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A COMPREHENSIVE REVIEW OF EMERGING PARADIGMS IN THE CLINICAL MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Significant advancements in the treatment of inflammatory bowel disease (IBD) over the past decade have focused on achieving sustained clinical remission and minimizing the side effects of conventional therapies. Traditionally, IBD management relies on aminosalicylates, corticosteroids, and antimicrobials. For patients who do not respond to these therapies, more targeted treatments such as calcineurin inhibitors (e.g., cyclosporine) and biologic agents, including TNF-α inhibitors (e.g., infliximab, adalimumab) and anti-cell adhesion molecules (e.g., vedolizumab, natalizumab), are utilized. These therapies specifically target pro-inflammatory cytokines such as TNF-α, IL-2, and integrin α4β7. Recent developments in IBD treatment have introduced novel biologics, small-molecule drugs, and biosimilars, which provide new therapeutic options with improved efficacy and safety profiles. Additionally, there is growing interest in the role of gut microbiome modulation through probiotics, prebiotics, and dietary interventions in the management of IBD. Stem cell transplantation and fecal microbiota transplantation are also being explored as promising therapeutic strategies for refractory cases. These advancements represent a significant shift towards more personalized and effective treatment approaches, offering hope for better outcomes and improved quality of life for patients with IBD. This review provides a comprehensive overview of these emerging therapies and their potential to revolutionize IBD management.

KEYWORDS: Inflammatory Bowel Disease, Crohn‘s Disease, Ulcerative Colitis, Biologics, Biosimilars, Stem cell transplantation, gut microbiome, probiotics, prebiotics, new treatment approaches. Biological agents, calcineurin inhibitors, novel biologics, small molecule drugs.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammation of the intestinal tract resulting due to an imbalance of the intestinal microbiota in a genetically susceptible individual. IBDs are a group of autoimmune diseases comprising two major forms, Crohn‘s disease and Ulcerative colitis. Patients with IBDs present with symptoms like diarrhea, abdominal pain, bloody stools and vomiting.[1] Several factors are responsible for development of IBD, which include imbalance of intestinal microbiota, change in immune system and genetic susceptibility. A mutation in the gene, NOD2 increases the susceptibility to IBD via production of proinflammatory cytokines.[2] Environmental factors also play a major role in the development of IBD.[3] Moreover, increased intake of milk proteins, animal proteins, and polyunsaturated fatty acids increase the risk for IBD.[4] and consumption of tobacco increases the risk for Crohn‘s disease.[5] The pathogenesis of IBD, including genetic and environmental factors and the inflammatory cascade induced is summarized in [Figure -1]. The incidence of inflammatory bowel disease (IBD) is rapidly increasing in India. The available evidence suggests that the burden of IBD in India is among the highest in the world. It is unclear exactly how many Indians have IBD as it is often misdiagnosed as intestinal tuberculosis. But, a 2017 study estimated that more than 1.1 million people have Ulcerative colitis and at least 30,000 people have Crohn‘s disease.[7]

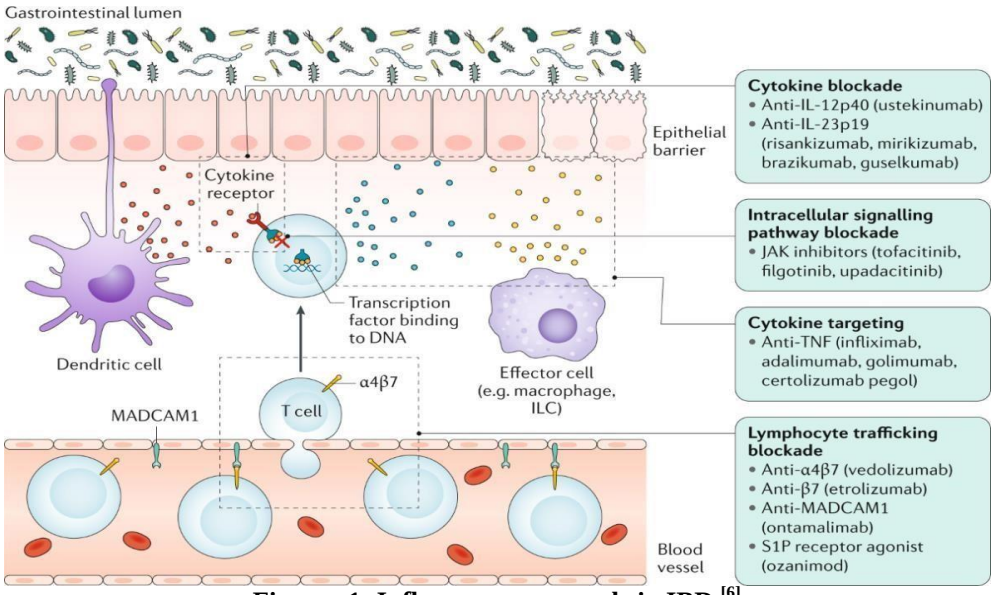

Figure –1: Inflammatory cascade in IBD.[6]

IFNγ, Interferon Gamma; IL, Interleukin; Th, T-helper cell; TLR, Toll-like Receptor; TNF, Tumour Necrosis Factor.

MANAGEMENT OF IBD

Conventional treatment of IBD

Treatment of the disease involves use of drugs that can significantly reduce the symptoms of the disease and help maintain its remission.[1] Medications for IBD are prescribed stage by stage. Firstly, less harmful drugs are prescribed; if these drugs do not provide the desired relief, other drugs are prescribed to achieve the desired effect.[8] Traditionally, the drugs used are Amino salicylates (ASA), Corticosteroids, Immunosuppressive agents, Anti Microbials and Biologics [Figure - 2]. [Table – 1] summarizes the drugs used in the treatment of IBD, their Mechanism of action and Side effects.

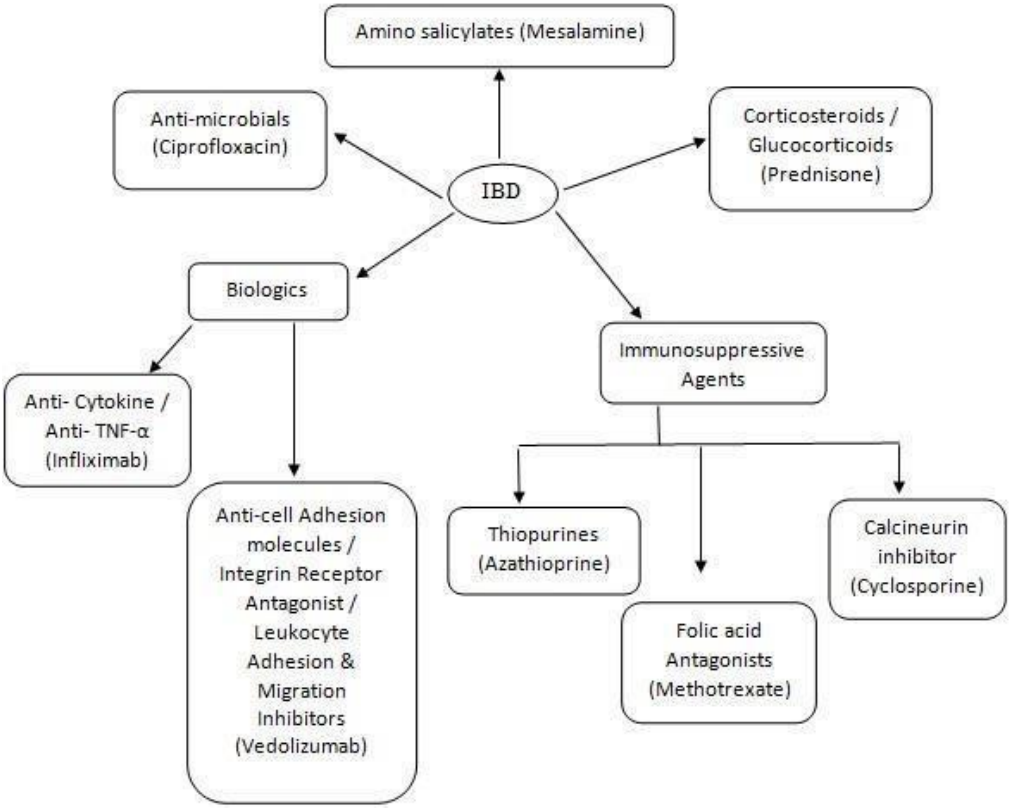

Figure – 2: Conventional Treatment for IBD.

Table 1: IBD Treatment – Drugs, Mechanism of action and Side Effects.

Treatment	Related drugs	Mechanism of action	Features	Potential Adverse effects
Amino salicylates[10-13]	Mesalamine Olsalazine Balsalazide	Inhibition of IL-1, TNF-α & PAF, decreased antibody	Locally immunosuppressive, non-specific	Headache, dizziness, dyspepsia, epigastric pain, nausea,
	Sulfasalazine	secretion.	inhibition of cytokines, medium cost.	vomiting & diarrhea.
Immuno - modulators/Immuno - suppressive agents [14-20]	Azathioprine 6-mercaptopurine Methotrexate	Blockage of de novo pathway of purine synthesis	Antiproliferative effects, reduction of inflammation	Black, tarry stools, bleeding gums, chest pain, fever, chills, swollen glands, pain, cough, & weakness.
Cortico steroids [21-22]	Prednisone Methyl-prednisolone Hydrocortisone Budesonide	Blockage of phospholipase A2 in the arachidonic acid cascade altering the balance between PGs & LKs; stimulation of apoptosis of lamina propria lymphocytes; suppression of transcription of cytokines.	High Immuno-suppression, risk of potential infection, adverse effects with long periods of use, low cost.	Full moon face, difficulty healing, acne, sleep & mood disturbances, glucose intolerance, osteoporosis, osteonecrosis, subcapsular cataracts, myopathy, infections, acute adrenal insufficiency, myalgia, malaise, arthralgia or intra cranial hypertension & pseudo rheumatism syndrome.
Biologicals: anticytokine drugs [23-46]	Infliximab Adalimumab Certolizumabpegol Golimumab Ustekinumab	Induction of apoptosis in proinflammatory cells; specificallynding TNF- α; of interaction receptckage	Specific inhibition of cytokine, Immunosuppression, high cost, advanced technology required.	Abdominal pain, chest pain, chills, cough, dizziness, fainting, headache, itching, muscle pain, nasal congestion, nausea, sneezing, weakness, vomiting, bloody urine, cracks, in skin, diarrhea, pain, constipation, falls, facial edema, general feeling of illness, hernia, irregular heartbeats, unusual bleeding, weight loss, increased risk of reactivation of latent TB & increased risk for developing infections & lymphoma.
Biologics: Anti- cell adhesion molecules[36,47-52]	Vedolizumab Natalizumab	Inhibition of migration.	Specific inhibition of cell adhesion molecules, high cost, advanced	Nasopharyngitis, headache, abdominal pain, increased risk of infections, serious
			technology required.	infections & Progressive Multifocal Leukoencephalopathy (Natalizumab)
Antimicrobials[53-60]	Ciprofloxacin Metronidazole Rifaximin Azithromycin Clarithromycin	Inhibits the growth & multiplication of specific bacteria that trigger an aberrant immune response that contribute to IBD.	Can be used to treat primary active disease and for secondary septic complications- like abscesses, post-operative infections; medium cost.	Ciprofloxacin- tendonitis, tendon rupture, photosensitivity, inhibition of cartilage growth in children, oral thrush, QTprolongation. Metronidazole- gastrointestinal disturbances, permanent peripheral neuropathy, Clostridium difficile infection & antibiotic resistance.

TNF-α: Tumor necrosis factor-α, IL-1: Interleukin-1, PAF: Platelet Activating Factor, PGs: Prostaglandins, LKs: Leukotrienes.

Recent Advancements in the Management of IBD

The ultimate goal of management of IBD is to achieve complete disease control and stop disease progression. The key therapeutics outcomes have changed from clinical symptom control to attain steroid free remission, biological remission and mucosal healing (or endoscopic remission).[61] Mucosal healing leads to significantly better clinical outcomes, reduced resource utilization and restored quality of life.[62,63,64] The management of IBD consists of two different therapeutic approaches known as ―Step-Up‖ or ―Top-Down‖ strategies. The former is a classical method in which the intensity of treatment increases along with the severity of disease. The latter strategy involves an early onset of intensive treatment (with biological therapy) in order to avoid the occurrence of future complications.[65] However, the current therapies are not totally curative, and patient may be unresponsive or refractory to the treatment. Moreover, there is a risk of side effects with these drugs and their use is limited by their cost.[66] Hence, the newer biologics & stem cell transplant may provide an alternative to the conventional therapy to overcome its short comings.

Biological therapy

Biological agents are targeted to inhibit pro-inflammatory cytokines, Chemokines and Integrins and hence block immune system activity.

Anti-TNF-α inhibitors

TNF is a cytokine that plays a major role in the pathogenesis of IBD and other immunological diseases such as Rheumatoid Arthritis, Ankylosing Spondylitis and Psoriasis.[67] Anti-TNF-α drugs are highly effective for the treatment of moderate-severe diseases, primarily as induction and maintenance therapy.[68] A number of different anti-TNF antibodies are available, they are.

1. Infliximab (IFX): The first commercially available anti-TNF molecule. It is a chimeric monoclonal IgG1 antibody formed by a segment of native mouse protein containing binding site for the TNF-α.[69]
2. Adalimumab (ADA): it is a fully humanized IgG1 monoclonal antibody emerged as an alternative molecule to treat patients non-responsive to IFX.[33,70]
3. Certolizumab pegol (CDP 870): It is a pegylated and fully humanized monoclonal antibody fragment, recently approved by the FDA for the treatment of Crohn‘s disease. This drug has found to be more effective & less immunogenic than IFX & ADA.[37]
4. Golimumab: It is a humanized IgG1 TNF-α antagonist monoclonal antibody that showed significant results in inducing & maintaining remission in IBD patients.[40]
5. AVX-470: It is an orally administered polyclonal immunoglobulin purified from the colostrum of cows immunized with recombinant human TNF.[71]
6. Thalidomide: It was originally used for its sedative & anti-emetic properties. Recently, it has shown to inhibit TNF-α production by monocyte & other cells. It is found to be effective in chronically active, steroid dependent Crohn‘s disease.[72,73]

Anti-Integrins / Anti-Adhesins / Leukocyte adhesion & migration inhibitor

Lymphocyte-endothelial interactions are mediated by adhesion molecules which play a role in the leukocyte migration to the site of inflammation such as the intestine.

1. Natalizumab: It is the first Anti-adhesin found to be effective for IBD. It causes nonspecific inhibition of integrins, α4β7 and α4β1. There is a risk of developing Progressive Multifocal Leukoencephalopathy (PML), a devastating & fatal neurological disorder caused by reactivation of John Cunningham virus.[74,75]
2. Vedolizumab: It is an anti-α4β7 integrin monoclonal antibody. This α4β7-integrin is an antiadhesion molecule expressed on the surface of gut specific lymphocytes. It binds to mucosal vascular addressin cell molecule-1 (MAdCAM-1) which exists on intestinal vasculature & mediates leukocyte migration to gut. The most common adverse effect reported were generally mild and included nasopharyngitis, headache, arthralgia & nausea.[76,77]
3. Ertolizumab: It binds selectively to the β7 sub-unit of α4β7 and also to αƐβ7 integrin hetero dimers. Thus, it antagonizes / blocks the interaction between α4β7 and MAdCAM-1 at the vascular level and also blocks the interaction between αƐβ7 and E-cadherin in the intra-epithelial compartment and inhibits the adhesion of intra-epithelial T-cell to the epithelial cells. It represents the next generation of anti-adhesion molecules. It offers an alternative to Vedolizumab. The adverse effects are mild to moderate and include influenza- like illness, arthralgia & rash.[74,78,79,80]
4. Abrilumab: It is a monoclonal antibody that selectively blocks α4β7 and can be administered subcutaneously with high bioavailability & long half-life.[74,81,82]
5. PF-00547659 (SHP647): It is a subcutaneously administered monoclonal antibody that inhibits binding of α4β7-integrin to MAdCAM with high affinity & selectively.[74,83]
6. AJM-300: It is a small oral molecule that blocks α4 integrin sub-unit.[84]
7. PTG-100: It is a small oral molecule that targets α4β7 integrin.[84]

Anti-Interleukin 12/23

Interleukin -12 is produced by phagocytic & dendritic cells in response to microbial stimulation and activates natural killer cells and T-lymphocytes.[85] Interleukin-23 causes differentiation of Th 17 and produce many pro-inflammatory cytokines like IL-17 & F, TNFα, IL-22, IL-26 and INF-γ.[86] By preventing IL-12 & 23 binding to the IL-12Rβ1 receptor on the surface of NK and T-cell, these drugs inhibit production of cytokines which is helpful in IBD treatment.[74]

1. Ustekinumab: It is a monoclonal antibody to the common p40 subunit of IL-12 & IL- 23.[74,87]
2. Risankizumab: It is a humanized monoclonal antibody to the p19 subunit of IL-23; hence it does not affect during infections and for cancer immunity.[74,88]
3. Brazikumab: It is a fully human m-Ab targeting the p19 subunit of IL-23.[84]
4. Briakinumab: It is a fully human m-Ab targeting the p40 subunit of IL-12/IL-23.[84]
5. Mirikizumab: It is a humanized m-Ab targeting the p19 subunit of IL-23.[84]

Small-molecule drugs

Small molecule drugs (SMDs) have a molecular weight <1kDa and are organic compounds composed of oxygen, carbon & nitrogen. Due to their low molecular weight, they can be easily diffused through cell membrane when compared to large macromolecule like Anti-TNF-α‘s (≤144 kDa). SMDs offer advantage over biologics because they can be taken orally which may be preferential to the patient, removing the need for hospital attendance, selfinjection & repeated cannulation. Moreover, they lack immunogenicity.[74]

Janus – kinase inhibitors

Janus-kinases (JAKs) are intracellular non-receptor tyrosine kinases that play a key role in signaling transduction for several extracellular moles such as cytokines & growth factors.

JAK1, JAK2, JAK3 and tyrosine kinase-2 (TYK2) are the four JAKs belonging to this family. Circulating cytokines activate the cell membrane receptors resulting in the phosphorylation of signal transducers and activators of transcription (STATs) by the JAKs. The JAK-STAT pathway is involved in an array of essential processes such as cell proliferation, growth, differentiation and migration. Blocking of JAK-STAT pathway results inhibition of several proinflammatory cytokines. Hence, JAK-STAT pathway is an important target in IBD.[84]

Tofacitinib: It is pan-JAK inhibitor (inhibits JAK1, JAK2, JAK3 & TYK2) with preferential inhibition of JAK1 & JAK3.

1. Filogtinib: It is a selective JAK1 inhibitor.
2. Upadacitinib: It is another selective JAK1 inhibitor.
3. Peficitinib: It is an inhibitor of JAK1, JAK2 & JAK3.

Sphingosine-1 phosphate receptor modular

Sphingosine –1 phosphate (S1P) is a chemoattractant that is shown to mediate angiogenesis, vascular tone & permeability and cancer growth & metastasis. There are five subtypes of S1P receptor (SIP1-5).[74]

1. Ozanimod: It is an oral S1P1 and S1P5 receptor agonist.[84]
2. Etrasimod: It is a S1P1, S1P4 & S1P5 receptor modulator.[84]
3. Fingolimod: It is a similar agent that has been associated with adverse events such as bradycardia, atrioventricular block, muscular oedema and serious infections like disseminated varicella zoster & herpes simplex infections. It has been used for multiple sclerosis.[74]

Phosphodiesterase-4 inhibitor

Phosphodiesterase-4 (PDE4) is an enzyme that degrade cAMP (cyclic AMP). cAMP has been shown to affect NF-K-β signaling in macrophages and T-cells therefore, it has antiinflammatory & immunosuppressive properties. Hence, PDEases act as pro-inflammatory enzymes. Increased expression of PDE-4 has been reported in inflammatory diseases such as psoriasis.[89] Apremilast: It is an inhibitor of PDE4 and is already approved for the treatment of psoriatic arthritis and plaque-psoriasis.[84,90]

Oral SMAD-7 antisense oligonucleotide

Mongersen (GED-0301): SMAD-7 is an intracellular protein that binds to the TGF-β receptor and prevents TGF-β1 associated & SMAD associated signaling. Mongersen is an oral formulation containing the SMAD7 antisense oligonucleotide the hybridizes to the human SMAD7 messenger RNA and facilitates ribonuclease (RNase) H-mediated RNA degradation through a classical antisense mechanism.[91] Invivo data involving a mouse model have shown that oral administration of SMAD7 antisense oligonucleotide can down regulate SMAD7 and alleviate crohn‘s disease like colitis.[76,92]

Serine protease inhibitor

Bowman Birk inhibitor (BBI): BBI are a class of naturally occurring serine protease inhibitors that are derived from legumes such as soyabeans, peas, lentils and chickpeas. BBI, have potential anti-inflammatory and chemo-preventive properties within the gastrointestinal tract (GIT).[93] BBI is an inhibitor of proteases like elastase, cathepsin G, mast cell chymase and trypsin. BBI has two distinct inhibitory domains. The first of these domains inhibits trypsin, which ‗prefers‘ positively charged amino acids side chains at the P1 location. The second domain inhibits chymotrypsin and other serine proteases, which ‗prefers‘ large nonpolar side chains. BBI places a leucine in the P1 position of the active sites of these proteases and inhibits them. BBI has been used to treat patients with active ulcerative colitis.[94]

Biosimilars

Biosimilars can be defined as a ―Biotherapeutic product‖ which is similar in terms of quality, safety & efficacy to an already licensed reference biotherapeutic product with similarity defined as absence of a relevant differences in the paranode of interest.[95] Biologics are made in living cell lines and are intrinsically complex proteins. They are sensitive to changes in the manufacturing process, including growth conditions, purification process, formulation and storage

conditions.[64] Hence, due to their highly complex nature, biosimilar agents may not be identical to the reference product, the active ingredients are essentially the same as those of the reference product.[76] The main advantage of biosimilars is that it can offer savings of up to 72% when compared to the original biological product.[96] A multi-country budget impact analysis of biosimilars for the treatment of Rheumatoid Arthritis has shown that the use of biosimilars resulted in significant cost savings.[97]

CT-P13: It is an infliximab biosimilar and the first monoclonal antibody biosimilar to be used in clinical practice. It is having been approved by the European medicines agency (EMA) for use in all indications for which infliximab is approved, including use in treatment of IBD.[98] Switching from originator infliximab to its biosimilar was shown to be safe and as effective as its originator.[99] However, patients with previous infliximab exposure exhibited lower response rales and were more likely to develop allergic reactions.[100,76]

Stem cell transplantation

Stem-cell therapy is used as an alternative method for treating the tissue damage caused by chronic inflammation in IBD through alteration of mucosal immune response.[74] At present, haemopoietic stem cell (HSC) and mesenchymal stem cell (MSC) transplantations have been used in clinical trials.

1. **Haemopoietic stem cell transplantation (HSCT):** Haemopoietic stem cells are multipotent cells isolated from the bone marrow, umbilical cord or peripheral blood and have the ability to differentiate into blood and immune cells. By migrating to the damaged tissue, they may differentiate to epithelial or immune modulatory cells and restore normal mucosal tissue & integrity.[74,101] HSCT may also be used in monogenic diseases, such as Interleukin-10 deficiency, where allogenic bone marrow transplant would correct the disease by reconstituting a new immune system. Use of HSCT is restricted to patients with severe crohn‘s disease, who do not respond to standard treatment and in whom surgery is not an option.[102]
2. **Mesenchymal stem cell transplantation (MSCT):** Mesenchymal stem cells are multipotent cells found in the bone marrow, umbilical cord and adipose tissues. They have immuno-modulatory capacity and down regulate mucosal immune reactivity by promoting regulator T-cell formation and inhibition of proliferation & function of Th1 & Th17 cells and promoting tissue healing.[74,103] Major advantages of MSCT over HSCT are their low immunogenicity properties, non-myeloablative technique, without total body irradiation and eliminating the need for chemotherapy.[104]

Faecal Microbiota transplantation (FMT) or Faecal bacteriotherapy

After (FMT) was successful in the treatment of clostridium difficile infection.[105] efforts were made to use it for the treatment of IBD, since gut microbiota play an important role in the pathogenesis of IBD. There is clinical evidence that enteric bacteria can induce chronic, immune-mediated intestinal inflammation in genetically susceptible hosts. This depends on the relative balance between beneficial and detrimental bacteria in the intestines. Faecal bacteria (Escherichia coli, campylobacter species, mycobacterium avium) to commensal bacterial flora (Bacteroides and Firmicutes phyla).[74] This abnormal composition is called as dysbiosis.[64] FMT is a process where faecal bacteria are transplanted from a healthy individual to a recipient.[64] Siblings who are close in age are the best faecal microbiota donors for patients with ulcerative colitis.[106]

Microbiome targeting diet

The imbalance in the gut bacteria contributes to the inflammation in IBD. Researchers at UMASS Medical school developed a diet, IBD anti-inflammatory diet to restore the balance between the pathogenic and commensal bacteria in the gut while promoting good nutrition.[107] This microbiome targeting diet helps in improving the symptoms for IBD patients. The diet focuses on increased intake of prebiotic and probiotic foods and other beneficial foods while substituting certain carbohydrates and other adverse foods. In their trial, the majority (61.3%) of patients who compiled with the diet for at least 8 weeks reported a dramatic decrease in the severity of the disease.[108]

Table 2: List of probiotic and prebiotic foods.[107]

Probiotic foods	Prebiotic foods
Plain yogurt Aged cheese Fermented vegetables Kefir Miso Microalgae	Oat groats Steel-cut oats Bananas Ground flax seeds Chia
Pickles Raw honey Fermented cabbage Kimchi Tempeh (grain free)	Hemp seeds Garlic Onions Chicory roots Artichokes Leeks Asparagus All vegetables and some fruits Legumes

CONCLUSION

This review critically examines the recent advancements in therapeutic strategies for managing Inflammatory Bowel Disease (IBD), which includes- Crohn's Disease (CD) and Ulcerative Colitis (UC). The increasing global prevalence of IBD has highlighted the limitations of conventional therapies, such as aminosalicylates, corticosteroids, and immunomodulators. While these traditional treatments have been foundational in IBD management, a significant proportion of patients either

fail to achieve remission or lose responsiveness over time, thereby necessitating the development of alternative therapeutic approaches.

Recent innovations in IBD treatment have led to the emergence of biologic agents and small molecules that target specific pathways involved in the disease's pathogenesis. Biologics, including anti-TNF agents, integrin inhibitors, and IL-12/23 antagonists, have shown substantial efficacy in both inducing and maintaining remission in patients with moderate to severe forms of the disease. Additionally, small molecule therapies, such as Janus kinase (JAK) inhibitors, represent a promising new option, particularly for patients who do not respond to biologics.

These novel therapies mark a significant shift in the approach to IBD management, offering renewed hope for patients with refractory disease. The growing emphasis on precision medicine, informed by a deeper understanding of the genetic and molecular mechanisms underlying IBD, is enabling more personalized treatment strategies. By tailoring interventions to the specific characteristics of individual patients, these advancements aim to optimize therapeutic outcomes, reduce the incidence of complications, and enhance the quality of life for those affected by IBD. As ongoing research continues to refine these approaches, these innovative therapies are poised to play a central role in the long-term management of IBD, with the potential to achieve sustained remission and improved outcomes for a broader patient population.

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