Original Article

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Cost-utility analysis of romiplostim for the treatment of chronic primary immune thrombocytopenia in China

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SUMMARY This study aimed to assess the cost-utility of romiplostim (ROMI) compared to eltrombopag (EPAG) as a second-line treatment for chronic primary immune thrombocytopenia (cITP) in Chinese adults. A decision tree-embedded Markov model with a lifetime horizon was used to estimate the quality-adjusted life years (QALYs) and costs for ROMI versus EPAG from the perspective of the Chinese health care system. The model was driven by platelet response with a 4-week cycle. Both QALYs and costs were discounted 5% per year. Clinical data comparing ROMI and EPAG were obtained by matching-adjusted indirect comparison (MAIC), utilizing individual patient data on ROMI and published Chinese Phase III trial data on EPAG. Costs were reported in 2022 US dollars and included drug acquisition costs, monitoring costs, bleeding-related costs, and costs associated with adverse events. Deterministic and probabilistic sensitivity analyses were performed. The CEA model indicated that treatment with ROMI resulted in an average of $4,344.4 higher costs for 0.004 QALYs. One-way sensitivity analysis (OSA) indicated that the model was most sensitive to the high bleeding rate in response (Markov stage) for EPAG and ROMI. Probabilistic sensitivity analysis (PSA) indicated that ROMI was likely to be cost effective in 0.16% cases at a willingness-to-pay threshold of $12039.1 (China per capita GDP in 2022) per QALY. If the price of ROMI is either lower than or equal to that of EPAG, ROMI could likely be considered cost-effective as a second-line treatment for Chinese adults with cITP.

Keywords immune thrombocytopenia, romiplostim, eltrombopag, cost-utility analysis

1. Introduction

Primary immune thrombocytopenia (ITP) is a hematological disorder characterized by isolated thrombocytopenia (platelet count < 100×10^9/L (< 100×10^3/microliter)) in the absence of a clear cause. The annual incidence of ITP in adults is (2-10)/100,000 worldwide (*1*), and the condition predominantly affects people over 60 years old (*2*). cITP (one of ITP, ≥ 12 months' duration) is an autoimmune disease, and a significant proportion of patients may suffer from other complications, such as recurrent and persistent disease, a high risk of bleeding, and unpredictable disease progression. These complications, along with cITP, lead to a serious reduction in the quality of life (QoL) of patients. At the same time, frequent use of medications to maintain platelet counts at safe levels poses a significant long-term economic and QoL burden on patients with cITP in China (*2*).

According to ITP guidelines and an expert consensus in China (*2*), the US (*3*), Japan (*4*), South Korea (*5*), Italy (*6*), and Spain (*7*), intravenous immunoglobulin (IVIg), prednisolone, or anti-D immunoglobulin are commonly regarded as first-line therapies for cITP. These drugs have a rapid onset of action, but they do not result in durable remission in most patients. If first-line therapy is ineffective or not tolerated as a result of long-term use, patients with cITP need to be switched to a second-line regimen. The goal of second-line therapy is to maintain platelet counts at safe levels in order to achieve disease remission. Thrombopoietin receptor agonists (TPO-RAs) are recommended as the first choice for second-line treatment of cITP, including recombinant human thrombopoietin (rhTPO), EPAG, ROMI, herombopag, and avatrombopag.

ROMI is a long-acting TPO-RA that is administered subcutaneously once a week. It works by stimulating the production of platelets, which are blood cells that help to clot blood. Clinical studies have demonstrated ROMI's effectiveness in increasing platelet counts and reducing bleeding episodes in patients with cITP. Alongside ROMI, eltrombopag (EPAG) is another TPO-RA that

is generally accepted as a therapeutic alternative with comparable safety and efficacy(*8*). However, despite their widespread use, ROMI and EPAG have not been directly compared in head-to-head clinical trials to treat cITP.

Given the growing attention on the value of innovative cITP drugs, it is essential to evaluate their economic impact. Understanding the cost-utility of these treatments can inform healthcare decision-makers and ensure optimal resource allocation. This study aims to fill this gap by assessing the cost-utility of ROMI compared to EPAG in the treatment of cITP in Chinese adults. The findings furnish evidence supporting the clinical use of ROMI and offer empirical data for cost-effectiveness assessments conducted by healthcare technology assessment (HTA) agencies globally. By evaluating both the clinical and economic aspects of ROMI and EPAG, this study aims to support informed decision-making and contribute to the broader discussion on the value of innovative treatments for cITP.

2. Patients and Methods

2.1. Population and perspective

Subjects were consistent with the instructions for ROMI, *i.e.*, adults (≥ 18 years of age) with cITP who have not responded well to other treatments (*e.g.*, corticosteroids and immunoglobulins). Potential subjects with a mean body weight of 60 kg were included. An analysis was performed from the perspective of the Chinese health care system.

2.2. Comparators

A model compared ROMI versus EPAG. ROMI dosing data were obtained from a Chinese phase III clinical trial (CTR20150395) where patients were given intramuscular injections once a week at a mean dose of 3.1 μg/kg (*9*). The average daily dose of EPAG was 42.1 mg, which was based on a Chinese phase III clinical trial (*10*).

2.3. Model construction

A short-term decision tree was embedded in a Markov model over a lifetime horizon (33 years, a cohort from 45 years of age and older). The model cycle was 4 weeks. Both QALYs and costs were discounted at a rate of 5% per year. The incremental cost-effectiveness ratio (ICER) of ROMI versus EPAG for the second-line treatment of adults with chronic ITP was calculated using Microsoft Excel (Version 16.72).

As shown in Figure 1, the 6-week decision-tree stage considered two treatment options: ROMI and EPAG. Based on treatment results, participants were divided into platelet response and non-response branches, and the definition of platelet response is any platelet count ≥ 50 × 10^9/L. Platelet response was further divided into non-bleeding and mild bleeding branches; platelet non-response was divided into non-bleeding, mild bleeding, and severe bleeding branches. Non-bleeding patients were those with a score of 0 on the World Health Organization Bleeding Scale, while scores of 1 and 2 were considered mild bleeding and scores of 3-4 were considered severe bleeding.

As shown in Figure 2, the long-term Markov model included three health states: "Response", "Non-response", and "Dead". In this model, a "Response" state is defined as patients achieving a platelet count of ≥ 50 × 10^9/L, while a "Non-response" state refers to patients with a platelet count of < 50 × 10^9/L.

Figure 3 shows the model of the drug treatment pathway. After 4 weeks of nonresponse to treatment with ROMI or EPAG; participants were switched to rhTPO combined with rituximab (rhTPO + RTX) and then switched to all-trans retinoic acid combined with danazol (ATRA + danazol). After 4 consecutive cycles of ATRA + danazol (*11*), participants were finally switched to best

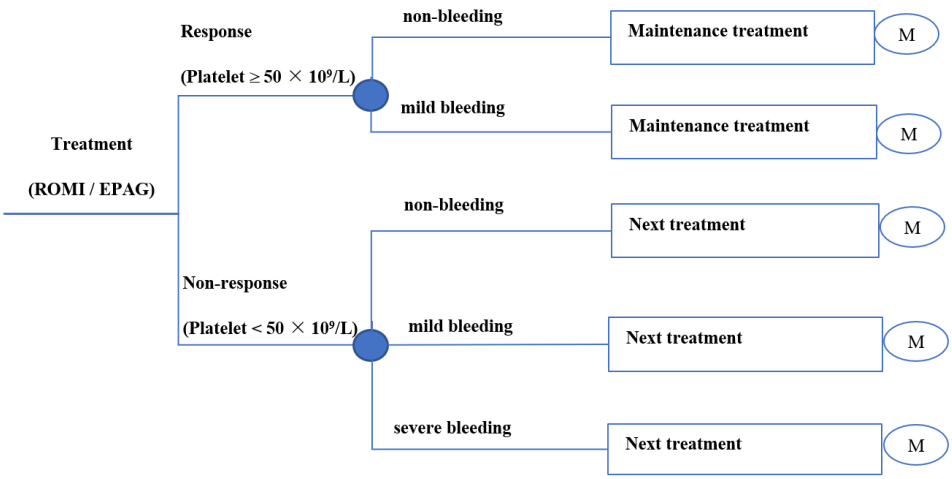

Figure 1. Overview of an embedded decision tree. EPAG: eltrombopag; ROMI: romiplostim; Next Treatment: rhTPO + Rituximab.

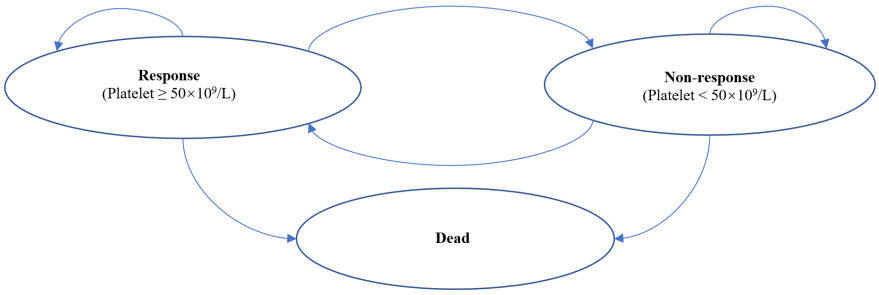

Figure 2. Overview of a long-term Markov model driven by platelet response.

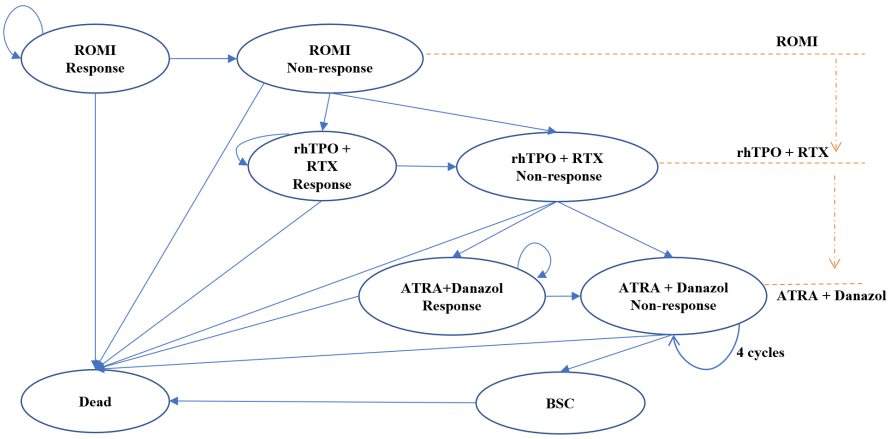

Figure 3. Treatment pathway (ROMI as an example). ROMI: romiplostim; RTX: rituximab; ATRA: all-trans retinoic acid; BSC: best supportive care.

Table 1. Clinical efficacy inputs for the short-term decision tree stage

Inputs	ROMI	Reference	EPAG	Reference
Probability of response	47.6%	(*11*)	48.8%	P_{ROMI}*ORs
Low bleeding rate in response	11.4%		13.2%	
Low bleeding rate in non-response	35.1%		40.4%	
High bleeding rate in non-response	1.30%		1.9%	

EPAG: eltrombopag; ROMI: romiplostim.

supportive care (BSC).

2.4. Assumptions

i) Splenectomies: According to expert clinical opinion, splenectomy for treatment of ITP declined in prevalence (less than 10%) in recent years. All patients in this study cohort were assumed to have not undergone a splenectomy.

ii) Treatment pathway: The drug treatment was assumed to be platelet non-response for one cycle before moving on to the next treatment. The sequence of drug changes was only from ROMI/ EPAG to rhTPO + RTX and then to ATRA+ danazol.

iii) Mortality: Patient mortality was not considered in either group during the decision tree stage. It was assumed to be equivalent to natural mortality for patients without bleeding or those experiencing mild bleeding. The risk ratio (RR) between severe bleeding and the natural population is 2.6 (*12*). Mortality was higher in the non-responders treated with ATRA combined with danazol after several lines of treatment, consequently, we assumed that the mortality rate ratio (RR) of this group and the BSC group versus the natural mortality rate was 2.6.

2.5. Clinical inputs

Clinical efficacy data on ROMI were obtained from a clinical trial (*11*) in China, including the platelet response rate, low bleeding rate, and high bleeding rate in each health state. Due to the lack of head-to-head clinical RCT studies comparing ROMI and EPAG, the odds ratios (ORs) for the clinical effect data between the ROMI and EPAG groups were obtained by MAIC. Efficacy data for the EPAG group were calculated by multiplying the absolute values for the ROMI group (P_{ROMI}) by the ORs (Table 1).

Table 2. Clinical efficacy inputs for the long-term Markov stage

Inputs	To		
	Response	Non-response	Dead
From			
ROMI/EPAG response	0.79983	0.19996	0.00021
ROMI/EPAG non-response; rhTPO + RTX response	0.54379	0.45594	0.00027
rhTPO + RTX non-response; ATRA + Danazol response	0.61984	0.37980	0.00036
ATRA + Danazol non-response; BSC	0	0.99946	0.00054
dead	0	0	1

EPAG: eltrombopag; ROMI: romiplostim; RTX: rituximab; ATRA: all-trans retinoic acid; BSC: best supportive care.

Table 3. Utility inputs

Inputs	Mean	SE	Reference
Non-bleeding in response	0.86	0.15	Agota 2010
Mild bleeding in response	0.73	0.19	Agota 2010
Non-bleeding in non-response	0.84	0.19	Agota 2010
Mild bleeding in non-response	0.73	0.19	Agota 2010
Severe bleeding in non-response	0.45	0.06	Leontiadis 2007
Dead	0.00	/	
Disutility	-0.1	0.03	Jamali 2009

The analysis indicated that ROMI had a slightly lower platelet response rate compared to EPAG (ROMI *vs*. EPAG, OR: 0.976, 95% confidence interval (CI): 0.13-6.83). However, ROMI was superior to EPAG in terms of the low bleeding rate (ROMI *vs.* EPAG, OR: 0.85, 95% CI: 0.27-2.74) and high bleeding rate (ROMI *vs.* EPAG, OR: 0.67, 95% CI: 0.02-15.05).

In the long-term Markov stage, the effectiveness of ROMI was assumed to be the same as that of EPAG because MAIC of the response rates suggested no significant differences between the 2 TPO-RAs, as evinced by a wide CI that included 1. The response rate to EPAG was based on the RAISE trial (*12*), and ROMI performed as well as EPAG. The response rates for all other treatments (*13*) were obtained from the published literature (Table 2). As mentioned in the previous hypothesis, the model included both natural mortality and high-risk mortality.

2.6. Utility

The patient utility values were collected in different bleeding groups (Table 3). Due to lack of utility data for Chinese adults with ITP, utility values from a time trade-off (TTO) survey (*13*) conducted in the UK were included in this study, and disutility values associated with serious bleeding and adverse effects were obtained from the published literature (*14,15*).

2.7. Costs

The full course of treatment for a patient with cITP was considered in this study (Table 4). Drug prices were from the Yaozhi database (*16*), and drug daily doses from clinical trials (*2,11,13,17*). The costs of adverse effects were derived from the published literature in China. Administration and monitoring costs were obtained from a catalog of prices for medical care in representative cities, such as Shanghai, Guangzhou, Beijing, Zhengzhou, and Chengdu. All costs were assessed in US dollars (USD), using the average RMB/USD exchange rate of 6.7261 in 2022. This comprehensive cost assessment ensures an accurate and realistic evaluation of the economic impact of cITP treatments within the Chinese healthcare system.

2.8. Sensitivity analysis

One-way and probabilistic sensitivity analyses were used to test the uncertainty of the model. OSA was performed to identify the most sensitive parameters of this model. In OSA, all key model inputs were varied around the base-case values by ± 20%. PSA was performed using 5,000 iterations by simultaneously sampling from estimated probability distributions of model parameters to examine parameter uncertainty over the entire model, and cost-effectiveness acceptability curves (CEACs) were then calculated.

3. Results

3.1. Base case

The lifetime horizon Markov model indicated that treatment with ROMI resulted in an average of $4,344.4 higher costs for 0.004 QALYs (Table 5). The ICER in this model was $1,135,779.46/QALY, which was higher than $36,117.2/QALY (3 GDP per capita) in China.

3.2. OSA

Figure 4 shows the results of the OSA, presented as the net monetary benefit (NMB) considering a willingness-to-pay threshold of $12,039.1 per QALY. The variables with the largest effect on the model were a high bleeding rate due to EPAG in response (Markov stage), a high bleeding rate due to ROMI in response (Markov stage), the average daily dosage of rhTPO (15,000 U/ampoule), days of weekly rhTPO (7,500 U/ampoule), and the

Table 4. Direct costs per cycle (USD)

Costs	ROMI	EPAG	rhTPO + RTX	ATRA + Danazol/BSC
Drug acquisition cost	2334.2	1307.1	3439.7	138.4
Administration cost	54.5	5.7	152.0	24.9
Costs of a bleeding disposition in response	2.1	2.4	601.8	601.8
Costs of a bleeding disposition in non-response	40.9	58.5	990.4	990.4
Costs of adverse events	3.1	57.9	25.2	-
Monitoring costs	63.2	63.2	63.2	63.2
Total fee in response	1036.3	1436.2	4281.8	828.2
Total fee in non-response	1075.1	1492.3	4670.4	1216.8

EPAG: eltrombopag; ROMI: romiplostim; RTX: rituximab; ATRA: all-trans retinoic acid; BSC: best supportive care.

Table 5. Base case cost-effectiveness

Drug	Total costs ($)	Total QALYs	Incremental costs ($)	Incremental QALYs	ICERs ($/QALY)
EPAG	22,366.2	9.787			
ROMI	26,704.1	9.791	4344.4	0.004	1135779.46

EPAG: eltrombopag; ROMI: romiplostim.

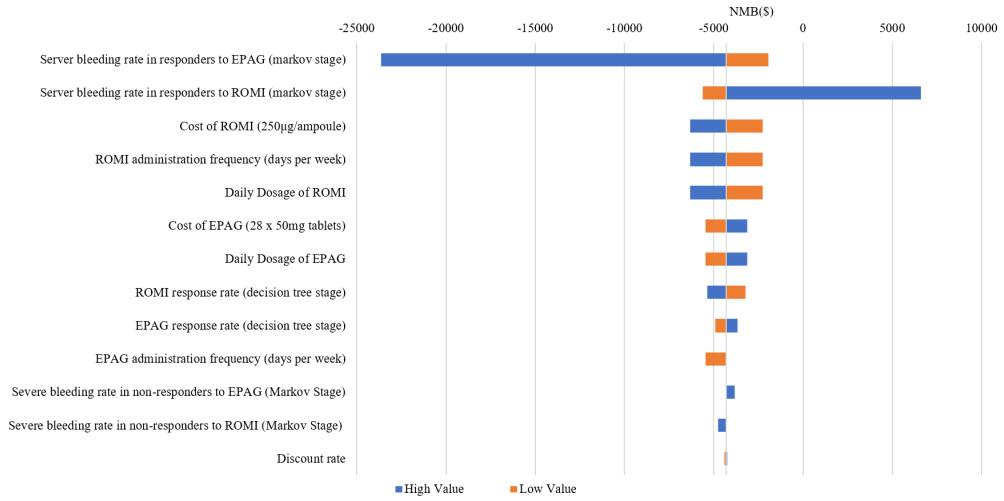

Figure 4. One-way sensitivity analysis. ROMI: romiplostim; EPAG: eltrombopag. NMB: net monetary benefit, NMB=(λ×ΔEffectiveness)−ΔCost, λ=1 times GDP per capita.

average daily dosage of rhTPO (7,500 U/ampoule).

3.3. PSA

PSA results are presented on the cost-effectiveness planes in Figure 5. CAECs demonstrated that at a cost-effectiveness threshold of $0-$36,117.2 (3 times GDP per capita)/QALY, the probability that ROMI is cost-effective versus EPAG was 0.68% and 0.16% (Figure 6).

3.4. Scenario analysis

Based on the pre-negotiation prices, ROMI is not cost-effective compared to EPAG. In the scenario analysis, we examined the probability of ROMI being cost-effective at different prices while keeping other conditions constant. When the monthly drug cost of ROMI ($326.8) is equal to EPAG, under a willingness-to-pay threshold of 0.5 times GDP per capita in China, the probability of ROMI being cost-effective exceeds 50% (Table 6). Moreover, as the price of ROMI decreases, the probability of ROMI being cost-effective increases. This analysis highlights the importance of price adjustments in determining the cost-effectiveness of ROMI in treating cITP.

4. Discussion

4.1. ROMI's cost-effectiveness relative to EPAG under specific pricing conditions

This study aimed to evaluate the cost-utility of romiplostim (ROMI) compared to eltrombopag (EPAG) for the treatment of chronic immune thrombocytopenia (cITP) in Chinese adults, specifically addressing the

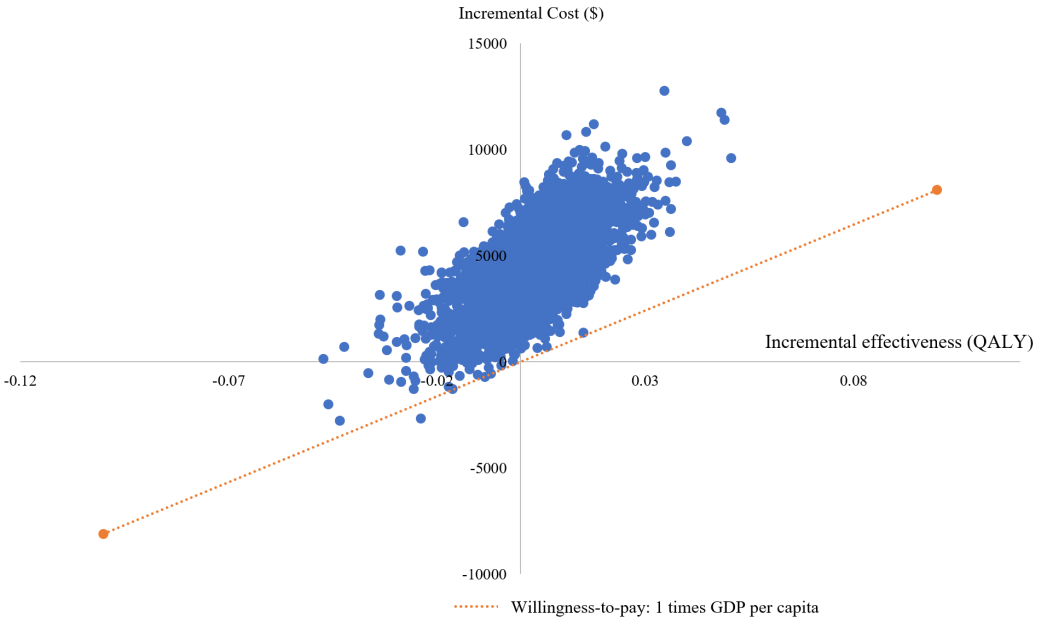

Figure 5. Probabilistic sensitivity analysis (5,000 simulations).

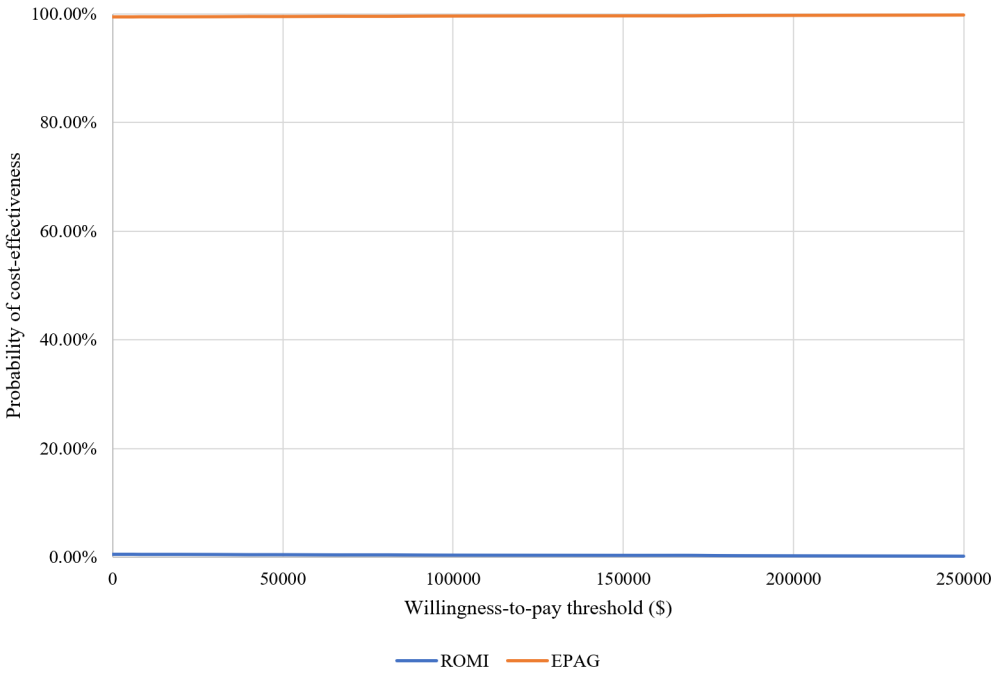

Figure 6. Cost-effectiveness acceptability curves. ROMI: romiplostim; EPAG: eltrombopag.

Table 6. Probability of ROMI being cost-effective compared to EPAG at different price points

Price of ROMI ($/ampoule)	Willingness-to-pay threshold		
	(0.5 times GDP per capita)/QALY	(0.8 times GDP per capita)/QALY	(1 times GDP per capita)/QALY
583.5*	0.54%	0.44%	0.44%
326.8	55.7%	56.4%	56.7%
294.4	74.8%	75.5%	76.2%
264.6	87.5%	88.2%	88.7%
234.9	95.8%	96.2%	96.5%

*$583.5/ampoule: the price used in the base case analysis, resulting in a drug acquisition cost of $2,334.2 per cycle.

economic impact of these treatments. In evaluating the pharmacoeconomic aspects of cITP treatment in China, a point warranting acknowledgement is that this analysis is specifically based on the pre-negotiation list price of ROMI. This context is essential as it underlines that the economic insights and conclusions are contingent upon these initial pricing assumptions before any pricing negotiations or adjustments. If the pricing of ROMI is in line with or lower than that of EPAG, ROMI emerges as a better choice, providing both economic and therapeutic advantages. This dominance of ROMI is predominantly attributed to its comparative affordability, without compromising efficacy, and an enhanced safety profile. Moreover, the similarity in platelet response rates between ROMI and EPAG, as highlighted in a comprehensive review of 14 randomized controlled trials (RCTs) by Puavilai *et al.* (2020) (*18*), corroborates the pharmacoeconomic benefit of ROMI when priced competitively. Our findings provide valuable guidance for clinical practice, emphasizing the importance of cost considerations in therapeutic choices for ITP.

4.2. Contribution to clinical economic evaluation in China

The current findings added to the existing evidence and models while remaining in line with prior models (*19-21*). First, EPAG is commonly used as a comparator in the economic evaluation of ROMI. Second, a lifetime horizon was thought to be appropriate, since adult ITP tends to be a chronic disease and the median age of patients is 45. Third, a one-month cycle was used to match the clinical trial involving ROMI. Costs and outcomes were discounted at a rate of 5% annually, as recommended by the China Guidelines for Pharmacoeconomic Evaluations (*22*). The treatment pathway used in this model was based on the Chinese guidelines on the diagnosis and management of adult ITP (version 2020) (*2*). Above all, this study stands out as one of the few model-based approaches being adopted in developing countries, bridging a critical knowledge gap and offering substantial insights for the evaluation of relevant drugs in this context.

4.3. Limitations

While providing valuable insights, this study had several limitations that warrant consideration. First, the key effectiveness outcomes rely on indirect comparisons between ROMI and EPAG, as direct head-to-head clinical trials are not available. This reliance introduces a degree of uncertainty, but this methodology remains the most feasible and is representative for the Chinese context. Due to simplifications in the model, this study focused on patients who have not undergone a splenectomy, and the cost-effectiveness of ROMI in a small subset of patients who have undergone a splenectomy for ITP remains unknown. More clinical efficacy and cost data are necessary to draw conclusions in this regard. Additionally, this cost analysis is confined to direct medical expenses, drawing primarily from existing literature, and didn't account for broader societal perspective, including the indirect costs related to lost productivity. A more comprehensive analysis incorporating these indirect costs would offer a more holistic understanding of ROMI's economic impact. These limitations highlight the need for ongoing research from diverse perspectives to fully comprehend the pharmacoeconomic implications of ROMI and EPAG in the treatment of cITP.

5. Conclusion

Under the current pre-negotiation pricing, ROMI is not a cost-effective option. However, ROMI could be cost-effective if its price is reduced to be lower than or equal to EPAG. This study highlights the critical role of pricing in treatment cost-effectiveness and suggests that future research and pricing negotiations are needed to make ROMI a viable economic alternative for ITP treatment in China.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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