The Cost-Effectiveness of Vedolizumab for Inflammatory Bowel Disease: A Review of the Current Literature

Yecheskel Schneider, MD, Monica Saumoy, MD, Shirley Cohen-Mekelburg, MD, Adam F. Steinlauf, MD, and Ellen J. Scherl, MD

Dr Schneider, Dr Saumoy, and Dr Cohen-Mekelburg are clinical fellows; Dr Steinlauf is an assistant professor of medicine; and Dr Scherl is a professor of clinical medicine in the Division of Gastroenterology and Hepatology at NewYork-Presbyterian/Weill Cornell Medical Center in New York, New York.

Address correspondence to:
Dr Yecheskel Schneider
1305 York Avenue, 4th Floor
New York, NY 10021
Tel: 646-962-4800
Fax: 646-962-0399
E-mail: Yss9003@nyp.org

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Abstract: The United States spends a greater share per gross domestic product on health care than any other developed country in the world. Cost-conscious, high-value care has an important role in the practice of medicine. Inflammatory bowel disease (IBD) affects 1.6 million people in the United States and is responsible for significant health care costs, with estimates as high as $31.6 billion annually, a large portion of which is attributable to the use of biologic therapies. As the number of therapeutic targets for IBD expands, gastroenterologists can anticipate the arrival of novel therapeutic agents on the market, and these may carry significant costs. Vedolizumab, a monoclonal antibody directed against the gut-selective integrin α4β7, is a novel biologic agent approved for the treatment of Crohn's disease and ulcerative colitis. Cost-effectiveness is an area of research that aims to assess the added value (in terms of both cost and utility) of diagnostic or therapeutic interventions. This article reviews the current literature evaluating the cost-effectiveness of vedolizumab for the treatment of IBD.

Inflammatory bowel disease (IBD) is a chronic, systemic, immune-mediated inflammation of the gastrointestinal tract, and can be subdivided into Crohn's disease (CD) and ulcerative colitis (UC). Although the underlying etiology of IBD has yet to be elucidated, multiple immunoregulatory pathways influenced by the environment, genetics, and microbiome have been implicated in UC and CD and are the focus of novel immune-mediated targeted therapies.[1] Most patients present between the ages of 15 and 40 years.[2] As chronic diseases, both CD and UC can cause significant impairment in quality of life.[3] In the United States, the incidences of CD and UC are 20.2 and 19.2 per 100,000 person-years, respectively, and a systematic review of the literature from 2012 suggests that the incidences of both diseases are rising.[4] The course for each individual patient can be highly variable[5]; many patients have relapsing and remitting disease, which may necessitate different therapies during the course of their lifetime.[6,7]

Table 1. Comparison of Base Case Characteristics, Competing Strategies, and Study Results

Study	IBD Type	Disease Severity	Therapy Type	Competing Strategies to VDZ	Preferred Strategy
Wilson et al[17]	UC	Moderate to severe	First-line and second-line	First-line: anti-TNF agents (ADA, IFX, GLB) and conventional therapy (IMMs, 5-ASA, corticosteroids) Second-line: ADA	VDZ (first- and second-line)
Jansen et al[18]	UC	Moderate to severe	First-line and second-line	First-line: IFX, ADA, GLB Second-line: ADA	VDZ (first- and second-line)
Yokomizo et al[19]	UC	Moderate to severe	First-line	IFX, ADA	IFX
Liu et al[20]	UC and CD	Unclear	Unclear	ADA	ADA
Bounthavong et al[21]	CD	Moderate to severe	First-line	IFX, ADA, CZP	IFX
Liu et al[22]	CD	Moderate to severe	First-line	IFX, ADA, NTZ	ADA
Erim et al[23]	CD	Moderate to severe	Third-line	Dose escalation of ADA	VDZ

5-ASA, 5-aminosalicylic acid; ADA, adalimumab; CD, Crohn's disease; CZP, certolizumab pegol; GLB, golimumab; IBD, inflammatory bowel disease; IFX, infliximab; IMMs, immunomodulators; NTZ, natalizumab; TNF, tumor necrosis factor; UC, ulcerative colitis; VDZ, vedolizumab.

Treatment of IBD is aimed at decreasing inflammation. Current therapies include aminosalicylates, corticosteroids, immunomodulators (eg, azathioprine or 6-mercaptopurine), and biologic agents.[8] The goals of biologic therapy are mucosal healing (MH) and reversal of the natural history of progressive structural damage due to chronic inflammation. Biologic agents currently approved for use in CD or UC can be divided into 2 main categories: anti–tumor necrosis factor (TNF) agents (eg, infliximab [Remicade, Janssen], adalimumab [Humira, AbbVie], golimumab [Simponi, Janssen], and certolizumab pegol [Cimzia, UCB]), and anti-integrins (eg, natalizumab [Tysabri, Biogen], which targets α4, and vedolizumab [Entyvio, Takeda Pharmaceuticals], which specifically targets the gastrointestinal-selective integrin α4β7).[9,10] With the rising use of biologic agents, there has been an increase in the cost of IBD management.[11] Both CD and UC carry significant economic burdens for individual patients and for the health care system in general.[12] In the United States, the direct and indirect costs of IBD management in 2014 were estimated to range from $14.6 billion to $31.6 billion.[13] A 2012 study estimated that direct health care insurer and out-of-pocket expenditures for CD were responsible for over $2 billion per year.[14] A study by Park and colleagues evaluated the health-related costs of CD in the context of the current era of biologic use, and found that anti-TNF agents accounted for approximately 29.5% of total costs.[15] The distribution of costs reveals significant contributions from medications, including biologic agents, which are significantly more expensive than other therapies for IBD.[12] As new therapies are approved for IBD, it is important to balance the increase in cost with the increase in effectiveness gained. The economic burden of IBD is significant, and cost-consciousness when choosing appropriate therapy is a necessary component of management.

Cost-effectiveness analysis is a research tool to compare 2 or more potential treatment options. The goal is to determine whether the increase in effectiveness (often represented by quality-adjusted life year [QALY]) and its associated increase in cost are below a set willingness-to-pay threshold. These outcomes are thought of in terms of the incremental cost-effectiveness ratio, defined as the difference in cost divided by the difference in effectiveness.[16] Often, a clinical scenario is simulated in a predictive model, and the study can then be calculated from payer, societal, or patient perspectives. Each perspective will alter the costs that are input into the model. This review evaluates the current evidence regarding the cost-effectiveness of vedolizumab for the treatment of IBD.

Literature Review

Literature exploring the cost-effectiveness of vedolizumab can be divided into studies for CD and studies for UC. In each group, studies vary upon where within the treatment algorithm vedolizumab is being utilized. It is important to evaluate each cost-effectiveness study by considering the clinical scenario proposed by the authors. (Table 1 has a summary of base case characteristics.) For example, one study may obtain very different results by studying vedolizumab for UC after anti-TNF failure as opposed to studying vedolizumab for first-line therapy of CD in

Table 2. Comparison of Study Design Characteristics

Study	Model Type	Time Horizon	Perspective (Currency Reported)	Choice of Effectiveness Measure or Outcome
Wilson et al[17]	Markov model	5 years and lifetime	Payer (US dollars)	QALY, total number in remission, total number of surgeries
Jansen et al[18]	Network meta-analysis	1 year	Unclear (British pounds)	Cost per response, cost per remission
Yokomizo et al[19]	Decision tree	1 year	Payer (US dollars)	Cost per remission
Liu et al[20]	Network meta-analysis	1 year	Unclear (US dollars)	Cost per response, cost per remission
Bounthavong et al[21]	Markov model	Lifetime	Payer (US dollars)	QALY
Liu et al[22]	Network meta-analysis	52-60 weeks	Unclear (US dollars)	Cost per remission
Erim et al[23]	Markov model	1 year	Payer (US dollars)	QALY

QALY, quality-adjusted life year.

anti-TNF–naive patients. Additionally, one has to consider which treatment options are being compared (eg, specific anti-TNF agents, corticosteroids, surgery). Of equal importance is to evaluate the study characteristics, such as the choice of model, the time horizon, and the perspective of the study. (Table 2 has a summary of study characteristics.)

Cost-Effectiveness Studies of Vedolizumab for Ulcerative Colitis

Several studies have examined the cost-effectiveness of vedolizumab for UC. Wilson and colleagues compared 3 treatment options for moderate to severe UC in anti-TNF–naive patients from a payer's perspective using a Markov model (a time transition model that can cycle between different health states) with a 5-year time horizon.[17] The 3 treatment arms included vedolizumab, anti-TNF agents (specifically adalimumab, infliximab, and golimumab), and conventional therapy (immunomodulators, aminosalicylates, and corticosteroids). The authors also compared vedolizumab and adalimumab as second-line treatment for patients who previously failed anti-TNF therapy. Effectiveness outcomes were calculated QALY, remission, and total number of surgeries. The authors found that patients on vedolizumab spent more time in the clinical response and remission health states and experienced fewer surgeries than patients in the other treatment arms. When the time horizon was extended to that of an individual's lifetime, the incremental cost-effectiveness ratio for vedolizumab was cost-effective (below the set willingness-to-pay threshold) when compared with the other treatments. The study group also created a second model for patients who had previously failed anti-TNF therapy. In this model, vedolizumab was more cost-effective compared to adalimumab as second-line therapy over both 5-year and lifetime horizons.[17]

Similar findings were reported in a study by Jansen and colleagues.[18] The authors evaluated the cost per clinical outcome of vedolizumab vs anti-TNF agents for the treatment of moderate to severe UC. They performed a systematic literature search and included randomized, controlled trials that studied infliximab, adalimumab, golimumab, or vedolizumab in order to perform a network meta-analysis. The study was performed calculating costs in British pounds. Evaluated outcomes included clinical response and clinical remission (each defined by Mayo score, as reported in the individual trials that were evaluated). The authors found that the cost per patient and number needed to treat (NNT) for sustained response and remission at 52 weeks were lowest for vedolizumab in anti-TNF–naive patients. For anti-TNF–experienced patients, the authors compared vedolizumab to adalimumab; similar to Wilson and colleagues,[17] Jansen and colleagues found that vedolizumab had lower costs and NNT.[18] The authors concluded that vedolizumab may potentially provide better clinical and economic value than other biologic agents.[18]

Although the previous 2 studies found vedolizumab to be more cost-effective than other biologic agents for both anti-TNF–naive and –experienced patients, additional studies have shown vedolizumab to be less cost-effective than other biologic agents for the treatment of UC. Yokomizo and colleagues[19] created a decision analytic model to compare cost per remission (defined as MH) for infliximab, adalimumab, or vedolizumab

as first-line therapy in patients with moderate to severe UC, from a payer's perspective. The authors found that infliximab had the lowest cost per MH at $99,171/MH; vedolizumab was $301,969/MH.[19] Additionally, a probabilistic sensitivity analysis indicated that infliximab was more cost-effective in 95% of the 10,000 simulations.[19] The authors concluded that infliximab was the most cost-effective option for first-line therapy of moderate to severe UC.

Liu and colleagues performed an indirect comparison of cost per responder and remitter comparing adalimumab and vedolizumab.[20] The authors utilized data found in published randomized, controlled trials comparing the respective biologic medications with placebo, and created a network meta-analysis. The main outcomes were the cost per incremental responder and the cost per incremental remitter. The authors calculated costs for both UC and CD based on their respective market share (23% for UC and 77% for CD). The study found that the 1-year treatment costs per incremental responder in patients with IBD were greater for vedolizumab at $406,629 vs adalimumab at $197,902. Similarly, the cost per incremental remitter for vedolizumab was $336,332 vs $197,874 for adalimumab. These findings were consistent with sensitivity analyses that were performed. The authors concluded that costs per responder and remitter for patients with CD and UC were lower for patients who received adalimumab compared with patients who received vedolizumab. Notably, the authors did not state if these patients were anti-TNF–naive.

Cost-Effectiveness Studies of Vedolizumab for Crohn's Disease

Cost-effectiveness studies have evaluated the use of vedolizumab in CD, although in fewer numbers than studies for UC. Bounthavong and colleagues performed a cost-effectiveness study using a Markov state transition model with a lifetime horizon to evaluate the most cost-effective biologic agent for patients with moderate to severe CD from a US payer's perspective.[21] The comparator treatments included infliximab, adalimumab, certolizumab pegol, and vedolizumab. The model did not specifically state whether these patients were biologic-naive, although this is likely the case given the treatments that the authors evaluated, which included mostly anti-TNF agents. Bounthavong and colleagues concluded that infliximab was the most cost-effective strategy, and vedolizumab was eliminated because the incremental cost-effectiveness ratio was above the set willingness-to-pay threshold.[21]

Liu and colleagues also performed a study evaluating the cost-effectiveness of vedolizumab for first-line treatment of CD.[22] They evaluated the choice of biologic therapy (infliximab, adalimumab, natalizumab, or vedolizumab) for patients with moderate to severe CD, who were presumably anti-TNF–naive. They examined the relative efficacy and cost per remitter for each of the biologic agents being compared. The study utilized data from published randomized, controlled trials to perform a network meta-analysis, comparing 1-year clinical remission rates for patients who responded to the induction phase of treatment. By using the NNT, Liu and colleagues calculated the cost per incremental remitter and found that the cost was lowest for adalimumab ($189,891) and highest for vedolizumab ($281,508), although this difference was not statistically significant.[22] The authors concluded that adalimumab costs per remitter were numerically lower than for vedolizumab for patients with moderate to severe CD.

Erim and colleagues created a Markov model to evaluate the role of vedolizumab as a third-line, rescue therapy for patients with moderate to severe CD who have failed infliximab and adalimumab.[23] The model assessed patients from a US payer's perspective over a 12-month period with 2-week cycles between state transitions. The authors designed the model to study the most cost-effective option for patients who failed infliximab and were then placed on adalimumab; patients could either respond, be a primary nonresponder, or be a secondary nonresponder to adalimumab. All nonresponders (primary or secondary) could then undergo 2 competing strategies: adalimumab dose intensification (40 mg weekly) or switching classes to vedolizumab. Patients in the adalimumab dose intensification arm could switch over to vedolizumab if they did not respond to the increased dose or if they failed to maintain response. The study found that the strategy that used vedolizumab initially, rather than dose escalating, was most cost-effective. The strategy of dose escalation of adalimumab followed by vedolizumab had an incremental cost-effectiveness ratio of $611,974/QALY, which was well above the authors' set willingness-to-pay threshold of $100,000/QALY.[23]

Conclusion

Comparing cost-effectiveness studies is challenging and requires paying close attention to model construction, probability and cost inputs, and the choice of outcomes. Current literature suggests that from a cost-effectiveness perspective, vedolizumab might be a reasonable option for first- and second-line therapy for moderate to severe UC. To date, there are no studies to suggest that vedolizumab would be the most cost-effective option for first-line therapy for moderate to severe CD. However, studies suggest that vedolizumab has a role later on in an individual's treatment course. Current treatment algorithms are

limited; more studies are warranted to evaluate the role of vedolizumab as either second- or third-line therapy for CD, as well as to evaluate the comparative effectiveness of novel therapies that have not yet been approved for the treatment of IBD, such as ustekinumab (Stelara, Janssen) and tofacitinib (Xeljanz, Pfizer). Many factors must be considered when faced with the real-time clinical decision of choosing biologic therapy for a patient, including the patient's individual preferences, unique medical history, and the potential side effects of each therapy. There are unmet needs for individualized treatment in IBD and for approaches that improve delivery and response to therapy while simultaneously providing cost-conscious care.

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References

1. Yadav V, Varum F, Bravo R, Furrer E, Bojic D, Basit AW. Inflammatory bowel disease: exploring gut pathophysiology for novel therapeutic targets [published online May 6, 2016]. *Transl Res.* doi:10.1016/j.trsl.2016.04.009.
2. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. *Scand J Gastroenterol*. 2015;50(8):942-951.
3. Irvine EJ. Quality of life of patients with ulcerative colitis: past, present, and future. *Inflamm Bowel Dis*. 2008;14(4):554-565.
4. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology.* 2012;142(1):46-54.e42; quiz e30.
5. Liverani E, Scaioli E, Digby RJ, Bellanova M, Belluzzi A. How to predict clinical relapse in inflammatory bowel disease patients. *World J Gastroenterol*. 2016;22(3):1017-1033.
6. Fell JM, Muhammed R, Spray C, Crook K, Russell RK; BSPGHAN IBD Working Group. Management of ulcerative colitis. *Arch Dis Child*. 2016;101(5):469-474.
7. Kammermeier J, Morris MA, Garrick V, Furman M, Rodrigues A, Russell RK; BSPGHAN IBD Working Group. Management of Crohn's disease. *Arch Dis Child*. 2016;101(5):475-480.
8. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology.* 2015;148(5):1035-1058.e3.
9. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab [published online June 1, 2016]. *J Crohns Colitis*. doi:10.1093/ecco-jcc/jjw092.
10. Iskandar HN, Dhere T, Farraye FA. Ulcerative colitis: update on medical management. *Curr Gastroenterol Rep*. 2015;17(11):44.
11. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. *Nat Rev Gastroenterol Hepatol*. 2015;12(9):537-545.
12. Park KT, Bass D. Inflammatory bowel disease-attributable costs and cost-effective strategies in the United States: a review. *Inflamm Bowel Dis*. 2011;17(7):1603-1609.
13. Mehta F. Report: economic implications of inflammatory bowel disease and its management. *Am J Manag Care*. 2016;22(3)(suppl):s51-s60.
14. Gunnarsson C, Chen J, Rizzo JA, Ladapo JA, Lofland JH. Direct health care insurer and out-of-pocket expenditures of inflammatory bowel disease: evidence from a US national survey. *Dig Dis Sci*. 2012;57(12):3080-3091.
15. Park KT, Colletti RB, Rubin DT, Sharma BK, Thompson A, Krueger A. Health insurance paid costs and drivers of costs for patients with Crohn's disease in the United States. *Am J Gastroenterol*. 2016;111(1):15-23.
16. Torrance G, Siegel J, Luce B. *Framing and Designing the Cost-Effectiveness Analysis.* New York, NY: Oxford University Press; 1996.
17. Wilson M, Mody R, Ursan J, Carr S. Cost-effectiveness of vedolizumab compared with conventional therapy and biologics for treatment of moderately to severe active ulcerative colitis in the United States. *Gastroenterology*. 2015;148(4):S198-S199.
18. Jansen J, Mody R, Ursan I, Lorenzi M, Patel H, Alberton M. Cost per clinical outcomes with biologics for the treatment of moderately to severe active ulcerative colitis. *J Crohns Colitis*. 2015;9(1):S239-S240.
19. Yokomizo L, Limketkai B, Park KT. Cost-effectiveness of adalimumab, infliximab or vedolizumab as first-line biological therapy in moderate-to-severe ulcerative colitis. *BMJ Open Gastroenterol*. 2016;3(1):e000093.
20. Liu Y, Ozbay A, Skup M, Reichmann W, Diener M, Chao J. Comparison of cost per responder and remitter in patients with inflammatory bowel disease in the United States: an indirect comparison of adalimumab and vedolizumab. *Am J Gastroenterol*. 2014;109(suppl 2):S479.
21. Bounthavong M, Bao YH, Devine B, Veenstra DL. A cost-utility analysis of biologics for moderate-to-severe Crohn's disease: evidence synthesis using a Bayesian network meta-analysis. *Value Health*. 2015;18(3):A224-A225.
22. Liu Y, Ozbay A, Reichmann E, Revol C, Chao J, Skup M. Cost per remitter associated with biologic therapies for Crohn's disease. *Gastroenterology*. 2015;149(4):S862-S863.
23. Erim DO, Mahendraratnam N, Okafor PN, Wheeler SB. The value of vedolizumab as rescue therapy in moderate-severe Crohn's disease patients with adalimumab non-response in the USA. *J Crohns Colitis*. 2015;9(8):669-675.