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Is the New Approach in Inflammatory Bowel Disease Treat-to-Target?

*Vinod Kumar P**

Department of Pharmacology, Amala Institute of Medical Sciences, Thrissur, Kerala, India

Article info

Received 20 February 2021
Revised 15 March 2021
Available Online 05 April 2021

*Corresponding author: Vinod Kumar P, Department of Pharmacology, Amala Institute of Medical Sciences, Thrissur, Kerala, India

Abstract

Inflammatory bowel disease is a chronic inflammatory disease of which the etiology is unknown. Ulcerative colitis and Crohn's disease are the two main entities of inflammatory bowel disease that are challenging clinicians. In addition to tumor necrosis factor blockers, this overview summarizes current and future new drugs, in the treatment of inflammatory bowel disease according to their goals. The infiltration of lymphocytes into the intestinal lining is a target for therapeutic purposes in inflammatory bowel disease. The vascular cell adhesion molecule-1 and the mucosal addressin cell adhesion molecule-1 are a family of integrins for the alpha4 that are specifically expressed in the alimentary canal on vascular endothelial cells. In Crohn's disease, the alpha4beta7 integrin, and its endothelial receptor, the mucosal addressin cell adhesion molecule-1, have proven to be a relevant factor in the development of chronic intestinal inflammation. New biological and chemical drugs are emerging, with additional molecules pending approval.

Keywords: *Ulcerative colitis; Crohn's disease; Vascular cell adhesion molecule-1; Mucosal addressin cell adhesion molecule-1; Inflammatory bowel disease*

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main entities of IBD present a particular clinical and pathological feature (Figure 1) [1]. Inflammatory bowel disease (IBD) is a chronic inflammatory disease, where the etiology is unknown with structural damage to the gastrointestinal tract that deregulates the immune responses causing inflammation of the gut mucosa. Inflammation in all layers of intestinal walls with patchy discontinuous appearance from mouth till anus i.e., through the entire gastrointestinal tract is a characteristic feature of crohn's disease (Figure 1) [2].

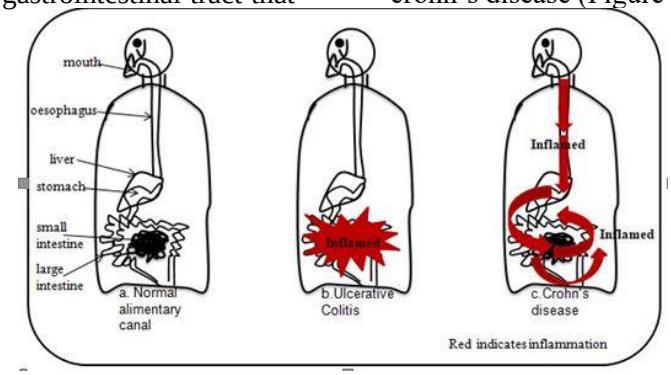

Figure 1: A. Normal. B. Ulcerative colitis C. Crohn's disease.

The superficial mucosal layer of the gut wall is mostly affected by ulcerative colitis, it arises from anus and extends throughout the colon [2]. Crohn's disease (CD) and Ulcerative colitis (UC) are the two main entities of IBD that have posed challenges for physicians over the years in the treatment of IBD having changed from relieving symptoms to healing the intestine, resulting in treating short-term complications with reduced hospitalization and surgery [3]. Biologics are target specific molecules which are involved in the inflammatory cascade triggered during irritable bowel disease, preclinical and clinical studies suggest their application in moderate to severe irritable bowel disease in patient who is not responding to conventional medicaments.

In the late 1990s, infliximab, an anti-TNF antibody was marketed for the treatment of IBD along with other anti-TNF blockers like adalimumab, certolizumab pegol, golimumab, with natalizumab available only in the United States because of their safety profile [4], was considered to be the gold standard treating moderate-to-severe IBD .With a consistent response rate for induction and maintenance, disease remission showing efficacy not only healing of the gut mucosa but also in the relief of symptoms, with reduced hospital admission with improvement in quality of living [5].

A new generation of small molecules called biologics, minimizes hospital stay [6], with more molecules underway for approval. This review summarizes the treatment of IBD according to their targets. The infiltration of lymphocytes into the intestinal mucosa is a target for therapeutic purposes in IBD characterized by integrins, which have low-affinity bonds, ligands in the endothelium of intestinal cells, inducing rolling and adhesion effect, resulting in circulating leukocyte to slow down.

The infiltration of lymphocytes includes extravasation and priming of cells from the vasculature, migration, and homing of activated cells into the intestinal tissues, and retention of leukocytes within the gut mucosa [7]. The surface of the vascular endothelial cells expresses the cellular adhesion molecules (CAMs). Both vascular cell adhesion molecule-1 (VCAM-1) and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) are receptors for the α4 family of integrins, specifically expressed on vascular endothelial cells of the alimentary canal. Integrin/CAM is disrupted by blocking leukocytes across the endothelium and into the inflamed parenchymal tissues. In CD, α4β7 integrin and its endothelial receptor, MAdCAM-1, demonstrated as a relevant factor for the development of chronic intestinal inflammation [8]. The first gut-selective integrin blocker vedolizumab indicated for patients with Crohn's disease (CD) and ulcerative colitis (UC). A recombinant humanized IgG4κ monoclonal antibody natalizumab interferes with lymphocyte homing that binds to the α4 subunit of two different integrins expressed on the surface of T and B cells and by binding to the α4 subunit, wherein natalizumab inhibits α4-mediated adhesion of leukocyte. Etrolizumab inhibits by binding to the β7 subunit and α4β7 and αEβ7 integrins.

Anti-TNF antibody

An orally administered antibody is isolated from the colostrums of cows and in the alimentary tract it negates the TNF locally. Delayed-release enteric-coated capsules have been formulated where, in the small intestine and colon, it is released at pH 6 after administration orally. Two preliminary studies in moderate-to-severe ulcerative colitis (UC), exhibited the safety and clinical efficacy [9,10]. 25.9% in the AVX-470 groups experienced clinical response with 11.1% with placebo. Adverse effects were comparatively less to placebo and further studies are required to evaluate higher doses and duration of long-term treatment.

Integrin α4 β7, MAdCAM-1

Leukocyte's infiltration plays a crucial role by inhibiting integrins and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), intervening with the migration of the cells [11]. The α4 subunit on lymphocytes is inhibited by natalizumab liable for the immune response and is effective in both induction and maintenance therapy with a risk for progressive multifocal leukoencephalopathy (PML) [12]. The second generation of anti-adhesion agents developed for gut specificity. Vedolizumab was first to be approved by the US Food and Drug Administration (FDA) for Crohn's disease (CD) and UC, which inhibits the gut-specific MAdCAM-1, α4, and β7. The drug has displayed effect in both the randomized controlled trials GEMINI I and GEMINI II for CD and UC [13,14], with no PML reported with vedolizumab [14]. Three large phase III clinical trials: ENACT-1, ENACT-2, and ENCORE demonstrated the clinical efficacy of natalizumab. ENACT-1 investigated the efficacy of natalizumab for the induction and ENACT-2 the maintenance of remission in moderate-to-severe CD patients. The induction study in ENACT-1 trial, showed a significant difference in response and remission rate, but only in the subset of patients with

high CRP levels. In the ENACT-2 trial, clinical response and remission were significantly higher compared with placebo [12]. The efficacy of natalizumab in the induction of remission in patients, confirmed by the ENCORE trial showed a response and remission rates significantly higher in the treatment compared to placebo [15,16]. Despite the positive results, the occurrence of PML with natalizumab is currently used only in patients with serology negative for the JC virus, limited by safety issues restricting the use of natalizumab therapy for CD, approved only for CD in the United States and Switzerland, under a specific regulatory and distribution program, also approved for the treatment of multiple sclerosis (MS). In CD, inhibition of engagement between the α4β7 integrin and MAdCAM-1 that are expressed on the vascular endothelium in the actively inflamed gut is associated with the clinical effect of natalizumab and the α4β1 integrin/VCAM-1 pathway may play a role for the inhibitory effects since VCAM-1 expressed on the submucosal vessels of the inflamed intestinal mucosa [4].

AJM300 oral administration suppresses the α4 integrin subunit. In moderately active UC, treated with placebo or AJM300 a good clinical response of 62.7% and 25.5%, was displayed, in a phase 2a study with 102 patients. AJM300 group reported good clinical respite with mucosal healing compared to placebo. To date, no serious adverse events, specifically PML have been reported [17]. In Japan, an ongoing phase 3 studies are being conducted.

AMG 181 (abrilumab) targets α4β7, which inhibits the MAdCAM-1 receptor, is an IgG2 human monoclonal antibody. A study was conducted in 68 healthy subjects and 4 subjects with active UC where out of the 4 subjects, 3 received active drugs and 1 received placebo, for its pharmacokinetic properties in patients [18]. Remission with mucosal healing achieved of UC patients treated with the drug with no report of serious adverse events recognized. This was followed by pharmacokinetic and pharmacodynamic studies [19]. Clinical response rates were high in patients who received subcutaneous injection of placebo, at dose of 21 mg, 70 mg, and 210 mg every 4 weeks in CD. At week 12, response was high in the active treatment group, despite the absence of statistical significance in the 210 mg abrilumab group [20]. And similarly, moderate-to-severe UC were studied [21,22] in 354 patients and both the studies hardly reported any death and or PML cases.

Etrolizumab is a humanized monoclonal antibody, and the inhibition is because β7 subunit and α4β7 and αEβ7 integrins binds preferentially in the intestine. Etrolizumab was studied for its safety in patients with moderate-to-severe UC [23,24] and in 2014, a phase 2 study was conducted, to receive one of two doses of etrolizumab subcutaneously or placebo with different doses like at 0, 4, and 8 weeks 100 mg or at week 0, 420 mg loading dose and at weeks 2, 4, and 8 by 300 mg. Clinical remission was attained after 10 weeks of therapy compared to placebo and adverse events observed in each group [24]. Presently a study comparing etrolizumab with adalimumab and placebo is ongoing with regards to efficacy and safety in UC. PF-00547659 is another therapeutic target which is a fully human anti-MAdCAM IgG2 antibody, located on the vascular endothelium on the lamina propria of the intestine. In 2011, one RCT evaluated the safety and preliminary efficacy in 80 patients with active UC who received PF-00547659 or placebo intravenously or subcutaneously at an interval of 4 weeks with no related adverse effects with PF-00547659 [25]. A phase 2 randomized, double-blind, placebo-controlled study, TURANDOT [26,27] was conducted with PF-00547659 in 357 patients who were evaluated for their usefulness and safety in moderate-to-severe UC. The study of the OPERA [28] involved patients with CDs that were intolerant to immunosuppressants or anti-TNF drugs in phase 2. The response shown by PF-00547659 and placebo did not show importance at 12 weeks.

Cytokines (Interleukin-12 and Interleukin-23)

The proliferation of Th1 and Th17 in CD could be due to cytokines like interleukin -12(IL-12) and interleukin -23 (IL-23) associated with inflammation. Ustekinumab acts against the p 40 subunit. Ustekinumab is an IgG1 antibody [29]. In Phase 3 study [30] in moderate-to-severe CD, the efficacy of ustekinumab was evaluated. At week 6, UNITI-1 patients displayed a higher response than UNITI-2 those who received 130 mg of ustekinumab compared to placebo displaying good clinical response. Patients who received maintenance dose every 8-12 weeks of ustekinumab (IM-UNITI) displayed good response at 44 weeks with the treatment group displaying similar adverse effects.

In two retrospective observational studies clinical response rate of 65% and 81% in efficacy studies and at 3 months [31,32] the endoscopic response of around 77% was observed. The study to evaluate the safety

and efficacy of ustekinumab in moderate-to-severe UC is ongoing.

Brazikumab (MEDI2070) without affecting IL-12 [33] interferes with p19, a subunit of IL-23. In a phase 2a study, its efficacy was investigated [34] at 8 weeks, displaying no significance with drug and placebo in 59 CD treated patients. At 8 and 12 weeks, levels of biomarkers like C-reactive protein (CRP) and fecal calprotectin (FCP) displayed no significant difference compared to placebo, reporting headache and nasopharyngitis as the adverse effects. Patients did not undergo any endoscopic or radiologic evaluation.

Risankizumab is used in moderate-to-severe CD, interferes with the p19 subunit. In a randomized study, at 0, 4, and 8 weeks, 121 patients received risankizumab or placebo, intravenously in a dose of 200 mg or 600 mg [35]. No difference in adverse effects was observed in both groups, with no death reported. Nausea and worsening of the condition were common and serious adverse effects. Recently clinical remission was seen in 62of 121 patients at week 26 [36]. At week 52, clinical remission and clinical response of 80% were observed. At week 52 the endoscopic response and remission were 54.8% and 35.5%. A phase 3 study is currently active and in recruiting phase.

Transforming growth factor β1 (TGF-β1)

CD patients exhibit the bizarre activity of suppressing the cytokine transforming growth factor (TGF) β1 that results in high levels of an intracellular protein, Smad7, which binds to the cytokine receptor blocking the signal. Smad7 impairment restores TGF-β1 activity, thus inhibiting cytokine production. Mongersen (GED-0301) binds and inactivates Smad7 RNA that restores TGF-β1 signaling mechanism is an antisense oligonucleotide administered orally [37]. In 2015, assessment for its efficacy was evaluated in 160 CD patients in phase 2 randomized control trials. 40 mg and 160 mg groups achieved 55% and 65% clinical remission compared to 10% of the placebo on the fifteenth day.

A phase 3 clinical trial revolve was discontinued, where the safety profile, clinical and endoscopic effect of mongersen in patients with CD was evaluated [38-40].

JAK/STAT pathway

The Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling pathway is a new target. JAK inhibitors block cytokine signaling involved in the pathogenesis of IBD. A JAK1 and JAK3 A non-selective inhibitor is tofacitinib [41,42], and the first IBD phase 2 studies were conducted in 2012 for assessing moderate-to-severe UC within different doses was published [43]. At higher doses primary outcome displayed by the treatment group in comparison to placebo. In patients who received tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, and 15 mg respectively, compared to 10% in placebo. The effectiveness of the drug was displayed in OCTAVE 1, 2, and OCTAVE Sustain [44] studies in phase 3. In the treatment groups at 52 weeks, the mucosal healing progression was higher compared to placebo with no difference in adverse effects observed in tofacitinib compared to placebo.

Tofacitinib is a drug with a short half-life, low antigenicity, with the ability to dampen several pro-inflammatory pathways, in UC, but results in treatment of CD of a phase 2 study were less reassuring. After 4 weeks of treatment, reduction in biomarker levels (CRP and FCP) were seen in both treated and placebo groups at the higher doses [44] and displaying no difference. The primary endpoint was not achieved for induction and maintenance therapy of CD in two, phase 2b studies even after follow-up [45].

Filgotinib is found to be highly selective for JAK1 than JAK2 and is administered orally. The drug was also found to be effective in patients with RA [46,47]. An RCT study FITZROY involving 174 patients, meant to evaluate the efficacy and safety of filgotinib for the treatment of moderate-to-severe CD [47], where the efficacy of filgotinib was shown in CD patients, irrespective to their prior exposure to anti-TNF [48]. In previously exposed patients to anti-TNF therapy, the effect was much less. Patients who achieved endoscopic remission in the 10th week with filgotinib compared to placebo showed no statistical significance and adverse effects.

Upadacitinib is a selective JAK1 inhibitor administered orally, in patients with moderate-to-severe CD. A phase 2 studies, published results of 180 patients who completed 16 weeks of induction [49], and in endoscopy significant effect was seen in a dose of 12 mg twice daily and higher.

Sphingosine-1 phosphate receptor (S1PR)

A structural protein found in humans, sphingosine, which makes up sphingomyelin, that is involved in the signaling pathway is sphingosine-1 phosphate (S1P) [50-52]. Ozanimod (RPC1063) is a selective agonist administered orally, and it modulates 1 and 5 S1PR subtypes [53].

By binding to S1PR subtype1 by ozanimod causes a negative feedback mechanism, blocking the effects of inflammation and the drug effect is reversible when discontinued, with 14-day duration. The S1PR type 1 expresses the effect related to chronic inflammation, and sheds light on the pathogenesis of IBD [54].

S1P plays a role in chronic inflammatory conditions as it acts against the leukocyte trafficking property. The safety and efficacy of ozanimod [55] was studied in 197 UC patients in a double-blind study named TOUCHSTONE, in phase 2. In 16% of patients with ozanimod 1 mg, clinical remission was significantly higher compared to placebo display improvement in mucosal healing and clinical remission [56,57]. Nasopharyngitis, upper respiratory tract infections and higher transaminase levels were reported as some of the adverse effects of ozanimod. Presently, a phase 3 trial is being conducted in UC on induction and maintenance therapy.

Pattern recognition receptors - toll-like receptors

In inflammatory bowel disease, a new target is toll-like receptors (TLR) which are pattern recognition receptors that recognize pathogens, activate mucosal healing via toll like receptor-9 [58], where it also plays an important role in immunity. DIMS0150 is a topical agent that is expected to be used in the treatment of colitis. The collect study in Europe, a phase 3, randomized, double-blind, placebo-controlled clinical trial, evaluated the safety and efficacy of DIMS0150 in UC [59]. DIMS0150 displayed remission when combined with mucosal healing in moderate-to-severe UC in 131 patients, in treatment, and to placebo groups. DIMS0150 showed improved outcomes, for the investigators to consider patient-reported outcomes (PRO) when DIMS0150 was evaluated for its efficacy [60]. The safety and efficacy of DIMS0150 in patients with refractory UC were due to improved sensitization to steroids [61-64]. A multicenter, randomized, double-blind, placebo-controlled trial of 156 patients with UC, the use of PC was investigated [65]. LT-02 displayed a significant reduction in Simple Clinical Colitis Activity Index (SCCAI), with a modified release form drug. It displayed no significant improvement in mucosal healing. Presently a phase 3 trial is being conducted with oral preparation of this drug.

Phosphodiesterase 4 (PDE4)

Currently, apremilast is approved in psoriasis, is an inhibitor phosphodiesterase 4 (PDE 4) [66] where in a phase 2 study effectiveness of apremilast in UC [67], was demonstrated displaying marked improvement in symptoms and mucosal healing compared to placebo.

Gut microbiota/fecal microbiota transplantation (FMT)

The immune response plays an important role but the relationship to microbiota is unclear and an inflammatory response could be due to any change in the gut mucosa environment. Clinical studies related to the effects on the microbiota are being conducted for a better understanding.

Fecal microbiota transplantation (FMT) may contribute to disease remission in ulcerative colitis, and the factors that determine the effects of treatment remain unknown. Out of the 661 IBD patients who underwent FMT, clinical remission that was observed in patients with CD and pouchitis was around 50.5% and 21.5%. A higher number of FMT infusions showed improved remission in UC patients when administered throughout the lower GI tract [68-71] and a randomized control trial was conducted in 2015, wherein FMT was administered via a nasoduodenal tube [72] .

In patients with severe, resistant UC, the effect of FMT was evaluated [73] where in 27% patients receiving FMT compared to 8% patients receiving placebo displayed no difference in adverse effects. In a study conducted on mild-to-moderate UC patients who were transplanted with donor FMT enemas or autologous FMT as a placebo, results indicated that patients who received FMT achieved around 50% remission clinically with no difference in adverse effects in treatment and placebo [74], with more studies required to understand a better treatment modality in IBD.

In a study conducted in 2019 a total of 20 patients with ulcerative colitis were included in this prospective, uncontrolled study. Once every 3 weeks patients underwent gastroscopy five times. To evaluate the extent of intestinal mucosal lesions in patients with ulcerative colitis, clinical indices were used to assess the efficacy of fecal microbiota transplantation, also the Mayo score. 16S ribosomal RNA-sequencing detected changes in the gut bacteria and the analyses were done to know if there was any relationship between ulcerative colitis and intestinal flora. Clinical index scores for diarrhoea, abdominal pain, and blood stool decreased significantly after treatment. No significant change was observed in erythrocyte sedimentation rate and C-reactive protein levels, with a significant decrease in the clinical index score for intestinal mucosal lesions and according to the Mayo

score. The 16S ribosomal RNA-sequence revealed that the intestinal flora in patients diagnosed with ulcerative colitis was different from that of donors. Improvement in the scores for diarrhoea, abdominal pain, and mucous membrane lesions changes due to abundance of bacterial flora and for patients with this disease, fecal microbiota transplantation would be of great therapeutic benefit [69].

In a study on UC patients has conducted wherein 73 adults with mild-moderate active ulcerative colitis in 2019. Anaerobically prepared pooled donor FMT or autologous FMT via colonoscopy that was followed by 2 enemas over 7 days in 38 and 35 patients respectively. Autologous FMT participants at 8 weeks were offered open-label therapy and they were followed up for 12 months. Steroid-free remission was the primary outcome of UC defined as a total Mayo score of ≤ 2 with an endoscopic Mayo score of 1 or less at week 8 and was reassessed after one year. Adverse events included secondary clinical outcomes. 69 (95%) among 73 patients who were randomized completed the trial. 32% achieved the primary outcome who received pooled donor FMT compared to 9% receiving autologous FMT. 42% of those who achieved the primary endpoint at 8weeks, following donor FMT, remission was maintained at 12 months. 3 serious adverse events in the donor FMT group and 2 in the autologous FMT group were observed. Further studies regarding the safety and longer-term maintenance of remission are required [75].

Multi-Matrix System (MMX)

A recently developed formulation, multi-matrix system (MMX), is, being studied in inflammatory bowel disease, with drugs like budesonide, a second-generation corticosteroid is administered by enteral route. This formulation was said to have a minimal first -pass effect. In RCT studies, budesonide MMX was well tolerated in a study in mild-to-moderate UC in a dose between 3-9 mg showing significant improvement with adverse effects same as corticosteroids [76,77]. CORE I and CORE II studies conducted on mild-to-moderate UC patients with budesonide MMX had greater effectiveness than mesalamine and placebo in phase 3 trials [78,79].

Anti-IL-17A

One human anti-IL-17A monoclonal antibody is secukinumab, blocks IL-17A, and is effective in rheumatoid arthritis [80], autoimmune uveitis, and psoriasis [81] with disappointing results in CD. This could be due to differences in pathogenesis and maintenance of homeostasis that depend on the host's immune response to microbiota [82].

Omics

Omic approaches are just starting to be applied in IBD. The immunocytes in the gut mucosa and T cells are involved. These cells are likely candidates for appropriate targets for therapeutic intervention [83]. Single omics will not provide a complete picture of IBD, no matter how precise and informative it is and all relevant omics data, referred as integrated Personal Omic Profiling (iPOP), must determine, risk assessment of disease, early and accurate diagnosis, disease progression, targeted therapeutic treatments and prevention of disease [84]. The results of iPOP, is crucial information when and where to intervene for therapeutic success for example as in case of the new therapies for drug-resistant breast cancer where transcriptional signatures and epigenetic links correlate a strong link to inflammation [85,86] leading to the subsequent discovery that metformin, an antidiabetic medication, selectively targeting cancer stem cells, [87,88] leading to phase 2 clinical trials [89].

Genomics

Over past two decades, advances in genomics and genomic data have contributed to understand the link between specific gene loci and their contribution to IBD susceptibility [90,91]. More than 300 genetic variants affecting various host functions have identified in genome-wide association studies in IBD patients [92]. Around 30% of the IBD-related genetic loci are shared by both CD and UC indicating, that a common disease-related pathway may be associated with cytokine, chemokine signaling and T helper (Th) cell response in the host [90-92].

Microbiomics

In the healthy state, the gut homeostasis is maintained [93] and the changes in the gut microbial compositions, results in an imbalance promoting excessive inflammation [94]. There is increasing evidence supporting microbial imbalance in the GI tract influences the development and progression of IBD [95-102].

Immuno-transcriptomics

Immuno-transcriptomics signatures can differentiate between healthy subjects and IBD patients or between

the different IBD subtypes can serve as reliable, clinically prognostic, or diagnostic biomarkers. Such signatures are still not correctly defined. The large number of genes involved in IBD pathogenesis makes identifying a targeted, manageable list of genes to define a signature is extremely difficult. The number of potential target genes has grown steadily. The immune network is made up of hundreds of immune cells, including their subpopulations, which are involved in the pathogenesis of the disease along with their overly complex gene signatures and associated functions [103].

Nanomedicine

Nanomedicine (NM) has generated much excitement and promise for the development of novel therapeutics and diagnostics [104]. The potential of nanomedicine for targeting, diseased areas, protect molecules from degradation, and control drug release over time is attractive. This holds good for oral drug delivery, especially in case of IBD [105-109]. NMs are used as carriers, having the ability to incorporate both hydrophilic and hydrophobic drugs and to be administered by various routes [110]. In NMs carrier material, particle size and surface charge play a key role that determines cellular uptake and interaction with biomolecules and NMs have a high surface area-to-volume ratio. Small particles possess more interaction sites as compared to large size particles which may help to regulate pharmacokinetics of drug release [111]. Nanoparticles can be either colloidal dispersions of solid excipient particles in which the drug is dispersed, adsorbed, or dissolved in the matrix, or nano capsules in which the drug is confined to an aqueous or oily core surrounded by a shell-like wall [112]. Various approaches such as emulsion evaporation/diffusion, nanoprecipitation have been reported for the preparation of nanoparticles [113].

Rolipram, a phosphodiesterase 4 inhibitor (PDE 4), loaded into poly lactic-co-glycolic acid (PLGA) nanoparticle and was tried as a first model drug to passively target the inflamed intestine in a study conducted [114] and in vitro results, initially showcased biphasic release that was followed by a slow and sustained release for one week. In addition to PLGA, polycaprolactone (PCL) can be used as matrix material for rolipram loaded nanoparticles [115]. Rolipram PCL NP released 80% of the drug after 48 h while PLGA NP released only 50% after 48 h and 80% after 7 days. Apart from this, the use of liposomes, have also been applied to IBD treatment because of stability issues, liposomes are administered parenterally.

What is new?

Low molecular-weight heparin (LMWH) is shown to be effective in IBD when administered parentally [116], but the mechanism in its prevention is yet to be determined [117]. A local delivery strategy for LMWH to locally target the inflamed intestinal mucosa to reduce this risk since heparin displayed minimal tendency to cross the intestinal mucosa, thus reducing the adverse effects [118]. Orally delivered LMWH microspheres and rectally administered LMWH solution have shown promising results showing superiority of the orally delivered microspheres [119] and the rectally administered solution over subcutaneously administered LMWH. The bioavailability studies of LMWH of orally delivered LMWH microspheres showed low systemic availability indicating a low potential for adverse effects. Another sophisticated system for the delivery of biologics is based on thioketal nanoparticles (TKN) [119] a novel polymer poly-(1-4 phenylenacetone dimethylene thioketal) that is sensitive to reactive oxygen species (ROS) but resistant to degradation by acid-base-and protease-catalysed pathways.

Summary of the targets for IBD

This gives an overview of the new targets for IBD that affects the gastrointestinal tract. With new targets in site, let us hope for better personalised treatment for IBD. Despite the recent advances extremely limited options, remains the main limitation (Figure 2).

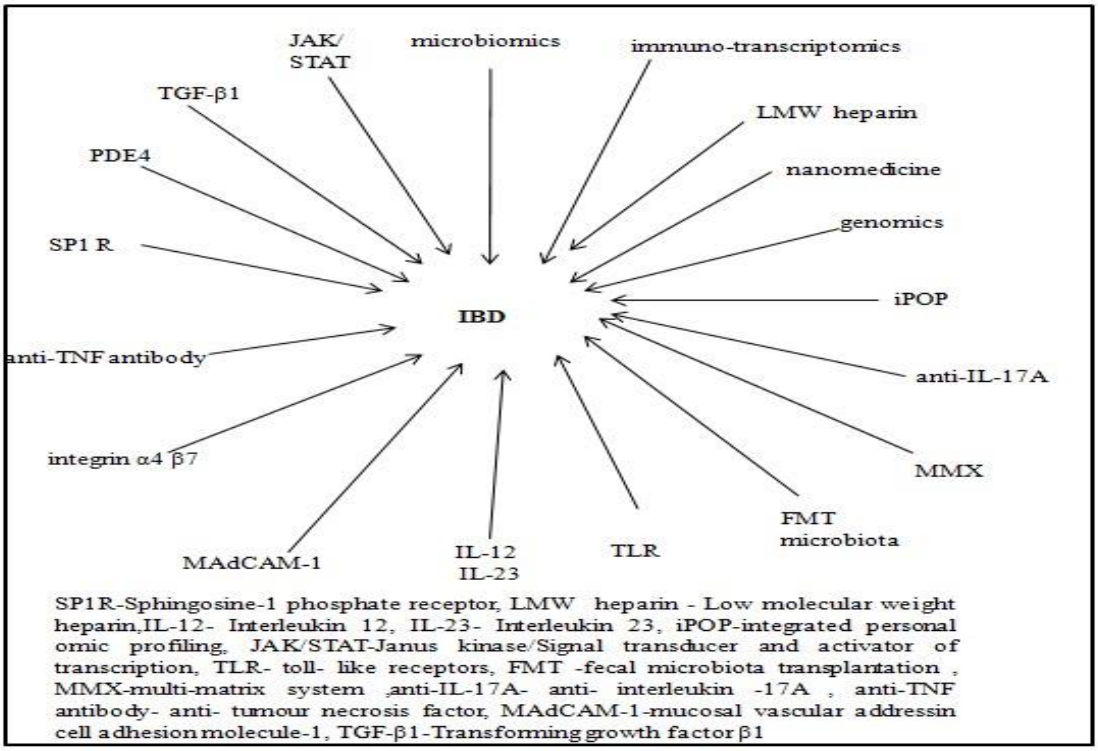

Figure 2: Summary of targets in IBD.

Conclusion

At present, no animal models represent the exact pattern and complexity of human IBD. Targeted drug delivery is one of the major attractions in nanomedicine. With many treatment modalities recently approved, other drugs commonly used for other indications are currently being investigated to be part of the IBD treatment regimen. Despite the recent advances and extremely limited options, the inability to personalize the specific treatment to a specific patient is the main limitation. With the understanding of the etiology of IBD, better disease control in the treatment for the IBD patients, the future lies in a promise with different targets, the mechanism behind the inflammation needed to transfer this targeting concept successfully.

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