

Use of Biologics in Inflammatory Bowel Disease: Combination and Sequential Therapy

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ABSTRACT

Inflammatory bowel disease (IBD) in the form of ulcerative colitis (UC) and Crohn's disease (CD) has multifactorial etiology and multiple inflammatory pathways. Newer treatments with biologic agents are used as an adjunct to conventional therapy. Biological agents such as anti-tumor necrosis factor (TNF), anti-integrin, and anti-interleukin are believed to be able to overcome the inflammation that underlies the occurrence of inflammatory bowel disease (IBD). The "step up" approach in IBD therapy uses conventional drugs with low potency but fewer side effects as the first line, followed by biologic agents as second line therapy. However, the result is often a delay in the management of severe complications of IBD. A "top down" approach is currently being used to successfully prevent severe complications of IBD by using biologic agents early. Biological agent therapy can be initiated in moderate to severe IBD either in combination or sequentially. But in the end, various parameters must be considered before starting the use of biologic agents such as drug effectiveness, safety profile, drug availability, price, and patient preferences.

Keywords: *Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologic agent*

ABSTRAK

Inflammatory bowel disease (IBD) dalam bentuk ulcerative colitis (UC) dan Crohn's disease (CD) memiliki etiologi multifaktorial dan melalui jalur inflamasi yang multipel. Pengobatan terbaru dengan agen biologik digunakan sebagai pilihan tambahan pada terapi konvensional. Agen biologik seperti anti tumor necrosis factor (TNF), anti integrin, dan anti interleukin dipercaya dapat mengatasi inflamasi yang mendasari terjadinya inflammatory bowel disease (IBD). Pendekatan "step up" pada terapi IBD menggunakan obat konvensional dengan potensi rendah namun efek samping yang lebih sedikit sebagai lini pertama, dilanjutkan dengan agen biologik sebagai terapi lini kedua. Namun hasilnya seringkali terjadi keterlambatan dalam tatalaksana komplikasi berat IBD. Pendekatan "top down" digunakan saat ini agar berhasil melakukan pencegahan terhadap komplikasi berat IBD dengan menggunakan agen biologik lebih awal. Terapi agen biologik dapat dimulai pada IBD derajat sedang berat baik secara kombinasi atau sekuensial. Namun pada akhirnya, berbagai parameter harus tetap diperhatikan sebelum memulai penggunaan agen biologik seperti efektivitas obat, profil keamanan, ketersediaan obat, harga, dan preferensi pasien.

Kata kunci: *Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologic agent*

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract that has two main forms, namely ulcerative colitis (UC) and Crohn's disease (CD). The etiology of IBD is still unclear but is thought to have a multifactorial etiology. The influence of genetics, the environment, the immune system, and the balance of the microbiota in the gut play an important role in the occurrence of IBD. This disease is characterized as a chronic recurrent inflammatory bowel disease with main symptoms such as diarrhea, hematochezia, and abdominal pain.¹

The health burden due to IBD was found increased from 1990 to 2017. The prevalence of IBD increased globally from 79.5 per 100,000 population in 1990 to 84.3 per 100,000 population in 2017. In Indonesia alone, the prevalence of IBD in Cipto Mangunkusumo Hospital was from 1541 colonoscopy by 8.3%. IBD can be diagnosed at any age, including infancy to the elderly. Most cases are diagnosed in adolescence or young adulthood. The increase in prevalence in recent years can be seen in countries in South America, Asia, and the Middle East.^{2,3}

Management of IBD depends on the degree of disease and the location of the involved lesion. Current routine therapy of IBD uses conventional agents such as aminosalicylate, steroids, and immunomodulators. Although administration of the conventional agents mentioned above can improve symptoms in patients, the inflammatory activity that occurs in patients does not completely stop. Currently, biologic agents such as anti-TNF, anti-integrin, and anti-interleukin agents are being used to treat IBD. This biologic agent works regarding to the molecular pathophysiology of IBD. It is believed that biologic agents not only improve symptoms but can also stop the underlying inflammation.²

Pathophysiology of Inflammatory Bowel Disease (IBD)

Gastrointestinal tract is the organ with the most amount of chronic exposure, whether caused by antigens in bacteria or in food. Under normal conditions without inflammation, gut homeostasis is maintained by suppressing the immune response to antigens. Inflammatory bowel disease (IBD) is an idiopathic disorder caused by excessive and chronic inflammation of the digestive tract. This chronic inflammation can result in gastrointestinal bleeding and significant weight loss.⁴

IBD disease is classified into two main phenotypes, namely ulcerative colitis (UC) and Crohn's disease (CD). On CD there is transmural inflammation that can affect all parts of the gastrointestinal tract. The most common area is the terminal ileum. The shape of the CD lesion itself is a skip lesion, in contrast to the continuous UC. Complications of CD are formation of abscess, fistulas, and strictures. On the other hand, UC causes mucosal inflammation and is confined to the large intestine.⁵

Clinically the two are different but closely related risk factors can occur in both types of disease. Genetic, environmental, and gut microbiota factors play an important role in the occurrence of IBD. The imbalance of homeostasis in the intestine causes the intestinal mucosa to become fragile. Furthermore, antigens in food or bacteria will enter the intestinal lining and activate dendritic cells and macrophages. Activation of these two cells is the main mechanism for the release of various pro-inflammatory cytokines such as interleukins, TNF-alpha, and NFK-beta resulting in chronic inflammation.⁶

Inflammatory Bowel Disease (IBD) Therapy

The cause of IBD is still unknown for sure. Pharmacological management of IBD is done by giving various drugs with different mechanisms but having non-specific anti-inflammatory mechanisms of action. Drugs used in IBD are selected based on the severity of the disease in the patient. The therapeutic pyramid in IBD uses a step up approach, namely by starting therapy with an agent that has lowest potency but has fewest side effects or a top down approach that is directly using drugs with high potency.⁷

One of the management agents for mild to moderate IBD is 5-aminosalicylic acid (5-ASA). This agent can be used to induce remission in mild cases and as a remission maintenance agent. Sulfalazine is a drug that has a 5-ASA component bound to a sulphyridine. The nature of 5-ASA itself is known to be very well absorbed in the small intestine therefore it often does not reach the large intestine. The target of action of 5-ASA in IBD is the large intestine where inflammation occurs. The addition of sulphyridine to sulfalazine is useful for inhibiting the absorption of the small intestine so that 5-ASA can reach the large intestine. The use of sulfalazine however has several side effects that sometimes can not be tolerated by the patient. Currently another type of 5-ASA, mesalamine, is used in patients who are unable to tolerate the side effects of sulfa on sulfalazine. Mesalamine has a microgranular

formulation that only releases when it reaches the ileum and large intestine. Mesalamine is believed to be able to provide an appropriate topical mechanism of action in inflammatory areas in the large intestine.⁷

The use of antibiotics in IBD is controversial and the available evidence is not strong. However, in developing countries such as Indonesia, which has a high prevalence of infectious diseases, it is necessary to first eliminate the cause of infection in intestinal inflammation. Tuberculosis, clostridium difficile, and other bacterial infections can cause colitis.⁸

In patients who do not respond well to 5-ASA, corticosteroids such as oral prednisone, budesonide, intravenous hydrocortisone, or methylprednisolone are said to be effective in inducing remission in patients with moderately severe IBD. In distal colitis, the use of topical steroids such as enemas or foams can still be given. If the patient has achieved remission, the use of corticosteroids cannot be continued as maintenance therapy for remission. Corticosteroids should be reduced in dose and discontinued. Often for maintenance of the remission phase in patients maintained with 5-ASA or immunomodulators.⁷

Some immunomodulatory agents that can be used in IBD are azathioprine, methotrexate, and cyclosporin. Azathioprine is rapidly absorbed and converted to 6-mercaptopurine. Furthermore, 6-mercaptopurine inhibited RNA synthesis and cell proliferation. The effects of these agents take 3-4 weeks before their efficacy appears. Azathioprine is often used as a steroid-sparing agent in IBD. Another drug, namely methotrexate, can inhibit DNA synthesis and cell proliferation as well as the action of IL-1. These drugs are used for the induction and maintenance of remission in CD patients, but their effect on UC is unclear. Cyclosporine is also an immunomodulator that can be used in steroid-refractory IBD patients. Cyclosporine inhibits calcineurin, an enzyme for T cell activation. The use of cyclosporine requires regular monitoring of renal function because it can cause kidney damage.⁷

Of the several agents mentioned above, a step-up approach is important because the cause of infection must first be removed. Management of mild IBD generally uses 5-ASA, antibiotics, and topical corticosteroids. Then, in moderate IBD, systemic corticosteroids and immunomodulators can be used. In patients who do not improve with these drugs or patients with severe IBD, treatment should switch to last line, namely surgery or administration of biologic agents.

Definition and Types of Biologic Agents

Biological agents are all kinds of products produced by extraction or semisynthetic from biological sources. Biological agents include vaccines, blood components, gene therapy, and protein monoclonal antibodies. Therapy with biologic agents is used to specifically target our immune cells for the treatment of a disease. Molecules commonly used for treatment with biologic agents are interleukins and cytokines that play a direct role in our body's defense system. When talking about IBD, there are already several types of drugs that are included in biologic agents and have been approved for use as a modality of IBD therapy. Its use does have great potential, but the side effects that can arise must also be considered.⁹

Broadly speaking, currently approved biologic agents for the treatment of IBD are anti-TNF, anti-integrin, and anti-interleukin groups. Anti-TNF drugs include infliximab, adalimumab, golimumab, and certolizumab. Anti-integrin drugs include natalizumab and vedolizumab. Then the anti-interleukin group consists of only one drug, namely ustekinumab. There are still some drugs that are currently in trials with a different mechanism of action than the drugs mentioned above.⁹

Biologic Agents Mechanism

Anti-TNF works by inhibiting the pro-inflammatory cytokine TNF. TNF cytokines are proinflammatory agents produced by macrophages, monocytes, and T lymphocytes. In a person's intestines, transmembrane TNF (igen can cause proinflammatory effects such as angiogenesis, Paneth cell death, fibrogenemTNF) and soluble TNF (sTNF) can be found. An increase in the amount of TNF triggered by antis (MMP production), and impaired intestinal epithelial cell function. Anti-TNF drugs include infliximab, adalimumab, golimumab, and certolizumab.⁹ Anti-integrins work by inhibiting integrins. Integrins are receptors that facilitate adhesion. Integrin in leukocytes is used for the process of leukocyte migration at the site of inflammation. Anti-integrins prevent the influx of inflammatory cells into the intestinal tissue. Drugs that include anti-integrins are natalizumab and vedolizumab.⁹

Anti-interleukins are newer biologic agents in the management of IBD. Interleukin (IL) plays an important role in the pathogenesis of IBD. Cytokines IL-12 and IL-23 are said to be one of the main pathways of inflammation. they have a similar structure and are

responsible for the production of 1 (Th1) and 17 (Th17) helper T cells. Initially, macrophages and dendritic cells produce IL-12 and IL-23 when antigen-induced activation occurs. Furthermore, IL-12 activates STAT 4, causing the conversion of naive T cells to Th1 which can produce IFN-gamma. On the other hand, IL-23 activates STAT 3 and STAT 4, causing the conversion of naive T cells to Th17 which can produce IL-17 and TNF-alpha. Drugs that include anti-interleukins are ustekinumab.⁹

Biologic Agents Effectiveness and Side Effects

There have been quite a number of studies assessing the effectiveness of using biologic agents in IBD. Several meta-analyses have been performed for both CD and UC comparing the efficacy between biologic agents. Most studies have reported the superiority of biologic agents over placebo. Several studies have also examined more specifically on the use of biologic agents in the induction or maintenance phase of remission.

The meta-analysis by Vickers et al assessed the efficacy of biologic agents used in UC. It was found that all biologic agents were superior to placebo in the induction of clinical response, remission, and mucosal repair. In the remission induction phase, infliximab showed significant improvement compared to adalimumab. In addition, no significant difference was found compared to other biologic agents. In the maintenance phase, vedolizumab showed significant differences in clinical response and mucosal repair compared to other biologic agents.¹⁰

Another meta-analysis by Hazlewood et al showed that infliximab, including the combination of infliximab with azathioprine, adalimumab and vedolizumab was superior to placebo for the induction and maintenance of remission in CD. The results of this meta-analysis also showed that the best agents for the induction and maintenance of remission in CD are adalimumab and the combination of infliximab with azathioprine.¹¹

In addition to effectiveness, the side effects of using biologic agents should also be assessed. The limitations of anti-TNF are related to safety issues, high cost, and diminishing effectiveness. The use of anti-TNF increases the risk of infection. It is known that TNF itself is used for granuloma formation therefore the use of anti-TNF can increase the risk of active tuberculosis infection. In addition, anti-TNF is also closely related to reactivation of hepatitis B therefore hepatitis screening should be carried out in every patient who will receive anti-TNF treatment.

The risk of developing non-melanoma skin cancer and non-Hodgkin's lymphoma has also been reported in association with anti-TNF use, especially when used in combination with other immunosuppressants.

Management Approach and Use of Biologic Agents in Inflammatory Bowel Disease (IBD)

IBD treatment itself has two types of approaches, namely step up and top down. The step up approach is the use of drugs with low potency but fewer side effects as the first line. If this treatment fails, then the agent used is changed to a more potent agents but the side effects are also more severe. The top-down approach is done the other way around, that is, first, the agent with the strongest potency is used and then it goes down periodically to become a drug with a low potency so that the side effects do not get worse.

Consideration of step-up therapy is to minimize the occurrence of side effects in the patient and hope that low-potency therapy is sufficient to improve the patient's symptoms. However, this approach often causes delays in treating chronic inflammatory complications of IBD, especially CD. Currently, many studies support a top-down approach for the successful prevention of severe chronic inflammatory complications of IBD such as strictures, fistulas, and permanent intestinal damage requiring surgery.¹²

On CD, multiple times of infliximab is recommended for direct use on moderate-to-severe CDs. Results from the TOP-DOWN trial found that taking infliximab with azathioprine on CD earlier than steroids followed by infliximab with azathioprine as needed, showed better results in the infliximab group with azathioprine earlier. The mean of remission in this group was higher than the group that used steroids first. Another study also found that remission was easier to achieve with the early use of adalimumab (CHARM, ADHERE, and EXTEND trials) and certolizumab (PRECISE 2 trial).¹²

Early use of anti-TNF was indeed found to have a better effect on CD. However, the use of other classes such as anti-integrins and anti-interleukins has not been widely studied. On the other hand, fewer studies have been conducted on the early use of biologic agents in UC. It has not yet been determined whether the early use of biologic agents in UC provides more benefits than side effects.

The last therapeutic modality that can be done in IBD patients is surgery. Often the damage to the bowel is permanent (usually from CD) and requires resection of that part. Indications for surgery in IBD patients include unresponsiveness to all medications,

strictures, abscesses, fistulas, developmental disorders in children, cancer, and emergencies such as massive acute bleeding.¹²

Currently, IBD therapy prioritizes the use of strategies based on the pathophysiology of IBD. However, the immunologic mechanism of IBD is always evolving and identification of the appropriate therapeutic modality is required to achieve maximum results. Various inflammatory pathways are activated simultaneously until inflammation occurs in IBD. Currently, therapies aimed at multiple inflammatory pathways are expected to help induce remission. Therapy in combination and sequential form of biologic agents is believed to provide a better cure rate in IBD patients. Biological agents can be started in patients with moderate to severe IBD.

Combination and Sequential Therapy Using Biologic Agents

The combination therapy of infliximab and thiopurine has been studied in several randomized controlled trials (RCTs) that have assessed its efficacy. The SONIC RCT study demonstrated that infliximab and thiopurine were more effective in inducing steroid-free clinical remission and mucosal healing after 26 weeks of therapy compared to monotherapy of the two drugs. The study population was CD patients who were naive to thiopurine and infliximab.¹³ Another study, UC-SUCCESS RCT, showed that the combination of infliximab and azathioprine was better at inducing steroid-free clinical remission after 16 weeks of use in naive UC patients.¹⁴ Good effect in patients who experienced secondary loss after the use of TNF-alpha. Immunomodulators can suppress the presence of antibodies to infliximab and adalimumab thereby helping to improve clinical response.^{15,16}

Changes in therapy are often used only in IBD patients who experience primary or secondary failure of treatment with these drugs. However, in some cases, maintenance therapy can use a simpler regimen than the initial therapy. In patients on the combination therapy of thiopurine and infliximab, further administration of the two drugs is not necessary once the patient has reached the target of therapy. Discontinuation of immunosuppressants in stable patients (clinical remission > 6 months) does not lead to clinical deterioration in later life.¹⁷ In patients with steroid-refractory severe acute ulcerative colitis, a combination of thiopurines and calcineurin inhibitors is often used. Calcineurin inhibitors are advised to be discontinued after 6-12 months, while thiopurine

therapy can be continued as monotherapy.¹⁸ Recent studies have also shown that vedolizumab can be used as a substitute for thiopurine in combination with a calcineurin inhibitor.¹⁹

The use of dual targeted therapy (DTT) is currently used in 2 scenarios, namely concomitant IBD with extraintestinal comorbidities or patients with refractory IBD. In cases of concomitant IBD with extraintestinal manifestations, often administration of one type of biologic agent can control IBD but fail to control other diseases. A 2018 study by Buer et al showed 10 IBD patients (4 CD and 6 UC) who received vedolizumab after administration of anti-TNF-alpha (9 infliximab and 1 adalimumab). All patients achieved clinical remission after a median of 17 months. Biomarkers improved in all UC patients and half the CD patients. Improvement on endoscopy was found in all UC patients and 3 of 4 CD patients.²⁰

Another study in Italy showed 16 IBD patients (11 CD and 5 UC) who received DTT. A total of 7 patients had uncontrolled IBD and 9 patients had extraintestinal manifestations. The patient was given a combination of vedolizumab and anti-TNF-alpha, ustekinumab and anti-TNF-alpha, and vedolizumab and ustekinumab. After 2 months, all patients had clinical improvement and did not need steroids.²¹

In patients who failed to treat biologic agents, follow the algorithms in Figure 1 and Figure 2. In patients with moderate-to-severe CD who received infliximab or adalimumab therapy, if they experience primary failure, the therapy can be switched to vedolizumab or ustekimumab. In case of secondary failure, the trough level (TL) and antibody to the drug were assessed. Patients with low TL and negative antibodies, can be done escalating drug dose before. Patients with low TL and antibody positive, can be replaced with drugs of the same class. In patients with normal TL and antibody negative, it can be changed to ustekimumab or vedolizumab.²²

In UC patients receiving anti-TNF-alpha or vedolizumab, if they experience primary failure, the drug can be changed to ustekimumab, tofacitinib, or vedolizumab if previously using anti-TNF-alpha. If the patient has secondary failure, the TL and antibodies to the drug are assessed. Patients with low TL and negative antibodies, can be done escalating drug dose before. Patients with low TL and antibody positive, can be replaced with drugs of the same class. In patients with normal TL and antibody negative, can be changed to ustekimumab, tofacitinib, or vedolizumab if previously using anti-TNF-alpha.²²

CONCLUSION

Biological agents are currently expected to be new therapeutic modalities that can provide better effects than conventional agents. Pathophysiologically, biologic agents not only relieve symptoms in IBD patients but can also stop the underlying inflammatory process. Various types of biologic agents that can be used and included in various recommendations are anti-TNF such as infliximab, adalimumab, golimumab, and certolizumab, anti-Integrin such as natalizumab and vedolizumab, and anti-interleukin such as ustekinumab.

The use of biologic agents is generally given to IBD patients who do not respond to conventional treatment such as aminosalicylate, corticosteroids, and immunomodulators. However, currently the management of IBD with a top-down approach is more often used. Biological agents can be used directly in moderate to severe IBD, especially if the patient has the resources and there are no contraindications to the use of biologic agents. Several parameters must be considered before starting the use of biologic agents such as drug effectiveness, safety profile, drug availability, price, and patient preferences. In Indonesia itself with a fairly large prevalence of infectious diseases, the use of biologic agents is closely associated with tuberculosis infection, reactivation of hepatitis B, fungal infections, and psoriasis.

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