World Journal of Gastroenterology

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World J Gastroenterol 2020 November 7; 26(41): 6455-6474

DOI: 10.3748/wjg.v26.i41.6455

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Real-world cost-effectiveness associated with infliximab maintenance therapy for moderate to severe Crohn's disease in China

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Supported by Zhejiang Medical and Health Science and Technology Project, No. 2020KY608; and Natural Science Foundation of Zhejiang Province, No. LQ19H030013.

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Abstract

BACKGROUND

Infliximab was the first approved biologic treatment for moderate to severe Crohn's disease (MS-CD) in China. However, the cost-effectiveness of infliximab maintenance therapy (IMT) for MS-CD relative to conventional maintenance therapy remained unclarified.

AIM

To assess the cost-effectiveness of IMT for MS-CD in Chinese patients from the perspective of Chinese public insurance payer.

METHODS

A cohort of MS-CD patients managed in a Chinese tertiary care hospital was created to compare IMT with conventional maintenance therapy (CMT) for clinical outcomes and direct medical costs over a 1-year observation time using conventional regression analyses. A decision-analytic model with the generated evidence was constructed to assess the cost-effectiveness of IMT relative to CMT using reimbursed medical costs.

statement: The study was reviewed and approved by the Sir Run Run Shaw Hospital Institutional Review Board.

Conflict-of-interest statement: Chen Y and Chen WD are employed by a consulting firm that receives industry funds to conduct health economics and outcome research. Other authors have none to declare.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at caoq@zju.edu.cn.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: July 2, 2020
Peer-review started: July 2, 2020
First decision: July 28, 2020

RESULTS

Based on the included 389 patients, IMT was associated with significantly higher disease remission chance [odds ratio: 4.060, P = 0.003], lower risk of developing new complications (odds ratio: 0.527, P = 0.010), higher utility value for quality of life (coefficient 0.822, P = 0.008), and lower total hospital costs related to disease management (coefficient -0.378, P = 0.008) than CMT. Base-case cost-effectiveness analysis estimated that IMT could cost Chinese health insurance payers ¥55260 to gain one quality-adjusted life year (QALY). The cost-effectiveness of IMT was mainly driven by the estimate of quality of life, treatment efficacy of maintenance therapy, mortality risk associated with active disease, and unit price of infliximab. The probability that IMT was cost-effective at a willingness-to-pay threshold of three times gross domestic product [2018 Chinese gross domestic product per capita (GDPPC)] was 86.4%.

CONCLUSION

IMT significantly improved real-world health outcomes and cost the Chinese public health insurance payers less than one GDPPC to gain one QALY in Chinese MS-CD patients.

Key Words: Infliximab; Crohn's disease; Maintenance therapy; Cost-effectiveness; Outcomes; Direct medical costs

Core Tip: Infliximab maintenance therapy significantly reduced disease severity, improved quality of life, and reduced outpatient clinic visits and hospitalization related to active disease in Chinese patients with moderate to severe Crohn's disease. Even though the drug acquisition costs of infliximab could not be fully offset by the saved medical costs, the cost-effectiveness of infliximab maintenance therapy was highly attractive from the perspective of Chinese health care payers.

Citation: Shi JH, Luo L, Chen XL, Pan YP, Zhang Z, Fang H, Chen Y, Chen WD, Cao Q. Real-world cost-effectiveness associated with infliximab maintenance therapy for moderate to severe Crohn's disease in China. *World J Gastroenterol* 2020; 26(41): 6455-6474
URL: https://www.wjgnet.com/1007-9327/full/v26/i41/6455.htm
DOI: https://dx.doi.org/10.3748/wjg.v26.i41.6455

INTRODUCTION

Crohn's disease (CD) is a chronic disease that can affect any part of the gastrointestinal tract[1]. Even though the causes of CD have not yet been fully clarified, current research has proven that tumor necrosis factor-α (TNF-α) is the proinflammatory cytokine enhancing leukocyte migration, activating leukocytes, inducing acute-phase reactants and metalloproteinases, and inhibiting apoptosis of inflammatory cells in CD patients[2-4]. As the first developed TNF-α blocker, infliximab has been shown to be effective across the spectrum of CD, including refractory luminal CD, steroid-dependent CD, and refractory fistulizing CD. The ACCENT 1 trial demonstrated the clinical benefits of infliximab used as a maintenance therapy. In this trial, there was a significantly higher clinical remission rate, a higher mucosal healing rate, and a lower hospitalization rate associated with 1-year infliximab maintenance therapy (IMT) when compared to placebo[5].

Using a conservative estimate, CD affects at least 200000 patients across China[6]. Similar to CD patients in western countries, Chinese CD patients are relatively young, and their quality of life and social function are significantly impaired by CD. Even though infliximab was approved to treat CD in China shortly after its launch in 2005, access to infliximab in Chinese CD patients was highly limited due to the lack of reimbursement coverage. Thus, anti-inflammatory drugs and immunosuppressants are still the mainstay treatment for CD in China, and the limited clinical benefits and side effects associated with these drugs are still the main concern regarding the

Revised: August 5, 2020
Accepted: September 18, 2020
Article in press: September 18, 2020
Published online: November 7, 2020

P-Reviewer: Hansson-Hedblom A
S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Ma YJ

utilization of these drugs for moderate to severe Crohn's disease (MS-CD). The purpose of this study was to clarify the real-world health outcomes, medical costs, and cost-effectiveness associated with IMT for MS-CD in Chinese patients and generate real-world evidence to support reimbursement decision making related to the treatments for MS-CD in China.

MATERIALS AND METHODS

This study consisted of a real-world study and cost-effectiveness analysis comparing IMT and conventional maintenance therapy (CMT) for health outcomes and direct medical costs in a clinical cohort of MS-CD patients. Research ethics approval for this study was obtained from Sir Run Run Shaw Hospital, Hangzhou, China.

Real-world study

This study identified MS-CD patients who visited the Inflammatory Bowel Disease clinic of Sir Run Run Shaw Hospital in two time windows: January 1, 2014 to December 31, 2014 and July 1, 2017, to June 30, 2018. This study included all patients with a diagnosis of MS-CD who received maintenance therapy in Sir Run Run Shaw Hospital. To minimize the risk of selection bias, this study only excluded patients with insufficient information for data analysis. Hospital medical records associated with the included patients during the 1-year observation time period were reviewed to extract patient demographics including age, gender, body mass index, socio-economic status (employment, residence, and marital status), lifestyle (smoking and drinking), disease site, history of CD-related surgery, CD-related complications, extraintestinal manifestations, and comorbidities. The prescription records associated with the included patients during the 1-year observation period were the data source for the therapy pattern. The documented telephone follow-up questionnaires of the identified patients from the time window from July 1, 2017 to June 30, 2018 were the data sources to assess disease activity using Harvey-Bradshaw Index and rate quality of life on a 0 to 100 scale (0 indicated the worst health status, and 100 indicated the best health). The measured disease activity and quality of life associated with the followed-up patients were used to develop the prediction formulas from the multiple linear regression analyses that used patient characteristics and treatment pattern as independent variables. The developed prediction formulas for disease activity and utility for quality of life were used to estimate the disease activity and quality of life associated with the identified patients from the time window between January 1, 2014 and December 31, 2014. The billing records associated with the included patients' outpatient clinic visits and hospitalizations in Sir Run Run Shaw Hospital during the 1-year observation period were used to extract the health resources utilization (outpatient visits, hospital admissions, and hospital stay length) and direct medical costs.

This study stratified the included patients into two groups for the data analysis. The included patients receiving infliximab-contained maintenance therapy were assigned into the IMT group. The other included patients receiving maintenance therapy without containing infliximab were assigned into CMT group. The patient baseline characteristics associated with the two groups were summarized using descriptive statistical methods. Student *t* test, chi square test, and Wilcoxon rank sum test were used to compare the two groups for their patient characteristics and measured outcomes, which included disease remission, quality of life, health resources utilization, and direct medical costs over 1-year observation time. To adjust the potential confounding effects associated with patient baseline characteristics, this study conducted multivariable conventional regression analyses, including logistic regression analysis, linear regression analysis, Poisson regression analysis, beta-binomial regression analysis, and generalized linear regression analysis, with adjustment of patient baseline characteristics to compare IMT *vs* CMT for disease remission (defined as Harvey-Bradshaw Index score < 5)[7], utility for quality of life, health resources utilization, and direct medical costs. The statistical significance in these analyses was defined as the two-sided *P* value less than 0.05.

Cost-effectiveness analysis

A decision-analytic model was constructed to simulate health outcomes and direct medical costs associated with two model maintenance therapy scenarios: IMT *vs* CMT. For each model scenario, the decision-analytic model used a Markov model design to simulate treatment cycles between induction therapy and maintenance therapy for treatment response, disease relapse, surgery, and mortality associated with MS-CD

patients. The decision analytic model defined the induction therapy as any treatments used with the goal to achieve disease remission in the MS-CD patients who were relapsed from maintenance therapies, which were regularly given to patients to maintain disease remission after induction therapy. The introduction therapies used in real-world study cohort, including steroids (55.2%), infliximab monotherapy (14.3%), a combination of infliximab and immunosuppressant (9.7%) or enteral nutrition (11.7%), and enteral nutrition monotherapy (9.1%), were applied to the decision analytic model to simulate the distribution of introduction therapies in the model cohort. The identified maintenance therapies in the IMT group and CMT group from the real-world study were used to simulate the distributions of IMT and CMT in the model cohort. The administration of infliximab as introduction therapy and maintenance therapy in the real-world study cohort was based on the product monograph of infliximab for MS-CD (5 mg/kg administrated at 0, 2, and 6 wk for introduction therapy, subsequent administration using the same treatment dosage every 8 wk for maintenance therapy). The constructed decision-analytic model allowed patients to receive repeatedly induction therapy and maintenance therapy after disease relapse. The model also assumed that the surgical treatment for the complications only occurred in patients with active CD. The post-surgery patients entered another treatment cycle including induction and maintenance therapy until the occurrence of another surgical treatment in the model.

The decision-analytic model took into account the mortality associated with surgical treatment, disease remission, and active disease to estimate the survival rate associated with each model cycle. The cycle length of the Markov models in the decision-analytic model was 3 mo to align with the patients' regular follow-up frequency. The simulation time horizon in the decision-analytic model was set to lifetime to estimate overall survival, quality-adjusted life years (QALY), cumulative risk of CD-related surgery, and reimbursed medical costs under the reimbursement policy for CD patients in Zhejiang province (annual co-payment: ¥20000; reimbursement percentage: 80%; annual reimbursement cap: ¥40000). The structure of the decision-analytic model is illustrated in Figure 1.

A literature review was conducted to estimate model variables for the treatment response associated with induction therapy[8-13], risk of disease relapse associated with maintenance therapy[14], surgery risk associated with active CD, perioperative mortality associated with surgery, and the hazard ratio of mortality associated with active CD relative to age and gender-matched general population[15-30]. Meta-analysis was used as the main approach to synthesize the identified evidence from the literature review. The constructed decision analytic model was used to conduct cost-effectiveness analysis, which included base-case analysis, one-way sensitivity analyses, and probabilistic sensitivity analysis (PSA). The point estimates of QALY gains and lifetime reimbursed medical costs from the base-case analysis were used to calculate the incremental cost-effectiveness ratio (ICER) per gained QALY associated with IMT relative to CMT. One-way sensitivity analyses assessed the change of ICER associated with IMT by varying each model variable within its 95% confidence interval (CI) or ± 25% of its baseline value. PSA was conducted using a Monte Carlo simulation method to run 10000 iterations of cost-effectiveness analyses based on the distributions of model variables (beta distributions for probability and utility variables; gamma distributions for cost variables). The cost-effectiveness proportion associated with IMT relative to CMT was calculated under the willingness-to-pay (WTP) of one, two, and three times of the 2018 Chinese gross domestic goods per capita (GDPPC) (¥64644 or $9769)[31], respectively.

RESULTS

The real-world study initially identified 593 MS-CD patients. Of the identified MS-CD patients managed in the study hospital, 393 patients received maintenance therapy for MS-CD. After further exclusion of 4 patients without sufficient information for data analysis, this study eventually included 389 patients to conduct the data analysis. Of the included 389 patients, 259 patients received IMT, including the combination of infliximab and immunosuppressant (38.2%), infliximab monotherapy (44.6%), the combination of infliximab and enteral nutrition (12.4%), and the combination of infliximab, immunosuppressant, and enteral nutrition (4.8%). The other 130 patients received CMT that included immunosuppressant (61.7%), 5-aminosalicylates (25.8%), enteral nutrition (7.0%), the combination of immunosuppressant and enteral nutrition (3.1%), and the combination of immunosuppressant, 5-aminosalicylates, and/or

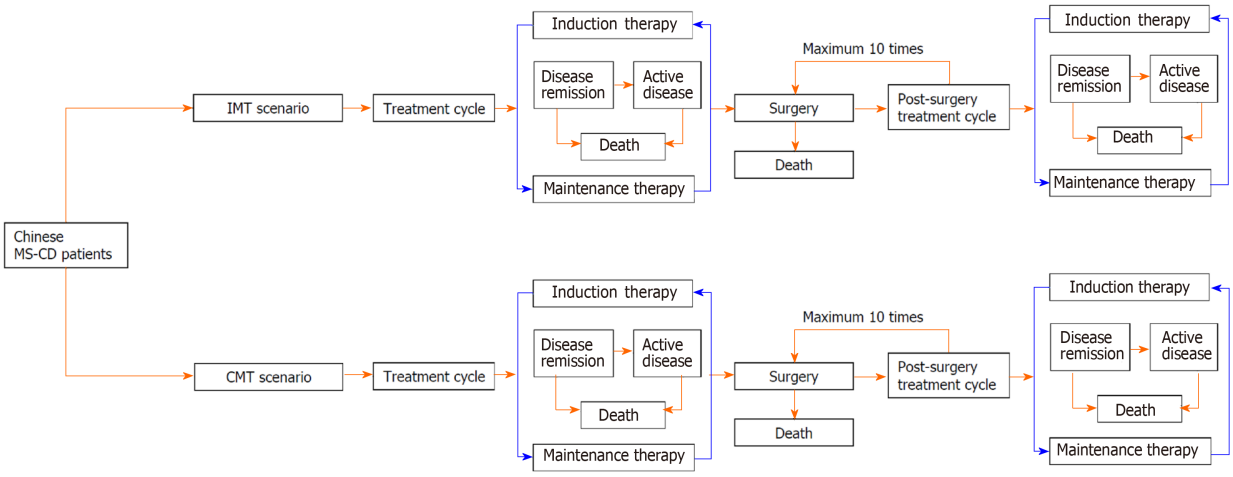

Figure 1 Structure of the decision analytic model assessing the cost-effectiveness of infliximab maintenance therapy relative to conventional maintenance therapy for moderate to severe Crohn's disease in China. CMT: Conventional maintenance therapy; IMT: Infliximab maintenance therapy; MS-CD: Moderate to severe Crohn's disease.

enteral nutrition (2.4%).

Real-world outcomes associated with IMT and CMT

The comparisons of the patient baseline characteristics associated with the two study groups for IMT *vs* CMT identified significantly younger age (34.1 ± 10.9 years *vs* 37.2 ± 11.2 years, $P = 0.004$), lower rate of married patients (56.0% *vs* 67.7%, $P = 0.026$), higher unemployment rate (6.9% *vs* 1.5%, $P = 0.023$), higher proportion of disease site at ileocolon (52.5% *vs* 33.8%, $P < 0.001$), higher proportions of historical complications for anus fistula (36.3% *vs* 14.6%, $P < 0.001$), perianal abscess (27.4% *vs* 13.8%, $P = 0.003$), and intestinal fistula (10.4% *vs* 3.1%, $P = 0.012$); and lower proportions of comorbidities including chronic hepatitis B (3.1% *vs* 8.5%, $P = 0.020$), gastroenteritis (1.5% *vs* 4.6%, $P = 0.071$), and kidney diseases (0.4% *vs* 3.8%, $P = 0.009$) in the IMT group. The patient baseline characteristics associated with the two study groups are summarized in Table 1.

The unadjusted comparisons of the measured clinical outcomes, health resources utilization, and hospital costs associated with the two created study groups for IMT *vs* CMT from the included 389 patients are summarized in Table 2. The multivariate regression analyses with the adjustment of patient demographics, social economic status, disease site at diagnosis, history of CD-related complications, history of CD-related surgery, and extraintestinal manifestation at baseline confirmed that IMT was associated with significantly higher disease remission chance [odds ratio (OR): 4.060, 95%CI: 1.643 to 10.753, $P = 0.003$], lower risk of developing any new complications (OR: 0.527, 95%CI: 0.323 to 0.858, $P = 0.010$), and higher utility value for quality of life (coefficient: 0.822, 95%CI: 0.218 to 1.426, $P = 0.008$) than CMT; IMT was associated with significantly lower outpatient clinic visits (coefficient: -0.564, 95%CI: -0.703 to -0.425) and shorter hospital stay length related to active disease management (coefficient: -4.725, 95%CI: -7.112 to -2.337, $P < 0.001$) than CMT; and IMT was associated with significantly lower outpatient costs (coefficient: -1.248, 95%CI: -1.651 to -0.850) and total medical costs related to active disease management (coefficient: -0.378, 95%CI: -0.659 to -0.101, $P = 0.008$) than CMT. The results of multivariate regression analyses are summarized by clinical outcomes (Table 3), health resources utilizations (Table 4), and medical costs (Table 5).

Cost-effectiveness of IMT relative to CMT

Based on the model variables that are summarized in Table 6, the comparisons of the point estimates of the model outputs associated with two model scenarios in the base case analysis without discounting the measured outcomes estimated that the IMT model scenario was associated with the increase of overall survival by 2.871 years (43.815 years *vs* 40.944 years), QALY by 2.476 years (33.365 QALY *vs* 30.889 QALY), and reimbursed medical costs by ¥96201 (¥ 469958 *vs* ¥373757). The cumulative CD-related surgery risk associated with the IMT model scenario was reduced by 39.7%. The discounted point estimates of QALYs and reimbursed medical costs associated with the two model scenarios in the base-case analysis estimated that the ICER

Table 1 Patient characteristics associated with the included moderate to severe Crohn's disease patients in real-world study

	IMT, *n* = 295		CMT, *n* = 130		*P* value
Patient characteristics	**Mean/%**	**SD**	**Mean/%**	**SD**	
Demographics					
Male proportion	72.2%		64.6%		0.125
Age in yr	34.1	10.9	37.2	11.2	0.004[b]
BMI range					
< 18.5	32.8%		40.0%		0.162
18.5-23.9	56.0%		53.8%		0.689
≥ 24	10.4%		6.2%		0.165
Lifestyle					
Non-smoker	85.7%		87.7%		0.592
Non-drinker	81.9%		88.5%		0.093
Marital status					
Unmarried	43.2%		32.3%		0.037[a]
Married	56.0%		67.7%		0.026[a]
Employment status					
Student	13.5%		7.7%		0.090
Full-time	59.1%		54.6%		0.401
Part-time	2.7%		2.3%		0.816
Unemployed	6.9%		1.5%		0.023[a]
Farmer	1.5%		1.5%		0.996
Retired	3.9%		4.6%		0.724
Unknown	5.8%		18.5%		< 0.001
Missing	6.6%		9.2%		0.345
Disease site at diagnosis					
Distal colon	52.9%		34.1%		< 0.001
Terminal ileum	19.5%		48.8%		< 0.001
Colon	9.7%		10.9%		0.729
Upper gastrointestinal and back colon	4.3%		3.1%		0.572
Upper gastrointestinal and ileum end	4.7%		0.8%		0.045[a]
Upper gastrointestinal tract	0.0%		0.8%		0.158
Previous surgery	29.0%		30.0%		0.831
Previous complication					
Perianal abscess	27.4%		13.8%		0.003[b]
Intestinal fistula	36.3%		14.6%		< 0.001
Intestinal obstruction	18.1%		13.1%		0.203
Extra-intestinal manifestation					
Aphthous stomatitis	8.9%		3.8%		0.070
Joint pain	3.1%		3.1%		0.995
Comorbidities					
Gallbladder diseases	3.9%		5.4%		0.488
Chronic hepatitis B	3.1%		8.5%		0.020[a]

Lung nodes	3.9%	2.3%	0.421
Gastroenteritis	1.5%	4.6%	0.071

[a]$P < 0.05$.
[b]$P < 0.01$. BMI: Body mass index; CMT: Conventional maintenance therapy; IMT: Infliximab maintenance therapy; SD: Standard deviation.

associated with the IMT scenario relative to the CMT scenario was ¥55260, 85.5% of the 2018 Chinese GDPPC. The results of the base case analysis before and after discounting are summarized in Table 7.

One-way sensitivity analyses indicated that the cost-effectiveness of IMT could be more attractive, indicated by the reduction of ICER over ¥20000, as shown by increasing the following model variables: Quality of life associated with disease remission, relapse risk associated with CMT, treatment discontinuation risk associated with IMT, relapse risk after treatment discontinuation, and hazard ratio of mortality associated with active disease relative to the general population. The cost-effectiveness of IMT was less attractive, indicated by the increase of ICER over ¥20000, when increasing the following model variables: Treatment response of induction therapy with enteral nutrition, steroids plus 5-aminosalicylates, and steroids alone, distribution of induction therapy using steroids, disease relapse risk after the discontinuation of IMT, quality of life associated with active disease, and unit price of infliximab. The impacts of these key model variables on the cost-effectiveness of IMT relative to CMT are illustrated in Figure 2.

The 10000 generated ICER values associated with IMT from the Monte Carlo simulations were ranked to identify the median ICER (¥68512) and its 95% credible interval (¥-238869 to ¥601293). The cost-effectiveness proportions of IMT relative to CMT under the WTP of one, two, and three times of the 2018 Chinese GDPPC were 47.6%, 74.7%, and 86.4%, respectively.

DISCUSSION

This study observed that IMT was highly effective in a real-world setting by achieving a 94.6% disease remission rate. This is much higher than the reported disease remission rate of infliximab in randomized trials[9,32,33], which reported about 60% disease remission rate associated with 1-year infliximab monotherapy in MS-CD patients. Because the IMT group consisted of approximately 60% of patients receiving a combination of infliximab and immunosuppressants or enteral nutrition in the real-world study, the MT containing infliximab and traditional treatments could be more effective in MS-CD patients. The superior treatment effects associated with the combination of infliximab and immunosuppressants for MS-CD have been proven in randomized clinical trials. However, the reported disease remission rate in these randomized trials was not as high as what was observed in this study. Because the treatment efficacies of infliximab were mainly assessed in randomized clinical trials conducted in western countries, the observed treatment effects of infliximab in this study might suggest that patient ethnicity might play a role in the treatment effects of infliximab. This speculation was supported by another retrospective study that observed nearly the same disease remission rate (97.1%) associated with 1-year treatment with infliximab for MS-CD in Korean patients[34]. Additionally, male gender was found to predict better treatment response of infliximab[35], and the high male proportion in the patient cohort in this study could further increase the disease remission rate. Thus, IMT could gain more clinical benefits and have more attractive cost-effectiveness in Chinese MS-CD patients.

Similar to previous studies reporting reduced health resource utilization associated with infliximab in CD patients, this study confirmed that the high disease remission rate associated with IMT reduced health resources utilization related to active disease management during the 1-year observation period. According to the multivariate regression analysis, IMT significantly reduced outpatient clinic visits and hospital stay days related to active disease management. These impacts on health resources utilization could save direct medical costs and partially offset the high drug acquisition costs of infliximab. However, the drug acquisition costs of infliximab were much higher than conventional medications used for CMT. The overall direct medical costs associated with IMT was about four times of the direct medical costs associated with CMT. Because the cost-effectiveness was assessed by ICER, which is the ratio

Table 2 Unadjusted comparisons of the measured clinical outcomes, health resources utilization, and direct medical costs associated with infliximab maintenance therapy and conventional maintenance therapy during 1-year observation time

	IMT, *n* = 295			CMT, *n* = 130			*P* value
Outcome measure	**Mean/%**	**SD**	**Median**	**Mean/%**	**SD**	**Median**	
Clinical outcomes							
Surgery rate	12.7%			25.4%			0.002[b]
Disease remission rate	94.6%			86.9%			0.008[b]
Utility for quality of life	0.890	0.080	0.900	0.757	0.093	0.748	< 0.001
Newly developed complications							
Any complications	27.0%			42.3%			0.002[b]
Anus fistula	17.4%			14.6%			0.489
Intestinal fistula	3.5%			4.6%			0.582
Intestinal obstruction	4.2%			12.3%			0.003[b]
Perianal abscess	5.8%			6.2%			0.886
Bowel perforation	1.9%			3.8%			0.260
Health resource utilization							
Outpatient clinic visits	1.9	3.3	1.0	3.7	5.2	2.0	< 0.001
Hospital admissions	5.3	2.2	6.0	1.4	1.0	1.0	< 0.001
Hospital admissions for infliximab administration	4.4	2.2	5.0	0.0	0.0	0.0	< 0.001
Hospital admissions for active disease management	0.9	1.0	1.0	1.4	1.0	1.0	< 0.001
Hospital stay days	15.2	11.1	14.0	14.8	12.4	9.5	0.207
Hospital stay days related to infliximab administration	5.7	3.8	6.0	0.0	0.0	0.0	< 0.001
Hospital stay days for active disease management	9.5	11.3	9.0	14.8	12.4	9.5	< 0.001
Direct medical costs for outpatient clinic visits							
Outpatient costs for drugs	¥710	¥4,268	¥0	¥2,342	¥4698	¥644	< 0.001
Outpatient costs for others	¥232	¥589	¥0	¥130	¥446	¥0	0.008[b]
Total outpatient costs	¥942	¥4371	¥54	¥2473	¥4777	¥810	< 0.001
Direct medical costs for hospitalizations							
Hospital costs related to infliximab administration	¥5,305	¥7650	¥3577	¥0	¥0	¥0	< 0.001
Drug acquisition costs of infliximab	¥39018	¥9610	¥39200	¥0	¥0	¥0	< 0.001
Hospital costs for active disease management	¥11041	¥17982	¥4090	¥24274	¥29285	¥9321	< 0.001
Total hospital costs	¥55365	¥22337	¥52155	¥24274	¥29285	¥9321	< 0.001
Total direct medical costs	¥56307	¥23866	¥52476	¥26747	¥30541	¥12503	< 0.001

[b]$P < 0.01$. CMT: Conventional maintenance therapy; IMT: Infliximab maintenance therapy; SD: Standard deviation.

between the difference in lifetime medical costs and difference in QALY associated with IMT and CMT, the drug acquisition costs of infliximab were likely to be the main driving factor for the cost-effectiveness of IMT for MS-CD in China.

This study constructed a comprehensive decision-analytic model that fully accounted for the induction and maintenance treatment cycles, surgery related to developed complications, and mortality risk related to disease status and surgery to

Table 3 Summary of the multivariable regression analyses for clinical outcomes in the included moderate to severe Crohn's disease patients

Outcome type	Disease remission					CD-related surgery					CD-related complications					Utility, quality of life				
Regression analysis method	Logistic regression analysis					Logistic regression analysis					Logistic regression analysis					Beta-binomial regression analysis				
Independent variables	Sample size	OR	95%CI		*P* value	Sample size	OR	95%CI		*P* value	Sample size	OR	95%CI		*P* value	Sample size	Coefficient	95%CI		*P* value
			Lower	Upper				Lower	Upper				Lower	Upper				Lower	Upper	
IMT *vs* CMT	389	4.060	1.643	10.753	0.003[a]	389	0.658	0.349	1.249	0.196	389	0.527	0.323	0.858	0.010[a]	389	0.822	0.218	1.426	0.008[a]
Demographics																				
Male gender											389	1.111	0.675	1.844	0.681	389	-0.008	-0.622	0.607	0.980
Age in yr	389	0.951	0.918	0.986	0.005	389	1.027	1.002	1.052	0.035[a]	389	0.990	0.968	1.011	0.351	389	-0.016	-0.041	0.010	0.223
BMI																				
< 18.5						389	1.936	0.682	6.535	0.244										
18.5-23.9						389	0.826	0.292	2.755	0.733										
Residence area																				
Urban city						389	0.521	0.246	1.035	0.073										
Insurance plan																				
Farmar	389	0.384	0.098	1.634	0.178															
Other plans						389	2.578	1.034	6.247	0.038[a]										
Disease site at diagnosis																				
Terminal ileum						389	1.350	0.612	3.042	0.460	389	1.246	0.732	2.104	0.414	389	-0.227	-0.847	0.392	0.472
Colon						389	0.812	0.385	1.762	0.590	389	1.581	0.756	3.247	0.216					
History of CD-related complications																				
Intestinal fistula	389	0.307	0.098	0.976	0.042[a]															
Intestinal obstruction	389	0.831	0.322	2.293	0.709															
Extraintestinal abscess						389	5.766	1.277	25.741	0.020[a]										
Anal fistula						389	0.747	0.350	1.509	0.431						389	0.142	-0.546	0.829	0.687
Joint pain	389	0.318	0.059	1.866	0.187															

History of CD-related surgery	389	0.158	0.056	0.407	0.000					389	0.488	0.282	0.824	0.009[b]	389	-0.304	-0.908	0.299	0.323
Comorbidities																				
Gallbladder disease										389	3.812	1.343	11.494	0.013[a]						
Kidney disease						389	5.015	0.826	31.142	0.070										

[a]$P < 0.05$.

[b]$P < 0.01$. BMI: Body mass index; CD: Crohn's disease; CI: Confidence interval; CMT: Conventional maintenance therapy; IMT: Infliximab maintenance therapy; OR: Odds ratio; SD: Standard deviation.

simulate lifetime health outcomes and reimbursed medical costs associated with IMT and CMT. This study leveraged the generated evidence from the real-world study for the estimation of the model variables to maximize the generalizability of the cost-effectiveness analysis. Consistent with real-world studies with long-term follow-ups and the cost-effectiveness analyses assessing IMT for MS-CD in high-income countries[36], the constructed decision-analytic model confirmed that IMT could gain more clinical and health benefits than CMT by increasing overall survival, increasing QALY, and reducing the risk of surgery for CD-related complications. Additionally, IMT was only associated with a modest increase of reimbursed medical costs under current Chinese reimbursement policy. In this case, the cost-effectiveness of IMT relative to CMT for MS-CD in China was highly attractive by having the ICER value less than the 2018 Chinese GDPPC. This result also suggested that the reimbursement coverage in Chinese patients was unlikely to substantially reduce the out-of-pocket costs associated with the disease management. Thus, the affordability of IMT could be still a significant barrier for patient access to infliximab even with reimbursement support. Since the cost-effectiveness of IMT was highly sensitive to the price of infliximab, it might be beneficial to use our constructed decision-analytic model to identify further the appropriate price of infliximab and reimbursement policy to improve patient access to IMT.

This study conducted one-way sensitivity analysis and probability sensitivity analysis to assess the impact of uncertainty associated with the model variables on the cost-effectiveness of IMT relative to CMT in MS-CD patients. The one-way sensitivity analyses clearly demonstrated that quality of life, measured as utility in our study, associated with disease remission and active disease, could substantially change the ICER due to their wide 95%CIs. Thus, the validity of the utility associated with disease remission and active disease in our study was critical for the robustness of our cost-effectiveness analysis. Because the estimated utilities for disease remission and active disease were highly comparable as previously reported results of a meta-analysis[37] based on 17 studies (utility for disease remission: 0.829 *vs* 0.840; utility for active disease: 0.743 *vs* 0.753), the utility variables in cost-effectiveness analysis should have sufficient external validity. Our PSA took into account overall uncertainty associated with utility variables and also other model variable to estimate the distribution of the

Table 4 Summary of the multivariable regression analyses for health resources utilization in the included moderate to severe Crohn's disease patients

Outcome type	Outpatient visits					Hospital admissions related to active disease					Hospital stay length related to active disease				
Regression analysis method	Poisson regression analysis					Poisson regression analysis					Linear regression analysis				
Independent variables	Sample size	Coefficient	95%CI		*P* value	Sample size	Coefficient	95%CI		*P* value	Sample size	Coefficient	95%CI		*P* value
			Lower	Upper				Lower	Upper				Lower	Upper	
IMT *vs* CMT	238	-0.564	-0.703	-0.425	0.000	291	-0.074	-0.276	0.128	0.470	389	-4.725	-7.112	-2.337	0.000
BMI															
< 18.5						291	0.244	-0.122	0.643	0.209	389	5.510	1.587	9.433	0.006[b]
18.5-23.9						291	-0.020	-0.382	0.375	0.917	389	-0.759	-4.449	2.932	0.686
Lifestyles															
Smoker	238	0.073	-0.231	0.355	0.623										
Residence area															
Urban city	238	0.693	0.558	0.830	0.000										
Insurance plan															
Urban workers	238	-0.070	-0.230	0.092	0.392										
Urban residents	238	-0.442	-0.696	-0.196	0.001[b]										
Disease site at diagnosis															
Terminal ileum	238	0.113	-0.086	0.314	0.268						389	-2.100	-5.085	0.884	0.167
Colon															
Ileocolon	238	0.128	-0.057	0.317	0.179						389	-2.505	-5.099	0.089	0.058
End ileum + upper digestive tract						291	0.222	-0.359	0.731	0.421					
Ileocolon + upper digestive tract	238	0.502	0.162	0.825	0.003[b]	291	0.253	-0.218	0.670	0.263					
History of CD-related complications															
Pyloric obstruction	238	-0.247	-1.698	0.815	0.690	291	0.819	0.080	1.450	0.018[a]					
Intestinal fistula	238	0.028	-0.272	0.312	0.850										
Intestinal obstruction	238	0.372	0.183	0.555	0.000										
Extraintestinal abscess											389	11.363	4.696	18.030	0.001[b]
Anal fistula						291	0.241	0.007	0.468	0.040[a]	389	-0.316	-2.710	2.078	0.795

Perianal abscess						291	0.150	-0.091	0.383	0.214					
Extraintestinal manifestations															
Joint pain	238	-0.438	-0.919	-0.013	0.057										
Mouth ulcers	238	-0.465	-0.936	-0.053	0.038[a]										
History of CD-related surgery	238	-0.117	-0.291	0.054	0.184										
Comorbidities															
HP infection	238	1.168	0.588	1.672	0.000										
Rhinitis	238	1.439	0.221	2.966	0.034[a]										
Gallbladder disease	238	-0.233	-0.640	0.133	0.235										
Tuberculosis											389	6.773	-2.555	16.100	0.154
Peritonitis	238	1.986	1.438	2.471	0.000	291	0.872	-0.321	1.759	0.091	389	53.048	32.426	73.671	0.000
Abdominal abscess	238	NA	NA	NA	NS	291	NA	NA	NA	NS	389	NA	NA	NA	NS
fracture						291	1.213	0.030	2.080	0.017[a]					
Osteoporosis	238	-0.159	-1.626	0.945	0.802										
Muscle atrophy											389	45.956	23.426	68.486	0.000
Arrhythmia	238	-1.109	-2.919	0.055	0.123										
Hepatitis B virus carriers	238	-0.358	-1.062	0.235	0.275										

[a]$P < 0.05$.

[b]$P < 0.01$. BMI: Body mass index; CD: Crohn's disease; CI: Confidence interval; CMT: Conventional maintenance therapy; IMT: Infliximab maintenance therapy; NA: Not available; NS: Not significant.

cost-effectiveness of IMT relative to CMT under the 10000 Monte Carlo simulations. Our base-case analysis indicated that IMT was highly cost-effective by having an ICER less than 2018 Chinese GDPPC (85.5%). Our PSA estimated that 47.6% of simulated ICERs less than 2018 Chinese GDPPC. Thus, base-case analysis was likely to overestimate the cost-effectiveness of IMT. As the cost-effectiveness proportion associated with IMT relative to CMT was 86.4% under the recommended cost-effectiveness threshold, both base case analysis and PSA supported the attractive cost-effectiveness of IMT in Chinese MS-CD patients.

Except infliximab, the other launched TNF-alpha inhibitors, such as etanercept and adalimumab, were launched in China as well. However, the approved indications of etanercept and adalimumab did not include MS-CD when this study was conducted. The other biologics indicated for MS-CD, including vedolizumab and ustekinumab, were recently launched in China. Thus, our cost-effectiveness analysis did not include

Table 5 Summary of the multivariable regression analyses for direct medical costs in the included moderate to severe Crohn's disease patients

Outcome type	Outpatient medical costs					Hospital costs related to active disease					Total medical costs				
Regression analysis method	Generalized linear regression analysis					Generalized linear regression analysis					Generalized linear regression analysis				
Independent variables	Sample size	Coefficient	95%CI		*P* value	Sample size	Coefficient	95%CI		*P* value	Sample size	Coefficient	95%CI		*P* value
			Lower	Upper				Lower	Upper				Lower	Upper	
IMT *vs* CMT	237	-1.248	-1.651	-0.850	< 0.001	293	-0.117	-0.387	0.150	0.384	342	-0.378	-0.659	-0.101	0.008[b]
BMI															
< 18.5						293	0.753	0.240	1.225	0.003[b]	342	0.513	0.013	0.972	0.035[a]
18.5-23.9						293	0.214	-0.276	0.657	0.367	342	-0.002	-0.486	0.435	0.992
Lifestyles															
Smoker	237	0.563	-0.529	1.824	0.263										
Heavy drinker						293	-1.519	-2.805	0.515	0.057	342	-1.714	-2.835	0.009	0.013[a]
Residence area															
Urban city	237	0.741	0.365	1.127	< 0.001										
Insurance plan															
Urban residents	237	-0.562	-1.038	-0.030	0.028[a]										
Other plans						293	0.395	-0.071	0.915	0.111	342	0.248	-0.235	0.784	0.325
Disease site at diagnosis															
Terminal ileum											342	0.183	-0.204	0.564	0.343
Colon	237	-0.116	-0.728	0.569	0.707										
Ileocolon	237	-0.279	-0.662	0.102	0.158	293	-0.252	-0.513	0.010	0.060	342	-0.163	-0.517	0.178	0.347
Ileocolon + upper digestive tract											342	0.600	-0.073	1.397	0.106
CD-related complications															
Intestinal obstruction	237	1.270	0.680	1.901	< 0.001										
Gastric fistula											342	-2.351	-4.061	1.308	0.049[a]
Intestinal abscess						293	-1.183	-2.224	0.372	0.064	342	-1.180	-2.174	0.261	0.050
Bowel perforation											342	0.570	-0.048	1.314	0.094
Perianal abscess	237	-0.058	-0.495	0.409	0.795										

Intestinal-cutaneous fistula						293	-2.539	-4.153	0.711	0.022[a]					
Extraintestinal manifestations															
Psoriasis											342	NA	NA	NA	NS
Mouth ulcers	237	-0.089	-0.933	1.004	0.852	293	-0.781	-1.253	-0.241	0.002[a]	342	-0.680	-1.166	-0.121	0.010[a]
History of CD-related surgery	237	0.019	-0.407	0.466	0.929										
Comorbidities															
Intestinal ulcer	237	-4.250	-6.471	0.449	0.004[b]										
Shingles						293	-2.464	-4.080	0.786	0.026[a]					
Joint pain											342	-3.952	-5.675	-0.291	0.001[a]
Esophageal disease											342	-2.696	-4.467	0.976	0.026[a]
Diabetes											342	-2.147	-3.910	1.523	0.076
Asthma											342	-3.391	-5.092	0.265	0.005

[a]$P < 0.05$.

[b]$P < 0.01$. BMI: Body mass index; CD: Crohn's disease; CI: Confidence interval; CMT: Conventional maintenance therapy; IMT: Infliximab maintenance therapy; NA: Not available; NS: Not significant.

these biologic treatments. Even though the maintenance therapy with these newly approved biologics were reported to have a higher disease remission rate than IMT, the higher acquisition costs associated with these biologics could make their cost-effectiveness relative to IMT unlikely attractive in MS-CD patients. Thus, the newly approved biologics are mainly recommended in the second-line treatment setting after the failure with infliximab treatment.

Even though the cost-effectiveness analysis based on the real-world data minimized the uncertainty and variability associated with the model variables, the real-world observation period was only 1 year, which was not sufficiently long to assess the impact of IMT on long-term clinical outcomes, such as the development of complications, surgeries, and mortality. The predictions of these long-term clinical outcomes in the cost-effectiveness analysis were based on literature evidence. Thus, the generalizability of the cost-effectiveness analysis needs further improvement by future real-world studies assessing these long-term outcomes associated with IMT in Chinese patients with MS-CD. Another main limitation in this study was the small sample size of the study cohort from one tertiary care hospital. The study cohort might not be large enough to represent fully the MS-CD patients across China. As the incidence rate of CD in China was as low as 0.46/1000000[38], it is challengeable to identify a large cohort of MS-CD patients from a single center. However, our study cohort had comparable patient baseline characteristics as the Chinese MS-CD patients

Table 6 The summary of the main model variables in the decision analytic model assessing the cost-effectiveness of infliximab maintenance therapy relative to conventional maintenance therapy for moderate to severe Crohn's disease in China

Model variable	Base line value	95%CI	
		Lower limit	Upper limits
Treatment efficacies of induction therapy			
Disease remission rate of steroids (reference)	0.347	0.247	0.447
Disease remission rate ratio for infliximab relative to reference	1.476	0.620	2.090
Disease remission rate ratio for infliximab plus immunosuppressant relative to reference	2.331	1.639	3.315
Disease remission rate ratio for infliximab plus enteral nutrition relative to reference	1.743	1.523	2.986
Treatment efficacies of maintenance therapy			
Quarterly risk of disease relapse associated with no treatment	0.207	0.146	0.284
Relative risk of disease relapse associated with infliximab relative to no treatment	0.040	0.000	0.140
Relative risk of disease relapse associated with immunosuppressant relative to no treatment	0.360	0.170	0.630
Mortality			
Perioperative mortality rate associated with surgery	0.014	0.007	0.030
Hazard ratio of mortality associated with active disease relative to age and gender-matched general population	3.047	2.195	4.230
Utility ratio between CD patients and general population			
Disease remission	0.829	0.622	0.994
Active disease	0.743	0.565	0.926
Direct medical costs			
Annual medical costs related to disease reemission management	¥9512		
Annual medical costs related to active disease management	¥14436		
Surgery costs per episode	¥16781		
Annual drug acquisition costs of infliximab used as induction therapy	¥49000		
Drug acquisition costs of infliximab used as MT in the first year	¥39200		
Drug acquisition costs of infliximab used as MT beyond the first year	¥29400		

CD: Crohn's disease; CI: Confidence interval; MT: Maintenance therapy.

in other observational studies[39,40]. Similar to the Chinese MS-CD patients in previously published observational studies, our study cohort was characterized by younger age, more male patients, higher proportion with disease site at colon, and one-third patients with history of surgery for CD-related complications.

CONCLUSION

In summary, this study confirmed that IMT was superior to CMT regarding disease remission rate, quality of life, and health resources utilization in real-world Chinese patients with MS-CD. The extremely high disease remission rate associated with IMT suggested that Chinese patients might have better treatment response to infliximab. Based on the generated real-world evidence, the cost-effectiveness of IMT relative to CMT was highly attractive as IMT cost the Chinese public health insurance payers less than the 2018 Chinese GDPPC to gain one QALY in Chinese MS-CD patients.

Table 7 Summary of the results of undiscounted and discounted point estimations of measured outcomes in base case analysis comparing infliximab maintenance therapy *vs* conventional maintenance therapy in the constructed decision analytic model

Model outputs	Results of base-case analysis without discounting			Results of base-case analysis with discounting		
	IMT	CMT	Difference	IMT	CMT	Difference
Overall survival in yr	43.815	40.944	2.871	23.858	22.947	0.911
Disease remission before surgery	30.433	13.157	17.276	18.102	9.392	8.710
Active disease before surgery	1.398	2.540	-1.142	0.803	1.788	-0.985
Disease remission after surgery	11.407	20.893	-9.486	4.709	9.701	-4.993
Active disease after surgery	0.576	4.354	-3.777	0.244	2.066	-1.821
Total QALY	33.365	30.889	2.476	18.392	17.491	0.901
Disease remission before surgery	23.450	10.220	13.230	14.066	7.288	6.778
Active disease before surgery	0.973	1.803	-0.831	0.566	1.278	-0.711
Disease remission after surgery	8.553	15.889	-7.335	3.592	7.492	-3.900
Active disease after surgery	0.389	2.977	-2.588	0.168	1.433	-1.266
Total reimbursed medical costs	¥469958	¥373757	¥96201	¥242107	¥192336	¥49771
Drug costs	¥156606	¥48359	¥108246	¥84553	¥25062	¥59491
Surgery costs	¥8261	¥28346	-¥20085	¥4019	¥14511	-¥10492
Disease remission management	¥284675	¥226987	¥57687	¥143601	¥116897	¥26704
Active disease management	¥20417	¥70065	-¥49648	¥9934	¥35866	-¥25932
Total patient out-of-pocket costs	¥726433	¥163918	¥562515	¥431392	¥109111	¥322281
Drug costs	¥629970	¥27629	¥602340	¥374967	¥18346	¥356622
Surgery costs	¥2526	¥11736	-¥9210	¥1452	¥7840	-¥6387
Disease remission management	¥87695	¥95541	-¥7846	¥51383	¥63547	-¥12165
Active disease management	¥6243	¥29012	-¥22769	¥3590	¥19378	-¥15789
Total medical costs	¥1196392	¥537676	¥658716	¥673499	¥301447	¥372052

IMT: Infliximab maintenance therapy; CMT: Conventional maintenance therapy; QALY: Quality-adjusted life years.

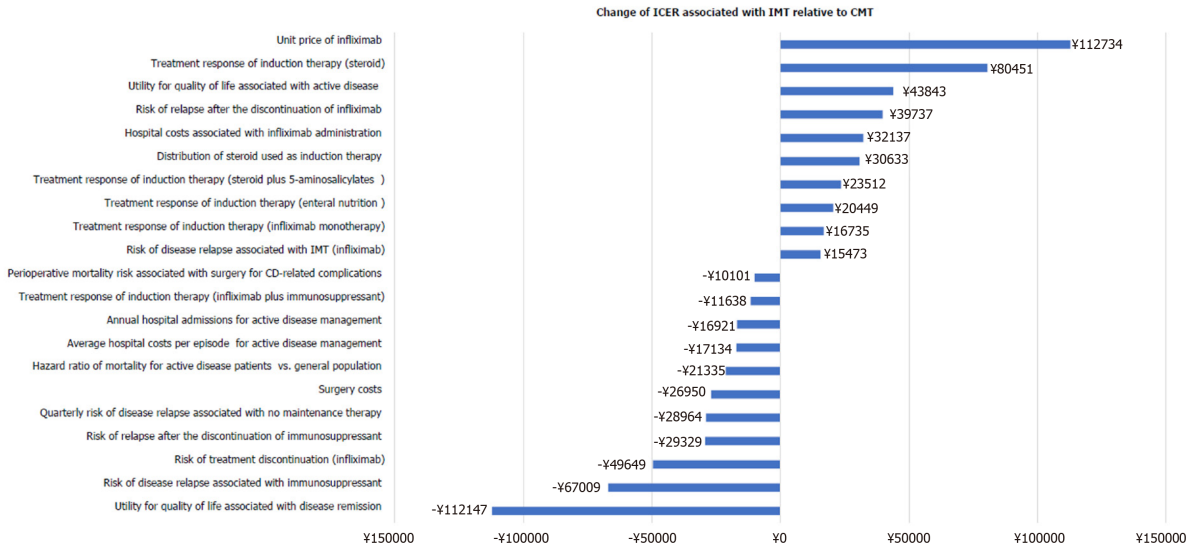

Figure 2 Impact of key model variables on the cost-effectiveness of infliximab maintenance therapy relative to conventional maintenance therapy for moderate to severe Crohn's disease in one-way sensitivity analyses. CD: Crohn's disease; CMT: Conventional maintenance therapy; ICER: Incremental cost-effectiveness ratio; IMT: Infliximab maintenance therapy.

ARTICLE HIGHLIGHTS

Research background

Infliximab was the first approved biologic treatment for moderate to severe Crohn's disease (MS-CD) in China. Even though infliximab was proven to be clinically more effective and safer than conventional treatments, Chinese MS-CD patients still had limited access to infliximab due to lack of reimbursement for their infliximab treatment.

Research motivation

The conventional treatments could not meet the medical needs of Chinese MS-CD patients. However, the patients could not afford regular infliximab-contained maintenance treatment (IMT) without reimbursement support. Reimbursement decision makers needed evidence to support the reimbursement coverage of infliximab used as maintenance therapy for MS-CD.

Research objectives

This study was designed to leverage the real-world evidence from a clinical cohort of patients with MS-CD in a Chinese tertiary care hospital and existing literature evidence to assess the cost-effectiveness of IMT relative to conventional maintenance therapy (CMT) in Chinese MS-CD patients.

Research methods

This study conducted a retrospective cohort study to compare IMT *vs* CMT for disease remission, quality of life, health resource utilizations, and direct medical costs in MS-CD patients who were followed up over one year in a Chinese inflammatory bowel disease treatment center. The generated evidence from the retrospective cohort study were further used to construct a decision analytic model to assess the cost-effectiveness of IMT relative to CMT in Chinese MS-CD patients.

Research results

The retrospective data analysis in this study observed significantly better clinical outcomes, including disease remission rate, CD-related complications, and quality of life, and less utilization of health resources associated with IMT. The base case cost-effectiveness analysis estimated that IMT was associated with attractive incremental cost-effectiveness ratio per gained quality-adjusted life year, which was less than one gross domestic products per capita in China. Probabilistic sensitivity analysis confirmed the attractive cost-effectiveness of IMT relative to CMT in Chinese MS-CD patients under the recommended cost-effectiveness threshold.

Research conclusions

IMT was confirmed to be superior to CMT in Chinese real-world MS-CD patients. With the overall uncertainty associated with clinical effectiveness, quality of life, and direct medical costs associated with IMT and CMT in Chinese MS-CD patients, the cost-effectiveness of IMT relative to CMT was attractive from the perspective of Chinese health care payers.

Research perspectives

This study only followed up a relatively small cohort with MS-CD patients from a single treatment center. The generalizability associated with generated evidence in this study needs confirmation by future studies with large sample size of patients enrolled from more treatment centers. Additionally, this study followed up MS-CD patients for only 1 year. Future studies are needed to follow up patients longer to assess the impact of IMT on long-term clinical outcomes, which should include survival outcomes and CD-related to surgery and complications.

ACKNOWLEDGEMENTS

We want to thank Professor Krahn M from THETA Collaborative at the University of Toronto to help with reviewing the statistical methods and proofreading the manuscript of this study.

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