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IBD: Emerging Treatment Landscape

Inflammatory bowel disease (IBD), comprising of ulcerative colitis (UC) and Crohn's disease (CD), is a complicated, uncontrolled, and multifactorial disorder.[1] It is characterized by chronic, disabling, relapsing, or progressive idiopathic inflammation leading to mucosal damage that may involve the entire gastrointestinal tract. Common symptoms include abdominal pain, diarrhea, rectal bleeding, gut/ perianal fistulas or abscesses, weight loss, malnutrition, and fever.[2,3,4] Additionally, it may be associated with an increased risk of colitis-associated neoplasia.[5]

The chronic nature of inflammatory bowel disease (IBD) has an enormous economic burden on patients, and the treatment is far from optimal due to the limited understanding of IBD pathogenesis. Personal genetic susceptibility, external environment, internal gut microbiota, and the host immune response have a role in IBD pathogenesis. IBD may be triggered by an aberrant and continued immune response to altered gut flora in genetically susceptible individuals with an impaired barrier function.[2,3]

IBD Incidence and Prevalence Trends[4,5,6,7,8,9,10,11,12]

Industrialization, urbanization and associated environmental factors are key contributors to the growing disease burden. IBD is emerging as a global public health issue with increasing incidence in the developing countries.

IBD Prevalence# (Asia)								
Country	UC			Country	CD			
South Korea	7.57 (1997)	-	30.87 (2005)	Japan	2.9 (1986)	-	13.5 (1998)	
Hong Kong	2.26 (1997)	-	6.30 (2006)	Singapore	1.3 (1990)	-	7.2 (2004)	

#per 100,000 population

In the Western world, the incidence of UC is showing a downward trend whereas incidence of CD is either constant or shows a slight upward trend.

Countries with Stabilized Incidence# Trend in IBD						
Country	UC			CD		
US*	10.1 (1970-1979)	-	8.8 (1990-2000)	7.9 (1970-1979)	-	Constant (2000)
UK	10 (1980)	-	13.9 (1994)	3.9 (1980)	-	8.3 (1994)
Northern France	4.2 (1988)	-	3.5 (1999)	5.2 (1988)	-	6.4 (1999)
Germany	2.4 (1980-1984)	-	3.9 (2004-2006)	4.5 (1980-1984)	-	4.8 (1991-1995)
Countries with Increasing Incidence# Trend in IBD						
Denmark	9.2 (1980)	-	13.4 (2003-2005)	4.1 (1980)	-	8.6 (2005-2006)
Sweden	9.2 (1980)	-	13.4 (2003-2005)	4.1 (1980)	-	8.6 (2005-2006)
Italy	3.8 (1978)	-	9.6 (1992)	1.9 (1978)	-	3.4 (1992)

*Olmsted County, Minnesota
per 100,000 population

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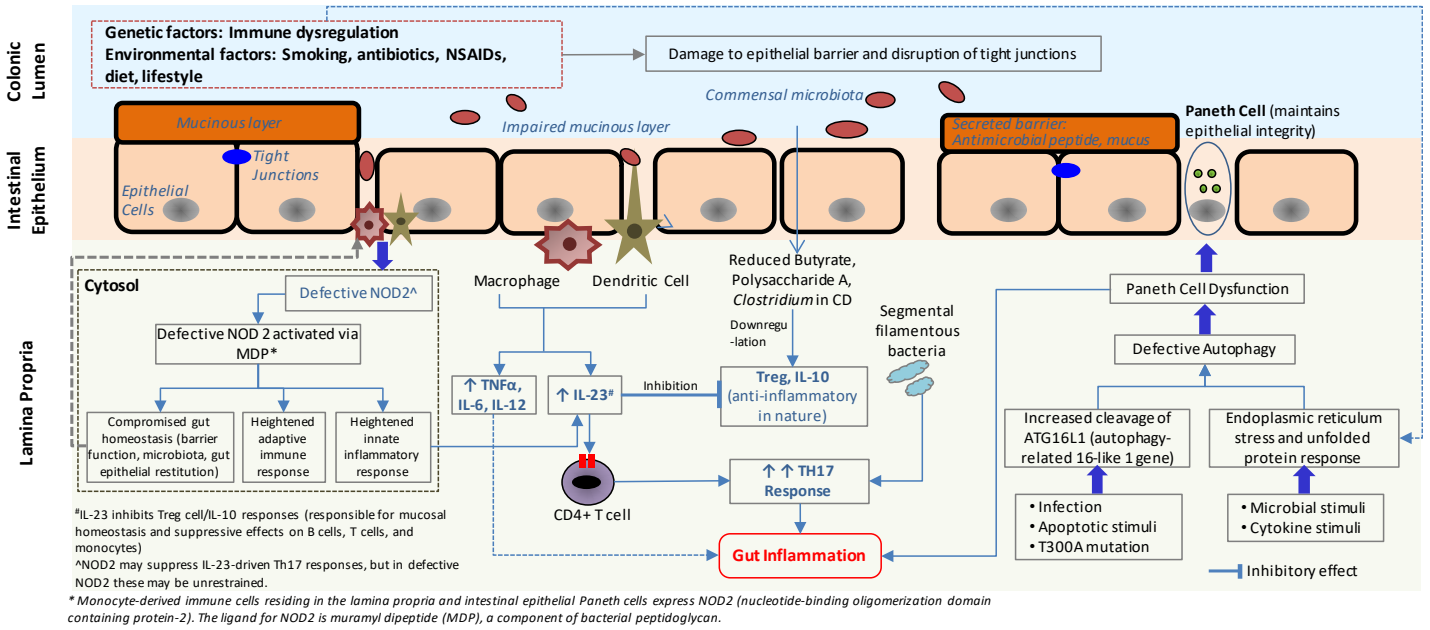
Crohn's Disease (CD) can affect any part of the GI tract and 30-40% of the patients have disease limited to the small bowel, 40-55% have disease involving the small and large intestine, and 15-25% have colitis alone. CD is segmental in nature with skip areas of normal gut between diseased segments, resulting in either a fibrostenotic obstructing pattern or a penetrating fistulous pattern of disease manifestation. CD is a transmural process resulting in a typical "cobblestone" appearance. Fistulas, ulcers, and abscesses in the abdomen and perianal region are commonly observed.

The localized release of cytokines, such as IL-12, IL-17, TNF-α, and IFN-ɣ, has been implicated in the chronic inflammation observed in CD patients. The production of IL-12 and IL-18 by antigen-presenting cells (APC) and macrophages generates a polarized differentiation toward Th1 lymphocytes, leading to an increased release of pro-inflammatory cytokines, including TNF-α and IFN-ɣ. Additionally, Th1 cytokines stimulate the APC to secrete more inflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, and IL-18, resulting in a self-sustained cycle.

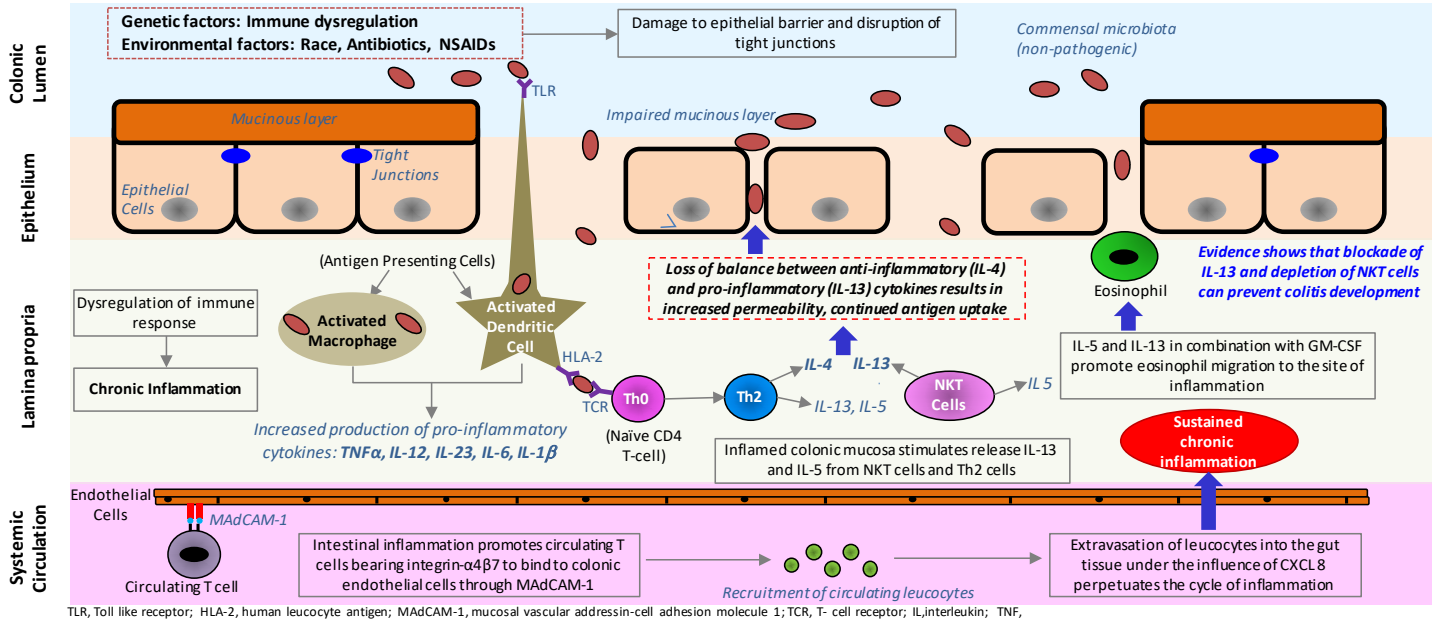
Aberrant and continued immune response to altered gut flora in genetically susceptibility individuals with an impaired barrier function may result in CD. *Defective NOD2 may result in compromised gut homeostasis and activation of inflammatory pathways, leading to excessive Th-17 response that eventually results in gut inflammation.*[13,14,15]



Ulcerative Colitis (UC)[13,16,17,18] is a mucosal disease that usually involves the rectum and extends proximally to involve a part or all of the colon. UC is limited to the rectum or the rectosigmoid area in 40-50% of the patients, 30-40% have disease extending into the sigmoid colon and 20% of the patients have pancolitis. Proximal spread of disease occurs in continuity leaving no areas of uninvolved mucosa. Clinical manifestations of UC include release of blood and mucus, petechial hemorrhages, and granulation tissue formation. During remission, the mucosa may have normal appearance. In severe forms of UC, deep ulceration and intestinal perforation may be observed.

Excess secretion of IL-13 in UC is responsible for the inflammation and chronicity. Apart from Th1 involvement, UC patients also show a Th2 response with increased secretion of IL-4, IL-5, and IL-9. Expression of the PU.1 transcription factor (a regulator of cellular communication), and the production of IL-9 block the proliferation of intestinal epithelial cells and regulate the expression of several tight-junction proteins. Together, they favor the translocation of specific bacterial species with subsequent activation of immune cells and mucosal inflammation in UC. Additionally, Th17-related cytokines are also increased in UC.

An impaired mucosal immune response to commensal gut flora and environmental factors in genetically susceptible individuals may damage colonic epithelium to result in ongoing inflammation[13,17,18]



TLR, Toll like receptor; HLA-2, human leucocyte antigen; MAdCAM-1, mucosal vascular addressin-cell adhesion molecule 1; TCR, T- cell receptor; IL,interleukin; TNF, tumour necrosis factor; Th, T-helper; NKT, natural killer T-cell; GM-CSF, granulocyte/monocyte colony stimulating factor; CXCL, chemokine

Management of IBD[5,13,19,20]

The goal of pharmacotherapy is to reduce the inflammation during relapses and to extend the period of remission. Physicians may adopt a "step-up" approach in which the intensity of treatment increases along with the severity of the disease or a ''top down'' approach, where an early intensive treatment (e.g., biologics) is used to avoid future complications.

Conventional Therapies

Aminosalicylates	Corticosteroids	Thiopurines	Folic Acid Antagonist	Calcineurin Inhibitors
Commonly prescribed aminosalicylates– mesalazine, sulfasalazine, olsalazine, and balsalazide • Used as first-line drugs to treat UC for both induction and maintenance of remission • Usually well tolerated	Corticosteroids provide significant symptom control of acute exacerbations in UC and CD • Corticosteroids act by: » down regulation of transcription of pro-inflammatory genes (e.g., NF-kB) involved in cytokine production » inhibition of the recruitment of immune cells and the expression of adhesion molecules in inflamed tissue • Long-term use is associated with severe adverse events	Thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6MP) are used for induction and maintenance of remission • Thiopurines preferred in glucocorticoid dependent IBD patients, active perianal and fistulizing CD	Methotrexate (MTX) is used for induction and maintenance of remission in CD in patients refractory or intolerant to thiopurines • Long-term efficacy is low	Calcineurin inhibitors have inhibitory effect on cellular and humoral immune systems • Cyclosporine (CSA) is effective in severe UC that is refractory to glucocorticoids and can prevent or delay surgery • Tacrolimus is effective in glucocorticoid dependent or refractory UC and CD and in patients with refractory fistulizing CD

Patients who are not candidates for conventional therapies due to intolerance or lack of response receive biologic therapies. These therapies were earlier reserved for moderate to severe IBD in patients who had failed on other therapies. Based on long-term safety and experience of treating physicians, these therapies are increasingly being used in moderate to severe IBD as initial therapy.

Biologics

Anti-TNF Therapies	• Infliximab (Chimeric IgG1antibody against TNF-α): for treatment of moderate to severe active CD and UC, refractory perianal and fistulizing CD • Adalimumab (recombinant human monoclonal IgG1 antibody): moderate to severe CD that has failed on conventional therapies or infliximab and moderate to severe UC that has failed on conventional therapies • Certolizumab pegol (pegylated anti-TNF Fab) for treatment of moderate to severe active CD with inadequate response to conventional therapies • Golimumab (fully human IgG1 antibody against TNF-α) for moderate to severe UC with an inadequate response or intolerant to prior treatment or requiring continuous steroid therapy
Anti-Integrins	• Natalizumab (recombinant humanized IgG4 antibody against α4-integrin): moderate to severe CD that has failed on conventional therapies or TNF-α inhibitors • Vedolizumab (antibody against α4β7 integrin): moderate to severe CD or UC that has failed on conventional therapies or TNF-α inhibitors
IL-12 and IL-23 Antagonist	• Ustekinumab: moderate to severe CD patients who have failed on conventional therapies and or TNF-α inhibitors

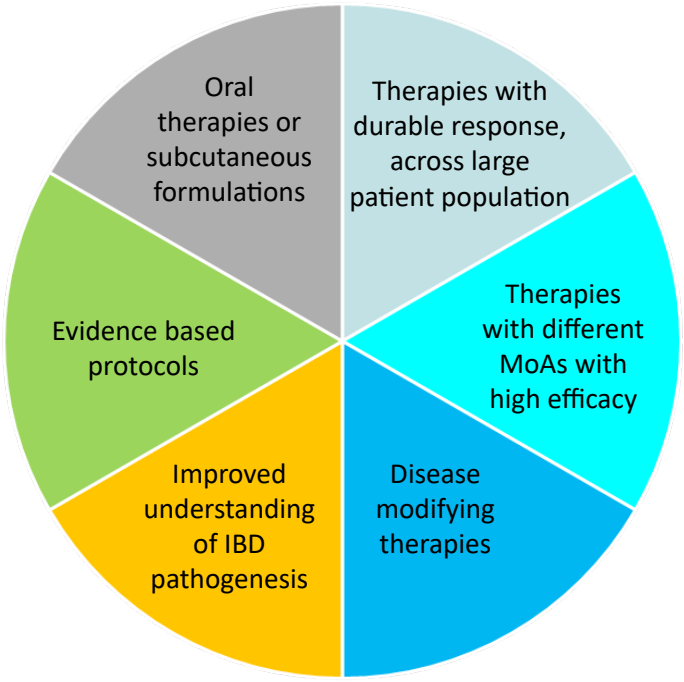
Challenges with Current SOC[13,21]

- Although several treatment options are available, slow onset of action and significant side effects are associated with most of the therapies.
- Aminosalicylates result in hypersensitivity reactions, hepatitis, agranulocytosis and impaired folic acid metabolism. Response is slow and may take 2 to 4 weeks and only 50-75% of mild to moderate UC patients respond and are able to maintain remission.
- Glucocorticoids can induce remission in 60-70% of patients but are not preferred for maintenance due to significant adverse effects with long-term use such as weight gain, osteoporosis, cataract, hyperglycemia, and emotional disturbances.
- Azathioprine and 6-mercaptopurine have a delayed onset of action. Some patients may develop pancreatitis, hepatitis, and dose dependent bone marrow suppression. Patients deficient in thiopurine methyltransferase are at increased risk of toxicity. IBD patients treated with azathioprine and 6-MP have a fourfold increased risk of developing a lymphoma.

- Patients on methotrexate may develop leukopenia, liver fibrosis and hypersensitivity pneumonitis.
- Cyclosporine is associated with nephrotoxicity, seizures, anaphylaxis, and serious opportunistic infections such a Pneumocystis carinii pneumonia.
- Anti-TNF therapies: Immunogenicity (antibodies to infliximab) may result in increased risk of infusion reactions and a decreased response to treatment, thereby necessitating a switch to another TNF inhibitor. Patients treated with anti-TNF therapies are also at increased risk of lymphomas, melanoma and opportunistic infections such as tuberculosis, atypical mycobacterial infections and invasive fungal infections such as histoplasmosis.
- Natalizumab use is associated with risk of developing progressive multifocal leukoencephalopathy (PML).

Unmet Needs[3,21,22,23]

Unmet needs in IBD



- 40-55% patients show no response to currently available biologic treatment options (primary failure), whereas 65-80% patients are unable to achieve full remission.
- Patients who respond to biologics may lose response over time due to antidrug antibodies (secondary failure), necessitating a switch.

- Patients who fail first-line biologics, usually have a suboptimal response of 20-40% to second-line agents with similar mechanism of action (e.g., anti-TNFs).
  - » Need disease modifying therapies that provide high efficacy even in later lines.
  - » Need to target other inflammatory pathways.

- Efficacious therapies that arrest or delay the onset of complications and lack risk of opportunistic infections and malignancies are needed.

- Improved understanding of IBD pathogenesis and predictive biomarkers for disease stratification to identify patients who benefit from aggressive therapy and to facilitate effective drug development.

- Identify relative positioning of individual agents or combinations in clinical practice as well as for clinical trial design purposes.

- Oral therapies or subcutaneous formulations with a less frequent dosing schedule would improve compliance and allow patients to maintain an active lifestyle.

IBD Pipeline Overview[24,25]

Ulcerative Colitis: The pipeline for ulcerative colitis is robust and diverse MoAs are under evaluation. Key MoAs include IL inhibitors, anti-TNFs, JAK inhibitors, immunomodulators, and anti-adhesion molecules. Targeted patient segments include patients not responding to conventional treatments (anti-TNF naïve patients), patients not responding to anti-TNFs and patients not responding to both anti-TNFs as well as vedolizumab. Key companies include Johnson & Johnson, Pfizer (multiple JAK inhibitors under development), AbbVie, Roche, Celgene (multiple assets), and GSK.

Development of several drugs for UC has been discontinued primarily due to lack of efficacy data. A few of the recently discontinued drugs are discussed below.

In 2016, Gilead discontinued the development of GS5745 due to insufficient evidence of treatment benefit in a Phase II/III study (NCT02520284).

Galapagos discontinued the development of GLPG1205 in 2016, based on negative efficacy results of a Phase II POC study (NCT02337608). GLPG0974 was discontinued in 2014 as it failed to show a measurable clinical difference from placebo in a Phase II POC study (NCT01829321).

AstraZeneca discontinued development of tralokinumab as add-on therapy in 2014, due to lack of significant improvement in clinical response in a Phase IIa study (NCT01482884).

Multiple assets in the pipeline are targeting UC patient sub-segments based on biomarkers, and are being developed along with companion diagnostics (e.g., Etrolizumab/ Roche, Bertilimumab/Immune Therapeutics, Cobitolimod/ InDex Pharmaceuticals). There are pipeline assets targeting a position in the treatment algorithm as a bridging therapy prior to the use of biologics (e.g., ozanimod/Celgene).

Among the assets in Phase III development, tofacitinib (Pfizer) and ozanimod (Celgene) appear to be promising, based on the results. Tofacitinib has completed three Phase III studies with positive results; data demonstrated that tofacitinib was effective as both induction and maintenance therapy in the treatment of moderate to severe UC. Phase III trial of ozanimod is underway and has demonstrated impressive efficacy in a Phase II trial. Positive Phase II data for cobitolimod (InDex), carotegrast methyl (EA Pharma), and LT-02 (NestleHealth) has been reported.

Ulcerative Colitis Pipeline (Phase II and above)

Drug	Developing Company	Selected MoA	Phase
Tofacitinib	Pfizer	JAK inhibitor	Pre-registration
Ustekinumab	Johnson & Johnson	Interleukin 12/23 antagonist	III
LT02	Nestle Health Science	Prostaglandin synthase inhibitor	III
Ozanimod	Celgene	S1P1/S1P5 receptor agonist	III
Etrolizumab	Roche	Alpha4beta7/ alphaEbeta7 integrin antagonist	III
Carotegrast methyl	EA Pharma	Alpha 4 integrin antagonist	III
Upadacitinib	AbbVie	JAK1 inhibitor	III
Alicaforsen	Atlantic Healthcare	ICAM-1 antagonist	III (planned)
Filgotinib	Gilead Sciences	JAK1 inhibitor	II/III
Risankizumab	AbbVie	Interleukin 23 antagonist	III (planned)*
Apremilast	Celgene	PDE4 inhibitor	III (planned)
Nanocort	Enceladus Pharmaceuticals	Glucocorticoid receptor agonist	II
Mongersen	Celgene	SMAD7 inhibitor	II
Cobitolimod	InDex Pharmaceuticals	Toll-like receptor 9 agonist	II
LT-0011	LTT Bio-Pharma	Superoxide dismutase stimulant	II
ILT-101	Iltoo Pharma	Interleukin 2 agonist	II
QBECO	Qu Biologics	Immunomodulator	II
SHP-647	Shire	MAdCAM Inhibitor	II
IBD98-M	Holy Stone Healthcare	Lipoxygenase inhibitor	II
LY-3074828	Eli Lilly	Interleukin 23 antagonist	II
KHK-4083	Kyowa Hakko Kirin	OX40 receptor antagonist	II
KAG-308	Kaken Pharmaceutical	EP4-selective agonist	II
INN-108	Innovate Biopharmaceuticals	Unidentified pharmacological activity	II
Etrasimod	Arena	Sphingosine 1-phosphate 1 receptor agonist	II
CyCol	Sigmoid Pharma	Immunosuppressant	II
Bertilimumab	Immune Pharmaceuticals	CC chemokine receptor 3 antagonist	II
TOP-1288	TopiVert Pharma	Kinase inhibitor	II
PTG-100	Protagonist Therapeutics	Alpha-4-beta-7 integrin-specific antagonist	II
GSK-2982772	GlaxoSmithKline	Receptor-interacting protein 1 kinase inhibitor	II
PRX-106	Protalix	Tumour necrosis factor alpha antagonist	II
E-6007	Eisai	Integrin activation inhibitor	II
LYC-30937	Lycera	ATPase Modulators	II
PF-06480605	Pfizer	TNFSF15 Blocker	II
STNM-01	Stelic Institute	Carbohydrate sulfotransferase 15 inhibitor	II
Bimekizumab	UCB	Interleukin 17A antagonist	II
PF-06651600	Pfizer	Janus kinase 3 inhibitor	II
PF-06700841	Pfizer	Janus kinase 1 inhibitor	II
DNVX-078	DeNovX	Unidentified pharmacological activity	II
Linaclotide delayed release	Ironwood Pharmaceuticals	Guanylate cyclase stimulant	II
ABX-464	Abivax	Interleukin 22 agonist	II
BI 655130	Boehringer Ingelheim	Unidentified pharmacological activity	II
YELIVA	RedHill Biopharma	SK2 selective inhibitor	II
Olamkicept	I-Mab Biopharma	Interleukin 6 antagonist	II
PF-06687234	Pfizer	Interleukin 10 agonist	II
Neihulizumab	AbGenomics	CD162 antagonist	II

(Pipeline updated as on January 24, 2018)

Note: *Risankizumab Phase II studies (M16-067 and M16-065) for UC are planned to be initiated in March 2018 and patients who respond to induction treatment in these Phase II studies will then be enrolled in a planned Phase III registrational study (M16-066) which is scheduled to be initiated in June 2018.

Crohn's Disease: The pipeline for Crohn's disease is intense and diverse MoAs are under evaluation. Key MoAs include IL inhibitors, JAK inhibitors, CCR9 receptor antagonists, immunomodulators, anti-adhesion molecules, and sphingosine receptor modulators. Targeted patient segments include patients not responding to conventional treatments (anti-TNF-naive patients), patients not responding to anti-TNFs (anti-TNF-refractory patients) and CD patients with fistulas. Key companies include AbbVie, Gilead Sciences, JNJ, Roche, Boehringer Ingelheim, Eli Lilly and Celgene.

Development of several drugs for CD has been discontinued primarily due to lack of efficacy data. Recently discontinued drugs include mongersen and AST-120.

Celgene discontinued the development of mongersen (GED-0301) in 2017 on the recommendation of the Data Monitoring Committee, based on interim futility analysis of Phase III trials REVOLVE (NCT02596893) and SUSTAIN (NCT02641392). Subsequently, Celgene decided not to initiate Phase III DEFINE trial (NCT02974322) in patients with active CD.

Ocera Therapeutics discontinued the development of AST-120 in 2014 as it failed to demonstrate significant benefit over placebo in Phase III FHAST-1 trial (NCT00321412) in CD patients with fistulas.

JNJ-64304500/Janssen is targeting fistulizing CD patients with perianal/enterocutaneous fistulas. Based on Phase II results, filgotinib (Gilead/Galapagos) appears to be promising among the assets in Phase III of clinical development.

Crohn's Disease Pipeline (Phase II and Above)

Drug	Developing Company	Selected MoA	Phase
Remestemcel-L	Mesoblast	Stem Cell Therapy	III
Vercirnon	Chemocentryx	CCR9 receptor antagonists	III
SAL-024	Valeant Pharmaceuticals	Unidentified pharmacological activity	III
Rifaximin-EIR	Valeant Pharmaceuticals	DNA-directed RNA polymerase inhibitors	III
Etrolizumab	Roche	Alpha4beta7/ alphaEbeta7 integrin antagonist	III
Myoconda	RedHill Biopharma	Anti-MAP therapy	III
Beclomethasone dipropionate	Soligenix	Steroid receptor agonists	III
Adalimumab	Boehringer Ingelheim	Tumour necrosis factor alpha antagonist	III
Filgotinib	Gilead Sciences	JAK1 inhibitor	III
L-fucose	ASDERA	Unidentified pharmacological activity	III
Guselkumab	MorphoSys	Interleukin 23 antagonist	III
Risankizumab	AbbVie	Interleukin 23 antagonist	III
SHP 647	Shire	Mucosal addressin cell adhesion molecule 1 antagonist	III Planned
Masitinib	AB Science	Tyrosine kinase inhibitor	IIb/III
Upadacitinib	AbbVie	JAK1 inhibitor	III
QBECO	Qu Biologics	Immunomodulator	IIb
Ozanimod	Celgene	S1P1/S1P5 receptor agonist	II
ILT-101	ILTOO pharma	Interleukin 2 agonist	II
Naltrexone	Jenken Biosciences	Opioid receptor antagonist	II
LY-3074828	Eli Lilly	Interleukin 23 antagonist	II
HMPL-004	Hutchison MediPharma	Tumour necrosis factor alpha antagonist	II
FFP-104	FF pharma	CD40 antagonist	II
CR-5/18	Ferring Pharmaceuticals	Interleukin 6 antagonist	II
Cenplacel-L	Celgene	Stem cell therapy	II
Bertilimumab	Immunepharma	CC chemokine receptor 3 antagonist	II
Amiselimod	Mitsubishi Tanabe Pharma	Sphingosine 1-phosphate receptor antagonist	II
Brazikumab (IV)	Allergan	Interleukin 23 antagonist	II
Alequel	Enzo Biochem	Immunosuppressant	II
Naltrexone	Cytocom	Opioid receptor antagonist	II
JNJ-64304500	Johnson & Johnson	Unidentified pharmacological activity	II
V-565	Vhsquared	Immunomodulator	II
Etrasimod	Arena Pharmaceuticals	Sphingosine 1-phosphate 1 receptor agonist	II
PRV-6527	Provention Bio	Colony stimulating factor 1 receptor antagonist	II

(Pipeline updated as on January 24, 2018)

Key Assets Under Development[1,4,5,26,27,28]

Tofacitinib is an oral JAK inhibitor that inhibits JAK1 and JAK3 and blocks the downstream effects of several pro-inflammatory cytokines such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-12, IL-15, IL-21, and IFN-γ. An sNDA filing for tofacitinib for the treatment of adult patients with moderately to severely active ulcerative colitis has been accepted by the FDA with an anticipated PDUFA action date in June 2018, based on three pivotal clinical trials. In the two completed pivotal Phase III induction trials (OCTAVE Induction 1-NCT01465763 and OCTAVE Induction 2-NCT01458951) patients were randomized to receive tofacitinib 10 mg twice daily or placebo for 8 weeks. For these trials at week 8, significantly more patients receiving tofacitinib 10 mg twice daily achieved remission ($p<0.01$ and $p<0.001$), mucosal healing ($p<0.001$ for both), and clinical response ($p<0.001$ for both) in both studies versus placebo. The third completed pivotal trial (OCTAVE Sustain-NCT01458574) evaluated oral tofacitinib 5 mg and 10 mg twice daily as a maintenance treatment in patients who previously completed and achieved clinical response in either the OCTAVE Induction 1 or OCTAVE Induction 2 studies. In this study, tofacitinib 5 and 10 mg twice daily had significantly greater effect versus placebo for the primary endpoint of remission, and secondary endpoints of mucosal healing, clinical response as well as sustained remission, sustained mucosal healing and sustained clinical response ($p<0.001$ all comparisons). A fourth pivotal trial (OCTAVE Open-NCT01470612) is currently evaluating long-term effects of tofacitinib in patients who had completed or demonstrated treatment failure in OCTAVE Sustain, or who were non-responders after completing OCTAVE Induction 1 or 2. The interim results from this ongoing study showed that there were no safety concerns and results support sustained efficacy with both tofacitinib 5 and 10 mg twice daily. JAK inhibition is a novel mechanism for IBD. Data of this oral agent is impressive and holds a lot of promise and could be a potential game changer. There is some concern about side effects that may need laboratory monitoring of lymphocytes, neutrophils, hemoglobin, liver enzymes, lipids, etc. Additionally, there is risk of lymphomas and GI perforation. Tofacitinib could open up this mechanism of action for IBD and other JAK agents in the pipeline would need to further improve the safety profile.

Filgotinib, an oral JAK1-selective inhibitor small-molecule is under evaluation in Phase III for CD and UC. Two Phase III studies for CD (NCT02914561 and NCT02914600) and two Phase III studies for UC (NCT02914522 and NCT02914535) are ongoing. Preliminary evidence points to a promising role of JAK inhibitors for the management of IBD patients.

Ustekinumab: IL-12 and IL-23 are heteromeric cytokines each consisting of two protein subunits – p35/p40 and p19/p40 subunits, respectively. They are upregulated in IBD patients. Ustekinumab is a fully human anti-p40 IgG1 antibody that can be given IV or SC. A Phase III randomized, double-blind, placebo-controlled, parallel-group, multicenter protocol to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderate to severe active UC is currently under way (NCT02407236; UNIFI). Based on physician experience with use of ustekinumab in CD, it is fairly well tolerated with no major side effects and has a dosing frequency of every 8 weeks, which is convenient for the patients. It could be a promising agent if the Phase III trials show significant efficacy.

Mongersen: TGF-β1 is a cytokine that is essential for cell homeostasis due to its anti-inflammatory properties. SMAD7 is an intracellular negative regulator of TGF-β1 signaling. High SMAD7 activity in IBD patients inhibits TGF-β1 signaling. Mongersen, an oral formulation, contains an anti-SMAD7 oligonucleotide that specifically targets SMAD7 mRNA. Mongersen facilitates RNase H-mediated degradation of SMAD7 mRNA, and inhibits the production and activity of SMAD7 thereby restoring the production of TGF-β1. Although clinical development of mongersen has been discontinued in CD, it has completed a multicenter open-label Phase II study to explore its efficacy and safety in subjects with active UC (NCT02601300) and Celgene is waiting to review the full dataset from the trial to determine next steps.

Etrolizumab is a humanized IgG1 monoclonal anti-β7 gut selective antibody that prevents the interaction of integrins α4β7 and αEβ7 with their ligands, MAdCAM-1 and E-cadherin, respectively. It is undergoing Phase III efficacy and safety trials in patients with CD (NCT02403323) and UC (NCT02118584) and for efficacy of the drug in patients with UC (NCT02163759, NCT02171429, NCT02136069, NCT02165215, and NCT02100696) and CD (NCT02394028) who are naive or refractory to, or intolerant of, TNF inhibitors. The results from these trials will determine the utility of etrolizumab in UC and CD and whether it will be used as a first- or second-line therapy.

Ozanimod is an oral selective small-molecule agonist of Sphingosine-1-Phosphate (S1P) receptor which is expressed on the surfaces of lymphocytes, and it blocks lymphocyte

egress from lymph nodes in to the systemic circulation. Binding of ozanimod to S1P1 results in internalization and degradation of the receptor and this prevents lymphocyte trafficking to the sites of inflammation. Ozanimod is in Phase III trials on induction and/or maintenance in UC (NCT02435992 and NCT02531126). For CD, results from a Phase II multicenter study for induction therapy (NCT02531113), demonstrated meaningful clinical improvement as early as Week 4 and endoscopic improvement at Week 12 in patients with moderate to severe CD. A Phase III trial to evaluate ozanimod in CD patients is expected to begin in early 2018.

Risankizumab, a monoclonal antibody, is directed against the p19 subunit of IL-23. In a Phase II trial in patients with moderate-to-severe CD, after 12 weeks, 24% (200 mg) and 37% (600 mg) of risankizumab-treated patients achieved clinical remission, compared with 15% of those receiving placebo. Endoscopic remission was achieved by 15% (200 mg) and 20% (600 mg) of patients receiving risankizumab compared to 3% of the placebo-treated patients. Currently, risankizumab is in two Phase III clinical trials for CD and an extension Phase III trial is planned to be initiated in Q1 2018. Based on preliminary data, risankizuamb appears to be promising for severe CD including fistulizing CD. For UC, two Phase II and one registrational Phase III trials are planned to be initiated in Q1 2018.

Stem cell based therapies are promising agents in the management of IBD. In IBD, regulatory T cells (Treg) are deficient or lack activity, in the background of an overactive immune system. Treg cells are highly potent immunosuppressants, and can distinguish self from non-self antigens. Therapies that enhance Treg cell production could have a potential role in the management of IBD. Mesenchymal stem cells (MSCs) are multipotent stromal cells that are present in various tissues such as bone marrow, and adipose tissue, and can promote Treg formation. Homing in and engrafting of MSCs only in the diseased bowel segments would be a novel approach in the management of IBD, thereby bypassing the serious side effects of the current treatment options while simultaneously providing a permanent cure. Migration of MSCs to the areas of injury and subsequent healing of colonic mucosa has been demonstrated in a mouse model. Cell-based therapies could be available as a combination of several cell types producing a synergistic response to heal lesions of IBD. Cenplacel-l (NCT01155362) is in Phase II clinical trial for CD and remestemcel-l (NCT00482092 and NCT00609232) is in Phase III clinical trial for CD.

Clinical Endpoints

Ulcerative Colitis: In line with the ongoing clinical trials in late phase of development, for induction phase, clinical response at 8 weeks to 12 weeks is an achievable target as some drugs may take longer to demonstrate an effect. However, response at 6 weeks, though aggressive, could be the key differentiator. The real test of clinical remission at 8 weeks should be steroid-free remission and that needs to be the target for emerging therapies to provide meaningful differentiation over the plethora of assets in the pipeline. For the maintenance phase, a key endpoint would be clinical remission coupled with an objective marker such as endoscopic mucosal healing, which is an inherent component of the current clinical trials for IBD. Given the challenges of endoscopic evaluation, a sustained decrease in fecal calprotectin could be a useful surrogate for endoscopic mucosal healing.

Crohn's Disease: The key endpoints for most of the current clinical trials in maintenance phase are clinical remission at weeks 26 and 56, coupled with endoscopic evaluation of mucosal healing. Corticosteroid-free remission at weeks 26 and 56 is another desirable endpoint.

Additional endpoints such as deep remission (clinical remission plus mucosal healing), transmural healing and histologic healing will eventually become critical and all future therapies are likely to be tested against these new strict endpoints, thereby raising the bar for future clinical development.

Conclusion

Management of IBD is challenging due to the complex and poorly understood disease pathogenesis and disease heterogeneity. The currently available treatment options are unable to control the multiple manifestations and complications of IBD. Therapies that have failed as a monotherapy may be utilized as a combination strategy to target multiple pathways in severe IBD but the efficacy of such combinations must be proven in clinical trials. An opportunity exists for efficacious and safe oral therapies that can be positioned prior to immunosuppressants/biologics. A few of the key promising oral agents include tofacitinib and ozanimod for UC and filgotinib for CD. Prognosis is poor for severe UC patients despite treatment. For patients who do not benefit from currently available treatment options, surgery is the only treatment option. Therapeutic options for severe UC to improve the quality of life are urgently needed. Currently, infliximab is approved for fistulizing CD and non-responders need surgical management.

Additional treatment options are needed for the management of fistulizing Crohn's disease. Due to significant side effects of immune suppression, therapies with steroid sparing and immunosuppressant sparing effects could be potential game changers.

Severe IBD has a significant impact on quality of life and healthcare expenditure. New biologics with path-breaking mechanisms are required to provide enhanced therapeutic value to patients who fail on the current standard of care.

Biomarkers that predict the disease course, response to therapy, risk of surgery etc. are needed for patient stratification in IBD. Such biomarkers would usher in an era of personalized medicine that would enable physicians to choose targeted therapies or therapy combinations at the time of diagnosis or flares. Close coordination among preclinical researchers, clinicians and the pharmaceutical industry is needed to further advance the remarkable progress achieved thus far towards the management of IBD.

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