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New Medical Therapies in Inflammatory Bowel Diseases In 2017

Atilla Ertan[1*] and Jamie Stewart[2]

[1]*Ertan Digestive Disease Center – Inflammatory Bowel Diseases Center, USA*

[2]*University of Texas Health McGovern Medical School (UTMMS) Gastroenterology, Hepatology and Nutrition Division and Memorial Hermann Hospital – Texas Medical Center, USA*

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Corresponding author: *Atilla Ertan, The UTMMS-MHH Ertan Digestive Disease Center and Gastroenterology Center of Excellence, 6400 Fannin, Suite 1400, Houston, Texas 77030, USA, Tel: 713-704-5928, 713-704-3450; Fax: 713-704-3485; E-mail: atilla.ertan@uth.tmc.edu*

Editorial

A significant progress has been made regarding the management of inflammatory bowel disease (IBD) over the past 38 years as shown in Table 1. Our therapeutic goals in IBD are summarized in Table 2. Only limited treatment options existed until the introduction of anti-tumor necrosis factor (anti-TNF) agents, which was a landmark in the management of these debilitating diseases. It is recommended that patients with IBD be treated with a combination of anti-TNF agents with immunomodulator therapy to increase the likelihood of steroid-free induction and mucosal healing with long–term remission. According to our own experience and general consensus, the IBD treat-to-target strategy with anti-TNFs is well-respected to change the natural history of IBD with a deep remission in a significant number of IBD patients [1-2]. Early intervention with top-down therapy may be the future direction in selected moderate to severe IBD patients with close follow-up and trough level monitoring as needed. Selected conditions for the top-down treatment with anti-TNFs are shown in Table 3.

Table 1: History of IBD Treatment

Year	Drug
1979	Sulfasalazine, Steroids
1980	Antibiotics, Azathioprine, 6-MP
1993	5-ASA
1994	Budesonide
1995	Methotrexate
1998	Infliximab
2007	Second generation anti-TNF agents
2014	New agents
2015	Biosimilars

Table 2: Therapeutic Goals in IBD

Clinical improvement
Clinical remission
Corticosteroid weaning
Maintenance of remission
Maintained tissue & transmural healing
Decrease in hospitalization & surgical interventions
Prevention of complications
Change natural course of the disease

Table 3: Selected conditions for the top-down treatment with anti-TNFs

Early age [<30 yrs] & young disease
Extensive anatomic involvement
Severe ano-rectal disease
Deep & extensive ulcerations
Stricturing and/or penetrating disease
Prior surgical intervention[s]
Family history of severe CD
Heavy smokers

Therapies with anti-TNFs have reduced relapse rates and allowed mucosal healing and, as a result, improved long-term outcomes in a substantial proportion of patients. According to a large amount of studies, anti-TNFs induced approximately 30% clinical remission and 50% clinical response in patients with moderate to severe Crohn's disease (CD) who are anti-TNF naïve or experienced. Moreover, the secondary loss of response may vary between 10 to 50% per year depending on studies and follow-up periods [3-6]. The "gut-selective" humanized, monoclonal antibody against alfa4beta7 integrin, [Vedolizumab] is now an established and FDA approved treatment option for patients with chronic ulcerative colitis (CUC) and CD either before or after anti-TNF therapy [7]. A recent study showed excellent rates of clinical remission at 12 months and mucosal healing, with no PML or other serious adverse events [8]. Recently, a fully human IgG1k monoclonal antibody that binds the p40 subunit of IL

 Corresponding author email: *atilla.ertan@uth.tmc.edu*

12/23 [Ustekinumab] was approved by the FDA for patients with moderate to severe CD [9]. In addition to initial very promising results with Ustekinumab, the phase III trials in patients with moderate to severe CD showed 34% clinical remission at week 6. Subsequent European studies with Ustekinumab revealed a relatively better clinical remission and continued to maintain clinical remission at 12 months [9-10]. Ustekinumab seems to be an attractive option with a relatively low immunogenicity, but its optimal dose has not been determined. All available biologic agents approved by the FDA are shown in Table 4.

Table 4: FDA Approved Biologic Agents in 2017

***Anti-TNF Agents*:**	
	Infliximab [Remicade]
	Adalimumab [Humira]
	Certolizumab [Cimzia]
	Golimumab [Simponi]
***Integrin Inhibitor Agents*:**	
	Natalizumab [Tysabri]
	Vedolizumab [Entyvio]
***Anti-IL-12/23 Agent*:**	
	Ustekinumab [Stelara]
***Biosimilars*:**	
	Pending

Despite the tremendous progress there are a significant number of patients who are refractory to these available biologic agents. Our understanding of the gut immune mechanism has become more sophisticated, but it still remains quite incomplete. The future looks more promising as several other novel treatment options have been identified and clinical studies are underway to determine the efficacy and safety of these therapies. Of note is the challenge of new clinical trials that have yielded positive early-phase results, but do not translate into positive late-phase study outcomes due to heterogeneity of patients and disease type, high placebo rates and other factors. Having a number of different agents available will allow us to offer the best therapies for an individual patient. The majority of the novel agents in phase of development of the treatment of IBD are summarized in Table 5. There are novel ways of reducing inflammation by targeting downstream signaling such as Janus kinase inhibitors, Tofacitinib and Filgotinib; the target lymphocyte trafficking as new anti-integrin agent, AJM300 and sphingosine1P1R, Fingolimod; and antisense oligonucleotides to transforming growth factor-beta, Mongersen. It is important to note that all above mentioned small molecules are oral agents [11-18] and extensive clinical research is pending in our Center and around the world. These agents may have huge implications and potentially less costly. We have to wait to see their late phase effectiveness and safety studies within the next 5-10 years.

Table 5: New Agents in Development for the Treatment of IBD

Name	Major Effect	Product
Etrolizumab	Anti-beta-7	GI spec. integrin antagonist
Tocilizumab	Anti-IL-6	Humanized MCA
Secukinumab	Anti-IL-17	Humanized MCA
Risankizumab	Anti-IL-23	Humanized MCA
Tofacitinib*	Anti-JAK	Immunomodulator
Fingolimod*	Sphingosine1P1R	Lymph. recept. agonist
Mongersen*	Targets SMAD7	Antisense oligonucleotide
AJM300*	Anti-alfa-4	Integrin antagonist
PPC*	Mucus	Phosphatidylcholine
*PO Agents		

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Conflicts of Interest

The authors are involved in clinical research with AbbVie, Janssen, Pfizer, Celgene, UCB, Takeda, F. Hoffman-LaRoche and Bristol-Myers Squibb. The research income stays in the Division for various other research and educational activities. There is no financial interest such as honoraria, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interests.

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