Cost-Effectiveness of Vedolizumab in the Treatment of Moderate-to-Severe Crohn’s Disease in China

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ABSTRACT

Introduction: To compare the cost-effectiveness of vedolizumab with that of conventional therapy in patients with moderate-to-severe active Crohn’s disease (CD) in China.

Methods: A decision tree and Markov model were built to predict the lifetime cost and health outcomes in the induction phase and maintenance phase of vedolizumab treatment and conventional therapy (a combination of corticosteroids, immunosuppressants, and aminosalicylates) in adult patients with moderate-to-severe active CD from the perspective of China’s healthcare system. Clinical efficacy and health utility were derived from the GEMINI 2 and GEMINI 3 trials and published literature. Costs were mainly obtained from clinical physician surveys in China and are presented in 2020 US dollars. Health outcomes (quality-adjusted life years, QALYs) and costs were discounted at an annual rate of 5%. The incremental cost per QALY gained was used to compare the cost-effectiveness of the two treatments. One-way and probabilistic sensitivity analyses (PSAs) were performed to test the robustness of the model.

Results: The model predicted more QALYs (9.92 vs 9.00 QALYs) and lower incurred costs ($288,284 vs $309,680) in vedolizumab than in conventional therapy in a mixed population (anti-TNF-naïve and anti-TNF-failure populations) over a lifetime horizon in the base-case analysis. Similar results were observed in the anti-TNF-naïve and anti-TNF-failure subgroups of patients with CD. One-way sensitivity analysis results suggested that health state cost was the most influential factor in the model. The PSA results supported the dominance of vedolizumab in the base-case analysis.

Conclusion: Vedolizumab appears to be a cost-effective strategy option in the treatment of adult patients with moderate-to-severe active CD in China in both anti-TNF-naïve and anti-TNF-failure populations.

Keywords: China; Conventional therapy; Cost-effectiveness analysis; Crohn’s disease; Vedolizumab
Key Summary Points

In recent years, cost-effectiveness analysis has been applied to determine entry onto the National Reimbursement Drug List in China. With the limited alternative drugs for the treatment of Crohn’s disease (CD), more than 90% of patients are treated with conventional therapy drugs. As a new-generation biological drug, vedolizumab (VDZ) was approved to treat CD in March 2020 in China and it provided a new option for the patients.

Economic evaluation evidence of vedolizumab is needed to support health decision-making in China. A hybrid decision tree and Markov model were first developed to compare the lifetime costs and health outcomes of VDZ and CT in the treatment of Chinese patients with moderate-to-severe active CD using published efficacy data of GEMINI 2 and GEMINI 3 trials in China.

Compared with CT, VDZ appears to be a cost-effective option in the treatment of adult patients with moderate-to-severe active CD in China in both anti-TNF- naïve and anti-TNF-failure populations.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.14627499.

INTRODUCTION

Crohn’s disease (CD) is a chronic progressive and relapsing inflammatory bowel disease (IBD) that affects the gastrointestinal tract and leads to bowel damage and disability with the development of disease [1]. The incidence and prevalence of CD have increased worldwide, especially in developed countries [2]. The incidence rate varies from 16.7 to 318.5 per 100,000 persons in North America, while it varies from 0.88 to 67.9 per 100,000 persons in Asia and the Middle East [2]. China is one of the developing countries facing a steady increase in patients with CD, and the incidence rate ranges from 0.07 to 1.31 per 100,000 persons [3]. Patients with CD suffer from a heavy disease burden, poor quality of life, and financial problems [4]. It is estimated that the direct costs of CD vary from $18,022 to $18,932 per patient-year in the USA and from €2898 to €6960 in European countries [5, 6]. In China, with the increasing usage of healthcare resources for IBD treatment, the mean direct cost rose to $11,669 per patient-year in 2019 [7].

Under current medical technology conditions, CD is an incurable disease. The treatment of CD mainly focuses on relieving symptoms and achieving long-term remission [1]. For conventional therapy (CT), corticosteroids, immunosuppressants and aminosalicylates are used to treat CD in most instances [1]. In China, more than 90% of patients are treated with CT drugs [8]. Compared with CT, biological regimens (e.g., anti-TNFα agents, anti-integrins) are effective in patients with CD in achieving clinical response and remission and are treatment alternatives, especially for patients who fail conventional treatment [9, 10]. However, 10–30% of patients with IBD have no response to initial anti-TNF therapy, and over 23% of patients with IBD lose response during the course of treatment [11]. As a new-generation biological drug, vedolizumab is an intravenously administered humanized immunoglobulin G1 monoclonal antibody that blocks α4β7 integrin and modulates the gut lymphocyte trafficking [1]. The post hoc analysis results of the GEMINI 2 and GEMINI 3 trials suggest that vedolizumab is effective for both anti-TNF-naïve and anti-TNF-failure patients with CD [12].

Economic evaluations play an important role in health decision-making and drug reimbursement in China [13]. Vedolizumab was approved by China’s National Medical Products Administration (NMPA) in adults with moderate-to-
severe active CD in March 2020 and is covered by Chinese national basic insurance. This study aimed to compare the cost-effectiveness of vedolizumab with that of CT in patients with moderate-to-severe active CD in China.

METHODS

Model Description

The model developed to perform cost-effectiveness analysis in this study was based on a previous model submitted to the National Institute for Health and Care Excellence (NICE) and subsequently revised [14]. This model consists of a decision tree (Fig. 1a) to simulate short-term induction therapy and a lifetime Markov model (Fig. 1b) to simulate maintenance therapy. Five health states are structured, three of which are defined by the Crohn’s Disease Activity Index (CDAI) score: remission (CDAI score less than 150), mild (CDAI score 150–220), and moderate-to-severe (CDAI score 220–600). The other two health states are surgery and death. During the induction phase, adults with moderate-to-severe active CD entered the model and initiated treatment with vedolizumab or CT. Patients who used biological therapy were monitored for response to the drug at the end of a 6-week induction phase, which was consistent with the duration in clinical trials [15, 16].

Patients on vedolizumab treatment who responded to therapy and did not discontinue because of adverse event intolerability entered

![Decision tree framework of induction phase. AEs adverse events, CT conventional therapy, MS moderate-to-severe, CDAI Crohn's Disease Activity Index. Response is defined as reduction in the CDAI score of at least 70 points or remission (CDAI score less than 150 points).](a)

![Markov model underlying the maintenance phase. R remission, M mild, MS moderate-to-severe, S surgery, D death](b)
the biological Markov model with 8-week cycles for maintenance therapy. In the Markov model, patients could transition among each of the four health states (remission, mild, moderate-to-severe, and surgery), transition to death, or remained in the same state at the end of each cycle. Patients in the moderate-to-severe health state after 1 year on vedolizumab treatment would discontinue because of a lack of response and switched to CT or surgery. Patients who discontinued because of adverse events (assumed to occur only in the biological arm) were assumed to switch to CT in the maintenance phase. In the CT arm, patients who responded in induction phase entered the Markov model for CT. Otherwise, patients were assumed to stay in a moderate-to-severe state until they required surgery if they failed to respond to induction treatment.

From China’s healthcare system perspective, this model simulated the disease progression of adult patients with CD over a lifetime horizon. Costs were adjusted to 2020 US dollar currency. Health outcomes (quality-adjusted life years, QALYs) and costs were discounted annually at 5% in line with the recommendation of Chinese guidelines for pharmacoeconomic evaluation [17].

Model Inputs and Data Sources

**Patient Characteristics**
The model focused on adult patients with moderate-to-severe active CD in China, which was defined as having CDAI scores over 220. The mean age of the patients was 37.3 years, and 55.4% were male, with an average weight of 50.83 kg [3]. A hypothetical mixed population cohort of 1000 anti-TNF-naïve and anti-TNF-failure patients were included in the simulation. Each subgroup of the mixed population was analyzed individually.

**Treatments**
In the biological arm, vedolizumab was given in 300-mg intravenous infusions at weeks 0, 2 and 6 (if had response) in the induction phase and every 8 weeks in the maintenance phase. In the CT arm, a combination of corticosteroids, immunosuppressants, and aminosalicylates was given (including mesalazine, prednisolone, azathioprine, sulfasalazine, budesonide, balsalazide, olsalazine, methotrexate, etc.), which was in line with the recommendation in Chinese guidelines for patients with CD [18].

**Clinical Efficacy and Transition Probability**
Clinical efficacy included the response and remission rate for the induction phase and the probability of staying in remission or mild disease during the maintenance phase. Response was defined as a decrease in the CDAI score of more than 70 points, while remission was defined as the CDAI score of 150 or less. The efficacy data of response and remission in each group were derived from two randomized clinical trials (RCTs) (GEMINI 2 and GEMINI 3) of comparisons of vedolizumab with CT plus placebo biological therapy [15, 16]. The probability of surgery was based on published literature [19, 20]. The transition probabilities for health states in each cycle are presented in Tables 1–3 in supplementary material.

**Adverse Events and Discontinuation**
The probabilities of adverse events and discontinuation were based on clinical trials [15, 16] and are presented in Table 1. In this model, discontinuation occurred when there was a lack of response to induction treatment, a loss of response in the maintenance phase, and adverse event intolerability in the vedolizumab arm [15, 16].

**Mortality**
Age- and sex-specific all-cause mortality was obtained from the Chinese general population [21]. Mortality was adjusted according to the patients’ baseline in this model, and an exponential distribution was estimated to predict mortality in each cycle with increasing age. The health-state-specific relative risk (RR) of mortality for each health state was estimated from published literature [22]. Compared with remission, the RRs of mortality for mild, moderate-to-severe, and surgery were 1.27, 2.26, and 3.22, respectively, with the progression of disease [22].
The health state utility and disutility applied in this model were systematically identified from published sources (Table 2) [23–29]. QALYs were calculated by using utility values multiplying by the duration in the health state.

**Costs**
Drug acquisition and administration costs, health state costs, and adverse event management costs were included in this model (Table 2). The price of vedolizumab was the shortlisted price of China’s National Reimbursement Drug List in 2020 [30]. The combination of treatments for CT was based on a

### Table 1 Model inputs of clinical efficacy, adverse events, and discontinuation

|                  | Vedolizumab | CT          | References |
|------------------|-------------|-------------|------------|
|                  | Mixed       | Anti-TNF naïve | Anti-TNF failure | Mixed | Anti-TNF naïve | Anti-TNF failure |
| **Clinical efficacy** |             |             |             |       |             |             |
| At the end of the induction phase |             |             |             |       |             |             |
| 6-week probability of response | 48.02% | 53.75% | 45.25% | 33.80% | 38.71% | 30.84% | [15, 16] |
| 6-week probability of remission | 16.78% | 21.88% | 13.31% | 9.86% | 10.32% | 9.69% | [15, 16] |
| During the maintenance phase |             |             |             |       |             |             |
| Annual probability of response | 47.40% | 65.15% | 29.27% | 35.29% | 42.25% | 26.92% | [15, 16] |
| Annual probability of remission | 38.96% | 51.52% | 28.05% | 21.57% | 26.76% | 12.82% | [15, 16] |
| **Incidence of AEs** |             |             |             |       |             |             |
| Serious infection | 0.69% | 1.49% | [15, 16] |
| Tuberculosis | 0.00% | 0.00% | [15, 16] |
| Malignancy (including lymphoma) | 0.00% | 0.05% | [15, 16] |
| Acute hypersensitivity reactions | 0.00% | 0.00% | [15, 16] |
| Skin site reactions | 0.93% | 4.50% | [15, 16] |
| Probability of discontinuation\* |             |             |             |       |             |             |
| Induction phase | 9.01% | 13.23% | 5.68% | – | [15, 16] |
| Maintenance phase per cycle | 34.65% | 15.49% | 68.29% | – | [15, 16] |

*VDZ* Vedolizumab, *CT* conventional therapy, *AE* adverse event

\* Discontinuation due to AEs is applicable only to responders on biological treatments because non-responders on biologics switch to CT and continue receiving such until the end of the model’s time horizon or until the patients require surgery.

**Health State Utility and Disutility**
The health state utility and disutility applied in this model were systematically identified from published sources (Table 2) [23–29]. QALYs were calculated by using utility values multiplying by the duration in the health state.
clinical physician survey of 18 doctors in 18 tertiary hospitals in China in 2019, as well as the related costs, summarized in Tables 4 and 5 in the supplementary material. Mesalazine (46%) was the most commonly used drug in CT, followed by prednisolone (41%), and the weighted cost was $362.5 per cycle in China. In addition, health state costs, administration fees, and adverse event treatment costs were derived from the clinical expert survey mentioned above.

### Cost-Effectiveness Analysis

In the base-case analysis, lifetime discounted costs and health outcomes were calculated for biological treatment and CT in a mixed population (anti-TNF-naive and anti-TNF-failure patients). The incremental cost per QALY gained was compared with the willingness-to-pay threshold in China, three times the Chinese GDP per capita in 2020 ($31,500). Values for the subgroups of anti-TNF-naive and anti-TNF-failure patients were estimated.

One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed to validate the robustness of specific parameter estimates, given their uncertainty. Variation in the parameter values of one-way sensitivity analysis was based on the 95% confidence interval or ± 20% when such data were not available. PSA was carried out by 5000 Monte Carlo simulations varying all input parameters at the same time on the basis of prespecified distributions. Cost and mortality RR, rate and utility, and transition probability parameters were assumed to follow gamma, beta, and Dirichlet distributions.

| Table 2 Model inputs of costs and health utility |
|-----------------------------------------------|
| Cost ($) | Utility | References |
| Drug cost per cycle | | |
| Vedolizumab induction phase | 1539.4b | – |
| Vedolizumab maintenance phase | 769.7 | – |
| Conventional therapya | 362.5 | – |
| Administration cost per cyclea | 50.7 | – |
| Health state costs per cyclea | | Health state utility |
| Remission | 386.8 | 0.83 |
| Mild | 440.9 | 0.69 |
| Moderate-to-severe | 1949.9 | 0.42 |
| Surgery | 10,601.8 | 0.42 |
| Costs of AEs per eventa | | AE utility decrement |
| Serious infection | 1504.2 | – 0.47 |
| Tuberculosis | 815.3 | – 0.50 |
| Malignancy (including lymphoma) | 1507.4 | – 0.18 |
| Acute hypersensitivity reactions | 234.0 | – 0.10 |
| Skin site reactions | 46.8 | – 0.03 |

**AE** adverse event

a The price information is based on the survey of 18 clinical physicians from 18 tertiary hospitals in China. b The cost was for weeks 0 and 2. A third injection was given if had response at week 6
This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. No patient identifiable data were involved in the analysis. Therefore, institutional review board approval was not required.

RESULTS

Base-Case Analysis

The results of the base-case analysis that compared vedolizumab and CT in patients with CD over a lifetime horizon are presented in Table 3. For the mixed (anti-TNF-naïve and anti-TNF-failure patients) population, treatment with vedolizumab resulted in 0.92 more QALYs (9.92 vs 9.00 QALYs) gained but lower discounted lifetime costs ($288,284 vs $309,680) than treatment with CT. In addition, vedolizumab therapy led to a higher QALY gained per patient (1.40 vs 0.58 QALYs) and a lower incremental cost ($33,484 vs $13,076) in the anti-TNF-naïve population than in the anti-TNF-failure population compared with CT. Therefore, biological treatment with vedolizumab appears to be a dominant strategy in patients with moderate-to-severe CD.

Sensitivity Analysis

The results of one-way sensitivity analyses are shown in Fig. 2. The incremental cost per QALY gained for vedolizumab was most sensitive to the health state costs, followed by average starting age entered in the model, for anti-TNF-naïve patients, anti-TNF-failure patients, and the mixed population. In addition, the one-way sensitivity analysis results were in line with the base-case analysis results; compared with CT, vedolizumab seemed to be a dominant strategy when the parameters varied with the estimated range.

The PSA results were robust to changes in all parameters at the same time following the pre-defined distribution and assumptions (Fig. 3). In the mixed population, vedolizumab was cost-effective in 100% of simulations and dominant in over 99% of all simulations (fourth quadrant) compared with CT. Similar PSA results were

Table 3 Results of base-case analyses

|                  | Vedolizumab | Conventional therapy | Difference |
|------------------|-------------|----------------------|------------|
| Mixed population |             |                      |            |
| Costs            | 288,284     | 309,680              | −21,397    |
| QALYs            | 9.92        | 9.00                 | 0.92       |
| ICER ($ per QALY gained) | | | Dominant |
| Anti-TNF-naïve population |         |                      |            |
| Costs            | 264,301     | 297,785              | −33,484    |
| QALYs            | 10.86       | 9.46                 | 1.40       |
| ICER ($ per QALY gained) | | | Dominant |
| Anti-TNF-failure population | | |            |
| Costs            | 303,551     | 316,627              | −13,076    |
| QALYs            | 9.32        | 8.74                 | 0.58       |
| ICER ($ per QALY gained) | | | Dominant |

ICER incremental cost-effectiveness ratio
obtained in the subgroups of anti-TNF-naïve and anti-TNF-failure patients.

DISCUSSION

To our knowledge, this study was the first cost-effectiveness analysis of vedolizumab versus CT in adult patients with moderate-to-severe active CD in China. The base-case analysis results suggested that vedolizumab was a dominant strategy to treat anti-TNF-naïve, anti-TNF-failure, and mixed patients with CD in China compared with CT. Health state costs and the average starting age were the most influential factors of cost-effectiveness. The results of one-way sensitivity analyses and PSAs were robust to those of base-case analyses. Compared with conventional therapy, vedolizumab resulted in 0.92 QALYs gained for patients with CD. In other words, it was equivalent to patients living in full health for 0.92 years. From this aspect, the absolute difference was not small and the improvement of health was acceptable. Besides that, more than 10,000 US dollars could be saved, which was roughly equivalent to the GDP per capita in China in 2020.

In this study, the clinical efficacy of response and remission in the induction and maintenance phases were mainly estimated from two RCTs [15, 16] (GEMINI 2 and GEMINI 3) comparing vedolizumab and CT plus placebo biological therapy. The GEMINI 2 trial [16] was designed to evaluate clinical efficacy and safety for induction and maintenance treatment, while the GEMINI 3 trial [16] focused only on induction therapy. The higher response and remission rates observed in vedolizumab arms resulted in an improvement in overall survival and more QALYs gained.

Discontinuation was defined as lack of response, a loss of response, or an intolerability of adverse events. In this model, discontinuation was assumed to occur only in biological therapy, while patients on CT would receive treatment until the end of the simulation horizon or transition to the surgery state. High discontinuation rates were observed in the anti-TNF-failure patients in the maintenance phase, reflecting the severity of disease in the subgroup population and the challenges in maintaining response. Approximately 68% of patients in GEMINI 2 lost response at week 52 [16].

Health state utility was calculated using a linear regression estimated by Buxton and colleagues [23] to map CDAI scores to EQ-5D utility values with the algorithm $\text{EQ-5D} = 0.9168 - 0.0012 \times \text{CDAI}$. The average of the CDAI range for each health state was applied to derive utility. For the surgery state, patients experience a period of decremental quality of life after transitioning from the moderate-to-severe state before the surgical procedure and then progressively improving to the remission or mild state after the surgical procedure for the remainder of the cycle in the maintenance phase. Thus, the surgery state was assumed to have the same utility value as moderate-to-severe disease in the model [22, 23].

Two health technology assessment (HTA) reports of vedolizumab in the treatment of adult patients with moderate-to-severe active CD were published by NICE [14] and Scottish Medicines Consortium (SMC) [31]. In the NICE single technology appraisal, the model structure submitted by the company was similar to that in this study. Compared with CT, the incremental cost-effectiveness ratio (ICER) of vedolizumab was £21,620 per QALY gained within the anti-TNF-failure population, while it was above £30,000 per QALY gained in the mixed population and anti-TNF-naïve population. However, vedolizumab therapy was a cost-saving strategy when the patient access scheme was proposed in the SMC report, which was in line with our study. Vedolizumab was recommended to be used in anti-TNF-failure populations in NHS England and Scotland [14, 31].

A universal health coverage policy has been applied in China for many years. To improve patient access to high-value drugs, China’s...
National Healthcare Security Administration started price negotiations with pharmaceutical manufacturers in 2017 [13]. To be listed on the National Drug Reimbursement List, the manufacturer of vedolizumab has reached an agreement with the Chinese government to decrease the price by 71% in 2020. Therefore, the agreement price of vedolizumab applied in this model from the perspective of China’s healthcare system incurred lower costs than those in other countries’ settings. In China, vedolizumab is accepted to cover both anti-TNF-naïve and anti-TNF-failure adult patients with moderate-to-severe active CD by national medical insurance. Moreover, under the current policy in China, renegotiation of the price will be carried out every 2 years by the government. Economic evaluation evidence is needed to support the decision of whether the drug will remain covered by national medical insurance or will be dropped from the reimbursement list in China. As a result of the lack of local economic evaluation information of vedolizumab in the treatment of patients with CD in China, this study is helpful and provides the evidence to inform decision-making.

There are some limitations in this study. Local costs were mainly derived from the clinical physician survey in 18 tertiary hospitals in China, and only direct medical costs were analyzed in the model, which may have impacted the cost-effectiveness, as the results illustrated in the one-way sensitivity analysis. The efficacy data simulated in the model were mainly from RCTs conducted in multiple centers, which may not reflect real clinical practice in China. The results of the sensitivity analysis showed the robustness of the model.

CONCLUSION

This study suggested that vedolizumab therapy appears to be a cost-effective strategy compared with CT in China. In all subgroups, vedolizumab was cost-effective compared with CT in the treatment of adults with moderate-to-severe active CD in China.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. All data applied in this study were obtained from published literature, public data and expert surveys. No patient identifiable data were involved in the analysis. Therefore,
institutional review board approval was not required.

**Data Availability.** All data generated or analyzed during this study are included in this published article/as supplementary information files.

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