The Role of Biologics Agent in the Treatment of Inflammatory Bowel Disease

Tri Hapsoro Guno, Marcellus Simadibrata***

*Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta
**Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:
Marcellus Simadibrata. Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No.71 Jakarta Indonesia. Phone: +62-21-3153957; Facsimile: +62-21-2454. E-mail:prof.marcellus.s@gmail.com

ABSTRACT

Inflammatory bowel disease (IBD), with major manifestations as Crohn's disease (CD) and ulcerative colitis (UC), is a chronic intestinal inflammatory disorder with an unknown etiology which pathogensis involving multifactorial immune disorder characterized by chronic relapsing inflammation of the intestine. Management of IBD depends on stage and location of the inflammation consist of the classic conventional treatment and the more new treatment with biologics agent. Biologics agent refers to monoclonal antibodies with activity directed against specific targets involved in the pathogenesis of chronic inflammatory conditions. Advances in the understanding of the specific mechanisms of pathogenesis IBD led to the development of targeted treatment. Today there are six biologics agent approved and used as therapy and there still many other biologics agent on research progress. Many reports show positive report about efficacy for the biological therapy compared with placebo and conventional treatment for the IBD. Limited by their cost and adverse effect that possibly happened, biologics agent is still promising therapy that change the course of IBD treatment.

Keywords: *Inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), biological therapy, biologics agent.*

ABSTRAK

Penyakit inflammatory bowel disease (IBD), terbagi menjadi penyakit Crohn dan kolitis ulseratif merupakan peradangan kronis inflamatorik dengan etiologi yang belum jelas diketahui dan melibatkan gangguan imunitas multifaktorial, dikarakteristikan dengan inflamasi usus yang berulang secara kronis. Tatalaksana dari IBD bergantung kepada derajat penyakit dan lokasi lesi, tatalaksana terdiri dari terapi konvensional dan terapi terbaru dengan agen biologis. Agen biologis merupakan antibodi monoklonal yang memiliki aktifitas menghambat target spesifik dalam proses inflamasi pada IBD. Dengan semakin berkembangnya pemahaman tentang mekanisme dari patogenesis IBD saat ini memicu perkembangan berbagai jenis agen biologis. Saat ini ada enam jenis agen biologis yang sudah disetujui dan digunakan sebagai terapi IBD dan banyak agen biologis lain sedang dalam tahap penelitian. Berbagai penelitian menunjukan efektifitas terapi biologis apabila dibandingkan dengan plasebo dan terapi konvensional. Walaupun penggunaanya masih terbatas dikarenakan masalah biaya dan efek samping yang mungkin terjadi, agen biologis tetap merupakan terapi yang menjanjikan dan dapat merubah tatalaksana IBD.

Kata kunci: *inflammatory bowel disease (IBD), penyakit Crohn, kolitis ulseratif, terapi biologis, agen biologis.*

INTRODUCTION

Health-care burden for management of inflammatory bowel disease (IBD) is substantially high but has been evolved since the introduction of biologics agent in the beginning of the twenty first century, since its impact on reducing the need of surgeries and improved quality of life for IBD patient.[1] Pathogensis on IBD involving multifactorial immune disorder characterized by chronic relapsing inflammation of the intestine. The two major manifestations of IBD were Crohn's disease (CD) and ulcerative colitis (UC) which share similar symptoms including diarrhea, hematochezia, and abdominal pain, whereas the location and depth of inflammation, as well as complications and prevalence can differ.[2,3]

Normally the immune system in gastrointestinal tract make a complex interaction between the innate, adaptive immune systems and intestinal microbes under homeostatic conditions. This homeostasis is disrupted with result of uncontrolled intestinal inflammation in IBD. Therapy with most non-biological drug (aminosalicylates, steroids and immuno-modulators) provide symptomatic improvement but fail to stop the underlying inflammatory process and do not change the disease course. Biologics therapy for IBD have been revolutionized the treatment of patients with Crohn's disease and have begun to have an impact on therapy for refractory ulcerative colitis. Biologics therapy proven to be highly effective.[2-4]

EPIDEMIOLOGY AND RISK FACTOR OF INFLAMMATORY BOWEL DISEASE

IBD can be diagnosed at any age from infancy to geriatrics population, with the majority of new cases are diagnosed in adolescence and early adulthood. In early twentieth century the incidence of IBD rose steadily in the western world but relatively rare in developing nations, but over the past few decades IBD also found emerged in newly industrialized countries such as in Asia, South America and Middle East and has evolved into a global disease with rising prevalence in every continent.[5,6]

Over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD, with substantial costs for health care. From ACCESS study, crude annual incidence of IBD per 100,000 individuals were 1.37 in Asia. Incidence of IBD case in Indonesia was 0.88 per 100,000 individuals, with CD incidence was 0.33 and UC incidence was 0.55.[7] Epidemiological differences in IBD between the western world and newly industrialized countries are primarily explained by genetic and environmental influences on disease development. Advances in health-care infrastructure and methodological challenges in reporting epidemiological data also influence differences in reported incidence between countries and world regions. The figure below summarize the historical of IBD from the first introduce.[1]

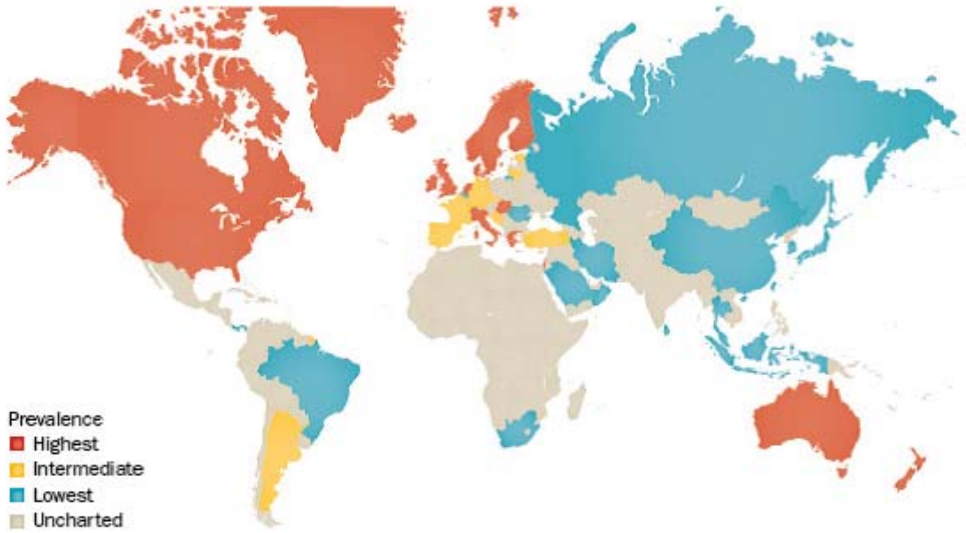

Figure 1. The global prevalence of IBD in 20151

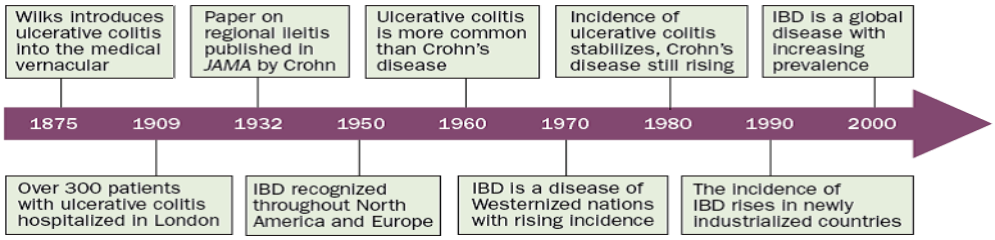

Figure 2. Historical timelines of inflmmatory bowel disease (IBD) throughout the world[1]

IBD is a chronic intestinal inflammatory disorder with an unknown etiology. IBD has been thought to be idiopathic but influenced by genetic and environmental factors.[2] It is believed to manifest in genetically predisposed individuals who has an abnormal immune response toward intestinal microbes after exposure to environmental triggers. Untill now 163 loci are known to confer susceptibility to Crohn's disease and/or ulcerative colitis. Genes with the strongest associations are involved in the immune response to microbes, such as innate sensing of bacteria (NOD2), the inflammatory response to microbes (IL23R) and autophagy (ATG16L1).[1]

Environmental exposures contribute to the etiology of IBD. Many of them have been studied, but none fundamentally can explain the truth pathogenesis of IBD. In the western world, smoking is the most consistently studied environmental determinant of IBD. The hygiene hypothesis postulates that children in industrialized and high urbanization society have less exposure to microbes early in life, such that infections later will trigger an abnormal host immune response. Risk of IBD associated with antibiotic use in childhood, breast-feeding prove the role of the intestinal microbiota in modulating inflamation. Dietary factors such as a low-fibre diet and high dietary fat in diets are associated with IBD, whereas consumption of tea was protective for IBD in Asia.[1]

PATHOGENESIS AND IMMUNE MECHANISMS IN INFLAMMATORY BOWEL DISEASE (IBD)

Human intestine service as a immune system with complex interaction occured. Idiopathic intestinal inflammations such as IBD occur when balance of this immune system disrupted. Initially T-helper-1 (Th1) cells have been thought to play an important role in pathogenesis related to the chronicity of intestinal inflammation, especially in CD, whereas Th2 cells have been thought to play an important role mainly in UC. Recently, additional factor like activation of Th17 cells and imbalance of Th17/T regulatory (Treg) cells are recognized to be an important component of IBD pathogenesis. Some other cells show to involved in the pathogenesis of IBD as can be viewed in this Figure below.[2,3]

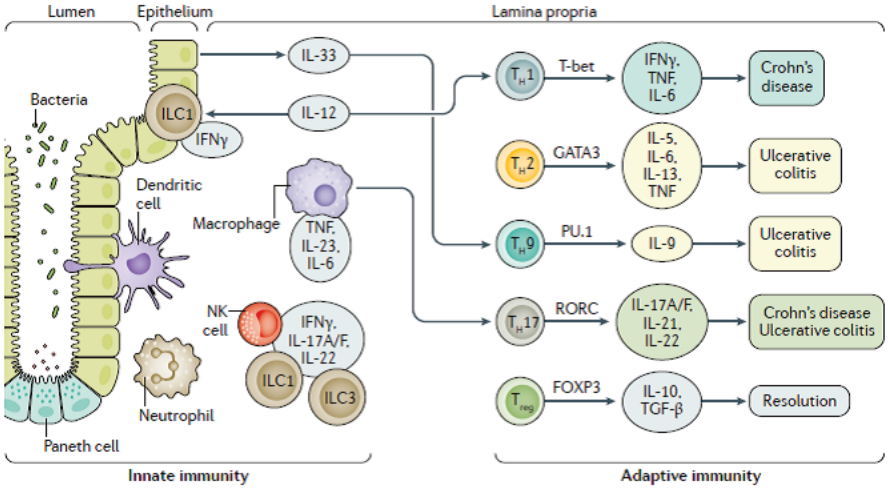

Figure 3. Proinflammatory immune cells and their crosstalk in patients with IBD.[3]

T_{reg} cell: regulatory T cell; TGF: transforming growth factor; T_H1: type 1 T helper cell; T_H2: type 2 T helper cell; T_H9: type 9 T helper cell; T_H17: type 17 T helper cell; NK cell: natural killer cell; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor.

Epithelial and Commensal Bacteria

Epithelial surface of intestine acts as a barrier from harmful pathogens and place where commensal microorganisms live. The imbalance interaction between imune system with microbes develop chronic intestinal inflammation when certain environmental factors triggers the genetically susceptible hosts. The intestinal epithelial cell (IEC) layer make crypts and villi of intestine which contain different cells including enterocytes, goblet cells, neuroendocrine cells, Paneth cells, M cells, and epithelial resident intestinal stem cells. These layers composed a single columnar cell lining with a tight junction and the ability to secrete mucus that contain anti-microbial peptides. This IEC layer separate intra-luminal pathogens from the subepithelial lamina propria. The mucus layer covers the outer epithelial surface, with major constituent is glycosylated mucin produce from goblet cells and defensins from Paneth cells (A-defensin) and IECs (B-defensin). Reduced mucus production can be from dysfunction of paneth cell or depletion of goblet cell are finding in patient with IBD and increased suscepibility to develop inflamation.[2,3]

Epithelial integrity depends on tight junctions function between IEC. Increase permeability of IEC layer make external pathogens are easily introduced, as happened on IBD. IEC also play a role as communicator between pathogens and lamina propria, normally small amounts of bacteria can translocate to submucosa to make antigen sampling and immune surveillance. High influx of intestinal contents and microorganisms occur when there is disruption of tight junction that thought to initiate and maintain a sustained inflammatory response in IBD.[2,3]

Approximately 10^{11}-10^{14} enteric commensal microorganisms from 300-500 bacterial species live in human intestine. The majority of commensal bacteria consist of gram-negative bacteria like Bacteroidetes and gram-positive bacteria like Firmicutes. Other minor bacteria such as Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicrobia. Commensal bacteria play role in protecting intestinal homeostasis by affecting crucial nutrient provision, development of the immune system, and modulation of energy metabolism. There are some clues that commensal bacteria play an important role in the development of IBD. In IBD there is reduce of diversity and amount of commensal compared to that in healthy humans.[2,3]

Innate and Adaptive Immunity in Inflammatory Bowel Disease (IBD)

The innate immune system serve as first line defensive against external pathogens. It provides rapid and non-specific protection from pattern recognition of pathogens. Human intestine innate immune system is composed of intestine epithelia, macrophages, monocytes, neutrophils, eosinophils, basophils, dendritic cells (DCs), and natural killer cells. Intraluminal pathogens communicate with innate immune cells through some receptors such as Toll like receptor (TLRs), nucleotide binding oligomerization domain leucine rich repeat receptors (NLRs), C-type lectin receptors (CLRs), and retinoic acid-inducible gene 1-like receptors (RLRs). Intestinal macrophages and DCs sense pathogen-associated molecular patterns (PAMPs) of microbes, activated signal pathways, such as NF-kB, produce proinflammatory cytokines, chemokines, and anti-microbial peptides. This activation of macrophages by these process than lead to direct elimination of pathogens through release of free radicals and proteases. Further process results in antigen presentation to the adaptive immune system by DCs and macrophages, connecting the innate and adaptive immune system.[2]

Activated DCs present intraluminal pathogens to naive CD4+ T cells which pooled at secondary lymphoid organs of the intestine and modulate the polarization of naive CD4+ T cells to Treg cells and T helper cells, including Th1, Th2, and Th17 cells. In normal conditions, TLR signaling leads tolerance to luminal pathogens through down-regulation of pattern-recognition receptors and promotes mucosal wound healing. However in IBD, impaired TLR signaling leads to increased intestinal permeability and inappropriate mucosal healing.[2]

The accumulation of both macrophages and DCs is observed in the lamina propria of IBD patients and in experimental colitis models. If interactions between DCs and T cells are interrupted, experimental T cell-mediated colitis is prevented. Impaired innate immune response might promote IBD development via inappropriate stimulation of adaptive immunity through failure to control microorganisms.[2]

Chronic inappropriate activation of the adaptive immune system against commensal microorganism has been thought to be the main pathogenesis of IBD. In Crohns disease patient there are increased production of IFN-g from Th1 cells and cytokines related with

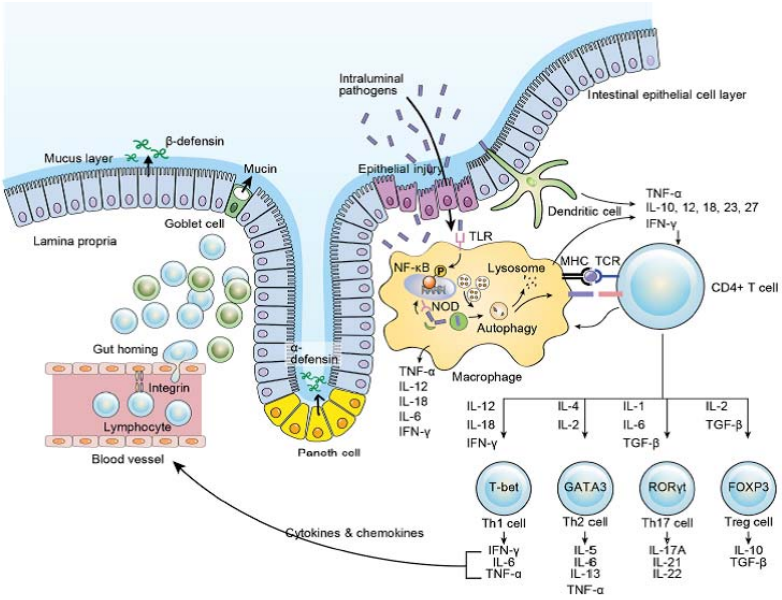

Figure 4. Summary of intestinal immune process.[2]
IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; TGF: transforming growth factor; Th: helper T cell; Treg: regulatory T cell; TCR: T cell receptor; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cell; TLR: toll-like receptor; NOD: nucleotide oligomerization domain.

Th17 cell, such as IL-17A/F, IL-21, IL-22, and CXCL8. While on UC patients there are increase production of Th2 cell-related cytokines, such as IL-5 and IL-13.[2]

MANAGEMENT OF INFLAMMATORY BOWEL DISEASE (IBD)

Management of IBD can be distinguished to two major groups, the classic conventional treatment and the more new treatment with biologics agent. The classical treatments consist of therapy with aminosalicylates, steroids and immuno-modulators drugs. These treatments differs for UC and CD and also differs for various stage of the disease. Treatment of UC is depend on the stage of the disease, patients with mild manifestations are usually treated with aminosalicylates, corticosteroids are given for those with moderate disease and cyclosporine is given to patients with severe disease. In CD therapy are depend on both location and behavior of the disease. The medication for crohns usually includes aminosalicylates and antibiotics to treat mild mucosal disease, corticosteroids to moderate disease, and biological molecules to treat fistulizing disease. Other therapy includes aminosalicylates, azathioprine, mercaptopurine, methotrexate, metronidazole can be used as maintenance therapies for both disease.[6]

Classically, immune-modulating treatments of IBD have focused on adaptive immunity. Corticosteroids have been widely used to treat acute flares of IBD and clinicaly effective. Suppression of proinflammatory cytokines, such as TNF-a and IL-1b, is known to be the primary mechanism underlying how corticosteroids control IBD. Corticosteroids also play an important role in regulation of T helper cell differentiation and type I interferon (IFN) production. Other immunomodulators to down-regulate the proinflammatory cytokines of T cells have been a well-established as treatment for IBD like cylosporine A, tacrolimus, methotrexate, azathioprine and 6-mercaptopurine. Non-specific immunosuppression using immunomodulators is generally safe and effective for disease control.[6]

Advances in the understanding of the specific mechanisms of IBD led to the development of targeted treatment, the biologics therapy. The biologic therapies as new therapy for IBD are still develop aim to reduce the side effects and to treat patients who do not respond satisfactorily to conventional therapies to improving the patient's life quality.[2,6]

THE BIOLOGICAL THERAPY

The biological therapy refers to monoclonal antibodies with activity directed against specific targets involved in the pathogenesis of chronic inflammatory conditions. In IBD based on the site of action of biologics agent, it can be divide to two major class of drugs: biologics agent that modulate

Table 1. Inflammatory bowel disease (IBD) treatments and their characteristic[6]

Treatment	Related drugs	Mechanism of action	Features
Aminosalicylates	Mesalamine Olsasalazine Balsalazide Sulfasalazine	Inhibition of IL-1, TNF-α, and PAF,decreased antibody secretion	Locally immunosupressive, nonspecific inhibition of cytokines. Medium cost
Immunomodulators	Azathioprin 6-mercaptopurin Methotrexate	Blockage of *de novo* pathway of purine synthesis.	Antiproliferative effects, reduction of inflammation.
Corticosteroids	Budesonide Hydrocortisone Methylprednisolone Prednisone	Blockage of phospholipase A2 in the arachidonic acid cascade altering the balance between prostaglandins and leukotrienes; Stimulation of apoptosis of lamina propria lymphocytes; Suppression of the transcription of cytokines.	High immunosuppression, Risk of potential infections, Adverse effects with long periods of use, Low cost.
Biologicals: Anticytokine drugs	Infliximab Adalimumab Certolizumabpegol Golimumab Ustekinumab	Induction of apoptosis in Proinflammatory cells; Binding specifically to TNF-α, Blockage of the interaction the receptor.	Specific inhibition of cytokine, Immunosuppression, high cost, Advanced technology required.
Biologicals: anti-cell adhesion molecule	Vedolizumab Natalizumab	Inhibition of migration.	Specific inhibition of cell adhesion molecules, High cost, Advanced technology required.

IL: interleukin; PAF, platelet activating factor; TNF, tumor necrosis factor

anti-inflammatory cytokines including agents that target or anti-tumor necrosis factor (TNF) (infliximab, adalimumab, certolizumab, golimumab), agents that target interleukin (IL)-12/23 (ustekinumab) and agents that target integrins/anti-cell adhesion molecule (natalizumab, vedolizumab). To understand the mechanism of biologics agent, we need to look back on the pathogenesis of the IBD and potential of therapy that can be applicable. Dozens of novel agents based on recent advances in the understanding of the mucosal immune system for IBD pathogenesis have been developed. [2]

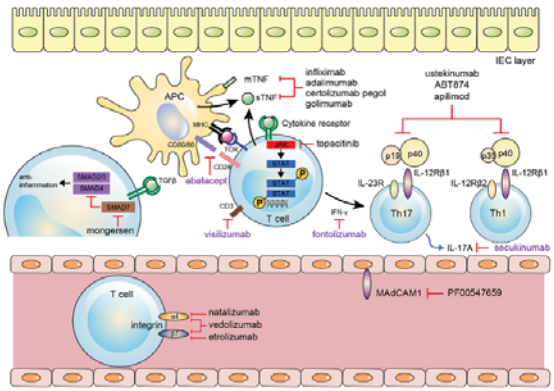

Figure 5. Biologics agent and target action related to inflammatory process (black: showed benefits; violet: no benefits)[2]

APC: antigen presenting cell; IEC: intestinal epithelial cell; TNF: tumor necrosis factor; MHC: major histocompatibility complex; TCR: T cell receptor; JAK: Janus kinase; TGF: transforming growth factor; IL: interleukin; MAdCAM: mucosal vascular addressing cell adhesion molecule

Biologics Agent that Modulate Anti-inflammatory Cytokines

The era of biologic therapy began with an anti-TNF agent infliximab for patients with CD. TNF-α has been thought to play an important role in patogenesis of IBD. TNF-α is a proinflammatory cytokine that produced by activated macrophages, monocytes, and T lymphocytes. Human intestine has two forms of TNF-α: the transmembrane TNF (mTNF) and soluble TNF (sTNF). mTNF is expressed on the surface of CD14+ macrophages and targets TNF-R2 of T cells, and sTNF is secreted by several immune cells as a signaling molecule and targets TNF-R1 of effector cells. In IBD, increased levels of both mTNF and sTNF support the pro-inflammatory effect of inflamed gut, such as angiogenesis, Paneth cell death, production of matrix metalloproteinase from myofibroblasts, and the undermining of the barrier function of IECs.[2,3] Several anti-TNF-α monoclonal antibodies have been developed and showed effectiveness for induction and maintenance of remission, as well as mucosal healing of IBD. These antibodies may activate various mechanisms involved in the immune response, such as induction of apoptosis as well as the blockage of growth factors for theTh cells, antibody production, and complement activation. However, another anti-TNF agent that targets sTNF, showed no benefits regarding treatment of IBD.[2,6]

Other important cytokines involved in the pathogenesis of IBD are related to Th17 cells (IL-17A,

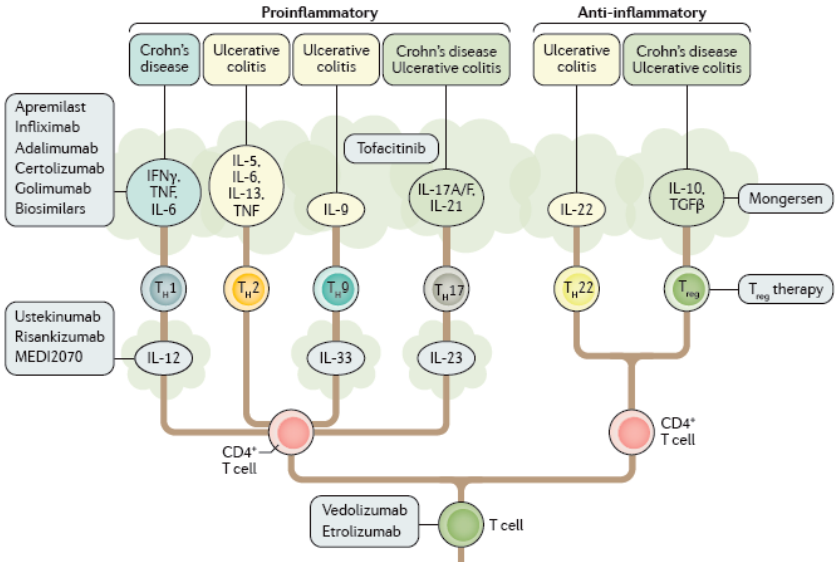

Figure 6. The T-cell cytokine tree in IBD and potential biologic treatment.[3]
TGF: transforming growth factor; TH1: type 1 T helper cell; TH2: type 2 T helper cell; TH9: type 9 T helper cell; TH17: type 17 T helper cell; TH22: type 22 T helper cell; Treg: regulatory T cell

IL21, IL-22, and IL-23). Th17 cells are differentiated from naïve CD4+ T cells that are stimulated with transforming growth factor (TGF). The inflamed intestinal tissue of IBD patients was shown to contain higher levels of Th17 cells and its cytokines. Exact role of Th17 cells and their cytokines in regards to intestinal inflammation has not yet been fully understood. Based on those mechanism, recently new drugs have been emerged such as IFN-γ antibody fontolizumab, anti IL-17A secukinumab.[2,3] Therapy such as Ustekinumab, ABT-874, and apilimod mesylate designed to targeting multiple cytokines in inflamatory process and it is thought to be a reasonable approach in the treatment of IBD since complex interactions between various cytokines happened in its pathogenesis.[2]

Biologics Agent that Targeting Inter-/intra-cellular Signaling Pathways

Proinflammatory cytokines promote activation of intracellular signal transduction and end result is production of inflammatory proteins. Janus kinase (JAK) and Signaling transducers and activator of transcription (STAT) cytokine signaling pathways are recently thought to be a potential therapeutic target of IBD. Various key cytokines such as IFN-γ, IL-2, IL-4, IL-7, IL-9, IL-15, IL-12, IL-21, IL-22, and IL-23 depend on the JAK-signaling pathway. JAK inhibition might result in downregulation of multiple inflammatory cytokines. The JAK family consists of four intracellular proteins, JAK1, JAK2, JAK3, and tyrosine kinase (TYK) 2. Some drugs develop to Targeting inter-/intra-cellular signaling pathways prove to be effective such as JAK 1/3 tofacitinib, oral SMAD7 anti-sense oligonucleotide-mongersen. Other drugs showed no clinical benefit on IBD such as visilizumab and abatacept.[2]

Biologics agent that inhibit the lymphocyte trafficking

Pathogenesis of IBD involving the role of lymphocytes and this cell must travel from their pool to the intestine. Lymphocytes express specific cell surface adhesion molecules targeting specific organs to facilitate the travel process. From this concept, selective agent to inhibition of those adhesion molecules potentially change the development of IBD. Those drugs such as natalizumab (monoclonal antibody against α4ß1 integrin), vedolizumab (monoclonal antibody against α4ß7 integrin), etrolizumab (monoclonal antibody against the ß7 subunit of integrin) and PF-00547659 (monoclonal antibody against MAdCAM-1).[2]

New biologics agent

A variety of new biologics specific to IBD pathogenesis are now emerging and under clinical investigation. The basic mechanism targeting different process from pathogenesis that involved, these can be seen on figure 7 below.[3]

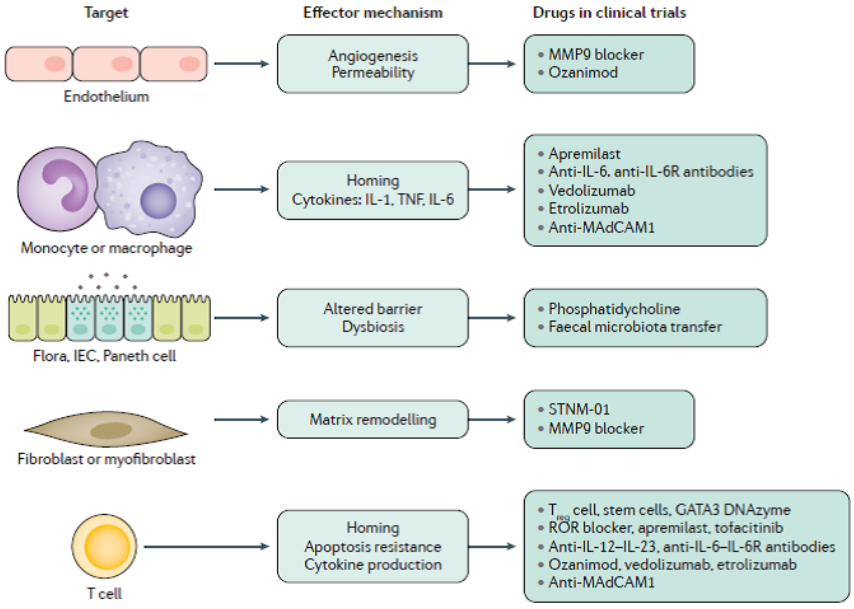

Figure 7. New therapeutic approaches in IBD with their specific targets.[3]
IEC: intestinal epithelial cell; IL-6R: IL-6 receptor; MAdCAM1: mucosal addressin cell adhesion molecular 1; MMP9: matrix metalloproteinase 9; ROR: RAR-related orphan receptor; Treg cell: regulatory T cell.

Tissue remodelling and destruction in patients with IBD is controlled by matrix metalloproteinas (MMPs). In IBD expression of MMP9 was found to be increased, particularly in patients with UC. Experimental models of inflammation have suggested an important role of MMP9 in impairing colonic epithelial permeability and augmenting inflammation via activation of myosin light chain kinase (MLCK). MMP9 favoured angiogenesis and created a proteolytic environment in the inflamed gut of a mouse model of colitis that stimulated the influx of myeloid cells into the colonic epithelium and the production of TNF. Currently a potent and highly selective allosteric MMP9 inhibitor (humanized monoclonal antibody GS-5745) has been developed and is currently being tested in clinical trials in patients with IBD but insufficient evidence of treatment benefit.[3]

Another drugs target to ameliorate tissue fibrosis in IBD through enzymes controlling degradation of matrix compounds. Carbohydrate sulfotransferase 15 (CHST15) is a specific enzyme biosynthesizing chondroitin sulfate E that binds to various pathogenic mediators and favours tissue fibrosis. CHST15 reduced colitis activity and intestinal accumulation of F4/80+ macrophages and ER-TR7+ fibroblasts. STNM01, a synthetic double-stranded RNA oligonucleotide directed against CHST15 showed a reduction of endoscopic inflammation as compared with placebo therapy and also histological analyses revealed that STNM01 reduces tissue fibrosis in Crohn's disease.[3]

CURRENT BIOLOGICS AGENT USED

The current use of biologic therapy is limited by their cost. With the expiration of patents for certain biologics, and the development of biosimilars (biological products that are highly similar to the reference product but can be produced at a lower cost with similar efficacy) will change the course of IBD treatment. Anti-tumor necrosis factor (anti-TNF) agents are the first and currently the most widely used biologic agents.[8] Several parameters should be considered when choosing a first-line biologic agent including the efficacy, safety profile, route of

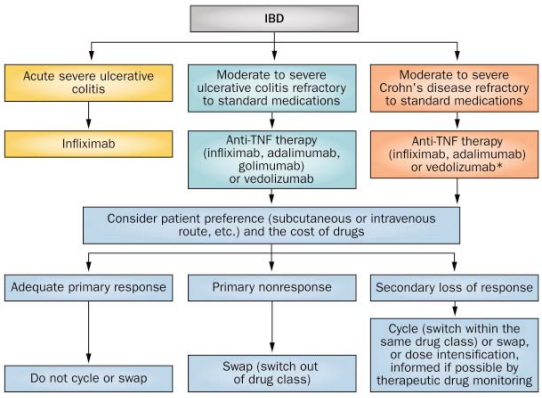

Figure 8. A proposed algorithm for clinical practice of Biologic agents in IBD.[10]
*For perianal fistulas the level of evidence is weak for vedolizumab. TNF, tumor necrosis factor.

administration, patient preference and cost. A proposed algorithm for using biologic agents in IBD can be seen in figure below.[10]

Patients with Crohn's disease who are refractory to standard medications, infliximab or adalimumab could be initiated. Vedolizumab has been approved for induction and maintenance therapy for Crohn's disease and ulcerative colitis. The use of natalizumab and certolizumab pegol is still restricted to a few countries due to an unclear between risk and benefit in IBD treatment.[10]

Response for the treatment can be adequate response or non-response. In patient with adequate primary response to a first-line anti-TNF therapy no switch between anti-TNF agents should be proposed, as switching is associated with loss of tolerance and efficacy. Non-responsive patient can be found up to 30% of total case. Non-response case divide into two type the primary non-response and secondary loss of response. If there is no response to initial treatment with anti-TNF it is called as primary non-responders. These type patient will unlikely to respond to another anti-TNF agent and require to switch to another class of biologic agent, such as vedolizumab. Secondary non-responders are patients who have a transient response but later will experience a loss of response to anti-TNF therapy. If this happened, the measurement of drug levels and anti-drug antibodies may help guide the next decision. Patients with subtherapeutic drug levels, require dose intensification, while patients with detectable antibodies against one anti-TNF may benefit from switching to another anti-TNF agent. Secondary non-responders with adequate drug levels should switch to a different class of biologic agent.[9,10]

Position of new biologics agent in the treatment of Inflammatory Bowel Disease (IBD)

New target molecules for biologics agent and cellular therapy have been develop and this may provide alternative therapy. As for many other biologics agent untill now still on research progress. Because of no data in long-term safety for ustekinumab, tofacitinib, and mongersen, the use of these medications in patients at high risk of infection is not recommended recently.[10]

EFFICACY OF BIOLOGICAL THERAPY

There are a lot of study about the using of biological therapy on IBD that has been published. Curently six biologic agents are approved for the treatment of IBD: infliximab, adalimumab, golimumab, certolizumab pegol, natalizumab and vedolizumab. Several meta-analyses have been conducted in both Crohn's disease and ulcerative colitis to compare the efficacy of the various biologic agents. Most of the results show positive report for biological treatment compared with placebo for the treatment of IBD. Some study also compares one biological treatment to another drugs to show which one more effective for inducing remission or maintanance therapy.[12,13]

Meta-analysis from vickers et al asses efficacy of Biologics agent used in ulcerative colitis showed that all biologics were superior than placebo in induction of clinical response, remission and mucosal healing (Figure 9). In induction of remission infliximab show significant improvement over adalimumab in clinical response, clinical remission and mucosal healing. With no other significant difference between other biologics exist. In maintenance study vedolizumab show significantly difference in durable clinical response and rates of mucosal healing compared with other biologics agent (Table 4).[12]

Meta-analysis from Hazlewood et al showed that infliximab, including combination of infliximab with azathioprine, adalimumab and vedolizumab were superior from placebo for induction and maintaining of remission on CD. This result also showed that the most effective agents for induction and maintaining

Table 2. Characteristics and dosage of biological treatments for IBD[4]

Drug	Type of monoclonal antibody	Target	Half-life (days)	Route	Induction phase		Maintenance phase	
					Dosage	Interval	Dosage	Interval
Infliximab	Chimeric IgG1	TNF-α	7.7-9.5	IV	5mg/kg	W0-W2-W6	5 mg/kg	Every 8 weeks
Adalimumab	Human IgG1	TNF-α	10-20	SC	160 mg	W0	40 mg	Every 2 weeks
					80 mg	W2		
Certozulimab pegol	Humanized pegylated Fab IgG4	TNF-α	14	SC	400 mg	W0-W2-W4	400 mg	Every 4 weeks
Golimumab	Human IgG1	TNF-α	8-16	SC	200 mg	W0	50-100 mg	Every 4 weeks
					100 mg	W2		
CPT-13	Chimeric IgG1	TNF-α	7.7-9.5	IV	5mg/kg	W0-W2-W6	5 mg/kg	Every 8 weeks
Natalizumab	Humanized IgG4	α4 integrin	7-15	IV	300 mg	W0-W2-W8	300 mg	Every 4 weeks
Vedolizumab	Humanized IgG1	α4ß7 integrin	15-22	SC	300 mg	W0-W2	300 mg	Every 4 weeks

Ig, immunoglobulin; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor; W, week

Table 3. Availability and drug labelling of biologics agent for inflammatory bowel disease (IBD)[10]

Agent	Primary Target	Route	Specific Labeling	
			Crohn's Disease	Ulcerative Colitis
Blockade pro-inflammatory cytokines				
Infliximab	TNF	IV	FDA and EMA approved	FDA and EMA approved
Adalimumab	TNF	SC	FDA and EMA approved	FDA and EMA approved
Certolizumab pegol	TNF	SC	FDA approved	-
Golimumab	TNF	SC	-	FDA and EMA approved
CT-P13	TNF	IV	EMA approved	EMA approved
TNF-Kinoid	TNF	IV	Phase II (-)	-
HMPL-004	TNF and IL-1ß	Oral	Ongoing Phase III	Ongoing Phase III
Ustekimumab	IL-12/IL-23 (p40 subunit)	IV/SC	Ongoing Phase III	-
AMG139	IL-23/IL-23R interaction	IV	Ongoing Phase II	-
BI 655066	IL-23 (p19 subunit)	SC	Ongoing Phase II	-
PF-04236921	IL-6	SC	Ongoing Phase I/II	-
Tralokinumab	IL-13	SC	-	Phase II (-)
Anrunkinzumab	IL-13 receptor	IV	-	Phase II (-)
QAX576	IL-13	IV	Ongoing Phase II	-
Bertilizumab	Eotaxin-1	IV	-	Ongoing Phase II
Vidofluidimus	IL-17 release	Oral	Phase II (+)	Phase II (+)
ATR-107	IL-21 receptor	IV/SC	Ongoing Phase I	-
NNC0114-0006	IL-21	IV	Ongoing Phase II	-
Blockade of the downstream signalling pathway mediated by cytokine				
Tofacitinib	JAK 1,2,3	Oral	Ongoing Phase III	Ongoing Phase III
Peficitinib	JAK 1	Oral	-	Ongoing Phase II
GLPG0634	JAK 1	Oral	Ongoing Phase II	-
GED0301 (mongersen)	Smad7 antisense oligonucleotide	Oral	Phase I (+)	-
BMS-936557	IP-10 antagonists	IV	Ongoing Phase II	Phase II (±)
Masitinib (AB1010)	Tyrosine kinase receptor	IV	Ongoing Phase II	-
Anti adhesion molecules				
Natalizumab	α4 Integrin	IV	FDA approved	-
Vedolizumab	α4ß7 Integrin	IV	Phase III (±)	Phase III (+)
Ertolizumab	ß7 Integrin	IV/SC	-	Phase II (+)
PF-00547659	MadCAM-1	IV/SC	Ongoing Phase II	Ongoing Phase II
AJM300	α4 Integrin	Oral	-	Phase II (+)
Alicaforsen	ICAM-1	Oral/ intra-rectal	Phase II (-)	Phase II (+)
Vatelizumab	α2ß1 Integrin	SC	-	Ongoing Phase II
Firategrast	α4 Integrin	Oral	Ongoing Phase II	-
GLPG0974	FFA-2	Oral	-	Ongoing Phase II
TRK-170	ß7 Integrin	Oral	Ongoing Phase II	-
Anti-inflammatory cytokine				
Low dose IL-2	IL-2	SC	Ongoing Phase II	Ongoing Phase II
Blockade of T-cell stimulation and induction of apoptosis				
SB-012	GATA-3	Intrarectal	-	Ongoing Phase I/II
VB-201	TLR-2 dependent innate cell activation	Oral	-	Ongoing Phase II
GSK1399686	Ribosomal 50S subunit	Oral	-	Ongoing Phase II
Laquinimod	?	Oral	Phase II (+)	-
DIMS0150	TLR9	Intrarectal	-	Ongoing Phase III
Other mechanism				
Fingolimod	Sphingosine 1-phosphate 1 receptor	Oral	Ongoing phase I	-
RPC1063	Sphingosine 1-phosphate 1 receptor	Oral	-	Ongoing Phase II
GSK 1399686	Ribosomal 50S subunit	Oral	-	Ongoing Phase II

EMA, European Medicines Agency; FDA, Food and drug administration; FFA-2, free fatty acid receptor-2; ICAM-1, InterCellular Adhesion Molecule-1; Ig, immunoglobulin; IL, interleukin; IP-10, interferon-γ-*inducible* protein-10; IV, intravenous; JAK, Janus kinase; MadCAM-1, mucosal address in cell adhesion molecule 1; NKG2D, natural killer group 2, member D; SC, subcutaneous; TNF, tumor necrosis factor; TGF, transforming growth factor; TLR, Toll-like receptor.

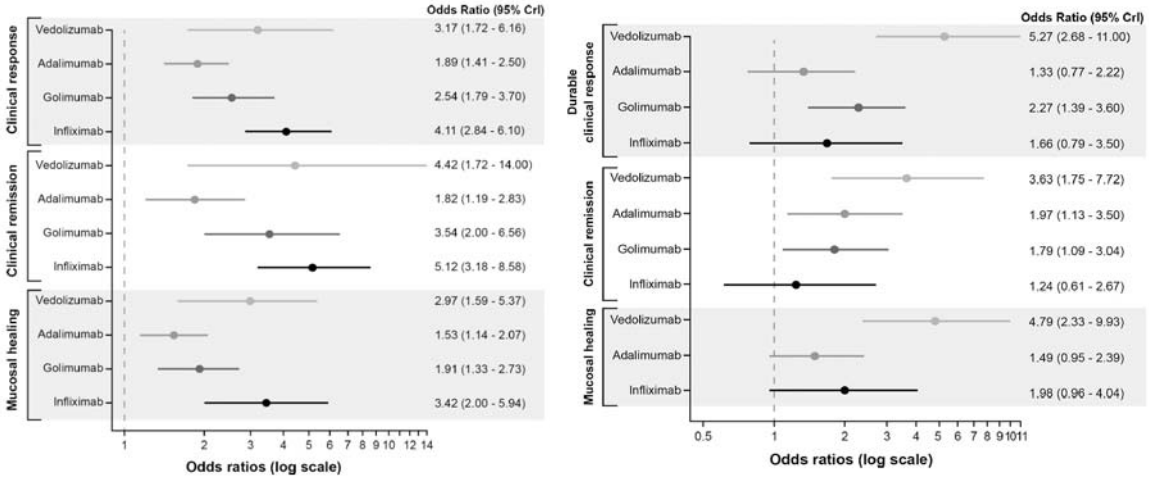

Figure 9. Forest plot of the odds ratio for biologics agent vs. placebo for ulcerative colitis. (A) Induction studies (B) Maintenance studies. *(CrI, credible interval).[11]

Table 4. Comparative efficacy of biologics agent as induction and maintenance therapy for anti-TNF therapy naïve subpopulation.[12]

Induction Therapy	Infliximab	Golinumab	Adalimumab
Clinical response			
Vedolizumab	OR = 0.78 (95% CrI: 0.39-1.64)	OR = 1.25 (95% CrI: 0.62-2.56)	OR = 1.69 (95% CrI: 0.86-3.43)
Infliximab	-	OR = 1.61 (95% CrI: 0.94-2.74)	OR = 2.19 (95% CrI: 1.35-3.55)
Golinumab	-	-	OR = 1.36 (95% CrI, 0.85-2.13)
Clinical Remission			
Vedolizumab	OR = 0.88 (95% CrI: 0.30-2.86)	OR = 1.26 (95% CrI: 0.4-4.43)	OR = 2.48 (95% CrI: 0.86-8.11)
Infliximab	-	OR = 1.44 (95% CrI: 0.65-3.14)	OR = 2.81 (95% CrI: 1.49-5.49)
Golinumab	-	-	OR = 1.95 (95% CrI: 0.96-4.10)
Mucosal Healing			
Vedolizumab	OR = 0.86 (95% CrI: 0.38-1.91)	OR = 1.54 (95% CrI: 0.76-3.09)	OR = 1.92 (95% CrI: 0.97-3.76)
Infliximab	-	OR = 1.79 (95% CrI: 0.96-3.42)	OR = 2.23 (95% CrI: 1.21-4.14)
Golinumab	-	-	OR = 1.24 (95% CrI: 0.79-1.98)
Durable Clinical response			
Vedolizumab	OR = 3.18 (95% CrI: 1.14-9.20)	OR = 2.33 (95% CrI: 1.04-5.41)	OR = 3.96 (95% CrI: 1.67-9.84)
Infliximab	-	OR = 0.73 (95% CrI: 0.31-1.77)	OR = 1.24 (95% CrI: 0.51-3.15)
Golinumab	-	-	OR = 1.69 (95% CrI: 0.85-3.70)
Clinical Remission			
Vedolizumab	OR = 2.93 (95% CrI: 1.03-8.28)	OR = 2.03 (95% CrI: 0.84-5.05)	OR = 1.81 (95% CrI: 0.74-4.90)
Infliximab	-	OR = 0.69 (95% CrI: 0.29-1.77)	OR = 0.63 (95% CrI: 0.24-1.63)
Golinumab	-	-	OR = 0.90 (95% CrI: 0.43-1.98)
Mucosal Healing			
Vedolizumab	OR = 2.43 (95% CrI: 0.87-6.66)	-	OR = 3.21 (95% CrI: 1.33-7.35)
Infliximab	-	-	OR = 1.31 (95% CrI: 0.57-3.12)
Golinumab	-	-	-

CrI: credible interval; OR: odds ratio; Note: Treatment effect estimates come from Bayesian mixed-treatment comparisson. ORs>1 favour the treatment in the column. Shading cell shown the significantly difference results.

remission in CD were adalimumab and combination of infliximab with azathioprine (Table 5).[13]

ADVERSE EFFECT OF BIOLOGICAL THERAPY

Besides effective for treating of both CD and UC, some obstacle happened in using biologics agent. Limitations of anti-TNF treatment is realated to safety issues, relatively high cost, and loss of effectiveness.[2,3] Anti-TNF treatment known to increase the risk of infection, the use of infliximab was associated with a 1.4- to 1.6-fold increase in serious infections. TNF is important for granuloma formation, and the use of anti-TNF agents has been reportedly associated with a fivefold increased risk of tuberculosis. Anti-TNF therapy also associated with hepatitis B reactivation. The use of anti-TNF drugs also has been associated with a small risk of malignancy, which dose-dependent, from non-melanome skin cancer and non-Hodgkin lymphoma. The rik will further increase in patient who also receive immunosuppressants therapy.[9,10] Physicians should be aware that anti-TNF antibodies may cause psoriasiform skin lesions in some patients with IBD. The anti-IL-12/IL-23 antibody, ustekinumab, is effective for the treatment of this paradoxical inflammation.[10]

Before starting anti-TNF treatment, a thorough evaluation is mandatory. Anti-TNF agent should be used with caution for patient with systemic lupus erythematosus and should not be used in patient with malignancy or premalignant disorder. The most common infections was bacterial and fungal infections including aspergillosis, cryptococcosis, candidosis, histoplasmosis, listeriosis, pneumocytosis and reactivated tuberculosis.[14]

BIOSIMILARS IN INFLAMMATORY BOWEL DISEASE (IBD)

Biologics medicines comprise proteins or other substances derived from a biological source. A biosimilar product is a biological product that is highly similar to a reference product. Biosimilar agent is not identical to the reference product, but the active ingredients are essentially the same as those of the reference product with no clinically meaningful differences in terms of safety or efficacy. These drugs are intended to be designed as a less expensive version of the reference product, biosimilars can reduce up to 72% budget compared to the original biological product in some countries. With the introduction of biosimilars, it is eagerly expected that patient access to biologics therapy will expand and the economic burden for health-care systems will decrease. Biosimilars represent a new generation of drugs for the treatment of IBD with comparable same efficacy and safety profile as original biologics agent, especially in countries with low economy capacity. Other biosimilar drugs that have been developed can be seen on figure below.[9-11]

Table 5. Result of network meta-analysis of biologics agent in treatment of Crohn's disease.[13]

Remission Induction	Comparator, OR (95% CrI), [a]probability intervention superior to comparator (greater odds of remission)					
Intervention	Placebo	Aza+6-mercap	Mtx	Certo	Inflix	Adal
Aza+ 6-Mercap	1.2 (0.76–2.1), 81%	-	-	-	-	-
Mtx	1.5 (0.72–3.2), 88%	1.3 (0.49–2.9), 71%	-	-	-	-
Certo	1.4 (0.95–2.0), 96%	1.1 (0.58–2.0), 63%	0.89 (0.40–2.1), 38%	-	-	-
Inflix	2.8 (1.4–7.2), >99%	2.3 (1.3–5.0), >99%	1.8 (0.69–6.4), 89%	2.1 (0.98–5.5), 97%	-	-
Adal	2.9 (1.6–5.5), >99%	2.4 (1.0–4.9), 98%	1.9 (0.76–4.8), 92%	2.1 (1.0–4.6), 98%	1.0 (0.32–2.4), 53%	-
Vedolizumab	2.0 (1.2–3.3), >99%	1.6 (0.78–3.2), 91%	1.3 (0.53–3.2), 71%	1.4 (0.77–2.7), 89%	0.70 (0.25–1.5), 20%	0.67 (0.33–1.5), 15%
[a]An OR greater than 1 favors the intervention (row) over the comparator (column), indicating a greater odds of induction of remission.						
Aza+ 6-Mercap	1.7 (1.3–2.6), >99%	-	-	-	-	-
Mtx	2.4 (1.1–4.8), 98%	1.4 (0.58–2.8), 78%	-	-	-	-
Certo	2.0 (1.4–3.0), >99%	1.2 (0.65–1.9), 72%	0.85 (0.39–2.1), 34%	-	-	
Inflix	2.8 (1.8–4.5), >99%	1.6 (1.0–2.5), 98%	1.2 (0.51–2.8), 65%	1.4 (0.77–2.6), 87%	-	-
Adal	5.1 (3.3–8.1), >99%	2.9 (1.6–5.1), >99%	2.1 (0.96–5.0), 97%	2.5 (1.4–4.6), >99%	1.8 (0.94–3.4), 96%	-
Vedolizumab	2.2 (1.3–3.7), >99%	1.3 (0.65–2.3), 76%	0.91 (0.39–2.3), 42%	1.1 (0.57–2.1), 59%	0.77 (0.39–1.5), 22%	0.42 (0.22–0.85), 1%

[a]An OR greater than 1 favors the intervention (row) over the comparator (column), indicating a greater odds of maintaining remission. Adal, adalimumab; Aza, azathioprine; Certo, Certolizumab; Inflix, infliximab; Mercap, mercaptopurine; Mtx, methotrexate.

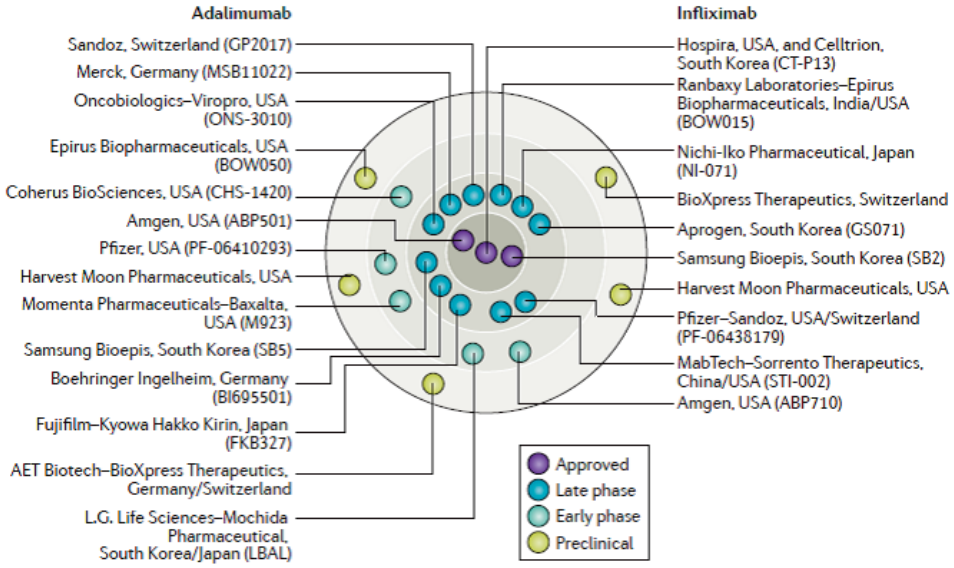

Figure 10. Biosimilars for adalimumab and inflixumab[11]

CONCLUSION

Immunological imbalance of the intestinal mucosa and inflammatory condition in IBD patients are the main target of these new biologics agent. With the more understanding in the pathological proccess in IBD recently the biological therapy is developing. These agents are used in IBD patients, who are refractory to standard medications. Several parameters about the drugs should be taken into account to help physicians through the decision-making process, including the comparative effectiveness and long-term safety profile, availability and labelling in the prescriber's country, international guidelines, and cost as well as patient preferences associated with the route of administration.

As an alternative, biosimilars are already available in the market and increased competition will lead to decreased costs and increased availability and accessibility of biological therapy. Although, it still need more research about efectivity, safety and applicability for this therapy. It is essential to provide patients with adequate, comprehensible and easily accessible treatment.

REFERENCES

1. Kaplan, GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12:720–7.
2. Kim DH, Cheon JH. Pathogenesis of Inflammatory Bowel Disease and Recent Advances in Biologic Therapies. Immune Netw 2017;17:25-40.
3. Neurath MF. Current and emerging therapeutic targets for IBD. Gastroenterol Hepatol 2017;14:269-78.
4. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. Therap Adv Gastroenterol 2015;8:66-82.
5. The American Gastroenterological Association (AGA). American Gastroenterological Association Consensus Development Conference on the Use of Biologics in the Treatment of Inflammatory Bowel Disease, June 21–23, 2006. Gastroenterology 2007;133:312-39.
6. Mattos BRRd, Garcia MPG, Nogueira JB, Paiatto LN. Inflammatory Bowel Disease: An Overview of Immune Mechanisms and Biological Treatments. Mediators Inflamm 2015;2015:1-11.
7. NG S, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's Disease and Colitis Epidemiology Study. Gastroenterology 2013;145:158-65.
8. Moss AC. Optimizing the use of biological therapy in patients with inflammatory bowel disease. Gastroenterol Rep (Oxf). 2015;3:63-8.
9. Chan HC-h, Ng SC. Emerging biologics in inflammatory bowel disease. J Gastroenterol 2017;52:141-50.
10. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Gastroenterol Hepatol 2015.
11. Danese S, Bonovas S, Peyrin-biroulet L. Biosimilars in IBD : from theory to practice. Nat Publ Gr [Internet]. 2016;14:22–31.
12. Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, et al. (2016) Systematic Review with Network Meta-Analysis:Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. PLoS ONE 11:e0165435.
13. Hazlewood GS, Rezaie A, Borman M, Remo Panaccione. Comparative Effectiveness of Immunosuppressants and Biologics for Inducing and Maintaining Remission in Crohn's Disease: A Network Meta-analysis. Gastroenterology 2015;148:344-54.
14. Stallmach A, Hagel S, Bruns T. Adverse effects of biologics used for treating IBD. Best Prac Res Clin Gastroenterol 2010;24:167–182.