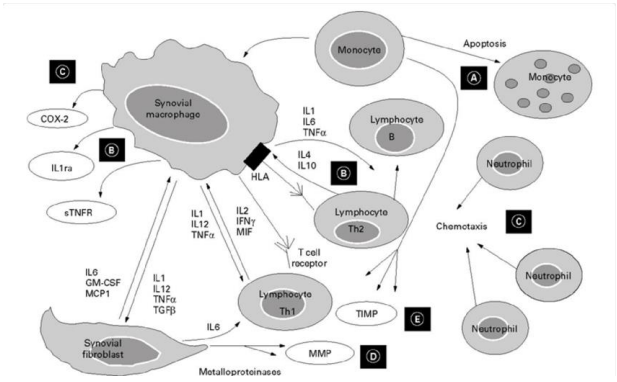
Indication, age, response, and TPMT activity are some of the factors that play a role in determining the individualised dose of azathioprine, which normally falls within the range of 1 to 3 mg/kg/day (for further information, see the following). The bioavailability of medication might vary depending on the formulation. It is possible that patients who are having problems in their liver and kidneys will require a reduction in their dosage. The individual has a previous record of experiencing serious adverse reactions to azathioprine or any of the other components. Acute inflammatory disease therapy during pregnancy. Treatment of rheumatoid arthritis in patients who have previously been exposed to alkylating medicines, such as cyclophosphamide, chlorambucil, or melphalan, due to the significant risk of developing cancer from these medications.

Methotrexate

Methotrexate is an immunosuppressant and an antimetabolite. It works by inhibiting dihydrofolate reductase, which in turn prevents DNA synthesis from occurring. This, in turn, leads to a reduction in the production of proinflammatory cytokines and ultimately results in the death of your lymphocytes.[26] in the[27] [27][28] in the The use of methotrexate in patients suffering from ulcerative colitis is still up for debate, despite the fact that it has been demonstrated to be helpful in treating Crohn's disease.a 44 According to a recent study [29], methotrexate induction therapy was successful in achieving a steroid-free response in 91 out of 179 individuals with active ulcerative colitis. This represents 51% of the total number of patients.There was no significant difference in the effectiveness of methotrexate and placebo in preventing relapse in the 84 patients who subsequently undertook maintenance therapy [[30]].(45) Patients who are being treated with methotrexate may experience adverse effects that are dose-dependent, including myelosuppression and hepatotoxicity.to [31] in [32]

In spite of this, there are no guidelines from society for the monitoring of hepatotoxicity, and there is a scarcity of data about the management of methotrexate in inflammatory bowel disease (IBD).[33] [33] According to the authors, a complete blood count and liver function tests must to be carried out prior to beginning methotrexate treatment, and then once more one month after the initial administration. When liver function test results show increased levels, the authors recommend reducing the dosage of methotrexate if the patient is experiencing these symptoms. Patients who continue to have normal test results while taking methotrexate should have these tests rechecked every two to four months, according to the authors' recommendation. If you are taking methotrexate, it is recommended that you take folic acid at the same time. This will reduce the likelihood that you will experience any adverse effects from the medication. The toxicity of methotrexate is associated to a large number of polymorphisms in the enzymes that are responsible for the metabolism of folic acid; nevertheless, research findings are conflicting.[36]

VI. MECHANISM OF ACTION



Adverse Drug Reaction

It is possible that liver problems are the cause of a yellowing of the skin or eyes, however it may be more difficult to detect in people with darker skin tones. An inflammation of the lungs may present itself in a variety of ways, including a persistent cough, chest pain, difficulty breathing, or shortness of breath. Renal diseases can be identified by a number of symptoms, such as swelling in the hands, ankles, or feet, change in the frequency of urine production or absence of urine production, and so on. A fever, chills, aches and pains in

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

the muscles, and a sore throat are some of the symptoms that may be associated with an infection. Gums that are bleeding, blood in the urine, blood vomiting, and bruises that cannot be explained are all signs that a blood problem is present.

Contraindications

This medicine should only be used to pregnant women who suffer from psoriasis or rheumatoid arthritis if the therapeutic advantages to both the mother and the unborn child outweigh the potential adverse effects.

VII. BIOLOGIC AGENTS

Anti-TNF Agents

Recent years have seen significant advancements in the treatment of inflammatory bowel disease, thanks to the introduction of biologic drugs.(46) However, primary nonresponse and subsequent loss of response are not only significant clinical concerns, but they are especially prevalent with anti-TNF drugs.[37] [37]It is [38] Ben-Horin and Chowers47 conducted a literature review in 2011 on the topic of anti-TNF drug resistance in Crohn's disease. Between 23 and 46 percent of patients who showed promise with anti-TNF drugs at the outset of treatment had experienced secondary loss of response by the 12-month mark, which required dose intensification. This was necessary since the responses had been lost.(47) There are a number of factors that might lead to nonresponse or loss of response in patients. Some of these factors include an elevated body mass index (BMI), female sex, advanced age (more than 50), and considerably active inflammatory bowel disease (IBD) that results in a high inflammatory load and drug loss in faeces. Also included in this category are patient features.

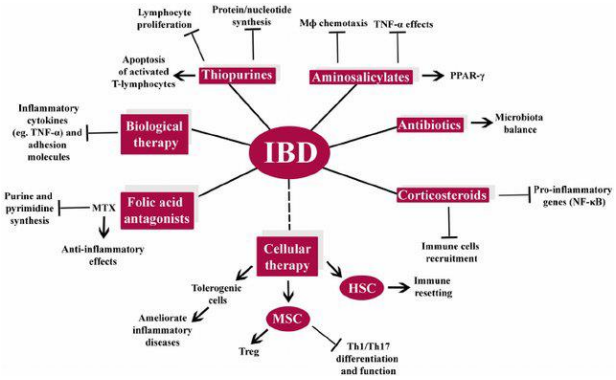


Fig: 4 Therapy options for inflammatory bowel disease (IBD) both now and in the future. Conventional methods of treating inflammatory bowel disease (IBD) have included the use of antibiotics, thiopurines, folic acid antagonists (methotrexate), corticosteroids, aminosalicylates, and anti-TNF-a biological agents. Each of these medications helps regulate the immune responses that are too active in people with Crohn's disease or ulcerative colitis in their own unique way. The dashed line pertains to the new cellular therapy, whereas the continuous lines represent the meds currently used to treat inflammatory bowel disease. The arrows represent events that induce or stimulate. The inhibitory actions of the prescribed therapy are represented by blocked arrows.

Table: 1 medication for treatment of IBD

Type of study	Patients	Treatment	Median treatment duration	Median follow-up duration	Results/Conclusion	Adverse events
Three phase 3, randomized, double-blind, placebo-controlled trials	Adults with UC	Tofacitinib (induction therapy: 10 mg twice daily for 8 weeks; maintenance therapy: either 5 or 10 mg twice daily for 52 weeks)	8, 8, 52 weeks	8, 8, 52 weeks	Tofacitinib appeared more effective in inducing and maintaining remission in patients with active CD compared with placebo	Increased lipid levels, infections, cardiovascular events
A phase 2, double-blind, randomized, placebo-controlled trial	Patients with moderate-to-severe CD	Filgotinib (GLPG0634, GS-6034) (200 mg once daily)	10 weeks	20 weeks	Filgotinib was more effective for inducing remission than placebo, and it had an acceptable safety profile	Infections
A multicenter, double-blind, phase 2b study	Adults with moderately to severely active UC and an inadequate response, loss of response, or intolerance to CSs, immunosuppressors, and/or biologics	Upadacitinib (7.5, 15, 30, or 45 mg once daily)	8 weeks	8 weeks	Upadacitinib (45 mg) was more efficacious as induction therapy than placebo	Increased serum lipid levels and creatine phosphokinase, herpes zoster, pulmonary embolism, deep venous thrombosis
A double-blind, placebo-controlled phase 2 trial	Adults with moderate-to-severe UC	Ozanimod (RPC1063) (0.5 or 1 mg daily)	32 weeks	32 weeks	Ozanimod at a daily dose of 1 mg resulted in a slightly higher rate of clinical remission of UC than placebo	Pyrexia, arthralgia, alanine aminotransferase increased, rash, vomiting, orthostatic hypotension, aspartate aminotransferase increased, hyperbilirubinemia, insomnia, nasopharyngitis, proctalgia
A phase 3, multicenter, randomized, double-blind, placebo-controlled trial	Patients with moderately to severely active	Oral ozanimod hydrochlorid (1 mg once daily) for induction therapy	10, 10, 52 weeks	10, 10, 52 weeks	Ozanimod resulted in significantly increased incidences of clinical response and clinical remission for both induction and maintenance period	Elevated liver aminotransferase levels, nasopharyngitis, headache, arthralgia
A single-arm, phase 2, prospective observer-blinded endpoint study	Adults with moderately to severely active CD	Ozanimod (0.25 mg daily for 4 days, followed by 3 days at 0.5 mg daily, then 1.0	12 weeks	112 weeks	Endoscopic, histological, and clinical improvements were seen within 12 weeks of initiating ozanimod therapy in patients with moderately to	CD (flare), abdominal pain, lymphopenia, arthralgia, nausea

Journal for Research in Applied Sciences and Biotechnology

www.jrasb.com

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

VIII. CASE STUDY AND REPORT

The use of dialectical behaviour therapy (DBT) in patients who have refractory inflammatory bowel disease (IBD) has been the subject of a significant number of case studies or series because of its effectiveness in treating these patients. When it comes to the bulk of these descriptions, the primary focus is on the incorporation of vedolizumab in conjunction with an anti-TNF-α. There were ten people who took part in the case series study, six of whom had been diagnosed with UC, and four of whom had been diagnosed with CD [50]. One of the participants had been diagnosed with UC. After undergoing a prolonged course of CT treatment with vedolizumab and either IFX or adalimumab, the authors are of the opinion that individuals with CD who have not reacted to prior treatments may be able to benefit from the treatment. Ustekinumab and vedolizumab were the two dialectical behaviour therapy (DBT) drugs that were given to two individuals who had been diagnosed with inflammatory bowel disease (IBD) in a study that was carried out by Biscaglia et al. [42]. As the findings reveal, there was a significant improvement in both the intestinal disease and the extraintestinal symptoms. This improvement was observed in both cases. Over the course of the two-year follow-up period, the patient who was on DBT medication did not experience any adverse events that were reported [43]. An other group of patients experienced clinical remission and an improvement in their extraintestinal symptoms after receiving vedolizumab and other biological treatments for a period of time ranging from five to thirty-seven months. The authors of this group of cases claimed that they had experienced these outcomes. Furthermore, despite the fact that there was a rate of infection, it was not very high and was not judged to be dangerous [44]. One of the patients who underwent IAPA was found to have refractory UC in addition to enteropathic seronegative spondyloarthritis, as stated by the findings of Bethge et al. [45]. This patient with refractory pouchitis was able to achieve endoscopic and histological remission, as well as complete alleviation of joint symptoms, by the administration of vedolizumab and etanercept in combination. Furthermore, there were no notable adverse effects detected in this patient [53]. There was a patient who had severe, treatment-resistant UC and spondyloarthropathy who was treated with vedolizumab and who tested positive for human leukocyte antigens-B27, as stated by Roblin et al. [46]. This patient was treated with vedolizumab. After the patient was given golimumab as part of the treatment plan, the patient exhibited a positive reaction to the medicine.

Vedolizumab plus golimumab CT for spondyloarthropathy and UC resulted in the symptoms remaining in remission for a period of at least one year over the course of extended treatment. This was the case across the entire duration of treatment. In a case study that was carried out by Liu et al. [48], the experience of a young patient who was diagnosed with ileocolic CD was documented from beginning to end. A combination of ustekinumab and vedolizumab was given to the patient for a period of ten months in order to address the patient's condition. The patient ultimately had mucosal healing as a consequence of this, which finally occurred after thirteen years of suffering from a chronic illness. There were no major adverse effects that were brought about by the combination of the two biological agents for a period of six months. Huff-Hardy et al. [49] reported that a patient who was diagnosed with refractory CD was treated with a combination of vedolizumab and ustekinumab. This combination was administered as a therapeutic regimen. The female patient, who was 22 years old, experienced a significant improvement in her perianal condition after she had received dialectical behaviour therapy (DBT) for a period of eight weeks. After undergoing treatment for her severe stenotic resistant fistula for a period of one year, she achieved a profound remission [50]. A recent multicenter study that was carried out in Finland analysed the data obtained from sixteen patients, fifteen of whom had been diagnosed with CD and were being treated with a combination of two biologic medications. In conclusion, the study was done in Finland. With a median follow-up time of nine months, the combination of adalimumab and ustekinumab was the deep brain stimulation (DBT) treatment that was employed the most frequently. By the time the follow-up period came to a close, seven patients, which is comparable to 32 percent of the total, had achieved remission from their cancer. Using DBT led to a reduction in the amount of corticosteroids that were required at each and every one of the data collection centres. It was shown that the combination of adalimumab and ustekinumab was the most effective treatment for patients who responded to dialectical behaviour therapy (DBT) at a rate of 56%. All nine of the DBT responders continued to take part in therapy when the follow-up period came to an end, which is a percentage of forty-one percent. The percentage of persons who had infections was 19%, and there were three of them. The findings of dialectical behaviour therapy (DBT) in this particular group of patients are particularly positive [51], despite the fact that the sample size is quite small.

Summary of the results

The findings of the research, which the authors feel to be pertinent and applicable to clinical practice, are summarised in the following paragraphs. Dual therapy refers to the practice of utilising two different biological agents in a single treatment. For the purpose of dual therapy (DT), the researchers Privitera et al.[52] used a combination of vedolizumab with either ustekinumab or vedolizumab + adalimumab for sixteen patients who were diagnosed with active inflammatory bowel disease (IBD) and/or substantial extraintestinal symptoms. The clinical state of gastrointestinal disease

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

and/or extraintestinal symptoms was improved in every patient who was treated with DT, and this improvement was achieved without the occurrence of severe adverse effects. Kwapisz et al. [53] conducted a trial in which they delivered a combination of two biological treatments to a CT in a total of seven patients: fourteen patients with CD and one patient with UC. Vedolizumab combined with an anti-TNF agent was administered to eight patients, vedolizumab combined with ustekinumab was administered to five patients, and ustekinumab combined with an anti-TNF- α agent was administered to two patients. In 73% of the cases, there was a noticeable improvement in the symptoms. Not only did 44% of patients have an improvement in endoscopic and imaging pictures, but 67% of patients were able to lower the amount of corticosteroids they were taking. The use of antibiotics allowed for the successful treatment of infections in four patients, three of whom had undergone surgical procedures.

The researchers Miyatani et al. [54] treated ten patients with CD who had active sickness that was resistant to treatment and had extraintestinal symptoms or not by using a combination of ustekinumab and upadacitinib, which is an oral selective Janus kinase inhibitor. Five out of six patients with active CD were able to achieve clinical remission, and two out of four individuals who had extraintestinal symptoms were able to bring their condition under control. At the end of the six-month follow-up, there were just a few minor adverse effects recorded, the most of which were upper respiratory infections. A retrospective analysis of 32 patients with chronic obstructive pulmonary disease (CD) and 18 patients with urological cancer (UC) who had CT with biologic or micromolecular treatments found that more patients were in clinical and endoscopic remission following CT compared to their baseline state [55]. Additionally, there was a significant decrease in the levels of erythrocyte sedimentation rate and C-reactive protein. Infections of the upper respiratory tract were the most common adverse event, involving 26% of patients.

Both intestinal homeostasis and inflammatory bowel disease (IBD) are thought to be considerably influenced by interleukins 12 and 23, according to current clinical research. They conducted a comprehensive investigation, which led to the development of monoclonal antibodies that target either the p40 subgroup (ustekinumab and briakinumab) or the p19 subgroup (risankizumab, guselkumab, brazikumab, and mirikizumab). Feagan et al. [56] conducted a study in which they examined individuals with moderate to severe UC to determine whether or not the combination of guselkumab and golimumab was superior to the use of either medicine exclusively. Golimumab alone was administered to 71 individuals, guselkumab with golimumab CT was administered to 72 patients, and guselkumab alone was administered to 72 patients. Sixty-three percent of patients who were getting combination treatment had reached clinical remission by the time the trial was twelve weeks old, while only sixty-one percent and seventy-five percent of patients in the other two groups had done so, respectively. Frequent side events were fever, anaemia, neutropenia, and upper respiratory infections. These were the most common adverse consequences. Since this is the case, it would appear that the combination of CT with guselkumab and golimumab is more efficacious than either medicine taken by alone.

According to the findings of the trials that have been reported up to this point, it appears that the combinations that are most preferred in patients with CD are vedolizumab combined with anti-TNF-α factors or vedolizumab combined with ustekinumab. When combined, these combinations produce clinical results that are good while also exhibiting an acceptable rate of side events. When it comes to persons who have UC, the most suitable combinations consist of administering either vedolizumab in conjunction with anti-TNF-α factor or vedolizumab in conjunction with tofacitinib.

When it comes to patients who have refractory inflammatory bowel disease (IBD) or IBD with extraintestinal indications, it seems that the combination of biological treatments with different mechanisms of action is both safe and beneficial. This is the case despite the fact that the research mentioned above only covered a small number of individuals. Additionally, research should be undertaken in rats using experimental models of colitis, as well as multicenter trials involving a large number of patients, in order to investigate the potential efficacy of the combination treatment, the appropriate dosage, and the length of treatment. Combined effort Utilising a combination of one immunosuppressive medication and one biologic agent is the treatment that is being administered: In patients diagnosed with chronic obstructive pulmonary disease (CD), it appears that the combination of azathioprine and a biologic anti-TNF-α agent, namely interferon-gamma (IFX) and, to a lesser extent, adalimumab, has a higher efficacy than either therapy alone [24,26,29,34]. When calcineurin inhibitors were administered in concert with vedolizumab, it appears that persons who were diagnosed with active inflammatory bowel disease (IBD) had a greater chance of achieving remission [36]. Vedolizumab combined with corticosteroids has been shown to be more successful than either treatment alone in producing remission, according to research [59].

This is the last but not the least of the findings. It is often acceptable to tolerate the side effects that were described in the aforementioned trials, provided that they are weighed against the therapeutic benefit. It has been known for a long time that the combination of IFX and azathioprine inhibits the formation of antibodies that are directed against the biological agent. This is an additional significant benefit. It is not suggested that clinicians refrain from using these drugs together when they are instructed to do so.[60]

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

IX. CONCLUSION

Clinical management of patients who have inflammatory bowel disease (IBD) continues to provide a number of significant challenges. Both the optimisation of the use of already available drugs, some of which have been in use for half a century, and the continuation of the development of novel agents to address these challenges are equally important.

REFERENCES

[1] Verdon C, Reinglas J, Coulombe J, Gonczi L, Bessissow T, Afif W, Vutcovici M, Wild G, Seidman EG, Bitton A, Brassard P, Lakatos PL. No Change in Surgical and Hospitalization Trends Despite Higher Exposure to Anti-Tumor Necrosis Factor in Inflammatory Bowel Disease in the Québec Provincial Database From 1996 to 2015. Inflamm Bowel Dis. 2021;27:655–661. doi: 10.1093/ibd/izaa166.

[2] Ungaro RC, Aggarwal S, Topaloglu O, Lee WJ, Clark R, Colombel JF. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. Aliment Pharmacol Ther. 2020;51:831–842. doi: 10.1111/apt.15685.

[3] Hirten RP, Iacucci M, Shah S, Ghosh S, Colombel JF. Combining Biologics in Inflammatory Bowel Disease and Other Immune Mediated Inflammatory Disorders. Clin Gastroenterol Hepatol. 2018;16:1374–1384. doi: 10.1016/j.cgh.2018.02.024.

[4] Grossberg LB, Papamichael K, Cheifetz AS. Review article: emerging drug therapies in inflammatory bowel disease. Aliment Pharmacol Ther. 2022;55:789–804. doi: 10.1111/apt.16785.

[5] Haider M, Lashner B. Dual Targeted Therapy for the Management of Inflammatory Bowel Disease. J Clin Gastroenterol. 2021;55:661–666. doi: 10.1097/MCG.0000000000001583.

[6] Privitera G, Pugliese D, Lopetuso LR, Scaldaferri F, Neri M, Guidi L, Gasbarrini A, Armuzzi A. Novel trends with biologics in inflammatory bowel disease: sequential and combined approaches. Therap Adv Gastroenterol. 2021;14:17562848211006669. doi: 10.1177/17562848211006669.

[7] Song YN, Zheng P. Efficacy and safety of tumor necrosis factor-α blockers for ulcerative colitis: A systematic review and meta-analysis of published randomized controlled trials. J Food Drug Anal. 2015;23:1–10. doi: 10.1016/j.jfda.2014.06.003.

[8] Baumgart DC, Le Berre C. Newer Biologic and Small-Molecule Therapies for Inflammatory Bowel Disease. N Engl J Med. 2021;385:1302–1315. doi: 10.1056/NEJMra1907607.

[9] Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383–1395. doi: 10.1056/NEJMoa0904492.

[10] Panaccione R, Ghosh S, Middleton S, Márquez JR, Scott BB, Flint L, van Hoogstraten HJ, Chen AC, Zheng H, Danese S, Rutgeerts P. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146:392–400.e3. doi: 10.1053/j.gastro.2013.10.052.

[11] Almon E, Shaaltiel Y, Sbeit W, Fich A, Schwartz D, Waterman M, Szlaifer M, Reuveni H, Amit-Cohen BC, Alon S, Chertkoff R, Paz A, Ilan Y. Novel Orally Administered Recombinant Anti-TNF Alpha Fusion Protein for the Treatment of Ulcerative Colitis: Results From a Phase 2a Clinical Trial. J Clin Gastroenterol. 2021;55:134–140. doi: 10.1097/MCG.0000000000001314.

[12] Almradi A, Hanzel J, Sedano R, Parker CE, Feagan BG, Ma C, Jairath V. Clinical Trials of IL-12/IL-23 Inhibitors in Inflammatory Bowel Disease. BioDrugs. 2020;34:713–721. doi: 10.1007/s40259-020-00451-w.

[13] Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV Jr, Dieleman LA, Katz S, Rutgeerts P UNITI–IM-UNITI Study Group. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375:1946–1960. doi: 10.1056/NEJMoa1602773.

[14] Sands BE, Sandborn WJ, Panaccione R, O'Brien CD, Zhang H, Johanns J, Adedokun OJ, Li K, Peyrin-Biroulet L, Van Assche G, Danese S, Targan S, Abreu MT, Hisamatsu T, Szapary P, Marano C UNIFI Study Group. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019;381:1201–1214. doi: 10.1056/NEJMoa1900750.

[15] Sands BE, Chen J, Feagan BG, Penney M, Rees WA, Danese S, Higgins PDR, Newbold P, Faggioni R, Patra K, Li J, Klekotka P, Morehouse C, Pulkstenis E, Drappa J, van der

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

Merwe R, Gasser RA Jr. Efficacy and Safety of MEDI2070, an Antibody Against Interleukin 23, in Patients With Moderate to Severe Crohn's Disease: A Phase 2a Study. Gastroenterology. 2017;153:77–86.e6. doi: 10.1053/j.gastro.2017.03.049.

[16] Sandborn WJ, D'Haens GR, Reinisch W, Panés J, Chan D, Gonzalez S, Weisel K, Germinaro M, Frustaci ME, Yang Z, Adedokun OJ, Han C, Panaccione R, Hisamatsu T, Danese S, Rubin DT, Sands BE, Afzali A, Andrews JM, Feagan BG GALAXI-1 Investigators. Guselkumab for the Treatment of Crohn's Disease: Induction Results From the Phase 2 GALAXI-1 Study. Gastroenterology. 2022;162:1650–1664.e8. doi: 10.1053/j.gastro.2022.01.047.

[17] Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, Kim KJ, Neurath MF, Schreiber S, Scholl P, Pamulapati C, Lalovic B, Visvanathan S, Padula SJ, Herichova I, Soaita A, Hall DB, Böcher WO. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2017;389:1699–1709. doi: 10.1016/S0140-6736(17)30570-6.

[18] Sandborn WJ, Ferrante M, Bhandari BR, Berliba E, Feagan BG, Hibi T, Tuttle JL, Klekotka P, Friedrich S, Durante M, Morgan-Cox M, Laskowski J, Schmitz J, D'Haens GR. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. Gastroenterology. 2020;158:537–549.e10. doi: 10.1053/j.gastro.2019.08.043.

[19] Nyarko, R. O., Roopini, R., Raviteja, V., Awuchi, C. G., Kumar, R., Faller, E. M., ... & Saha, P. (2022). Novel Sars-CoV-2 Variants & Therapeutic Effects. *Journal for Research in Applied Sciences and Biotechnology*, *1*(2), 25-34

[20] Awuchi, C. G., Saha, P., Amle, V. S., Nyarko, R. O., Kumar, R., Boateng, E. A., ... & Asum, C. (2023). A Study of various medicinal plants used in ulcer treatment: A review. *Journal for Research in Applied Sciences and Biotechnology*, *2*(1), 234-246.

[21] Sultana, A., Singh, M., Kumar, A., Kumar, R., Saha, P., Kumar, R. S., & Kumar, D. (2022). To identify drug-drug interaction in cardiac patients in tertiary care hospitals. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 146-152.

[22] Kumar, S., Keshamma, E., Trivedi, U., Janjua, D., Shaw, P., Kumar, R., ... & Saha, P. (2022). A meta analysis of different herbs (leaves, roots, stems) used in treatment of cancer cells. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 92-101.

[23] Kumar, R., Keshamma, E., Kumari, B., Kumar, A., Kumar, V., Janjua, D., & Billah, A. M. (2022). Burn injury management, pathophysiology and its future prospectives. *Journal for Research in Applied Sciences and Biotechnology*, *1*(4), 78-89.

[24] Kumar, A., Katiyar, A., Gautam, V., Singh, R., & Dubey, A. (2022). A comprehensive review on anti-cancer properties of Amaranthus viridis. *Journal for Research in Applied Sciences and Biotechnology*, *1*(3), 178-185.

[25] Kumar, R., Jangir, D. K., Verma, G., Shekhar, S., Hanpude, P., Kumar, S., ... & Kanti Maiti, T. (2017). S-nitrosylation of UCHL1 induces its structural instability and promotes α-synuclein aggregation. *Scientific reports*, *7*(1), 44558.

[26] Kumar, R., Register, K., Christopher-Hennings, J., Moroni, P., Gioia, G., Garcia-Fernandez, N., ... & Scaria, J. (2020). Population genomic analysis of Mycoplasma bovis elucidates geographical variations and genes associated with host-types. *Microorganisms*, *8*(10), 1561.

[27] Kumar, S., Yadav, S. P., Chandra, G., Sahu, D. S., Kumar, R., Maurya, P. S., ... & Ranjan, K. (2019). Effect of dietary supplementation of yeast (Saccharomyces cerevisiae) on performance and hemato-biochemical status of broilers.

[28] Hanna, D., Kumar, R., & Banerjee, R. (2023). A metabolic paradigm for hydrogen sulfide signaling via electron transport chain plasticity. *Antioxidants & Redox Signaling*, *38*(1-3), 57-67

[29] Keshri, S., Kumar, R., Kumar, D., Singhal, T., Giri, S., Sharma, I., & Vatsha, P. (2022). Insights Of Artificial Intelligence In Brain Disorder With Evidence Of Opportunity And Future Challenges. *Journal of Pharmaceutical Negative Results*, 10853-10867.

[30] Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353:1912–1925. doi: 10.1056/NEJMoa043335.

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

[31] Katsanos KH, Papamichael K, Feuerstein JD, Christodoulou DK, Cheifetz AS. Biological therapies in inflammatory bowel disease: Beyond anti-TNF therapies. Clin Immunol. 2019;206:9–14. doi: 10.1016/j.clim.2018.03.004.

[32] Peyrin-Biroulet L, Hart A, Bossuyt P, Long M, Allez M, Juillerat P, Armuzzi A, Loftus EV Jr, Ostad-Saffari E, Scalori A, Oh YS, Tole S, Chai A, Pulley J, Lacey S, Sandborn WJ HICKORY Study Group. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2022;7:128–140. doi: 10.1016/S2468-1253(21)00298-3.

[33] Zhang W, Scalori A, Fuh F, McBride J, She G, Kierkus J, Korczowksi B, Li R, Abouhossein M, Kadva A, Park KT, Tang MT. Pharmacokinetics, Pharmacodynamics, and Safety of Etrolizumab in Children With Moderately to Severely Active Ulcerative Colitis or Crohn's Disease: Results from a Phase 1 Randomized Trial. Inflamm Bowel Dis. 2022;28:1348–1356. doi: 10.1093/ibd/izab275.

[34] Yoshimura N, Watanabe M, Motoya S, Tominaga K, Matsuoka K, Iwakiri R, Watanabe K, Hibi T AJM300 Study Group. Safety and Efficacy of AJM300, an Oral Antagonist of α4 Integrin, in Induction Therapy for Patients With Active Ulcerative Colitis. Gastroenterology. 2015;149:1775–1783.e2. doi: 10.1053/j.gastro.2015.08.044.

[35] Sandborn WJ, Feagan BG, D'Haens G, Wolf DC, Jovanovic I, Hanauer SB, Ghosh S, Petersen A, Hua SY, Lee JH, Charles L, Chitkara D, Usiskin K, Colombel JF, Laine L, Danese S True North Study Group. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2021;385:1280–1291. doi: 10.1056/NEJMoa2033617.

[36] Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, Danese S, Feagan BG, Reinisch W, Niezychowski W, Friedman G, Lawendy N, Yu D, Woodworth D, Mukherjee A, Zhang H, Healey P, Panés J OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2017;376:1723–1736. doi: 10.1056/NEJMoa1606910.

[37] Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, DeMasi R, Soma K, Zhang R, Takiya L, Tatulych S, Mojcik C, Krishnaswami S, Menon S, Smolen JS ORAL Strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet. 2017;390:457–468. doi: 10.1016/S0140-6736(17)31618-5.

[38] Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, Klopocka M, Goldis A, Wisniewska-Jarosinska M, Baranovsky A, Sike R, Stoyanova K, Tasset C, Van der Aa A, Harrison P. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet. 2017;389:266–275. doi: 10.1016/S0140-6736(16)32537-5.

[39] Napolitano M, D'Amico F, Ragaini E, Peyrin-Biroulet L, Danese S. Evaluating Upadacitinib in the Treatment of Moderate-to-Severe Active Ulcerative Colitis: Design, Development, and Potential Position in Therapy. Drug Des Devel Ther. 2022;16:1897–1913. doi: 10.2147/DDDT.S340459.

[40] Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, Lespessailles E, Hall S, Hochfeld M, Hu C, Hough D, Stevens RM, Schett G. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis. 2014;73:1020–1026. doi: 10.1136/annrheumdis-2013-205056.

[41] Karner M, Kocjan A, Stein J, Schreiber S, von Boyen G, Uebel P, Schmidt C, Kupcinskas L, Dina I, Zuelch F, Keilhauer G, Stremmel W. First multicenter study of modified release phosphatidylcholine "LT-02" in ulcerative colitis: a randomized, placebo-controlled trial in mesalazine-refractory courses. Am J Gastroenterol. 2014;109:1041–1051. doi: 10.1038/ajg.2014.104.

[42] Neurath MF. Current and emerging therapeutic targets for IBD. Nat Rev Gastroenterol Hepatol. 2017;14:269–278. doi: 10.1038/nrgastro.2016.208.

[43] Schreiber S, Ben-Horin S, Leszczyszyn J, Dudkowiak R, Lahat A, Gawdis-Wojnarska B, Pukitis A, Horynski M, Farkas K, Kierkus J, Kowalski M, Lee SJ, Kim SH, Suh JH, Kim MR, Lee SG, Ye BD, Reinisch W. Randomized Controlled Trial: Subcutaneous vs Intravenous Infliximab CT-P13 Maintenance in Inflammatory Bowel Disease.

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

Gastroenterology. 2021;160:2340–2353. doi: 10.1053/j.gastro.2021.02.068.

[44] Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–2476. doi: 10.1056/NEJMoa050516.

[45] Singh S, George J, Boland BS, Vande Casteele N, Sandborn WJ. Primary Non-Response to Tumor Necrosis Factor Antagonists is Associated with Inferior Response to Second-line Biologics in Patients with Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. J Crohns Colitis. 2018;12:635–643. doi: 10.1093/ecco-jcc/jjy004.

[46] Ahmed W, Galati J, Kumar A, Christos PJ, Longman R, Lukin DJ, Scherl E, Battat R. Dual Biologic or Small Molecule Therapy for Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2022;20:e361–e379. doi: 10.1016/j.cgh.2021.03.034.

[47] Yang E, Panaccione N, Whitmire N, Dulai PS, Vande Casteele N, Singh S, Boland BS, Collins A, Sandborn WJ, Panaccione R, Battat R. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. Aliment Pharmacol Ther. 2020;51:1031–1038. doi: 10.1111/apt.15719.

[48] Glassner K, Oglat A, Duran A, Koduru P, Perry C, Wilhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. J Dig Dis. 2020;21:264–271. doi: 10.1111/1751-2980.12867

[49] Sandborn WJ, Lee SD, Tarabar D, Louis E, Klopocka M, Klaus J, Reinisch W, Hébuterne X, Park DI, Schreiber S, Nayak S, Ahmad A, Banerjee A, Brown LS, Cataldi F, Gorelick KJ, Cheng JB, Hassan-Zahraee M, Clare R, D'Haens GR. Phase II evaluation of anti-MAdCAM antibody PF-00547659 in the treatment of Crohn's disease: report of the OPERA study. Gut. 2018;67:1824–1835. doi: 10.1136/gutjnl-2016-313457.

[50] Kofla-Dłubacz A, Akutko K, Krzesiek E, Jamer T, Braksator J, Grębska P, Pytrus T, Stawarski A. Selective Forms of Therapy in the Treatment of Inflammatory Bowel Diseases. J Clin Med. 2022;11 doi: 10.3390/jcm11040994.

[51] Alayo QA, Fenster M, Altayar O, Glassner KL, Llano E, Clark-Snustad K, Patel A, Kwapisz L, Yarur AJ, Cohen BL, Ciorba MA, Thomas D, Lee SD, Loftus EV Jr, Fudman DI, Abraham BP, Colombel JF, Deepak P. Systematic Review With Meta-analysis: Safety and Effectiveness of Combining Biologics and Small Molecules in Inflammatory Bowel Disease. Crohns Colitis 360. 2022;4:otac002. doi: 10.1093/crocol/otac002.

[52] Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis. 2007;13:2–11. doi: 10.1002/ibd.20014

[53] Dolinger MT, Spencer EA, Lai J, Dunkin D, Dubinsky MC. Dual Biologic and Small Molecule Therapy for the Treatment of Refractory Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis. 2021;27:1210–1214. doi: 10.1093/ibd/izaa277.

[54] Kwapisz L, Raffals LE, Bruining DH, Pardi DS, Tremaine WJ, Kane SV, Papadakis KA, Coelho-Prabhu N, Kisiel JB, Heron V, Faubion WA, Loftus EV Jr. Combination Biologic Therapy in Inflammatory Bowel Disease: Experience From a Tertiary Care Center. Clin Gastroenterol Hepatol. 2021;19:616–617. doi: 10.1016/j.cgh.2020.02.017.

[55] Mosli MH, Sandborn WJ, Kim RB, Khanna R, Al-Judaibi B, Feagan BG. Toward a personalized medicine approach to the management of inflammatory bowel disease. Am J Gastroenterol. 2014;109:994–1004. doi: 10.1038/ajg.2014.110.

[56] Hazlewood GS, Rezaie A, Borman M, Panaccione R, Ghosh S, Seow CH, Kuenzig E, Tomlinson G, Siegel CA, Melmed GY, Kaplan GG. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology. 2015;148:344–54.e5; quiz e14. doi: 10.1053/j.gastro.2014.10.011.

[57] Zhao M, Bendtsen F, Petersen AM, Larsen L, Dige A, Hvas C, Seidelin JB, Burisch J. Predictors of response and disease course in patients with inflammatory bowel disease treated with biological therapy-the Danish IBD Biobank Project: protocol for a multicentre prospective cohort study. BMJ Open. 2020;10:e035756. doi: 10.1136/bmjopen-2019-035756.

[58] Kennedy NA, Heap GA, Green HD, Hamilton B, Bewshea C, Walker GJ, Thomas A, Nice R, Perry MH, Bouri S, Chanchlani N, Heerasing NM, Hendy P, Lin S, Gaya DR, Cummings JRF, Selinger CP, Lees CW, Hart AL, Parkes M, Sebastian S, Mansfield JC, Irving PM,

ISSN: 2583-4053

Volume-3 Issue-6 || December 2024 || PP. 126-139

https://doi.org/10.55544/jrasb.3.6.16

Lindsay J, Russell RK, McDonald TJ, McGovern D, Goodhand JR, Ahmad T UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019;4:341–353. doi: 10.1016/S2468-1253(19)30012-3.

[59] Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, Simoens S, Rutgeerts P, Gils A, Vermeire S. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148:1320–9.e3. doi: 10.1053/j.gastro.2015.02.031.

[60] Cheifetz AS, Abreu MT, Afif W, Cross RK, Dubinsky MC, Loftus EV Jr, Osterman MT, Saroufim A, Siegel CA, Yarur AJ, Melmed GY, Papamichael K. A Comprehensive Literature Review and Expert Consensus Statement on Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease. Am J Gastroenterol. 2021;116:2014–2025. doi: 10.14309/ajg.0000000000001396.

[61] Flamant M, Roblin X. Inflammatory bowel disease: towards a personalized medicine. Therap Adv Gastroenterol. 2018;11:1756283X17745029. doi: 10.1177/1756283X17745029.

[62] Mas EB, Calvo XC. Selecting the Best Combined Biological Therapy for Refractory . Inflammatory Bowel Disease Patients. J Clin Med. 2022;11 doi: 10.3390/jcm11041076.

[63] Privitera G, Onali S, Pugliese D, Renna S, Savarino E, Viola A, Ribaldone DG, Buda A, Bezzio C, Fiorino G, Fantini MC, Scaldaferri F, Guidi L, Danese S, Gasbarrini A, Orlando A, Armuzzi A. Dual Targeted Therapy: a possible option for the management of refractory Inflammatory Bowel Disease. J Crohns Colitis. 2020 doi: 10.1093/ecco-jcc/jjaa149.

[64] Glassner K, Oglat A, Duran A, Koduru P, Perry C, Wilhite A, Abraham BP. The use of combination biological or small molecule therapy in inflammatory bowel disease: A retrospective cohort study. J Dig Dis. 2020;21:264–271. doi: 10.1111/1751-2980.12867.

[65] Kwapisz L, Raffals LE, Bruining DH, Pardi DS, Tremaine WJ, Kane SV, Papadakis KA, Coelho-Prabhu N, Kisiel JB, Heron V, Faubion WA, Loftus EV Jr. Combination Biologic Therapy in Inflammatory Bowel Disease: Experience From a Tertiary Care Center. Clin Gastroenterol Hepatol. 2021;19:616–617. doi: 10.1016/j.cgh.2020.02.017.

[66] Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis. 2007;13:2–11. doi: 10.1002/ibd.20014.

[67] Yang E, Panaccione N, Whitmire N, Dulai PS, Vande Casteele N, Singh S, Boland BS, Collins A, Sandborn WJ, Panaccione R, Battat R. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. Aliment Pharmacol Ther. 2020;51:1031–1038. doi: 10.1111/apt.15719.

[68] Honap S, Netter P, Danese S, Peyrin-Biroulet L. An update on the safety of long-term vedolizumab use in inflammatory bowel disease. Expert Opin Drug Saf. 2023;22:767–776. doi: 10.1080/14740338.2023.2247976.

[69] Avedillo-Salas A, Corral-Cativiela S, Fanlo-Villacampa A, Vicente-Romero J. The Efficacy and Safety of Biologic Drugs in the Treatment of Moderate-Severe Crohn's Disease: A Systematic Review. Pharmaceuticals (Basel) 2023;16 doi: 10.3390/ph16111581.

[70] Miyatani Y, Choi D, Choi NK, Rubin DT. Dual-Targeted Therapy with Upadacitinib and Ustekinumab in Medically Complex Crohn's Disease. Dig Dis Sci. 2024;69:355–359. doi: 10.1007/s10620-023-08182-y

[71] Feagan BG, Sands BE, Sandborn WJ, Germinaro M, Vetter M, Shao J, Sheng S, Johanns J, Panés J VEGA Study Group. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. Lancet Gastroenterol Hepatol. 2023;8:307–320. doi: 10.1016/S2468-1253(22)00427-7.

[72] Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–2778. doi: 10.1016/S0140-6736(17)32448-0.