

Role of biologics and biosimilars in inflammatory bowel disease: current trends and future perspectives

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Abstract: Inflammatory bowel disease (IBD) is an idiopathic chronic inflammatory disease of the gastrointestinal system. The spectrum is of predominantly two types, namely, ulcerative colitis and Crohn's disease. The incidence of IBD has been increasing steadily since 1990, and so the number of agents used in their treatment. Biologics that are derived partly or completely from living biological sources such as animals and humans have become widely available, which provide therapeutic benefits to the IBD patients. Currently, monoclonal antibodies against tumor necrosis factor-alpha (infliximab, adalimumab, certolizumab, and golimumab), integrins (vedolizumab and natalizumab), and interleukin (IL)-12 and IL-23 antagonists (ustekinumab) are approved for use in IBD. Biosimilars of infliximab and adalimumab are also available for the treatment of IBD. This review summarizes the clinical pharmacology, studies leading to their approval, overall indications and their use in IBD, usage in pregnancy and lactation, and the adverse effects of these agents. This review also summarizes the recent advances and future perspectives specific to biologics and biosimilars in IBD.

Keywords: inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologics, biosimilars, tumor necrosis factor, integrin, interleukin, adalimumab, Humira[®], certolizumab, Cimzia[®], golimumab, Simponi[®], infliximab, Remicade[®], vedolizumab, Entyvio, natalizumab, Tysabri[®], ustekinumab, Stelara[®]

Introduction

The inflammatory bowel disease (IBD) comprises two types, namely, the ulcerative colitis (UC) and Crohn's disease (CD). They are a spectrum of chronic idiopathic autoimmune inflammatory disorders with remission and relapses, primarily affecting the gastrointestinal system.¹ It was traditionally regarded as the disease of the westernized nations, but in the 21st century, the epidemiology of IBD is fast changing.² A systematic review reports that the highest prevalence of IBD is seen in Europe (UC 505 per 1,00,000 in Norway and CD 322 per 1,00,000 in Germany) and North America (UC 286 per 1,00,000 in the USA and CD 319 per 1,00,000 in Canada).³ It also reports that the incidence has been rising since 1990 in newly industrialized countries of Africa, Asia, and South America. For example, the annual percentage change of UC and CD in Brazil was +14.9% (95% CI 10.4, 19.6) and +11.1% (95% CI 4.8, 17.8), respectively, whereas in Taiwan, it was +4.0% (95% CI 1.0, 7.1) and +4.8% (95% CI 1.8, 8.0), respectively.³ UC is characterized by confluent mucosal inflammation and erosions starting from the anal verge and extending to a variable extent.⁴ CD is a transmural inflammation of any part of the gastrointestinal tract with

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characteristic rectal sparing and skip lesions often associated with extraintestinal manifestations involving the joint, skin, or eyes.⁵ Patients often complain of diarrhea associated with rectal bleeding, abdominal tenderness, and weight loss.^{6,7}

Etiopathogenesis of IBD comprises genetic components, environmental factors, microbial flora of the gut, and immune responses.⁸ However, the main mechanism seems to be the bacterial antigens gaining access to the antigen-presenting cells through the impaired epithelial barrier. There are interleukin (IL)-12- and IL-18-mediated type 1 helper T-cell responses in CD and IL-4-mediated type 2 helper T-cell responses in UC.⁹ The balance between pro- and anti-inflammatory responses is governed by regulatory T_H 17 and T_{reg} cells as both of them serve to limit immune and inflammatory responses in the gut.⁹ The T cells further govern the release of IFN and tumor necrosis factor (TNF) that recruit macrophages, which in turn positively regulate T helper cells.⁹ Finally, the recruited inflammatory cells gain access to the site of inflammation with the help of cell adhesion molecules such as integrins.⁹

Medical therapy of IBD is complex as the disease etiology is multifactorial and the primary aim of pharmacotherapy is to dampen the generalized inflammatory response, thereby relieving symptoms.¹⁰ Off late importance has been given to mucosal healing as well.¹⁰ The specific goals of treatment in IBD include the control of acute exacerbation, maintenance of relapses, treatment of specific complications, and surveillance of malignant transformation.¹¹ Traditionally, the

drugs used in the treatment of IBD are mesalamine derivatives (mesalamine, sulfasalazine, olsalazine, and balsalazide), glucocorticoids (prednisolone, methylprednisolone, hydrocortisone, and budesonide), and immunomodulators (6-mercaptopurine, azathioprine, methotrexate, cyclosporine, and tacrolimus).¹⁰ With the advent of advances in medical science and technology, a new group of drugs emerged for various chronic disease conditions called the biologics that are derived partly or completely from living biological sources such as animals and humans.¹² The most widely used biologics are the TNF- α inhibitors such as adalimumab, certolizumab, golimumab, and infliximab, which are highly effective in the treatment of both UC and CD. The other biologic agents in IBD include the integrin receptor antagonists, namely, vedolizumab and natalizumab, and IL-12 and IL-23 antagonist, ustekinumab.¹³ This review summarizes the clinical pharmacology, overall indications and their use in IBD, usage in pregnancy and lactation, and the adverse effects of these agents and their biosimilars.

We have summarized various approved agents for current use in IBD and their recommended dosage regimen in Table 1. Some of the biologics in the Phases II and III of their development along with their mechanism of action as registered in the global clinical trial registry (www.clinicaltrials.gov) for use in IBD are summarized in Table 2. Similarly, the biosimilars in the pipeline at various stages of development for use in IBD and their status in various countries of the world are summarized in Table 3.

Table 1 Summary of biologics and biosimilars approved for treatment in IBD

Name (innovator agent/ biosimilar)	Brand name (company)	IBD indication	Route of administration	Dosage regimen	
				Induction	Maintenance
Adalimumab (innovator)	Humira® (AbbVie)	UC and CD	SC	160 mg on day 1 and 80 mg on day 15	40 mg every 4 weeks from day 29
Adalimumab-atto (biosimilar)	Amjevita™ (Amgen)				
Adalimumab-adbm (biosimilar)	Cyltezo® (Boehringer Ingelheim)				
Certolizumab pegol (innovator)	Cimzia® (Union ChimiqueBelge)	CD	SC	400 mg at weeks 0, 2, and 4	200 mg 2-weekly/400 mg 4-weekly
Golimumab (innovator)	Simponi® (Janssen Biotech)	UC	SC	200 mg at week 0 and 100 mg at week 2	100 mg every 4 weeks
Infliximab (innovator)	Remicade® (Janssen Biotech)	UC and CD	IV	5 mg/kg IV at weeks 0, 2, and 6 (in CD alone 10/kg may be given)	5 mg/kg every 8 weeks
Infliximab-dyyb (biosimilar)	Inflectra® (Celltrion)				
Infliximab-qbtx (biosimilar)	Ixifi™ (Pfizer)				
Infliximab-abda (biosimilar)	Renflexis™ (Merck)				
Vedolizumab (innovator)	Entyvio® (Takeda Pharmaceuticals)	UC and CD	IV	300 mg at weeks 0, 2, and 6	300 mg every 8 weeks
Natalizumab (innovator)	Tysabri® (Biogen)	CD	IV infusion over 1 hour	300 mg every 4 weeks	
Ustekinumab (innovator)	Stelara® (Janssen Biotech)	CD	IV for induction SC for maintenance	≤55 kg =260 mg; 56–85 kg =390 mg; >85 kg =520 mg	90 mg every 8 weeks

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IV, intravenous; SC, subcutaneous; UC, ulcerative colitis.

Table 2 Biologics in the pipeline and their current status

Serial number	Agent name	Mechanism of action	Current status
1	Etrolizumab	α 4 β 7 integrin antagonist	Phase III (UC and Crohn's disease)
2	Risankizumab	IL-23 inhibitor	Phase III (Crohn's disease)
3	Bertilimumab	Chemokine CCL11 inhibitor	Phase II (Crohn's disease and UC)
4	Bimekizumab	IL-17 inhibitor	Phase II (UC)
5	E6011	Chemokine CX3CL1 inhibitor	Phase I/II (Crohn's disease)
6	FFP104	CD40 antigen inhibitor	Phase II (UC)
7	Foralumab	CD3 antigen inhibitor	Phase II (Crohn's disease)
8	KHK4083	OX40 receptor antagonist	Phase II (UC)
9	Mirikizumab	IL-23 inhibitor	Phase II (Crohn's disease and UC)
10	PF04236921	IL-6 inhibitor	Phase II (Crohn's disease)
11	SHP 647	α 4 β 7 integrin antagonist	Phase II (Crohn's disease) and Phase III (UC)

Abbreviations: CCL, C–C motif chemokine ligand; CD, cluster of differentiation; CX3CL, C-X3-C motif ligand; IL, interleukin; UC, ulcerative colitis.

Table 3 Biosimilars in the pipeline and their current status

Company	Name of the agent	Status
Biosimilars of adalimumab		
Coherus Biosciences	CHS1420	Phase III (plaque psoriasis)
Fresenius Kabi	MSB11022	Preregistration (plaque psoriasis) and Phase III (UC, CD, and others)
Fujifilm Kyowa Kirin Biologics	FKB327	Preregistration (RA). Submitted to EMA in May 2017
LG Chem	LBAL	Phase III (RA)
Momenta Pharmaceuticals	M923	Phase III (RA and plaque psoriasis)
Oncobiologics	ONS3010	Phase III (plaque psoriasis)
Pfizer	PF06410293	Phase III (RA)
Prestige BioPharma	PBP1502	Preclinical (RA)
Merck & Samsung Bioepis	Imraldi	Registered (UC, CD, and others), EMA approved on June 23, 2016
Sandoz	GP2017	Preregistration (UC, CD, and others). Submitted to EMA in June 2017
Reliance Life Sciences	Adfrar	Launched in India for UC, RA, plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis in January 2016
Zydus Cadila	Exemptia	Launched in India for UC, CD, RA, juvenile RA, plaque psoriasis, psoriatic arthritis and ankylosing spondylitis, and hidradenitis suppurativa in December 2014
Biosimilars of infliximab		
Amgen	ABP710	Phase III (RA) and Phase I (UC, CD, and others)
Epirus Biopharmaceuticals	Infimab	Launched in India for RA in September 2014
MabTech/Sorrento Therapeutics	ST1002	Phase III (RA)
Nichi-Iko Pharmaceutical	NI071	Launched in Japan in September 2017. US Phase III trial in RA ongoing
Nippon Kayaku	Infliximab BS	Launched in Japan for UC, CD, RA, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis in November 2014
Reliance Life Sciences	BOW015	Launched in India for RA in December 2014
Sandoz/Pfizer	PF-06438179	Registered for UC, CD, RA, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis. Submitted to FDA in May 2017 and EMA in June 2017

Abbreviations: CD, Crohn's disease; EMA, European Medicines Agency; FDA, US Food and Drug Administration; RA, rheumatoid arthritis; UC, ulcerative colitis.

Review methodology

Studies were searched in electronic databases according to article titles, abstract contents, and relevance in the field of biologics and biosimilars in IBD. The database used in this review included PubMed, MEDLINE, Embase, Google Scholar, Scopus, ClinicalTrials.gov, US Food and Drug Administration (FDA), European Medicines Agency, and Cochrane databases. We also manually searched references to identify additional relevant studies. The “Keywords” above were used to locate relevant journal articles. Here, we provide a comprehensive narrative literature review of the role

of biologics and biosimilars in IBD as well as discuss and highlight the clinical pharmacology, overall indications and their use in IBD, usage in pregnancy and lactation, and the adverse effects of these agents and their biosimilars.

Discussion

TNF- α inhibitors

Adalimumab (Humira®)

Mechanism of action and indications

Adalimumab is the first fully human monoclonal antibody (MAb) that was approved by the FDA in 2002 for rheumatoid

arthritis (RA).¹⁴ It was initially named as D2E7 marketed by Abbott Laboratories (Chicago, IL, USA) and currently owned by AbbVie (Chicago, IL, USA).¹⁵ The name Humira stands for human MAb in RA. It is a recombinant human immunoglobulin (Ig)-G1 MAb created using the phage display technology.¹⁶ It inhibits TNF- α , which is a cytokine involved in normal inflammatory and immunological responses, and it inhibits its interaction with p55 and p75 cell surface TNF-alpha receptors. It does not have action on TNF-beta.¹⁶ It also causes changes in the levels of adhesion molecules that are responsible for leukocyte migration. Adalimumab is indicated for use in moderate-to-severe RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, moderate-to-severe CD and UC with inadequate response to conventional therapy, moderate-to-severe chronic plaque psoriasis, hidradenitis suppurativa, uveitis, and Behcet's disease.¹⁷ It is available as a sterile, preservative-free solution in the pen of 80 and 40 mg, the prefilled syringes of 80, 40, 20, and 10 mg, and a single use institutional vial of 40 mg, which are to be given subcutaneously (SC).¹⁴ The bioavailability of the agent is 64% with a half-life of ~2 weeks following linear kinetics of elimination.¹⁴

Dosing in CD

The recommended dose regimen for use in CD in adults is 160 mg on day 1, 80 mg on day 15, and a maintenance dose of 40 mg every alternate week starting at day 29 for not >1 year.¹⁴ The evidence for the use of adalimumab in CD stems from three main clinical trials, namely, CLASSIC (clinical assessment of adalimumab safety and efficacy studied as induction therapy in CD), CHARM (Crohn's trial of the fully human antibody adalimumab for remission maintenance), and GAIN (gauging adalimumab efficacy in infliximab nonresponders).¹⁸ The CLASSIC-I trial is a dose-ranging randomized controlled trial (RCT) with 299 moderate-to-severe CD patients naive to TNF- α inhibitor therapy who were randomized to receive adalimumab (40/20, 80/40, or 160/80 mg) or placebo at weeks 0 and 2. The remission rates (primary endpoint) defined as CD activity index (CDAI) <150 at week 4 were 18% ($P=0.36$), 24% ($P=0.06$), and 36% ($P=0.001$), respectively, and 12% in the placebo group.¹⁹ A total of 275 patients from CLASSIC-I entered the CLASSIC-II RCT where all patients received 40 mg adalimumab at weeks 4 and 6 of CLASSIC-I. A total of 55 patients who were at remission during both the dosing of CLASSIC-II were re-randomized into adalimumab 40 mg every other week (EOW), weekly, or placebo through 56 weeks. The rates of remission were 79%, 83%, and 44%, respectively. The remaining 204 patients who were not on

remission while entering CLASSIC-II were subjected to adalimumab 40 mg EOW open label with the option to increase the dose to 40 mg weekly in case of a nonresponse or flare, and at 56 weeks, 46% were at remission.²⁰ In CHARM trial, ~40% of the 499 patients with moderate-to-severe CD had clinical remission at 26 and 52 weeks suggesting long-term efficacy.²¹ In case of the GAIN trial conducted among patients who had either lost response or were intolerant to infliximab, patients were randomized to receive either adalimumab induction therapy or placebo and 21% achieved remission while approximately half demonstrated clinical benefit.²² A study done by Cote-Daigneault et al has shown the evidence for efficacy in fistulizing CD and in achieving mucosal healing in CD unlike certolizumab and in UC.²³ Adalimumab is indicated in pediatric CD. IMAGINE 1 and IMAGINE 2 are the two trials showing the evidence of efficacy and safety of adalimumab in pediatric population. The IMAGINE 1 trial was conducted in 192 children with CD not responding to conventional therapy. After an open-label induction therapy with SC adalimumab at weeks 0 and 2, 188 children at week 4 were randomized to receive double-blind maintenance therapy with either high dose (40 or 20 mg for body weight ≥ 40 or <40 kg; $n=93$) or low dose (20 or 10 mg for body weight ≥ 40 or <40 kg; $n=95$) of adalimumab alternate week for 48 weeks. At week 26, 63 (33.5%) of the 152 patients who completed 26 weeks were in clinical remission. High- and low-dose groups (36/93 [38.7%] versus 27/95 [28.4%]) showed no significant difference ($P=0.075$).²⁴ Patients who completed IMAGINE 1 were eligible to enroll in IMAGINE 2. A total of 100 children participated for up to 240 weeks. A total of 41% and 48% achieved remission (pediatric CDAI ≤ 10) and response (pediatric CDAI decrease ≥ 15 from IMAGINE 1 baseline) at 240 weeks, respectively. The safety profile was similar to those in adult CD trials with adalimumab and IMAGINE 1 trial.²⁵

Dosing in UC

The recommended dose regimen for UC is 160 mg SC on day 1 (or 80 mg on two consecutive days) followed by a dose of 80 mg on day 15 and, 2 weeks later (day 29), continues with a dose of 40 mg EOW.¹⁴ A meta-analysis of three RCTs reported that adalimumab 160/80 mg was more efficacious when compared with placebo for the induction of clinical remission (relative risk [RR] 1.62, 95% CI 1.15, 2.29) and clinical response (RR 1.37, 95% CI 1.19, 1.59). Similarly, adalimumab 40 mg EOW was more effective than placebo in maintaining clinical remission (RR 2.38, 95% CI 1.57, 3.59) and clinical response (RR 1.69, 95% CI 1.29, 2.21).²⁶

Side effects

The most serious adverse reactions encountered in clinical trials were serious infections due to immunosuppression, malignancies, and demyelinating neurological disease.¹⁴ Serious infections include pneumonia, septic arthritis, prosthetic/postsurgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis at an incidence rate of 0.04/patient-year (PY) when compared with 0.02/PY in the placebo arm.¹⁴ The most frequently encountered malignancies other than lymphoma and nonmelanoma skin cancers (NMSC) include breast cancer, colon cancer, lung cancer, melanoma, and prostate cancer at a rate of 0.6 (95% CI 0.3, 1.0)/100 PYs in 3853 adalimumab (Humira)-treated patients for a median duration of 5.5 months versus 0.4 (95% CI 0.2, 1.0)/100 PYs in 2183 controls for a medical duration of 3.9 months. However, based on a recent pooled estimate from 23,458 patients treated with adalimumab on comparison with age- and sex-matched populations, the observed number of malignancies in each disease population was reported to be similar to the expected number in the reference population.²⁷ The rates for lymphomas (0.1/100 PYs) and NMSC (0.2/100 PYs) were very low.²⁷ Some of the common side effects include injection site pain and reaction, hypersensitivity, and gastrointestinal disturbances. In contrast, rare adverse effects result in the reactivation of latent tuberculosis, autoantibody production leading to a lupus-like syndrome, blood dyscrasias, congestive cardiac failure, and interstitial lung diseases.²⁸ Humira comes under category B for its use in pregnancy as animal studies have proven to be safe but controlled studies in humans are lacking.¹⁴ Its use in lactation is based on the benefit–risk ratio as decided by the doctor because it is unknown if adalimumab is excreted in breast milk or absorbed systemically.¹⁴ Its use in children has not been evaluated, and it should be used judiciously in geriatric population as there is already an increased risk of infections and malignancies in elderly.¹⁴

Certolizumab pegol (Cimzia®)

Mechanism of action and indications

Certolizumab pegol is a monoclonal antibody (MAb) manufactured by Union Chimique Belge (UCB) Pharmaceuticals (Brussels, Belgium) and subsequently approved by the FDA in April 2008 for CD.²⁹ Certolizumab pegol is a recombinant antigen-binding fragment (Fab) antibody against TNF- α , which is conjugated to 40 kDa polyethylene glycol, thereby enhancing the bioavailability, drug stability, and plasma half-life.³⁰ The molecular mass of the Fab antibody frag-

ment alone is 47.8 kDa. It is the only crystallizable fragment (Fc)-free PEGylated TNF- α inhibitor, so it does not fix complement or cause antibody-dependent cell-mediated cytotoxicity.³⁰ The FDA-approved indications are moderate-to-severely active CD or RA, active psoriatic arthropathy, and ankylosing spondylitis.²⁹ It is available as powdered reconstitution form, which contains 200 mg of sterile, white, lyophilized powder, and as prefilled syringe, which is a single-use, 1 mL prefilled glass syringe with a fixed 25 G 1/2 in thin wall needle, providing a dose of 200 mg/1 mL.²⁹ Upon single SC dose or intravenous (IV) dose, there was a predictable dose-related plasma concentration. There is a linear relationship between the dose given and the maximum plasma concentration (C_{max}) and the area under the curve over time. Though metabolism studies have not been performed in humans, animal studies suggest that polyethylene glycol polymers are excreted unchanged in urine and the terminal plasma half-life is ~14 days.²⁹

Dosing in CD

The recommended regimen in CD is the SC administration of 400 mg initially and at weeks 2 and 4. If there is response, 400 mg SC is given once in every 4 weeks for maintenance.²⁹ The efficacy of certolizumab is proven by the PRECiSE-1 study, which was an RCT done at 171 sites where 331 patients with moderate-to-severe CD were randomized to receive 400 mg certolizumab and 328 patients received placebo. At week 6, clinical response (100-point reduction in CDAI score) was 35% when compared with 27% in the placebo group ($P=0.02$). At week 26, the clinical remission (CDAI ≤ 150 points) was 29% in the certolizumab group versus 18% in the placebo group ($P<0.05$).³¹ Fistula closure rates were same at short term and long term with certolizumab when compared with placebo.³¹ PRECiSE-2 study evaluated patients who had clinical response with certolizumab at week 6 and were randomized to receive certolizumab 400 mg ($n=216$) or placebo ($n=212$) every 4 weeks over weeks 8–24 for maintenance therapy. The remission rates were 48% and 29%, respectively, at week 26.³² Patients completing PRECiSE-1 and -2 received open-label certolizumab 400 mg every 4 weeks for 7 years in PRECiSE-3 trial, and the clinical remission rate was $\geq 68\%$ at each year based on observed cases.³³ Patients who relapsed in PRECiSE-1 and PRECiSE-2 received certolizumab re-induction followed by 400 mg every 4 weeks maintenance for 360 weeks and the overall remission rates at weeks 52, 156, and 362 were 64%, 64%, and 85%, respectively, based on observed cases.³⁴ WELCOME trial with 539 patients either intolerant or poor

responders to infliximab, which was given open-label induction, showed 62% response rates and 39.3% remission rates, despite being a difficult-to-treat group.³⁵

Side effects

The common adverse effects include injection site reactions and infections mainly of the respiratory tract and urinary tract; some of which can be very severe due to immune modulation. Similar to the other drugs in the class, reactivation of tuberculosis, hepatitis B, and malignancies have been reported, but hypersensitivity reactions are rare.³⁶ Some of the other rare adverse effects reported in controlled trials are blood dyscrasias, optic neuritis, hepatitis, alopecia totalis, anxiety, bipolar disorder, suicidal tendencies, nephrotic syndrome, renal failure, menstrual disorders, and dermatitis.²⁹ Certolizumab is a category B drug in pregnancy. Animal studies have proven no harm, but controlled human studies are not done.²⁹ Because of its large molecular weight, it neither crosses the placental barrier nor gets secreted in the milk. Even if present in milk, the biologics would get degraded in the intestinal tract, but the local effect in the mucosa is not known.²⁹ It is not recommended in pediatric use, and caution should be exercised regarding its use in elderly due to the risk of malignancy and opportunistic infections.²⁹

Golimumab (Simponi®)

Mechanism of action and indications

Golimumab is yet another fully human IgG1 kappa MAb first approved in 2009 by FDA for the treatment of RA. It was developed and marketed by Janssen Biotech, Inc (Horsham, PA, USA).³⁷ It was isolated from a hybridoma clone produced by transgenic mice, which were immunized with human TNF- α . The commercial product, which is produced in a recombinant cell line culture, binds to the soluble and transmembrane forms of TNF- α and acts as an inhibitor.³⁸ This agent has been approved for use in moderately to severely active RA, psoriatic arthritis, ankylosing spondylitis, and moderately to severely active UC.³⁹ The European Medicines Agency has further approved it for JIA in combination with methotrexate for children >40 kg body weight.⁴⁰ It is available as prefilled glass syringes (27G 1/2 in) providing either 50 mg/0.5 mL or 100 mg/1 mL of solution.³⁹ Upon SC administration, the bioavailability was 53% and gets primarily distributed in the circulatory system with limited extravascular distribution.³⁹ The terminal plasma half-life is ~2 weeks, and the metabolic pathway is not known.³⁹

Dosing in UC

The recommended dosage regimen for UC is 200 mg SC at week 0 followed by 100 mg at week 2 and maintenance therapy 100 mg once every 4 weeks.³⁹ In the PURSUIT-SC, a Phase II/III multicenter, placebo-controlled, induction RCT, anti-TNF-naïve patients with moderately to severely active UC were assigned randomly to receive placebo, or two golimumab regimens were given 2 weeks apart (200 mg followed by 100 mg or 400 mg followed by 200 mg). At week 6, both the golimumab regimens induced significant clinical response (30 versus 51 and 55%, both $P < 0.0001$) and clinical remission (6 versus 18 and 18%, both $P < 0.0001$).⁴¹ In the PURSUIT-M RCT, patients in clinical response were randomized to receive either placebo or two regimens of golimumab (50 or 100 mg every 4 weeks) for 52 weeks. At week 54, patients on golimumab achieved more continuous clinical response (31 versus 47 and 50%, $P = 0.01$ and < 0.001) and remission (16 versus 23 and 28%, $P = 0.12$ and 0.004).⁴²

Side effects

The common adverse events noted were infections and injection site reactions, which were similar in number to the placebo arm.⁴³ Golimumab as the other TNF- α inhibitors can rarely cause severe infections, opportunistic infection, reactivation of tuberculosis, malignancies, heart failure, autoimmunity, and demyelinating disorders.⁴³ It belongs to a category B drug in pregnancy as animal studies have shown no harm, but controlled human studies are lacking.³⁹ The information regarding secretion into human milk, the effect on breastfed infant, or lactation is not known.³⁹ Efficacy in children is not well established with one study on pediatric juvenile idiopathic arthritis demonstrating no efficacy but similar rate of adverse events when compared with adults.⁴⁴ Caution should be exerted while using in elderly due to increased risk of infections and malignancy with increasing age.³⁹

Infliximab (Remicade®)

Mechanism of action and indications

Infliximab is an engineered chimeric IgG1 MAb and created by combining mouse and human TNF that has increased the specificity and affinity to the TNF- α receptor. In 1988 at New York University's School of Medicine, this MAb against TNF has been discovered.⁴⁵ Remicade was the first TNF- α blocking agent approved by the FDA, initially for treating CD, in 1998. This is produced when the variable regions of a murine antibody (25%) are fused with the constant regions of a human antibody (75%) at the hinge region using genetic

engineering.⁴⁶ It is indicated for use in CD (pediatric and adult), UC (pediatric and adult), RA, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.⁴⁷ The agent is supplied as a sterile, white, lyophilized 100 mg powder for IV infusion in a 20 mL vial. Each single-dose vial contains infliximab (100 mg), dibasic sodium phosphate dihydrate (6.1 mg), monobasic sodium phosphate, monohydrate (2.2 mg), polysorbate 80 (0.5 mg), and sucrose (500 mg) and no preservatives.⁴⁷ In adults, single IV infusion of 3–20 mg/kg showed a linear relationship between the dose that was administered and the maximum serum concentration.⁴⁷ It acts by inhibiting the binding of TNF- α with its receptors. This results in the induction of proinflammatory cytokines such as IL-1 and IL-6. This causes an enhancement of leukocyte migration by increasing endothelial layer permeability and the expression of adhesion molecules by endothelial cells and leukocytes and results in the activation of neutrophil and eosinophil functional activities and the induction of acute-phase reactants and other liver proteins, as well as tissue-degrading enzymes produced by synoviocytes and/or chondrocytes.⁴⁷ Infliximab does not neutralize TNF- β , and the median terminal half-life of infliximab is 7.7–9.5 days.⁴⁷

Dosing in CD and UC

The recommended dose is 5 mg/kg at 0, 2, and 6 weeks, which is followed by the maintenance regimen of 5 mg/kg every 8 weeks after that for the treatment of CD or UC in both adults and children.⁴⁷ For adult patients with CD who respond and then lose their response, consideration may be given to treatment with 10 mg/kg.⁴⁷ In the Targan study, 65% of patients with active CD had a clinical response at weeks to doses 5, 10, and 20 mg/kg versus 17% for placebo with no dose–response effect. The remission rates were 33 versus 4%. In the ACCENT-1 trial with 573 patients and dose of 5 mg/kg, 58% achieved a clinical response and 28% achieved remission at week 2. It was also found that three loading doses at weeks 0, 2, and 6 had significantly higher response rate at week 10 when compared with a single infusion at week 0 (69 versus 59%, $P=0.035$).⁴⁸ In the ACCENT-1 maintenance trial, all patients received an induction dose of 5 mg/kg infliximab IV and then they were randomized to receive placebo or infliximab two doses (5 or 10 mg/kg) for 1 year once every 8 weeks. The proportion of patients who had remission at 2 weeks and continued to be in remission at 30 weeks was 21%, 44%, and 45%.⁴⁹ The evidence for the usefulness of infliximab in UC was mainly by two RCTs namely ACT-1 and ACT-2.⁵⁰ In ACT-1, 69% and 62% of patients who received infliximab 5 and 10 mg/kg, respectively, at weeks 0, 2, and 6,

had desired clinical response at week 8, in comparison to 37% of those receiving placebo ($P<0.002$ for both comparisons).⁵¹ In ACT-2, 65% and 69% of patients who received infliximab 5 and 10 mg/kg, respectively, achieved a clinical response at week 8, when compared with 26% of those receiving placebo ($P<0.001$ for both comparisons).⁵² A study done by Cote-Daigneault et al has shown the evidence for efficacy in fistulizing CD and achieving mucosal healing in CD unlike certolizumab and in UC.²³

Side effects

The main adverse effect includes the development of antibodies that may lead to the loss of response, infusion reactions, and serum sickness-like reactions.⁵⁰ Problems associated with immunomodulation as easy susceptibility to infections, reactivation of tuberculosis, certain malignancies, and opportunistic infections are similar as in other TNF- α inhibitors.⁵⁰ There have also been reports of hepatitis, CNS vasculitis, and hematological derangements that have been reported with the use of infliximab.⁴⁷ This agent belongs to category B in pregnancy, and its effect on a lactating infant or its presence in human milk is not known. However, as in other IgG antibodies, it is present in the placenta and the new born may face difficulties with immune suppression.⁴⁷ Its safety and efficacy has been well established in children older than 6 years for use in UC and CD. Use of infliximab in elderly is advised with caution due to an otherwise increased risk of malignancy and infections.⁴⁷

Integrin receptor antagonists

Vedolizumab (Entyvio)

Mechanism of action and indications

Vedolizumab is a humanized MAb, which was approved by the FDA in July 2014 after a priority review. It is essentially an integrin $\alpha 4\beta 7$ receptor antagonist, which blocks the binding of Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1) to the integrin receptor, thereby producing anti-inflammatory action by preventing T-cell adhesion and infiltration.⁵³ Since integrin $\alpha 4\beta 7$ receptors are found more in the gut epithelium, vedolizumab is indicated currently for moderate-to-severe CD and UC.⁵⁴ Clinical trials in pediatric population are also ongoing for UC and CD since November 2017.^{55,56} The agent is available in the market as 300 mg of lyophilized cake in a single-dose 20 mL vial for reconstitution.⁵⁷ The plasma half-life is ~25 days. The drug undergoes a rapid, saturable, and nonlinear elimination at low concentration and a slower, linear, and nonspecific elimination at therapeutic or higher concentration.⁵⁷

Dosing in CD and UC

Vedolizumab is given as a 300 mg IV infusion at 0, 2, and 6 weeks and then every 8 weeks after that, for both UC and CD. If no improvement is noticed, the drug is withdrawn.⁵⁷ In the GEMINI I induction therapy trial, 374 UC patients received either vedolizumab 300 mg (n=224) or only placebo (n=149) IV at weeks 0 and 2. The rates of clinical response (47% versus 26%) and clinical remission (17% versus 5%) at week 6 were statistically significant ($P<0.001$ for both).⁵⁸ Those with clinical response at week 6 were randomized to receive vedolizumab 300 mg IV every 4 weeks, or every 8 weeks or placebo for 52 weeks. The rates of clinical remission were 45% for the vedolizumab 4-weekly group, 52% for the vedolizumab 8-weekly group, and 16% for the placebo group ($P<0.001$).⁵⁸ The CD trials included the GEMINI II and GEMINI III, which showed mixed results of efficacy.⁵⁹ At week 6 in GEMINI II RCT, clinical remission was seen in 14.5% who received vedolizumab and 6.8% who received placebo and clinical response was seen in 31.4% who received vedolizumab and 25.7% who received placebo ($P=0.23$). Among patients who responded to induction therapy, 39.0% and 36.4% of those who received vedolizumab 8- and 4-weekly, respectively, were in clinical remission at week 52% versus 21.6% of those who received placebo ($P<0.001$ and 0.004, respectively, for the two vedolizumab groups versus placebo).⁶⁰ GEMINI III trial was conducted in patients with TNF antagonist failure, and the remission rates at week 10 were 26.6% in vedolizumab group versus 12.1% in placebo group (nominal $P=0.001$). The response rates at week 6 were 39.2% versus 22.3%, respectively (nominal $P=0.001$).⁶¹

Side effects

The most common adverse reactions seen with vedolizumab are infusion reactions and infections due to immunomodulation.⁵⁴ Safety data showed a similar adverse reaction rate to placebo.⁵⁵ Malignancies were reported in 0.4% of those treated with vedolizumab, but the long-term exposure was limited.⁵⁷ A potential for immunogenicity was found with 13% of the patients treated showing antivedolizumab antibodies at 24 weeks.⁵⁷ Safety and effectiveness in the pediatric population have not been established, while in geriatric population, no difference in safety and efficacy has been observed compared to the adult population.⁵⁷ Till date, no studies have been done with this drug in pregnant women and it is rated a category B drug.⁵⁷ No fetal harm was observed in studies done on rabbits and monkeys even at 20 times the recommended human dosage.⁵⁷ Animal studies detected vedolizumab in the milk of lactating monkeys, but it is still

unknown whether it can be generalized to humans. Hence, the drug should be used with caution in nursing mothers.⁵⁷

Natalizumab (Tysabri®)

Mechanism of action and indications

Natalizumab, the first among its drug family, is a humanized IgG4 MAb against the $\alpha 4$ chains of integrins and behaves as a selective adhesion molecule antagonist inhibiting the translocation of leukocytes across blood vessel membranes approved by FDA in year 2004.⁶² The agent is nonspecific to antagonize $\alpha 4\beta 1$ integrin (very late antigen [VLA]-4) and the $\alpha 4\beta 7$ integrin (lymphocyte Peyer's patch adhesion molecule [LPAM]-1).⁶³ VLA-4 is involved in regulating the trafficking of mononuclear leukocytes from the peripheral circulation to sites of inflammation, and this mechanism is tapped to treat multiple sclerosis.⁶³ The only other indication of use is in CD, and the mechanism of action is similar to vedolizumab.⁶³ It is available as 300 mg natalizumab in 15 mL (20 mg/mL) IV solution in a sterile, single-use vial with no preservatives.⁶⁴ Upon administration, the number of circulating leukocytes of all types is increased except the absolute neutrophil count.⁶⁴ The mean half-life was ~10–11 days, and a steady state concentration after a 4-weekly dose was achieved at 24 weeks.⁶⁴

Dosing in CD

The recommended dose in CD is 300 mg IV infusion over 1 hour 4-weekly, and the agent was discontinued at 12 weeks if no response. It should not be used with concomitant immunosuppressants (eg, 6-mercaptopurine, azathioprine, cyclosporine, and methotrexate) or concomitant inhibitors of TNF- α .⁶⁴ ENACT-1 trial with 905 adult patients with moderate-to-severe disease across 142 global centers proved the efficacy of natalizumab in CD. Patients randomly received 300 mg natalizumab 4-weekly (n=721) or placebo (n=181), and clinical response at week 10 was 56% versus 49% ($P=0.05$), respectively, while remission was seen in 37% versus 30% ($P=0.12$), respectively.⁶⁵ Those with clinical response at week 10 underwent the maintenance phase for 52 weeks, and the sustained response was 61% versus 28% in placebo arm ($P<0.0001$).⁶⁵ The next landmark trial was the ENCORE trial where 509 adult patients were randomized to receive natalizumab or placebo. At week 12, the clinical response rate was 60% versus 44% ($P=0.001$) and the remission rates were 38% versus 25% ($P=0.001$), respectively.⁶⁶

Side effects

The most common adverse effects encountered are a headache, abdominal pain, joint pain, colitis including worsen-

ing of CD, influenza syndrome, infection, gastrointestinal disturbances, fatigue, pharyngitis, and infusion reaction.⁶⁷ The serious adverse reactions as listed by the FDA include progressive multifocal leukoencephalopathy due to infection with John Cunningham virus, Herpes infections, hepatotoxicity, hypersensitivity, antibody formation, and immunosuppression.⁶⁴ Natalizumab is a category B drug in pregnancy with detection in human milk as well, though its effect on a breastfed infant is unknown.⁶⁴ It is not recommended for use in children, and sufficient data are not available to identify difference in responses among elderly.⁶⁴

IL-12 and IL-23 antagonist

Ustekinumab (Stelara®)

Mechanism of action and indications

Ustekinumab is a human IgG1κ MAb against the p40 subunit of IL-12 and IL-23 cytokines. It was first approved in Canada in 2008 for the treatment of plaque psoriasis in adult patients and later in 2009 by FDA.⁶⁸ IL-12 and IL-23 play an important role in the activation and differentiation of natural killer cells and CD4⁺ T lymphocytes. Hence, blocking their action helps in chronic inflammatory conditions such as plaque psoriasis, psoriatic arthritis, and CD.⁶⁹ It is available as IV 130 mg/26 mL (5 mg/mL) solution in a single-dose vial and SC 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe or 45 mg/0.5 mL in a single-dose vial.⁷⁰ Treatment has been shown to decrease the expression of mRNA of IL-12 and IL-23. Steady-state concentrations are achieved by week 28, and the mean elimination plasma half-life ranges from 15 to 45.5 days.⁷⁰

Dosing in CD

The recommended dosage regimen is a single IV dose, which is weight based (260 mg if weight is ≤55 kg, 390 mg if weight is >55–85 kg, and 520 mg if weight is >85 kg) followed by a maintenance dose of SC 90 mg administered 8-weekly.⁷⁰

The safety and efficacy of ustekinumab were evaluated in three randomized double-blind placebo-controlled clinical namely UNITI-1 and UNITI-2 for induction therapy and IM-UNITI for maintenance therapy.⁶⁸ In the UNITI-1 trial (n=741), the clinical response rate at week 6 was 33.7% and 21.5% ($P<0.01$) and the remission rate at week 8 was 20.9% and 7.3% ($P<0.001$) in the ustekinumab and placebo arms, respectively.⁷¹ In the UNITI-2 trial (n=628), the clinical response rate at week 6 was 55.5% and 28.7% ($P<0.001$) and the remission rate at week 8 was 40.2% and 19.6% ($P<0.001$) in the ustekinumab and placebo arms, respectively.⁷¹ IM-UNITI trial testing ustekinumab 90 mg SC maintenance

8-weekly and 12-weekly, 53.1% and 48.8%, respectively, were in clinical remission at week 44 when compared with 35.9% receiving placebo ($P=0.005$ and 0.04 , respectively).⁷²

Side effects

The most common adverse effects encountered were nasopharyngitis, injection site erythema, and vulvovaginal candidiasis besides other infections. Clinically significant and serious infections included anal abscess, gastroenteritis, and pneumonia.⁶⁹ A total of 0.2% of ustekinumab-treated patients and placebo-treated patients developed NMSC, whereas 0.2% of the ustekinumab-treated patients developed other cancers, which were none in the placebo group.⁷⁰ Approximately 6% of the patients in the psoriasis studies developed antiustekinumab antibodies whereas only 3% of the patients in the CD studies did so.⁷⁰ During the postmarketing phase, more incidents of hypersensitivity reactions such as anaphylaxis, angioedema, rashes, and urticaria have been reported.⁷⁰ Human data on effects in pregnancy are not well established due to the lack of data. Animal studies have not shown any adverse developmental effects on the fetus even at doses >100 times the recommended human dose.⁷⁰ Though studies in lactating monkeys have shown the presence of ustekinumab in the milk, no presence of the drug in human milk has been found.⁷⁰ Safety and efficacy have not been established in the pediatric population, and there are not enough data among elderly to determine any difference in the safety and efficacy as compared to the adult population.⁷⁰

Biosimilars in IBD

The treatment of IBD imposes a tremendous economic burden on the health care system as the cost utilization has seen a significant shift from hospitalization to medication, especially the biologics.⁷³ With the patent period of many of these drugs coming to an end, it is possible to produce a similar biologics that could be marketed at a much lower price than the innovator biologics, some of which are already available in developing countries such as India and developed countries such as South Korea.⁷⁴ These drugs are called as biosimilars, which may be defined as a biologic product that is highly like the reference biologic with no clinically meaningful differences in clinical safety or efficacy.⁷⁵ Biologics are a highly complex protein or other substances derived from a biological source, and hence, complete reproducibility of reference biologics is not possible. Thus, minor differences in clinically inactive components are permissible.⁷⁶ The current biosimilars approved for use in IBD belong to TNF-α inhibitors namely

adalimumab and infliximab.⁷⁷ Biosimilars of adalimumab include adalimumab-atto (Amjevita™) by Amgen Pharmaceuticals (Thousand Oaks, CA, USA) and adalimumab-dm (Cyltezo®) by Boehringer Ingelheim. Amjevita was created using recombinant DNA technology in a mammalian cell expression system resulting in an antibody with human IgG1:k constant regions and human-derived heavy- and light-chain variable regions. It was approved by FDA in September 2016.⁷⁸ Cyltezo is again a recombinant human IgG1 MAb, which was approved in August 2017.⁷⁹ The indications of these two agents are similar to Humira except in hidradenitis suppurativa and uveitis in the same dosage regimen with similar efficacy and side effects.^{78,79}

With regard to infliximab, there are again three biosimilars, which are approved by FDA namely infliximab-dyyb (Inflectra®) by Pfizer (New York City, NY, USA), infliximab-abda (Renflexis™) by Samsung Bioepis (Seoul, South Korea), and infliximab-qbtx (Ixifi™) by Pfizer in 2016, 2017, and 2017, respectively.^{80–82} Both chimeric IgG1κ MAb composed of human constant and murine variable regions, which are produced by a recombinant cell line cultured.^{80,81} These agents are used in the same indications as Remicade at same dose with similar efficacy and adverse effects.^{80,81}

Future paradigm

Biologics off late as mentioned has become an important modality of treatment in IBD and the mainstay of therapy in patients with fistulizing or perianal CD.⁸³ However, the available treatment has certain drawbacks, the most important of which is 30% primary nonresponders.⁸⁴ Some patients transiently show response but then experience a loss of response (secondary nonresponders).⁸⁵ Besides this, the available agents come with a myriad of serious adverse effects such as antibody formation, malignancies, reactivation of tuberculosis and hepatitis B as mentioned. Therefore, there is a need to develop newer agents that are more effective with fewer side effects and agents with novel targets and novel mechanisms of action. Some of these novel targets include Janus kinase inhibitors (eg, tofacitinib), IL inhibitors, antisense oligonucleotides (eg, mongersen), sphingosine-1-phosphate (S1P) receptor agonist (eg, ozanimod), anti-integrin inhibitors, and so on.⁸⁶ Janus kinase inhibitors interfere with the signaling pathway that is needed for inflammatory process, whereas the antisense oligonucleotides prevent translation process by binding to mRNA from which the protein is usually synthesized.^{87,88} S1P receptor agonists decrease the total lymphocyte count in circulation, especially CD4⁺CCR7⁺ and CD8⁺CCR7⁺ T cells.⁸⁹

Conclusion

As the burden of IBD is increasing with time, so is the plethora of novel agents under development for its treatment. Initially, biologics were prescribed much later in the course of the disease, but this paradigm has changed with the increasing availability of evidence that suggests early use of biological agents. Also, the focus of treatment has shifted from mere supportive or symptomatic to more therapeutic or curative. One of the significant hurdles faced currently with these newer biologics is the cost and adverse reactions. With the availability of biosimilars in the market now, the cost has come down drastically, and in the future with novel agents in the pipeline, one could expect to see agents with enhanced safety and tolerability.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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