Clinical Pharmacology & Biopharmaceutics

ISSN: 2167-065X

Maiti and Sharma, Clin Pharmacol Biopharm 2020, 9:6

Mini Review

Open Access

Gut Restricted Therapeutic Approaches to Inflammatory Bowel Disease

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Abstract

Inflammatory Bowel Disease (IBD), consisting of Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic intestinal disorder arises due to the damaged intestinal epithelium tissue which most often leads to relapsing. Major treatment options range from dietary intervention at an early stage of the disease, to the use of steroids or anti-inflammatory drugs for the severe most conditions. However, the side effects and associated comorbidities which bring disease recurrences points towards the unmet needs of the existing treatment options which are limited to their non-holistic mechanistic functionality. Among them, many drugs work specifically by acting locally on the gut tissue, in other words at the site of the disease; both to exert maximal efficacy as well as to avoid undesired side effects. Here we have reviewed the recent interests in the gut restricted therapeutic approaches for new IBD therapies.

Keywords: IBD; UC therapies; CD therapies; Gut-restricted compounds; Colon specific compounds; Non-systemic compounds

Introduction

IBD is a chronic disorder of gastrointestinal tract affecting severely the normal lifestyle of an individual. IBD comprises of CD and UC. While CD is characterized as an epithelial damage throughout the intestinal track from mouth to anus with multiple patches here and there in terms of their heterogeneous nature, morphology and size; UC is more restricted to the damage of the colonic epithelia with a leaky gut localized mainly from cecum to rectum [1,2]. Today an approximately 10 million people are living with IBD in different parts of the world in addition to many which are underreported or undiagnosed due to the nature of complexity of the disease [3]. Atpresent, there is no real ready-to-use non-invasive easy diagnostic tool available for a quick assessment of CD or UC. In recent time, the disease prevalence is growing at a faster rate due to the wide spread use of the modern food habits (western diet), environmental factors and genetic make ups; which might soon take an epidemic form of the disease [4].

UC is the major component of IBD with clinical symptoms of chronic abdominal pain, diarrhoea, bloody stool, fever and weight loss. In general people with stomach infection has a higher risk of developing UC, but chronic life habits and conditions like smoking, high sugar or high fat diet; and even anti-inflammatory or heavy antibiotic therapies are also the causes of developing UC [5]. Many patients develop colon cancer from UC. CD has a high prevalence form teenage group children to about 30 years old adults [6].

IBD Causes and Factors

Although the exact cause of the UC and CD are unknown, but epigenetic and environmental factors which affect the symbiotic ambience of gut microbiota and the overall immune status of the host body are the major causes thought to be theinitiators of IBD. The disruption in the intestinal wall integrity, by virtue of breakage of the tight junction between intestinal epithelial cells, compromises the differentiation between good and bad bacteria on two sides of the intestinal wall. And this in turn provides an immunologically flared up milieu of inflamed epithelial wall (Figure 1).

Human gut is the home for about hundreds of trillion of bacteria and is exposed to the constant flux of environmental bacteria which get ingested to our body through several ways [7]. The pathogenic and commensal bacteria get distinguished by our innate immune system

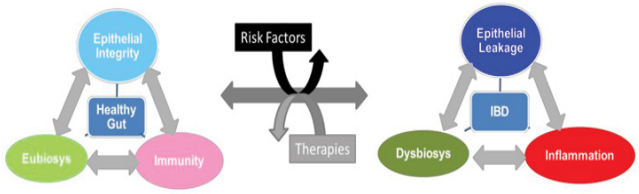

Figure 1: Causal relationship between healthy gut and IBD gut.

through the pattern recognition system. The pathogenic bacteria are eliminated by several mechanisms including the antimicrobial peptides secreted by intestinal epithelial cells in the gut epithelia. The commensal bacteria stays in symbiosis with the gut microbiota and protected from crossing the gut epithelia barrier by the integrity of epithelia cells through the protective mucous layer in the surface of the intestinal epithelial cells as well as by the tight junction protein which held epithelial cells tightly. The gut associated lymphoid cells constantly sample the composition of the luminal environment and provide the immunity to the gut barrier by pattern recognition and destroying pathogenic bacteria to maintain the integrity of the cellular lining [8]. But with the constant onslaught of different environmental factors on the intestinal epithelial cells by non-fibrous foods or dehydrations or low mucous production, the mucous barrier on the epithelial cells gets reduced and for other reason the tight junction proteins also gets lost. By these the integrity of the intestinal epithelial lining gets compromised. This loss of strict seal of mucous barrier and tight cellular integrity creates a leaky gut wall, which in turn allows commensal bacteria to enter into the basal side of the intestine, lamina propia.

In a leaky-gut-environment the innate immune system of the gut associated lymphoid system sends out macrophages and dendritic cells

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Received November 24, 2020; **Accepted** December 17, 2020; **Published** December 24, 2020

Citation: Maiti P, Sharma R (2020) Gut Restricted Therapeutic Approaches to Inflammatory Bowel Disease. Clin Pharmacol Biopharm 9: 209.

to destroy those pathogenicbacteria and activates T cells to alert the immune system through inflammatory signals. The composition of the bacterial community changes to during this instances. Although the interplay between leaky-gut, inflammation and dysbiosis of bacterial community is the real cause of the disruption or disease condition, but the true sequence of events or triggers are unknown. The gut associated lymphoid system, consisting of innate immune cells, is activated and produces more inflammatory cytokines to keep the systemic immune balance. This balance goes out of hand with a constant influx commensal bacteria in a leaky gut and slowly spreads all over part of the colon. A pan colitis kind of situation leads to the development of colon cancer [9].

Inflamed leaky gut lining is seen in the colonoscopies of the both CD and UC patients. Intestinal epithelial cells show almost no mucous barrier and lost tight junction between cells. Major inflammatory cytokines like tumor necrosis factor alpha (TNF), interlukine-8 (IL8), interlukine-6 (IL6) and interleukine-1-beta (IL1b) are seen in very high level in the circulating plasma of those patients [10].

Present Treatment Paradigm

The first line therapy of IBD, at present, is mesalamine for a mild to moderate condition of patients. Corticosteroids are used for severe conditions but with significant associated side effects. Immunosuppressants are also used for severe cases, but again with limitation as they have lot of side effects. The biologics like Infliximab are not widely popular due to its high cost and low level of response rate [11,12].

To a physician, the main goal of the treatment of IBD patient is to contain the remission. Reducing the inflammation to stop further damages and flare up the disease. Mucosal repair of the intestinal epithelial cells is another critical point of clinical significance to cure the disease and bring back the gut wall to its native form which are majorly investigated by colonoscopies during the treatment regimen [13]. Integrin inhibitors like Vedolizumab and Etrolizumab are used to limiting the infiltration of immune cells into lamina propia side of the gut wall. JAK inhibitors, IL23 antibody and IL22 antibody were used to contain the inflammatory signalling pathways [14,15]. Even the non-pathogenic good bacteria was used to limit the spread of inflammation and reverse the course of IBD in patients [16].

Gut-Restricted Function of Present Therapies

Several of the already approved IBD drugs exert their pharmacological action by modulating the components of factors present in the gut. The details of them are listed below in Table 1.

Mesalamine

Oldest among the drugs which acts predominantly through the mechanism at gut are the Asakol and Lialda. They are the two different formulatory compositions of mesalamine. They are prescribed as a first line therapy for mild to moderate UC and also as a combination therapy for moderate to severe UC patients. Mesalamine in its original form is absorbed maximally in the small intestine leading to a minimal exposure to the colon. The mechanism of action of mesalamine was through the modulation of multiple targets and was inconclusive as a major contributing pathway to the therapy. Few of the notables are effect on mucosal cells, anti-inflammatory effects on immune cells, as an antioxidant including COX2 inhibition, modulating nuclear hormone receptors like PPARg etc. The exposure proportional side effect to nephrosis, pancreatitis and cardiac effect was a major concern, besides the immune related side effects. But many clinical trials and their meta-analysis were inconclusive due to the heterogeneous complexity of patient population, nonadherence and their symptomic improvement without having a distinct molecular biomarker. During 1980s, a number of clinical trials were run on different formulations of mesalamine to evaluate the efficacy of the drug from its distributive properties in the intestine [17]. Time dependent enterocoatedmesalamines (Pentasa) was released in duodenum and matrix metalloenterocoated formulations (Lialda and Mezavant) were released in terminal ileum and entire colon. Prodrugs like salfasalzine, Osalazine and Balsalazine which primarily released in colon were also evaluated with comparable efficacy but with side effects. pH dependent mesalamine formulations (Asakol, Mesaaletc) havinga pH>6 were largely released in colon and showed maximal efficacy. Colonic delivery of mesalamine were also evaluated in the trial [18]. Presently several delayed release and enterocoatedmesalamine formulations are available in market, few of them are Asakol HD, Delzicol, Apriso etc. Considering the safety, efficacy and the adherence profile, presently gut-restricted or gut-released mesalamine is the most prescribed IBD medicine in the world.

Drug	Route	Type	Mechanism of Action	Approved for
Mesalamine (Asakol & Lialda)	Oral	Small Molecule	Anti-inflammatory	CD/UC
Vedolizumab	IV	Monoclonal antibody	4 7 integrin inhibition	CD/UC
Etrolizumab	IV	Monoclonal antibody	4 7 integrin inhibition	CD/UC
Rifaximine	Oral	Small molecule	Anti-bacterial	CD/UC

Table 1: Approved gut-restricted drugs for the treatment of IBD.

Antibodies acting on intestinal epithelial cells: Vedolizumab and Etrolizumab were two approved antibodies against 4 7 integrin for UC which functions by blocking the interaction between 4 7 integrin and MADCAM-1 and thereby stopping the leukocyte adhesion to the endothelium. MADCAM-1 is mostly expressed in the gut associated lymph nodes. Although given through the systemic route, these antibodies work at the site of inflamed intestinal epithelial where UC or CD exists [19].

Rifaximine

Rifaximine was approved in 2015 for the irritable bowel syndrome with diarrhoea. It's an antibacterial agent which works through the inhibition of the transcription process by binding to bacterial DNA. It has no absorption to the systemic circulation after oral administration and devoid of many side effect. Clinical studies have shown significant promise of remission in CD (69%) and UC (76%). Detailed studies are required to establish it for therapeutic use [20].

Upcoming Gut Restricted Drugs For the Treatment of IBD

List of Gut restricted drugs for the treatment of Inflammatory Bowel Disease (Table 2 and Figure 2).

TD1473

Theravance Biopharma initially tried to discover a unique formulation to make the pan JAK inhibitor tofacitinib to get restricted into the intestine and not to come into systemic circulation to reduce the toxicity of systemic tofacitinib. Initial efficacy data in anoxazolone induced colitis model showed that the intracecal delivery of tofacitinib

Drug	Company	Type	Mechanism of Action	Status
TD-1473	Theravance Biopharma	Small Molecule	Pan-JAK and TYK inhibition	Phase 2/3
PTG-100 PTG-943	Protagonist Therapeutics	Peptide	a4b7 integrin inhibition	Phase 2
JNJ67864238 (PTG 200)	JnJ (Protagonist Therapeutics)	Monoclonal Antibody	IL23 inhibition	Phase 2
BT-11	Landos Pharma	Small Molecule	LANCL2 activation	Phase 2
BBT-401	Bridge Therapeutics	Peptide	Pellino-1 inhibition	Phase 2
EB-8018	Enterome Biosciences	Small Molecule	FimH inhibition	Phase 1b
AVX-470	Avaxas Biologics	Polyclonal antibody	TNF inhibition	Phase 1
TD-5202	Theravance Biopharma	Small Molecule	Irreversible JAK3 inhibition	Phase 1
GB004 (AKB-4924)	Gossamer Bio	Small Molecule	HIF1a stabilizer	Phase 1
Tenapanor	Ardelyx Inc	Small molecule	NHE3 inhibitor	Phase 3 Approved (IBS-C)
ST-0529	Sublimity Therapeutics	Small molecule	Cyclosporin nano formulation	Phase 2
Safalcone	Korean Univ	Small molecule	NRF2 inhibition	Discovery
unknown	Inflamazome	Small molecule	NLRP3 inhibition	Discovery

Table 2: Upcoming gut restricted drugs for the treatment of IBD.

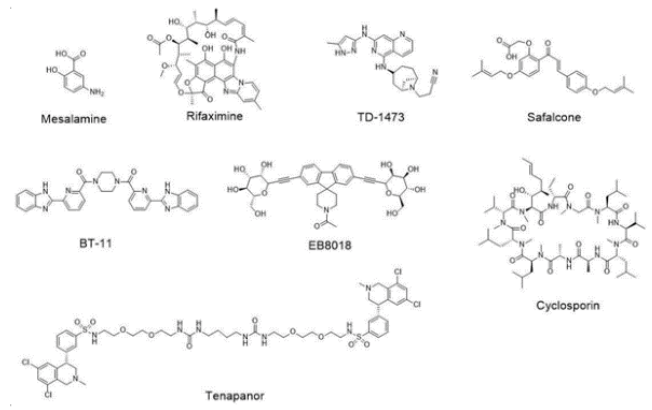

Figure 2: Structure of known or disclosed small molecules drugs.

with 15 times lower dose had the similar efficacy and colon exposure even with 80 times lower plasma exposure to its oral delivery; providing the proof of concept about the local effect of JAK inhibitors in colonic gut epithelium Although initially Theravance designed a gut restricted prodrug of tofacitinib, TD-3504; but discovered a chemically distinct new pan JAK TYK inhibitor TD-1473 with gut restricted properties. In an oxazolone induced colitis model TD1473 showed significant reduction of disease activity index at 1mpk oral dose which is comparable to the 15mpk oral dose of tofacitinib in the same model. The oral exposure of those corresponding drugs were 4ng. hr/ml to 4.7ug.hr/ml which indicates that a gut-restricted compound with more than 1000 fold lesser plasma drug concentration can elicit the same efficacy, but only through the local gut effect. It also showed no immunosuppression, as generally observed with tofacitinib, by penetrating the intestinal wall to exert anti-inflammatory effect locally on lamina propea and epithelial cells. It had slow absorption in the intestinal tract, but without any systemic plasma exposure [21].

Phase I clinical trial of TD-1473 with healthy volunteers for SAD (n=40) and MAD (n=32) showed tolerability upto 1000mg (SAD) and 300mg (MAD) for 14 days without any serious side effects. To extrapolate the similar observation from the preclinical pharmacokinetic pattern, in human also there was a low systemic exposure of the molecule and largely excreted through faeces. A placebo controlled exploratory phase Ib in 40 UC patient with 20 mg, 80 mg and 270 mg doses showed >30% clinical response along with endoscopic mucosal healing (>20% patients) when treated for 4 weeks. Also they had an improved histologic and rectal bleeding score [22]. Significant percent of patients (>30%) showed the reduction of CRP and calprotectin without any immunosuppression (reduction of lymphocytes, leukocytes andneutrophils) [23]. In collaboration with Jansen pharma, TD-1473 is now undergoing a phase 2 clinical trial in CD and phase 2b/3 UC patients [24].

PTG-100 and PTG-943

The clinical proof of principal of 4 7 integrin inhibition for the treatment of UC and AD was established with the approval of monoclonal antibodies Natalizumab, Vedolizumab and Etrolizumab. 4 7 integrin, majorly expressed in monocytes and macrophages, binds to the MAdCAM1 and VCAM1 in gut epithelial cells and Piears patches for T cell homing and thereby bacterial infiltration. Protagonist therapeutics discovered an oral small molecule cyclic peptide, PTG-100, as a 4 7 integrin antagonist whose exposure was restricted to gut. The molecule had a subnanomolar potency in inhibiting the 4 7 integrin and MAdCAM1 interaction while selective for VCAM and ICAM and in cellular adhesion assay as well [25]. This cyclic peptide showed great proteolytic and chemical stability in gastric fluid, intestinal fluid, plasma and liver. PTG-100 showed almost no plasma concentration in rodent and mostly found in Peyer's Patches and colon (about 4uM). The similar effect was observed in a monkey PK study with even higher level of colonic exposure of 15uM compared to any in plasma [26]. PTG-110 showed efficacy in rodent model on the prevention of T cell homing and mucus injury; most probably by local effect on lymphoid cells of intestine. In a placebo controlled phase I clinical trial PTG-100 showed safety and tolerability till 100 mg dose with a high faecal concentration and extremely low plasma concentration [27]. The initial phase II data showed a dose dependent target engagement saturating at about 60-70% level and receptor occupancy saturation at 300 mg dose. The histological remission was about 44% at 900mg dose. The further clinical testing washalted after an independent internal assessment of data predicted to be moderate efficacy of the molecule.

Instead, Protagonist placed a second generation molecule PTG-493 which is superior to PTG-100 in every aspect in preclinical studies and in early clinical studies. PTG-943 is about 5 times more potent and stays on target for about 3 times longer than PTG-100 in invitro assays. In monkey studies it showed higher level of target occupancy than PTG-100 although having similar low plasma exposure. In rat it had about 400-500 times higher intestinal concentration that plasma. In healthy mice, PTG-943 was more effective in donor T-cell homing in illeal Lamina Propia as well as preserving colon integrity. In a phase I clinical studies PTG-943 showed better target engagement of about 100% with a saturable receptor occupancy at 1000 mg dose [28]. A phase II clinical trial of PTG-943 is currently ongoing [29].

JNJ-67864238 (PTG200)

JnJ-67864238 (PTG200) is an IL23 antibody developed by Protagonist Therapeutics in collaboration with Jansen Biotech. The recent FDA approval of Ustekinuzumab confirmed the proof of concept of the IL23 inhibition for the treatment of IBD. In addition to that, few more IL23 antibodies (Brazikumab, MEDI2070, BI655066, Mirikizumab, Guselkumab, Risankizumab) are in advanced stages of clinical trial for their potential entry into market. While all those antibodies were injectables, Protagonist Therapeutics with their special peptide technology discovered and developed a gut restricted antibody, PTG200, to inhibit IL23 locally in the intestine for IBD treatment. A TNBS induced rat colitis model showed dose dependent improvement of the colitis parameters of body weight, colon length along with MPO, LCN2 and IL17concentration in faeces collected from distal colon and blood cytokines to validate hypothesis of local IL23 inhibition with an oral gut restricted antibody [30,31].

A randomised, double blinded placebo controlled phase I clinical trial of PTG200, demonstrated tolerability and safety of the molecule. Also this study showed the consistent pharmacokinetics and pharmacodynamics of the gut-restricted properties. A phase IIb clinical trial in underway with 90 patients in Australia [32].

BT-11

BT-11 is a first-in-class LANCL2 activator which is being developed by Landos Pharma [33]. CD4+ Treg cells controls the production of inflammatory cytokines IFN, IL17 and TNF to contain the flares of inflammation on intestinal wall and gut mucosa. LanthionineSynthetase Cyclase-like Receptor 2 (LANCL2) is majorly expressed in haematopoietic cells and gut specific Treg and colon epithelial cells. Although, abscicic acid is the natural ligand for LANCL2, a computational approach by an academic lab produced a hit which later optimized to give BT-11 [34].

BT-11 is a gut restricted and locally acting (intestinal epithelium) molecule which is well tolerated until 1000mpk tested in rats and dogs. A 500mpk rat exploratory PK suggested a small but rapid absorption of the molecule with a rapid clearance. The plasma concentration was very low, about 20 ng/ml at 500mpk dose [35]. A high volume of distribution (3.3L/kg) initially suggested a drug localization or non-systemic fractionation. BT-11 has been shown to be efficacious in various genetically and chemically induced rodent model of IBD along with the reduction of cytokines in the blood samples taken from CD patients; compared to the tofacitinib [36]. It showed thereduction of expression of TNF in intestinal cells to promise a better or similar effect in standard of care with TNF inhibition with this new mechanism of action. A randomised, double blind, placebo control phase I SAD and MAD study of BT-11 with CD and UC patients (n=70) showed that 100mg of once daily oral dose of BT-11 is safe. Drug concentration analysis showed a significantly low level (1:6000) of drug in plasma compared to the faeces and colon [37]. The faecal concentration increased dose proportionally. BT-11 showed significant decrease of TNF +, IFN + CD4+ T cells and increase of FOXP3+ CD4+ T cells in colonic mononuclear cells from patients with CD and UC. A phase II clinical of BT-11 is undergoing [38].

BBT-401

BBT-401 is a potent first-in-class, gut restricted pellino-1 inhibitor discovered by researchers at Sungkyunkwan University and Korea Research Institute of Chemical Technology and later licenced and developed by Bridge Biotherapeutics. Pellino-1 is a ligase which plays a key role in multiple immune receptor signalling pathways, including Toll-like receptors, interleukin-1 receptor and T-cell receptors [39]. BBT-401 is a lipidated tetra-peptide binds to Pellin-1 and thereby dissociates the multiprotein signalling complex comprising of MYD88, RIP1 and others. In preclinical cellular and animal models, the compound showed the inhibition of TLR-NF B signalling and pro-inflammatory cytokine expression. In animal model, it was shown to be safe in GLP tox studies. In animal models of colitis compound showed significant efficacy with improvement of colitis symptoms at a dose of 3mpk along with the mucosal healing. It was not systemically absorbed and hence the efficacy was mainly attributed to the local effect of the molecule [40]. In a phase 1 clinical trial with 80 healthy volunteer, BBT-401 was found to be safe and well tolerated till 1600 mg of daily doses for 7 days.

It was also shown that molecule has no systemic exposure. A randomised, placebo controlled, dose dependent phase 2 study is undergoing right now [41].

EB8018

Enterome Biosciences developed a first-in-class non-biological, non-steroidal and non-anti-inflammatory small molecule drug for CD by inhibiting the FimH binding of the gut bacteria. Bacteria like AIEC (Adherent and invasive E. Coli) and Klebsiela bind to proteins like CEACAM6 which are overly expressed in chronically inflamed epithelial cells of gut wall of CD and UC patients through the interaction of their FimH protein adhesion and thereby adhere to the gut cells and increases the bacterial concentration in gut mucosa [42]. FimH inhibition is also implicated in the urinary tract infection and other infections through the mechanism of biofilm formation [43]. Based on the available crystal structure of FimH and its natural ligand d-mannose, many efforts have been put to discover FimH inhibitors for therapeutics [44]. But most of the molecules suffered from the metabolic and chemical instability in GI tract. Disaccharides as well as monosaccharides with and without heterocycles were tried most. Many molecules showed unique physicochemical properties with high solubility but a very low systemic absorption and stayed mostly in the intestinal tract. In rodent model of CD, they showed reduction of pathogenic AIEC in faeces; and in the colonic and illeal mucosa showing early promise of the antiadhesive therapy [45]. Enterome developed EB8018 into phase I clinical trial and reported that the molecule is highly soluble and rapidly absorbed but only in small amount (123ng/ml at 1500 mg dose) and mostly (97%) excreted though faeces. The molecule was well tolerated till 1500 mg dose with noclinically significant adverse effects which led to the progression of the molecule into phase II clinical trial. Takeda Pharmaceutical has collaborated on this [46].

AVX-470

Avaxia Biologics [47] discovered AVX-470 (Avaximab), an oral gut restricted anti-TNF antibody for IBD. Although the systemic anti-TNF therapy for IBD was already approved (Adalizimab and Tofacitinib), but AVX-470 was designed to act only locally at the inflammation site of gut wall of CD and UC patients to reduce the immunogenic and immunosuppressive toxicity associated to systemic anti-TNF drugs. AVX-470 was a lactose-free formulation of polyclonal immunoglobin (Ig) obtained from the early milk of cows immunized with recombinant human TNF and later enterically coated to pH 6.0. It was stable in GI track, resistant to the cleavage and digestion by peptidases. It was localized into colon and had minimal systemic circulation. The molecule had a comparable in vitro potency to Infliximab. In a

chemically induced (DSS or TNBS) mice colitis model, AVX-470 showedsignificant reduction in disease activity score and inflammatory cytokines comparable to standard of care like Prednisolone and a matched murine antibody (AVX-470m). Also it was found to be penetrated into colonic mucosa to inhibited TNF driven mucosal inflammation [48].

A double blind, placebo controlled, phase I study (n=37) with 3 different doses of oral administration of AVX470 showed high intestinal localization of the drug and no traces in the blood circulation. The colonoscopic samples showed, the presence in both luminal and basal side as it penetrated through the inflamed leaky gut epithelia. Twice daily dosing (till 3.5mg/day) showed no black box warning which were generally present in systemic anti-TNF antibodies due to their immunosuppressive side effects. In moderate to severe IBD patients, it showed similar efficacy in initiating theremission, but better efficacy in maintaining the remission; comparable to systemic anti TNF antibodies. It showed significant reduction of CRP and IL6 [49].

TD-5202

Recently Theravance has disclosed another gut selective irreversible JAK3 inhibitor (TD-5202) by taking advantage of the differentiated structural feature of an active site cysteine of JAK3. The exact structure and the preclinical data of this molecule is not available in public domain. Again partnering with Jansen pharma, TD5202 is undergoing a phase I clinical trial indicating for inflammatory intestinal disease [50].

GB004 (AKB-4924)

Structure not disclosed yet: Aerpio Pharmaceuticals discovered AKB-4926, which later got licenced by Gossamer Bio to develop and commercialise for IBD as GB004. This is an oral gut restricted prolyl hydroxylase (PHD) inhibitor which selectively stabilizes Hypoxia-inducible factor 1-alpha (HIF1). In a hypoxic condition, when oxygen demand form stressed cells are far more than the supply; master regulators like HIF1 gets overexpressed to kick start induction of inflammatory genes to produce inflammatory cytokines and erythropoiesis [51]. In a disease condition like IBD where gut epithelial cells suffer from stress and high flux of inflammatory cytokines in a hypoxic condition, AKB-4924 plays a vital role to exert an anti-inflammatory effect and mucosal healing effect by stabilizing HIF1. Later on, they proposed the detailed mechanistic pathway of HIF-IL-12p40 involvement in the Th1/Th17 pathway for HIF1 mediated mucosal healing [52].

Importantly, this molecule is gut restricted when given orally, and hence doesn't inhibitthe systemic HIF1 which protects the renal and cardiac tissues which are of generally concern for this target to inhibit [53]. Also AKB-4924 selective against HIF2, which is otherwise known to cause inflammation. These were shown in a preclinical model of TNBS induced colitis in rat. Also molecule showed the improvement of parameters of colitis and inflammation along with the mucosal healing of protective effect of inflamed gut epithelial lining in this colitis model [54].

Gossamer Bio presently is running a placebo controlled phase 1 clinical trial on GB004 to evaluate the safety, tolerability and pharmacokinetics of the molecule on IBD patients [38].

Tenapanor

Tenapanor is an inhibitor of sodium/hydrogen exchanger 3 (NHE3), which is located in the apical surface of the small intestine and colon and responsible for the intestinal absorption of dietary sodium. ArdelyxInc[55] developed this compound for Irritable Bowel Syndrome with constipation (IBS-C) and got FDA approval in Nov 2019. By inhibiting the NHE3, Tenapanor decreases the sodium absorption and increases the moisture content of the mucosal surface. This effect results into the softening of the stool in patients. The molecule worked locally on the epithelial tissues of colon and intestine [56].

In a phase I clinical trial Tenapaor showed minimal absorption to the systemic circulation to below detectable limit of 0.5ng/ml. The major excretion of about 70-80% was through faeces. In phase III clinical trial, it showed significant efficacy in patients with IBS-C [57].

ST-0529

Sublimility Therapeutics developed a proprietary SmPill technology, unlike IV or oral, for specific delivery of cyclosporine to directly into the colon for moderate to severe UC patients. In a 100 patients phase 2a study it showed good tolerability and safety to progress into 280 patient phase 2b study [58]. Earlier, it was reported that the cyclosporine (through IV route) had about 80% disease response in acute severe UC patients which are refractory to steroid treatment and that effect was similar to TNF therapy [59]. ST-0529 is now undergoing clinical trial with the hope to provide a safe and more efficacious cyclosporine for UC patients without major side effect.

Safalcone

A recent publication from University of Korea showed that the anticolitic agent Safalcone when conjugated with natural amino acids to make it a gut-restricted compound, the inflammatory components and the disease index were improved significantly in a TNBS rat model of ulcerative colitis. The molecule showed almost no systemic exposure and was excreted through faeces. It was already known that the anti-colitis properties of Safalcone is achieved through the inhibition of NRF2 and HO-1 [60].

Inflazome

Recently Inflazome disclosed their pipeline with a molecule in the pipeline in discovery phase with a gut restricted NLRP3 inhibitor for the treatment of UC and CD [61].

Conclusion

As the prevalence of the IBD cases are growing rapidly worldwide due to the rapid industrialization, which causes major environmental changes and also the food habits of people especially living in the urban setting changes, the need for a real disease modifying therapy of IBD is of prime importance. Although presently there exists numerous therapies, but the response rate is not significant and coupled with the low adherence to the therapy creates a huge unmet need for patients suffering from this chronic disease. The remission of the disease is the most common factor in both UC and CD. Most of the present therapies come with lot of side effect and comorbidities. When the disease gets severe in nature, ultimately almost ~30% of the patient goes through the surgery for removal of intestine after the 15-20 years of the diagnosis of the disease. Also in very severe cases IBD leads to colon cancer.

To avoid side effects arising out of systemic exposure of the drug and also to limit the mechanism of action localized to the site of the disease, there are number of efforts underway to make those drugs delivered in a gut-restricted manner so that the efficacy can be achieved maximally as well as the side effects arising out of systemic circulation of drug can be contained. Considering the historical functioning of the existing drugs, mesalamine and antibodies; pharma companies' effort

on this unique mode of therapy could lead to a transformation to the therapy with more effective disease modification.

Conflicts of Interest

The authors declare that there is no conflict of interest. Both authors are employees of Cadila Healthcare Limited which fully owns Zydus Research Center.

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