Ministry of Higher Education

And Scientific Research

University of Diyala

College of Medicine

A Review Article in:

Role of biologics in treatment of inflammatory bowel disease

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

Submitted by: Abd Al-Qadir Qassim Muhammed

Supervised by: prof. Dr. Adil Hassan Al-Hussaini

2022-2021

Abstract

Inflammatory bowel diseases is a serious health issue because of their morbidity in the GIT and the other systems. They are divided into main two subtypes: ulcerative colitis and Crohn's disease. UC involve the large intestine and CD involve the whole GIT and they're difficult to differenciate clinically. There are many therapies in the treatment and the Biological treatment is the newest modality. There are many types and classes of drugs that classified as biologics and in this review we will discuss the biologics and their role in the treatment and maintenance of IBD.

Keywords: ulcerative colitis, Crohn's disease, biologics

Introduction

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease (CD). UC was first described in 1859, and CD in 1932. Both UC and CD are chronic and debilitating diseases without a real cure. As of 2017, 6.8 million IBD cases were reported globally, with an increase in age-standardized prevalence rates from 79.5 per 100,000 population in 1990 to 84.3 per 100,000 population in 2017 (1). The hallmark of IBD is chronic, uncontrolled inflammation of the intestinal mucosa, which can affect any part of the gastrointestinal tract. Diagnosis is based on the presence of architectural distortion (e.g., transmural or superficial patchy granulomatous infiltration) and/or acute inflammatory cells. However, chronic inflammation without any diagnostic abnormality can also be a feature of the normal gut (2). What distinguishes IBD from inflammatory responses seen in the normal gut is an inability to down-regulate those responses. In healthy people, the intestine becomes inflamed in response

to a potential pathogen, then returns to a state of tolerance once the pathogen is eradicated from the gut. In individuals with IBD, however, inflammation is not down-regulated, the mucosal immune system remains chronically activated, and the intestine remains chronically inflamed (3). Although UC and CD are generally accepted as clinically distinct conditions with distinguishing clinical, anatomical, and histological findings, a diagnostic gold standard remains elusive. In fact, these conditions probably represent a continuum of diseases, with UC and CD at opposite ends. Moreover, there may be a spectrum of illnesses within each disorder, making it likely that ‘‘ulcerative colitides’’ and ‘‘the Crohn’s diseases’’ will be the terms used to describe these illnesses in the future (4).

It is likely that a number of factors contribute to the development of mucosal inflammation. In addition, variations in influence may account for the clinical diversity seen in UC and CD. Current etiologic theories concerning IBD focus on environmental triggers, genetic factors, and immunoregulatory defects and microbial exposure (5). There are many roads to colitis. Whatever the trigger, neutrophils are early responders to all types of insult and play a central role in the inflammatory process. During the initial innate immune response, they are seen passing from the circulation through gaps in the vascular endothelium to infiltrate the tissues. Once there, neutrophils release antimicrobial peptides and reactive oxygen intermediates that may in themselves cause further tissue damage. Neutrophils also recruit and activate other white blood cells (e.g., macrophages) through the production of chemokines and the proinflammatory cytokines tumor necrosis factor (TNF)-a, interleukin (IL)-1b, IL-6, and IL-8 (6). At the microscopic level, Crohn’s disease affects the entire bowel wall, while ulcerative colitis is restricted to the

epithelial lining of the gut. Since the two diseases share similar symptoms, the diagnosis of one form of IBD over the other is often very difficult. Symptoms tend to vary depending on the type of IBD. A comparison of the key features in Crohn's disease and ulcerative colitis is shown in Table 1. Patients affected by ulcerative colitis tend to experience pain in the lower left part of the abdomen as well as diarrhea. As a result, they may experience weight loss and blood on rectal examination. In contrast, patients with Crohn's disease experience pain in the lower right abdomen, and bleeding from the rectum is less frequent than in ulcerative colitis (7).

Characteristics	Ulcerative Colitis	Crohn's Disease
Rectal bleeding	Common	Uncommon
Diarrhea	Often severe	Moderate to severe
Pain	Less frequent	Common
Anorexia	Mild or moderate	May be severe
Weight loss	Moderate	May be severe
Growth retardation	Usually mild	May be severe
Anal and perianal lesions	Rare	Common
Fistulas and strictures	Rare	Common
Rashes	Mild	Mild
Joint pain	Mild to moderate	Mild to moderate
Continuous?	No	Yes

Table 1. Comparison between CD and UC

There is no known medical or surgical cure for IBD. Treatment of the disease involves use of anti-inflammatory drugs that can significantly reduce the symptoms of the disease and help maintain its remission. Medications used to treat the symptoms of IBD include anti-inflammatory drugs, such as 5-aminosalicylic acid, and immunomodulators, such as azathioprine, mercaptopurine, methotrexate,and the new class known as

"biologics". These compounds regulate the immune system by efficiently triggering a Th2-mediated response that dampens Th1-mediated inflammation (8).

In this review, we will discuss the role of biologics in the management of inflammatory bowel disease.

Literature review

The introduction of biological agents – antitumour necrosis factor (TNF)-a and anti-integrin therapy – represents a new treatment paradigm for inflammatory bowel disease (IBD). Treatment goals have been discussed and partially redefined by gastroenterologists and their societies globally from focusing on clinical remission to focusingonmucosal healing and alteration of the clinical course of the diseases. Biologicals have been shown to reduce the need for both hospitalization and surgery in IBD patients (9). Biologicals are amongst the most thoroughly investigated agents prescribed by gastroenterologists, yet crucial questions persist regarding their true efficacy, when to use them and the treatment-associated risks. Randomized, controlled trials provide only a narrow view of the true effects of any agent and may raise new questions. Furthermore, the anti-TNF-a compounds have only rarely been evaluated in true clinical settings, which are compared with the best conventional therapy available, largely because of a regulatory requirement of a placebo arm in registration studies (10).

The main biological therapies for IBD are TNF-a antibodies and also anti-a4 integrin monoclonal antibodies. Initially, a chimeric (25% murine sequence and 75% human sequence) immunoglobulin (Ig)G1k subclass antibody (infliximab) was shown to be beneficial for patients with Crohn's disease (CD) (Table 2).In an attempt to reduce immunogenic responses

induced by chimeric antibodies, all murine sequences were removed to create a fully human monoclonal antibody (11).

	Infliximab	Adalimumab	Certolizumab pegol
Dosage	5 mg kg^{-1}	40 mg	400 mg
Route of administration	i.v.	s.c.	s.c.
Dosing intervals	8 weeks	2 weeks (e.o.w)	4 weeks
Induction	5 mg kg^{-1} weeks 0, 2, 6	160/80 mg (FDA) or 80/40 mg (EMA)	400 mg weeks 0, 2, 4
Dose escalation	10 mg kg^{-1} or every 4–6 weeks	40 mg e.w.	400 mg e.o.w.

i.v., intra venous; s.c., subcutaneous; e.w., every week; e.o.w., every other week; EMA, European Medicines Agency; FDA, Food and Drug Administration.

Table 2. Dosages and usage of biologicals

Anti-TNF agents have been a major advance in the management of acutely ill or corticosteroid-dependent individuals with CD or UC and in individuals with CD with fistulizing disease. There is little difference in efficacy between infliximab and adalimumab in CD; however, the data in UC seem to suggest an advantage for infliximab over adalimumab and the recently approved golimumab (12).

Methotrexate has not been shown to enhance the efficacy of infliximab, but it does reduce antibodies to infliximab development, suggesting that if used beyond a year it is possible that combining methotrexate with infliximab could enhance the durability of remission. The combination of methotrexate and anti-TNF has been especially popular among pediatricians who fear the potential of lymphoma seen (although rarely) in users of the combination of thiopurine plus anti-TNF (13). When anti-TNF agents were first introduced, there was much concern for the development of cancer and infection. These have not been borne out as major issues, although the risk for lymphoma, nonmelanoma skin cancer,

and some complex infections such as those secondary to mycobacteria and fungi remain a concern (especially as combination therapy with thiopurines is the optimal approach and they enhance the risk for those cancers and for infection). Practically, a major problem with anti-TNF therapy has been the need for alternate therapy among initial responders at a rate of ∼10% per year secondary to loss of response or intolerance (14). Individuals who lose response to one anti-TNF agent may respond to a second, although at a lower response rate. As these agents have been available for over 15 years, there has been increasing confidence in recommending anti-TNF therapy including where there is a lower degree of disease acuity compared with initial approaches reserving these agents only for the most ill patients. Furthermore, there has also been an increasing interest in determining the optimal timing and candidates for safely withdrawing anti-TNF therapy (15).

Since the application of biological drugs for treating IBD is a novel approach, there are several new biologic agents that have been recently approved or included in clinical trials or are under evaluation for determining their clinical efficacy and safety profile. Currently, therapies that manipulate leukocyte adhesion, costimulatory signaling and cytokine receptors are being evaluated as potential treatments for IBD. These alternative treatments emerged when it was observed that some of the patients under current biologic therapies with anti-TNF-α agents were primarily nonresponders or experience a loss of response, intolerance, or even presented side effects (16). Lymphocyte-endothelial interactions, mediated by adhesion molecules, are important in leukocyte migration and recruitment to sites of inflammation. The selective blockage of these adhesion molecules is a new and promising approach to treat CD. Recently approved by FDA, anti-α4 integrin monoclonal antibodies, specifically

natalizumab and vedolizumab, were effective in the treatment of moderately to severely active CD (natalizumab and vedolizumab) and for UC (vedolizumab) patients. The blockage of the T cell migration into the intestine by using anti-$\alpha 4\beta 7$ antibody vedolizumab, approved to treat adult patients, resulted in a selective barrier for the trafficking of CD4+CD45RO+ T cells. It also reduced the UC clinical score, presenting a successful remission in 33% to 50% of cases (17). Meanwhile, clinical efficacy of some therapeutic agents, such as inhibitors of leukocyte trafficking, including alicaforsen, an oligodeoxynucleotide that inhibits intercellular adhesion molecule 1 (ICAM-1) expression, are still under evaluation (18).

Among the new drugs being tested, ustekinumab, a monoclonal antibody against the p40 subunit of interleukin-12/23, approved to use in patients with moderate or severe psoriasis and psoriatic arthritis, was able to induce clinical response in patients with moderate-to severe CD, especially in those previously treated with IFX (19).

Etrolizumab, a humanized monoclonal antibody that selectively binds to the $\beta 7$ subunit of the heterodimeric integrins $\alpha 4\beta 7$ and $\alpha \mathrm{E}\beta 7$, was well tolerated in moderate to severe UC on phase II studies. Additionally, tofacitinib, a small molecule targeting Janus-activated kinase (JAK), was shown to particularly inhibit JAK1 and JAK3, also interfering with several cytokine receptors. However, there are no relevant clinical data related to this molecule (20). new clinical approaches have used the biological molecule abatacept, a fusion protein composed of the Fc portion of IgG together with the CTLA4 molecule (CTLA4-Ig), to treat different inflammatory disorders such as psoriatic arthritis, type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus. However, a phase III trial in moderateto-severe CD and UC showed no therapeutic benefits with the use

of the abatacept, indicating that blocking the T cell activation possibly compromises the activation of important regulatory T cells subsets in IBD patients (21).

Nowadays, five biologic agents are approved by FDA for the treatment of IBD: adalimumab, infliximab, golimumab, certolizumab pegol, and vedolizumab. In order to reach an effective disease remission of IBD patients, IFX standard dosage for UC and CD is usually 5 mg/kg by intravenous infusion at weeks 0, 2, and 6, followed by a maintenance regimen every 8 weeks. However, some data shows that the dosage of 10 mg/kg seems to maintain the remission for a longer period. On the other hand, ADA has shown to be effective to UC and CD by the subcutaneous administration with an initial dose of 160 milligrams, a second dose two weeks later of 80 mg, and a maintenance dose of 40 mg every other week, although it has also been shown that there is a dose-dependent effectiveness related to this drug (22). In patients with moderate to severe CD, subcutaneous administration of certolizumab pegol on subcutaneous doses of 400 mg once every 4 weeks was effective as induction and maintenance therapy. In case of lack of response, it should be given every 2 weeks. The recommended golimumab initial regimen for the treatment of UC is a 200 mg subcutaneous dose at week 0 followed by 100 mg at week 2. The maintenance therapy is 100 mg every 4 weeks. Vedolizumab was recently approved by FDA for the treatment of adults with moderately to severely active UC and CD. Dose regimen is 300 mg infused intravenously at 0, 2, and 6 weeks and the maintenance therapy at every 8 weeks thereafter (23-24).

Despite the fact that there are no suficient comparative trial data available between infliximab, adalimumab, and certolizumab pegol, they are considered as having comparable efficacy, especially when the

maintenance of remission is taking into consideration. An advantage of ADA, golimumab, and certolizumab in comparison with IFX and vedolizumab is that they can be administered by a subcutaneous injection. It is important to mention that patient's history, drug regimen, and drug efficacy create a singular scenario that should be taken into account before choosing the appropriate therapy (25).

Conclusion

Biologics provide great aid in the long term treatment of inflammatory bowel diseases but rhe loss of response and increases tolerance remain a hindrance the should be studied in the future.

References

1. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, Sadeghi A, Nixon MR, Abdoli A, Abolhassani H, Alipour V. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet gastroenterology & hepatology. 2020 Jan 1;5(1):17-30.
2. Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel diseases. Annu Rev Med. 2000;51:289–298.
3. Sands BE. From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. Gastroenterology. 2004; 126:1518–1532.
4. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. Inflammatory bowel diseases. 2006 Jan 1;12(suppl_1):S3-9.
5. Abreu MT. The pathogenesis of inflammatory bowel disease: translational implications for clinicians. Curr Gastroenterol Rep. 2002;4:481–489.
6. Cassatella M. The production of cytokines by polymorphonuclear neutrophils. Immunol Today. 1995;16:21–26.
7. Canavan C, Abrams KR, Mayberry J. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Alimentary pharmacology & therapeutics. 2006 Apr;23(8):1097-104.
8. Burger D, Travis S. Conventional medical management of inflammatory bowel disease. Gastroenterology. 2011;140:1827–1837.
9. D'haens GR, Panaccione R, Higgins PD, Vermeire S, Gassull M, Chowers Y, Hanauer SB, Herfarth H, Hommes DW, Kamm M, Löfberg R. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response?. Official journal of the American College of Gastroenterology| ACG. 2011 Feb 1;106(2):199-212.

10. Nielsen OH, Seidelin JB, Munck LK, Rogler G. Use of biological molecules in the treatment of inflammatory bowel disease. Journal of internal medicine. 2011 Jul;270(1):15-28.
11. Breedveld FC. Therapeutic monoclonal antibodies. The Lancet. 2000 Feb 26;355(9205):735-40.
12. Danese S , Fiorino G , Peyrin-Biroulet L . Biological agents for moderately to severely active ulcerative colitis: a systematic review and network metaanalysis . Ann Intern Med 2014 ; 160 : 704 – 11 .
13. Feagan BG , McDonald JW , Panaccione R *et al.* Methotrexate in combination with infliximab is no more effective than infliximab alone in patients with Crohn's disease . Gastroenterology 2014 ; 146 : 681 – 8 .
14. Targownik LE , Bernstein CN . Infectious and malignant complications of TNF inhibitor therapy in IBD . Am J Gastroenterol 2013 ; 108 : 1835 – 42 .
15. Molander P , Färkkilä M , Salminen K *et al.* Outcome after discontinuation of TNFα-blocking therapy in patients with inflammatory bowel disease in deep remission . Inflamm Bowel Dis 2014 ; 20 : 1021 – 8.
16. Danese S. Golimumab in ulcerative colitis: a'menage a trois' of drugs. Nature Reviews Gastroenterology & Hepatology. 2013 Sep;10(9):511-2.
17. De Mattos BR, Garcia MP, Nogueira JB, Paiatto LN, Albuquerque CG, Souza CL, Fernandes LG, Tamashiro WM, Simioni PU. Inflammatory bowel disease: an overview of immune mechanisms and biological treatments. Mediators Inflamm. 2015 Oct;493012(1155):2015.
18. Vegter S, Tolley K, Wilson Waterworth T, Jones H, Jones S, Jewell D. Meta-analysis using individual patient data: efficacy and durability of topical alicaforsen for the treatment of active ulcerative colitis. Alimentary pharmacology & therapeutics. 2013 Aug;38(3):284-93.
19. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. New England Journal of Medicine. 2012 Oct 18;367(16):1519-28.
20. Vuitton L, Koch S, Peyrin-Biroulet L. Janus kinase inhibition with tofacitinib: changing the face of inflammatory bowel disease treatment. Current drug targets. 2013 Nov 1;14(12):1385-91.
21. Mayer L, Kaser A, Blumberg RS. Dead on arrival: understanding the failure of CTLA4-immunoglobulin therapy in inflammatory bowel disease. Gastroenterology. 2012 Jul 1;143(1):13-7.
22. Press Announcements, FDA approves Humira to treat ulcerative colitis, 2015, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm321650.htm .
23. Blick SK, Curran MP. Certolizumab pegol. BioDrugs. 2007 May;21(3):195-201.
24. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I. Vedolizumab as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine. 2013 Aug 22;369(8):699-710.
25. Rutgeerts P, Vermeire S, Van Assche G. Biological therapies for inflammatory bowel diseases. Gastroenterology. 2009 Apr 1;136(4):1182-97.