ORIGINAL RESEARCH

Cost Per Response Analysis of Strategies for Chronic Immune Thrombocytopenia

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ABSTRACT

OBJECTIVES: This analysis estimated the cost per response and the incremental cost per additional responder of romplostim, eltrombopag, and the "watch-and-rescue" (monitoring until rescue therapies are required) strategy in adults with chronic immune thrombocytopenia (ITP).

STUDY DESIGN: The decision tree is designed to estimate the total cost per response for romiplostim, eltrombopag, and watch and rescue over a 24-week time horizon; cost-effectiveness was evaluated in terms of incremental cost per additional responder.

METHODS: Model inputs including response rates, bleeding-related episode (BRE) rates, and costs were estimated from registrational trial data, an independent Bayesian indirect comparison, database analyses, and peer-reviewed publications. Costs were applied to the proportions of patients with treatment response and nonresponse (based on platelet count). The total cost per response and the incremental cost per additional responder for each treatment were calculated. Sensitivity analyses and alternative analyses were performed.

RESULTS: With higher total costs and greater treatment efficacy, romiplostim and eltrombopag had a lower 24-week cost per response and a lower average number of BREs than watch and rescue. Eltrombopag was weakly dominated by romiplostim. The incremental cost-effectiveness ratio of romiplostim versus watch and rescue was $46,000 per additional responder. The model results are most sensitive to response rates of romiplostim and watch and rescue and the BRE rate for splenectomized nonresponders. Alternative analyses results were similar to the base case.

CONCLUSIONS: In adults with chronic ITP, romiplostim represents an efficient way to achieve response, with lower costs per response than eltrombopag; both romiplostim and eltrombopag had lower costs per response than watch and rescue.

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Chronic immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a low platelet count and increased risk of bleeding. Two thrombopoietin-receptor agonists (TPO-RAs), romiplostim (once-weekly subcutaneous injection)[1] and eltrombopag (once-daily oral agent),[2] are indicated for the treatment of adults with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.[1-4] In clinical practice, patients are sometimes monitored until rescue therapies, like intravenous (IV) immunoglobulin, are required, commonly referred to as the "watch-and-rescue" strategy.

Although some patients undergo splenectomy to treat their ITP, nonsplenectomized patients account for the majority of adult patients with ITP seen by clinical practices in the United States.[5] The primary goal of ITP therapy is to help achieve a platelet count that prevents major bleeding.[6] Both of the available TPO-RAs have been shown to increase and maintain platelet counts[3,4] and reduce the incidence of bleeding-related episodes (BREs). A BRE is defined as the occurrence of a bleeding event and/or use of rescue therapy, including intravenous immunoglobulin (IVIg), anti-D, corticosteroids, platelet transfusions, and dosage increases.[7,8] There is limited evidence related to the economics of TPO-RA therapy currently available in published literature.[9,10] This analysis was designed to evaluate the cost-effectiveness (in terms of incremental cost per additional responder) and cost per treatment response of the 2 TPO-RAs and the watch-and-rescue strategy for treating adults with chronic ITP in the United States.

METHODS

Overview and Model Structure

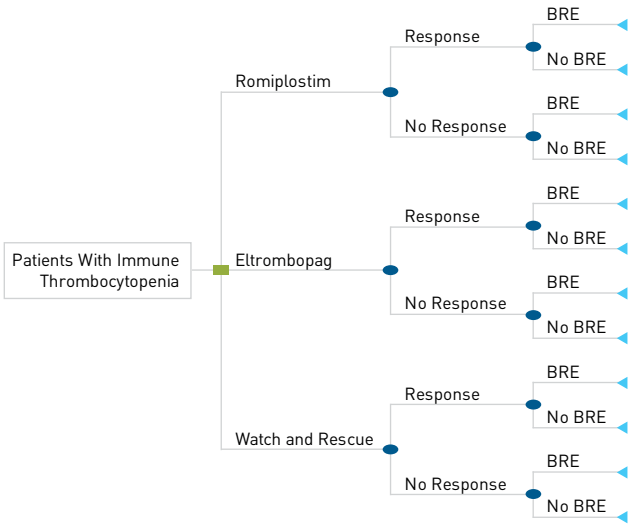
The target patient population consists of both splenectomized (51%) and nonsplenectomized (49%) adults with chronic ITP. Model comparators included romiplostim, eltrombopag, and watch and rescue. The model was developed in Microsoft Excel 2010 using Visual Basic for Applications (Microsoft Corp; Redmond, Washington).

The model begins with the decision to treat patients with ITP with either romiplostim or eltrombopag or to adopt the watch and rescue strategy. The analysis was based on a decision tree that stratified patients into response or no response, followed by the presence or absence of a BRE (**Figure 1**). Costs were applied to each group of patients in the decision tree. The patients were followed over a 24-week time horizon, consistent with the trial durations for romiplostim and eltrombopag.[3,4] For each strategy, the average number of BREs, BRE costs, percentage of patients who responded, and total costs, including drug, physician, and lab test costs, were estimated. The total cost per response for each treatment was calculated. Cost-effectiveness was evaluated in terms of incremental cost per additional responder from the US payer perspective.

TAKEAWAY POINTS

- Limited evidence evaluating the economic efficiency of thrombopoietin-receptor agonist (TPO-RA) therapy in the United States is currently available in published literature.
- Results of this analysis provide information on the efficiency (cost per response) and cost-effectiveness (incremental cost per additional responder) of the 2 available TPO-RAs (romiplostim and eltrombopag) and of "watch and rescue" in adults with chronic immune thrombocytopenia in the United States.
- Romiplostim represents an efficient way to achieve response, with lower costs per response than eltrombopag and watch and rescue.

FIGURE 1. Cost Consequence Analysis Decision Tree Structure



BRE indicates bleeding-related episode.

Treatment Response Rates

Overall platelet response was defined in the romiplostim trials as the percentage of patients with a platelet count ≥50 × 10^9/L for at least 4 weeks during the trial, excluding responses within 8 weeks after use of rescue medications.[3,11] Overall platelet response was defined in the eltrombopag trial as the percentage of patients: (1) with a platelet count of 50-400 × 10^9/L for at least 4 consecutive weeks during treatment, including all data up to time of withdrawal for patients who prematurely withdrew, excluding responses during rescue treatment and up to the time platelet counts fell below 50 × 10^9/L after cessation of rescue treatment; or (2) with a platelet count of 50-400 × 10^9/L for at least 6 of the last 8 weeks of treatment, excluding premature withdrawals and patients using rescue therapy at any time on treatment.[11-13] In the model, treatment response was defined by overall platelet response based on the number of weeks with a platelet count ≥50 × 10^9/L. The response rates for romiplostim were estimated using trial data.[3,13] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons Good Research Practices report suggests that data from head-to-head trials are preferred in economic evaluations of active comparators; in the absence of these data, evidence from an indirect treatment comparison may be considered.[14] The results from an independent Bayesian indirect comparison analysis suggested that the overall response rate with romiplostim was significantly higher than with eltrombopag (odds ratio [OR], 0.15).[11] Accordingly, the eltrombopag response rates (51.9% for nonsplenectomized and 35.5% for splenectomized patients) were estimated using the romiplostim response rates (87.8% for nonsplenectomized and 78.6% for splenectomized patients) and the OR of 0.15 estimated from Cooper et al.[11] The watch-and-rescue response rates for nonsplenectomized and splenectomized patients of 14.5% and 4.8%, respectively, were estimated from pooled placebo response rates.[3,4] Response rates are presented in **Table 1**.[1-4,8,11,15-18]

BRE Rates

A BRE was defined as a discrete and identifiable event of bleeding and/or the use of rescue therapy occurring within close proximity of one another (3 days).[8] A composite end point, such as a BRE, tends to be more clinically relevant because the bleeding events in phase 3 trials are likely to be confounded by increased use of rescue medication in the placebo arms.[8] According to Weitz et al, applying the BRE method to the romiplostim trial shows that treatment was associated with a reduction in the rate of unique clinical episodes related to bleeding compared with placebo. In the model, BREs were estimated from a post hoc analysis of 2 phase 3 placebo-controlled studies of romiplostim in patients with chronic ITP and were calculated by pooling the placebo and romiplostim data.[8] BREs were assumed to depend on response and splenectomy status only.

TABLE 1. Model Parameters[a]

	Base-Case Estimate	DSA Range (95% CI)	Reference
Eltrombopag vs romiplostim response OR	0.15	Did not vary	Cooper et al (2014)[11]
Response rates			
Nonsplenectomized			
Romiplostim	87.8%	73.0%-95.4%	Kuter et al (2008)[3]
Eltrombopag	51.9%	28.8%-75.8%[b]	Estimated based on data from Kuter et al 2008[3] and Cooper et al 2014[11]
Watch and rescue	14.52%	7.3%-26.3%	Kuter et al (2008)[3]; Cheng et al (2011)[4]
Splenectomized			
Romiplostim	78.6%	62.8%-89.2%	Kuter et al (2008)[3]
Eltrombopag	35.5%	20.2%-55.2%[b]	Estimated based on data from Kuter et al (2008)[3] and Cooper et al (2014)[11]
Watch and rescue	4.76%	0.8%-17.4%	Kuter et al (2008)[3]; Cheng et al (2011)[4]
Weekly BRE rates			
Nonsplenectomized			
Nonresponder	0.128	0.104-0.158	Weitz et al (2012)[8]
Responder	0.031	0.020-0.047	Weitz et al (2012)[8]
Splenectomized			
Nonresponder	0.151	0.126-0.179	Weitz et al (2012)[8]
Responder	0.039	0.026-0.059	Weitz et al (2012)[8]
Wholesale acquisition costs			
Romiplostim	$5.826/mcg	Not included	EncoderPro Database[15] (July 2015)
Eltrombopag (12.5 and 25 mg)	$4.082/mg	Not included	EncoderPro Database[15] (July 2015)
Eltrombopag (50 and 75 mg)	$3.988/mg	Not included	EncoderPro Database[15] (July 2015)
Eltrombopag (weighted average of all strengths/unit costs)	$4.008/mg	Not included	EncoderPro Database[15] (July 2015)
Dosing parameters			
Romiplostim (without top-coding)	317 mcg/week	Not included	Kuter et al (2008)[3]
Eltrombopag	54.875 mg/day	Not included	Cheng et al (2011)[4]
Physician and lab test costs			
Administration of romiplostim visit (injection)	$25.51/visit	Not included	CMS[17,c]
Physician visit	$73.30/visit	Not included	CMS[17,c]
Platelet count test	$6.09/test	Not included	CMS (Laboratory)[18,c]
Hepatic function panel	$11.11/test	Not included	CMS (Laboratory)[18,c]

(continued)

Because there were no published BRE data for eltrombopag, BRE rates were assumed to be the same as those for romiplostim and watch and rescue (Table 1).

Costs

Wholesale acquisition costs of eltrombopag (tablet strengths, 12.5 mg, 25 mg, 50 mg, and 75 mg) and romiplostim were obtained from the EncoderPro database.[15] Although the romiplostim prescribing information indicates that the maximum weekly dose of romiplostim is 10 mcg/kg per week,[1] in clinical trials of romiplostim, the maximum allowed dose was 15 mcg/kg per week.[3] Accordingly, in the base-case analysis, the maximum weekly dose of romiplostim was allowed to exceed 10 mcg/kg and an alternative analysis limiting the maximum weekly dose to 10 mcg/kg was also performed. It was assumed that patients in the watch and rescue treatment arm do not incur drug acquisition costs. Drug acquisition costs and dosing parameters for romiplostim and eltrombopag are presented in Table 1.

In the real-world setting, patients are on different tablet strengths of eltrombopag. Therefore, the proportions of patients utilizing the various eltrombopag tablet strengths were estimated from published

TABLE 1. *(Continued)* Model Parameters[a]

	Base-Case Estimate	DSA Range (95% CI)	Reference
Frequency of physician visits			
Romiplostim administration visits	1 per week	Not included	Assumption
Physician visits (for romiplostim, eltrombopag, and watch and rescue)	1 per week in weeks 1-4; 1 per 4 weeks in weeks 5-24	Not included	Romiplostim and eltrombopag prescribing information[1,2]
Frequency of clinical tests			
Platelet count test (for romiplostim, eltrombopag, and watch and rescue)	1 per week in weeks 1-4; 1 per 4 weeks in weeks 5-24	Not included	Romiplostim and eltrombopag prescribing information[1,2]
Hepatic function panel (for eltrombopag)	1 per 2 weeks in weeks 1-4; 1 per 4 weeks in weeks 5-24	Not included	Assumption
BRE cost (per event)			
Average total cost	$6022	$5421-$6623	Lin et al (2017)[16]

BRE indicates bleeding-related episode; CPT, Current Procedural Terminology; DSA, deterministic sensitivity analysis; OR, odds ratio.
[a]All cost estimates are in 2015 US$.
[b]DSA ranges for eltrombopag response rates were estimated using the upper and lower bounds for the romiplostim response rates[3] and applying the eltrombopag response OR (0.15).[11]
[c]The costs of administration/injection visits and physician office visits were estimated from the July release of the 2015 National Physician Fee Schedule Relative Value File,[17] using CPT codes of 96372 (therapeutic, prophylactic, or diagnostic injection [specify substance or drug]; subcutaneous or intramuscular) and 99213 (office or other outpatient visit for the evaluation and management of an established patient), respectively. The costs of platelet counts and hepatic function panels were estimated from the 2015 Clinical Diagnostic Laboratory Fee Schedule[18] using CPT codes of 85049 (blood count; platelet, automated) and 80076 (hepatic function panel), respectively.

literature (21.5% on 25 mg, 37.5% on 50 mg, and 41.0% on 75 mg).[4] The average cost of eltrombopag ($4.008 per mg) was estimated by calculating a weighted average of the unit costs and proportion of patients on each tablet strength. Patients on romiplostim incurred a weekly drug acquisition cost, whereas patients on eltrombopag incurred a daily drug acquisition cost. Both responders and nonresponders were assumed to receive treatment for the entire model horizon and accordingly incurred 24 weeks of drug costs.

The average treatment cost per BRE (Table 1) was estimated from a retrospective study of a large US administrative healthcare claims database that was sponsored by Amgen.[16] Adult patients with newly diagnosed ITP were identified between the years 2007 and 2012 by having at least 2 outpatient claims separated by at least 30 days or 1 inpatient claim with *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis code 287.31 for primary ITP. A BRE was defined as ≥1 actual bleeding event and/or use of rescue therapy (IV immunoglobulin and anti-D; IV steroids; and/or platelet transfusion). In the study, Lin et al did not consider an increase in dose or frequency of a concurrent ITP medication as rescue therapy. Average BRE costs for both nonsplenectomized and splenectomized patients were estimated; however, due to the high variability of the estimates, the difference in BRE costs between the 2 patient groups was not statistically significant. Therefore, the average total cost among both splenectomized and nonsplenectomized patients was used in the base-case analysis.[16]

The costs and frequency of physician office visits for administration of romiplostim and monitoring patients with chronic ITP, platelet count tests for patient monitoring, and hepatic function panels for patients on eltrombopag are also presented in Table 1.[1,2,17,18] The total costs of physician office visits and lab tests were calculated by multiplying the frequency of testing by the time horizon and the cost of individual visits. All cost estimates are presented in 2015 US dollars.

Model Analyses

In the model, the total costs at 24 weeks, proportion of patients with response, and average number of BREs were calculated for each comparator. The 24-week cost per response for each comparator was calculated by dividing the total cost at 24 weeks by the proportion of patients with response. The cost-effectiveness of the 2 TPO-RAs and the watch and rescue strategy for treating adults with chronic ITP in the United States was evaluated in terms of incremental cost per additional responder. An alternative analysis was also performed using incremental cost per BRE avoided as the outcome of interest.

When conducting cost-effectiveness analyses (CEAs), if a strategy is both more costly and less effective compared with an alternative strategy, then it is said to be dominated by the alternative strategy and no incremental cost-effectiveness ratio (ICER) is calculated.[19,20] If a more costly strategy provides additional benefit, then the 2 strategies are compared by dividing the additional cost (ie, incremental cost) by the additional benefit (ie, incremental effectiveness).[19,20] Weak dominance (also called extended dominance) occurs when the ICER for a strategy is greater (ie, the strategy is less cost-effective) than that of a more costly alternative.[19-21] Strategies that are weakly dominated are excluded, and then ICERs of the remaining strategies are recalculated.[19,20] Given the 24-week time horizon of the model, costs and outcomes were not discounted.

Deterministic, or 1-way, sensitivity analyses (DSAs) were performed to assess how changes in key model parameters, and parameter

TABLE 2. Base-Case and Alternative Analysis Results: Cost Per Response, by Treatment Strategy

Comparator	Proportion With Response	Average Number of BREs	24-Week Costs				24-Week Cost Per Response
			Drug	Visits and Tests	BREs	Total	
Base-case analysis							
Watch and rescue	9.5%	3.12	$0	$715	$18,788	$19,503	$204,403
Eltrombopag	43.5%	2.27	$36,949	$792	$13,684	$51,425	$118,113
Romiplostim	83.1%	1.27	$44,321	$1327	$7670	$53,318	$64,165
Alternative analysis 1: maximum dosage of 10 mcg/kg/week for romiplostim and corresponding response rate (80.8%)							
Watch and rescue	9.5%	3.12	$0	$715	$18,788	$19,503	$204,403
Eltrombopag	39.7%	2.34	$36,949	$792	$14,112	$51,853	$130,639
Romiplostim	80.9%	1.31	$43,762	$1327	$7915	$53,003	$65,541
Alternative analysis 2: response rates for eltrombopag (60.0% for splenectomized and 71.8% for nonsplenectomized) estimated using registrational trial data							
Watch and rescue	9.5%	3.12	$0	$715	$18,788	$19,503	$204,403
Eltrombopag	65.8%	1.71	$36,949	$792	$10,302	$48,043	$73,053
Romiplostim	83.1%	1.27	$44,321	$1327	$7670	$53,318	$64,165
Alternative analysis 3: patient population limited to nonsplenectomized patients only							
Watch and rescue	14.5%	2.74	$0	$715	$16,507	$17,222	$118,639
Eltrombopag	51.9%	1.87	$36,949	$792	$11,236	$48,978	$94,327
Romiplostim	87.8%	1.03	$44,321	$1327	$6180	$51,828	$59,027
Alternative analysis 4: platelet tests and physician visits are weekly during weeks 5 to 24 for watch and rescue, eltrombopag, and romiplostim							
Watch and rescue	9.5%	3.12	$0	$1905	$18,788	$20,694	$216,884
Eltrombopag	43.5%	2.27	$36,949	$1983	$13,684	$52,616	$120,848
Romiplostim	83.1%	1.27	$44,321	$2518	$7670	$54,509	$65,598
Alternative analysis 5: watch and rescue has zero physician visits and zero platelet count tests							
Watch and rescue	9.5%	3.12	$0	$0	$18,788	$18,788	$196,914
Eltrombopag	43.5%	2.27	$36,949	$792	$13,684	$51,425	$118,113
Romiplostim	83.1%	1.27	$44,321	$1327	$7670	$53,318	$64,165
Alternative analysis 6: response rates for eltrombopag (62.1% for splenectomized and 56.8% for nonsplenectomized patients) estimated from Bussel et al (2009)[22]							
Watch and rescue	9.5%	3.12	$0	$715	$18,788	$19,503	$204,403
Eltrombopag	59.5%	1.85	$36,949	$792	$11,163	$48,904	$82,188
Romiplostim	83.1%	1.27	$44,321	$1327	$7670	$53,318	$64,165

BRE indicates bleeding-related episode.

uncertainty, impact cost-effectiveness results. In the sensitivity analyses, parameters were varied using 95% CIs derived from the clinical trial data or database analyses (Table 1). The model was analyzed with each parameter varied individually to its corresponding upper or lower limit, and results were calculated. Results of the DSA are presented visually in the form of tornado diagrams. The DSA was performed with incremental cost per additional responder as the outcome measure. Alternative analyses examining the impact of differing assumptions related to romiplostim dosing, response rates, nonsplenectomized patients, and frequency of platelet count tests and physician visits were also performed.

RESULTS

Base Case

The total 24-week costs per patient ranged from $19,500 for watch and rescue to $53,300 for romiplostim (**Table 2**[22]). Compared with the watch and rescue strategy, use of either of the 2 TPO-RAs was associated with fewer BREs and thus a lower BRE treatment cost ($18,800 for watch and rescue; $13,700 for eltrombopag; and $7700 for romiplostim) and was associated with a lower cost per response ($204,400 for watch and rescue; $118,100 for eltrombopag; and $64,200 for romiplostim). With better treatment efficacy, romiplostim was associated with a

TABLE 3. Base-Case and Alternative Analysis Results: Incremental Cost Per Additional Responder[a]

Comparator	Total Costs	Proportion With Response	Incremental Costs	Incremental Proportion With Response	ICER
Base-case analysis					
Watch and rescue	$19,503	9.5%	Reference	Reference	Reference
Eltrombopag	$51,425	43.5%	$31,922	34.0%	Weakly dominated[b]
Romiplostim	$53,318	83.1%	$33,815	73.6%	$45,973
Alternative analysis 1: maximum dosage of 10 mcg/kg/week for romiplostim and corresponding response rate (80.8%)					
Watch and rescue	$19,503	9.5%	Reference	Reference	Reference
Eltrombopag	$51,853	39.7%	$32,350	30.2%	Weakly dominated[b]
Romiplostim	$53,003	80.9%	$33,500	71.3%	$46,966
Alternative analysis 2: response rates for eltrombopag (60.0% for splenectomized and 71.8% for nonsplenectomized) estimated using registrational trial data					
Watch and rescue	$19,503	9.5%	Reference	Reference	Reference
Eltrombopag	$48,043	65.8%	$28,540	56.2%	Weakly dominated[b]
Romiplostim	$53,318	83.1%	$33,815	73.6%	$45,973
Alternative analysis 3: patient population limited to nonsplenectomized patients only					
Watch and rescue	$17,222	14.5%	Reference	Reference	Reference
Eltrombopag	$48,978	51.9%	$31,756	37.4%	Weakly dominated[b]
Romiplostim	$51,828	87.8%	$34,607	73.3%	$47,219
Alternative analysis 4: platelet tests and physician visits are weekly during weeks 5 to 24 for watch and rescue, eltrombopag, and romiplostim					
Watch and rescue	$20,694	9.5%	Reference	Reference	Reference
Eltrombopag	$52,616	43.5%	$31,922	34.0%	Weakly dominated[b]
Romiplostim	$54,509	83.1%	$33,815	73.6%	$45,973
Alternative analysis 5: watch and rescue has zero physician visits and zero platelet count tests					
Watch and rescue	$18,788	9.5%	Reference	Reference	Reference
Eltrombopag	$51,425	43.5%	$32,637	34.0%	Weakly dominated[b]
Romiplostim	$53,318	83.1%	$34,530	73.6%	$46,945
Alternative analysis 6: response rates for eltrombopag (62.1% for splenectomized and 56.8% for nonsplenectomized patients; 59.0% for combined splenectomized and nonsplenectomized populations) estimated from Bussel et al (2009)[22]					
Watch and rescue	$19,503	9.5%	Reference	Reference	Reference
Eltrombopag	$48,904	59.5%	$29,401	50.0%	Weakly dominated[b]
Romiplostim	$53,318	83.1%	$33,815	73.6%	$45,973

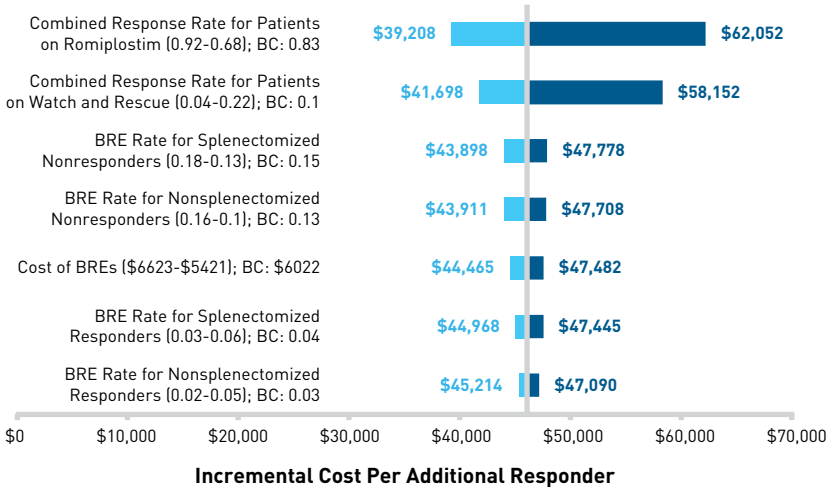
ICER indicates incremental cost-effectiveness ratio.
[a]Time horizon: 24 weeks. All costs presented in 2015 US$.
[b]Weak dominance occurs when the ICER for a strategy is greater than that of a more costly alternative (also called extended dominance).

lower cost per response than eltrombopag. The incremental cost per additional responder is presented in **Table 3**.[22] Eltrombopag was weakly dominated by romiplostim, and the ICER for romiplostim versus watch and rescue was $46,000 per additional responder.

Sensitivity Analyses

Given that romiplostim and watch and rescue are the 2 strategies on the cost-effectiveness frontier, the DSA was performed comparing romiplostim with watch and rescue only. Results of the DSA indicated that model results were most sensitive to the response rate of patients on romiplostim, the response rate of patients on watch and rescue, and the BRE rate for splenectomized nonresponders (**Figure 2**). Varying the response rate for patients on romiplostim to the lower and upper bounds of the 95% CI yielded ICERs of $62,100 and $39,200, respectively. Varying the response rate of patients on watch and rescue to the lower and upper bounds of the 95% CI yielded ICERs of $41,700 and $58,200, respectively. Varying the BRE rate for splenectomized nonresponders to the lower and upper bounds of the 95% CI yielded ICERs of $47,800 and $43,900, respectively.

FIGURE 2. Results of Deterministic Sensitivity Analysis (incremental cost per additional responder): Romiplostim Versus Watch and Rescue[a]



BC indicates base-case; BRE, bleeding-related episode; ICER, incremental cost-effectiveness ratio.

[a]The vertical axis represents the BC ICER, the horizontal bars represent the difference between the BC ICER and the ICER generated when the model is run using the high and low values of the plausible range, and the entire length of each horizontal bar represents the magnitude of variation in cost-effectiveness results. Bars that touch the vertical axis indicate parameters whose most favorable value results in dominance. Bars that extend off the tornado diagram (to the right) represent parameters whose least favorable value yields a dominated result.

TABLE 4. Alternative Analysis Results: Incremental Cost Per BRE Avoided[a]

Comparator	Total Costs	Average Number of BREs	Incremental Costs	Incremental BREs Avoided	ICER
Watch and rescue	$19,503	3.12	Reference	Reference	Reference
Eltrombopag	$51,425	2.27	$31,922	0.85	Weakly dominated[b]
Romiplostim	$53,318	1.27	$33,815	1.85	$18,278

BRE indicates bleeding-related episode; ICER, incremental cost-effectiveness ratio.

[a]Time horizon: 24 weeks. All costs presented in 2015 US$.

[b]Weak dominance occurs when the ICER for a strategy is greater than that of a more costly alternative (also called extended dominance).

Alternative Analyses

Results of all alternative analyses are presented in Table 2 (cost per response), Table 3 (incremental cost per additional responder), and Table 4 (incremental cost per BRE avoided). When a maximum dosage of 10 mcg/kg/week for romiplostim (ie, with top-coding) was considered and the corresponding response rate was included in the analyses, the cost per response for romiplostim increased from $64,200 (base-case) to $65,500 and the cost per response for eltrombopag increased from $118,100 (base-case) to $130,600. The cost per response for watch and rescue remained unchanged. The ICER for romiplostim versus watch and rescue was $47,000 per additional responder; eltrombopag was weakly dominated by romiplostim.

When the eltrombopag response rates were estimated using registrational trial data, the cost per response for eltrombopag decreased from $118,100 (base-case) to $73,100, and the cost per response results for the other strategies remained unchanged. As in the base-case analysis, eltrombopag was weakly dominated by romiplostim and the ICER for romiplostim relative to watch and rescue did not change from the base-case result.

When the patient population was limited to nonsplenectomized patients only, results were similar to those of the base-case analysis. The incremental cost per additional responder for romiplostim relative to watch and rescue was $47,200; eltrombopag continued to be weakly dominated by romiplostim. Cost per response estimates were $118,600 for watch and rescue, $94,300 for eltrombopag, and $59,000 for romiplostim.

When the frequency with which patients received platelet count tests and physician visits was increased to weekly during weeks 5 to 24, the cost per response for romiplostim increased from $64,200 (base-case) to $65,600; the cost per response for eltrombopag increased from $118,100 (base-case) to $120,900; and the cost per response for watch and rescue increased from $204,400 (base-case) to $216,900. The incremental cost per additional responder for romiplostim relative to watch and rescue remained unchanged from the base case; eltrombopag continued to be weakly dominated by romiplostim.

When the watch and rescue patients were not assigned costs for physician visits and platelet test counts throughout the 24-week period, the cost per response for watch and rescue decreased from $204,400 (base-case) to $196,900, and the cost per response results for the other strategies remained unchanged. The incremental cost per additional responder for romiplostim relative to watch and rescue increased from $46,000 (base-case) to $47,000, and eltrombopag continued to be weakly dominated by romiplostim.

When the eltrombopag response rates were estimated from Bussel et al,[22] eltrombopag was weakly dominated by romiplostim and the incremental cost per additional responder for romiplostim relative to watch and rescue did not change from the base-case result. The cost per response for eltrombopag decreased from $118,100 (base case) to $82,200, and the cost-per-response results for the other strategies remained unchanged. Additionally, when the eltrombopag response rates were varied according to the lower and upper

bounds of the CIs for the base case scenario (20.18% to 55.24% for splenectomized patients; 28.85% to 75.77% for nonsplenectomized patients), eltrombopag remained weakly dominated by romiplostim. Accordingly, the ICER for romiplostim relative to watch and rescue remained unchanged from the base-case scenario.

Lastly, when cost-effectiveness was assessed in terms of incremental cost per BRE avoided (Table 4), the ICER for romiplostim relative to watch and rescue was $18,300, and eltrombopag was weakly dominated by romiplostim.

DISCUSSION

The cost per response and the incremental cost per additional responder were evaluated for 2 TPO-RA treatments and a watch and rescue strategy in both splenectomized and nonsplenectomized adults with chronic ITP. The use of either TPO-RA resulted in lower costs per treatment response and fewer BREs than the watch and rescue strategy. In the base-case analysis, eltrombopag was weakly dominated by romiplostim and the ICER of romiplostim relative to watch and rescue was $46,000 per additional responder. DSA results suggest that model results are most sensitive to the response rates of romiplostim and the watch and rescue strategy, as well as the BRE rate for splenectomized nonresponders.

Results of alternative analyses examining (1) a maximum dosage of 10 mcg/kg/week for romiplostim (ie, with top-coding) and corresponding response rate, (2) eltrombopag response rates estimated using registrational trial data, (3) nonsplenectomized patients only, (4) additional platelet count tests and physician visits for patients on all treatments, (5) zero platelet count tests and physician visits for patients on the watch and rescue strategy, and (6) eltrombopag response rates estimated from Bussel et al[22] yielded similar results to the base case. An alternative analysis examining the incremental cost per BRE avoided found that eltrombopag was weakly dominated by romiplostim and the ICER of romiplostim relative to watch and rescue was $18,300.

Limitations

Results of this analysis should be interpreted in light of the following assumptions and limitations. The efficacy of eltrombopag was estimated using an OR obtained from an independent Bayesian indirect comparison performed by Cooper et al,[11] who noted that the clinical trials included in the analysis may have differed in terms of study population and design.[23] Despite these differences, Cooper et al concluded that the romiplostim and eltrombopag clinical trials included in the indirect comparison were sufficiently similar. Nonresponders were assumed to continue treatment for 24 weeks, which may overestimate drug costs. BRE rates were assumed to depend on platelet levels, independent of whether patients were on active TPO-RA treatment or watch and rescue. Adverse events were not included in the model due to limited evidence in the literature. Rituximab was not included in the model due to inconsistent use in treatment and the identification of literature to determine doses per patient that prevent bleeding events or predict a response. In the model, patients on watch and rescue were assumed to incur zero medication costs; however, in the real-world setting, patients might be receiving concurrent medication other than the TPO-RAs. Therefore, the model is likely to underestimate the total costs for patients on watch and rescue. There are currently no well-established willingness-to-pay thresholds for the incremental cost per additional responder in this clinical context; accordingly, it is ultimately up to the payer to determine whether TPO-RAs are cost-effective in the treatment of ITP. Finally, patients receiving TPO-RAs were assumed to be 100% compliant according to product labels. The eltrombopag prescribing information states that, due to drug–drug and drug–food interactions, patients must not take or ingest any antacids, dairy products, or mineral supplements within 4 hours of administration.[2] Noncompliance with these recommendations would cause a significant reduction of eltrombopag bioavailability,[2] consequently impacting the efficacy of the drug. According to the results for other drugs with similar drug–drug and drug–food interactions,[24,25] in which noncompliance was about 30%, it is unlikely that patients will be 100% compliant; however, data on eltrombopag compliance are not currently available.

CONCLUSIONS

In adults with chronic ITP, romiplostim represents an efficient way to achieve response, with lower costs per response than eltrombopag and watch and rescue. Eltrombopag was weakly dominated by romiplostim, and the ICER for romiplostim versus watch and rescue was $46,000 per additional responder. ■

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REFERENCES

1. NPLATE (romiplostim) [prescribing information]. Thousand Oaks, CA: Amgen, Inc; 2016. pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/nplate/nplate_pi_hcp_english.pdf. Accessed May 11, 2018.
2. PROMACTA (eltrombopag) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2015. pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/nplate/nplate_pi_hcp_english.pdf. Accessed May 11, 2018.
3. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet*. 2008;371(9610):395-403. doi: 10.1016/S0140-6736(08)60203-2.
4. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study [erratum in *Lancet*. 2011;377(9763):382]. *Lancet*. 2011;377(9763):393-402. doi: 10.1016/S0140-6736(10)60959-2.
5. Cetin K, Wasser J, Wettten S, Altomare I. Rate of bleeding-related episodes (BREs) in adult patients with primary immune thrombocytopenic pupura (ITP): a population-based retrospective cohort study of administrative medical claims data in the United States (US). *Blood*. 2014;124(21):202. bloodjournal.org/content/124/21/202. Accessed May 11, 2018.
6. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386-2393. doi: 10.1182/blood-2008-07-162503.
7. Stasi R, Murali M, Michel M, et al. Evaluation of bleeding-related episodes in patients with immune thrombocytopenia (ITP) receiving romiplostim or medical standard of care. *Int J Hematol*. 2012;96(1):26-33. doi: 10.1007/s12185-012-1088-8.
8. Weitz I, Sanz MA, Henry D, et al. A novel approach to the evaluation of bleeding-related episodes in patients with chronic immune thrombocytopenia. *Curr Med Res Opin*. 2012;28(5):789-796. doi: 10.1185/03007995.2012.684046.
9. Kikuchi K, Miyakawa Y, Ikeda S, Sato Y, Takebayashi T. Cost-effectiveness of adding rituximab to splenectomy and romiplostim for treating steroid-resistant idiopathic thrombocytopenic purpura in adults. *BMC Health Serv Res*. 2015;15:2. doi: 10.1186/s12913-015-0681-y.
10. Lee D, Thornton P, Hirst A, Kutikova L, Deuson R, Brereton N. Cost effectiveness of romiplostim for the treatment of chronic immune thrombocytopenia in Ireland [erratum in *Appl Health Econ Health Policy*. 2013;11(6):687]. *Appl Health Econ Health Policy*. 2013;11(5):457-469. doi: 10.1007/ s40258-013-0044-y.
11. Cooper K, Matcham J, Helme K, Akehurst R. Update on romiplostim and eltrombopag indirect comparison. *Int J Technol Assess Health Care*. 2014;30(1):129-130. doi: 10.1017/S0266462313000767.
12. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura. National Institute for Health and Care Excellence website. nice.org.uk/guidance/ta293. Published July 24, 2013. Accessed May 11, 2018.
13. Cummins E, Fielding S, Scott N, et al. Eltrombopag for the treatment of chronic immune thrombocytopenic purpura (ITP): a single technology appraisal. National Institute for Health and Care Excellence website. nice.org.uk/guidance/ta293/documents/thrombocytopenic-purpura-eltrombopag-rev-ta205-evidence-review-group-report2. Published October 19, 2012. Accessed May 11, 2018.
14. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health*. 2011;14(4):417-428. doi: 10.1016/j.jval.2011.04.002.
15. EncoderPro.com website. encoderpro.com/epro. Accessed July 2015.
16. Lin J, Zhang X, Li X, et al. Cost of bleeding related episodes in adult patients with primary immune thrombocytopenia: a population-based retrospective cohort study of administrative claims data for commercial payers in the United States. *Clin Ther*. 2017;39(3):603-609.e1. doi: 10.1016/j.clinthera.2017.01.023.
17. 2015 National Physician Fee Schedule relative value file (July release). CMS website. cms.gov/Medicare/Medicare-Fee-For-Service-Payment/PhysicianFeeSched. Accessed November 2015.
18. 2015 Clinical Diagnostic Laboratory Fee Schedule. CMS website. cms.gov/Medicare/Medicare-Fee-For-Service-Payment/Clinicallabfeesched. Accessed November 2015.
19. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford, UK: Oxford University Press; 2015.
20. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
21. Bala MV, Zarkin GA. Application of cost-effectiveness analysis to multiple products: a practical guide. *Am J Manag Care*. 2002;8(3):211-218.
22. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373(9664):641-648. doi: 10.1016/S0140-6736(09)60402-5.
23. Cooper KL, Fitzgerald P, Dillingham K, Helme K, Akehurst R. Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison. *Int J Technol Assess Health Care*. 2012;28(3):249-258. doi: 10.1017/S0266462312000414.
24. Vytrisalova M, Blazkova S, Palicka V, et al. Self-reported compliance with osteoporosis medication—qualitative aspects and correlates. *Maturitas*. 2008;60(3-4):223-229. doi: 10.1016/j.maturitas.2008.07.009.
25. Hamilton B, McCoy K, Taggart H. Tolerability and compliance with risedronate in clinical practice. *Osteoporos Int*. 2003;14(3):259-262. doi: 10.1007/s00198-002-1370-3.