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ROMIPLOSTIM AND ELTROMBOPAG FOR IMMUNE THROMBOCYTOPENIA: METHODS FOR INDIRECT COMPARISON

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Objectives: Immune thrombocytopenia (ITP) causes increased platelet destruction and suboptimal platelet production, increasing risk of bleeding. This analysis uses a Bayesian metaregression model to indirectly compare effectiveness of the thrombopoietin mimetics romiplostim and eltrombopag for increasing platelet counts, and contrasts the results with those of non-Bayesian approaches.
Methods: Ten databases were searched during 2010. Placebo-controlled trials of 24 weeks' duration were included. An indirect comparison was undertaken using Bayesian metaregression, which includes all trials in a single model. This was compared with previous analyses in which data for each intervention were combined using simple pooling, logistic regression or meta-analysis, followed by indirect comparison of pooled values using the Bucher method.
Results: Two trials of romiplostim and one of eltrombopag were included. The indirect evidence suggests romiplostim significantly improves overall platelet response compared with eltrombopag. Bayesian metaregression gave an odds ratio (OR) for eltrombopag versus romiplostim of 0.11 (95 percent credible interval 0.02–0.66); *p* values and Bayesian posterior probabilities ranged from 0.01 to 0.05 for all analyses. There was no significant difference in durable platelet response in any of the analyses, although the direction of effect favored romiplostim (OR = 0.15; 95 percent credible interval, 0.01–1.88); *p* values and Bayesian posterior probabilities ranged from 0.08 to 0.40 across analyses. Results were relatively consistent between analyses.
Conclusions: Bayesian metaregression generated similar results to other indirect comparison methods, and may be considered the most robust as it incorporates all data in a single model and accounts appropriately for parameter uncertainty.

Keywords: Idiopathic thrombocytopenic purpura, Romiplostim, Eltrombopag, Statistics as topic, Review, Systematic

Immune (idiopathic) thrombocytopenia (ITP) is an autoimmune condition characterized by increased platelet destruction and suboptimal platelet production, resulting in low platelet counts (thrombocytopenia) (21). Patients experience bleeding-related symptoms ranging from minor bruising to severe gastrointestinal or intracranial hemorrhage, which may be fatal. Adult ITP is generally a chronic condition (21); incidence was estimated as 3.9 per 100,000 person-years in a recent UK study (23). Management of adult ITP includes various therapies that interfere with platelet destruction through modulation of the immune system. Newly diagnosed patients usually receive corticosteroids, but may also require intravenous immunoglobulin (IVIg) to address dangerously low platelet counts. Long-term use of corticosteroids and immunoglobulins is associated with poor safety and tolerability and high costs (21). Potential second-line options include splenectomy or various drug treatments (21). Following splenectomy, approximately two-thirds of patients achieve sustained response for at least 5 years, with others having partial or transient responses. Approximately 14 percent do not respond, while 20 percent of responders later relapse. Complications of splenectomy include surgical morbidity and mortality, thrombosis, and lifelong increased risk of infection (21). Five-year mortality estimates for ITP patients with persistent low platelet counts ($<30 \times 10^9$/L) range from 2.2 percent for patients under 40 years to 47.8 percent for those over 60 years (7), with bleeding and infection contributing equally to mortality (20;21).

The glycoprotein hormone thrombopoietin regulates platelet production *via* the thrombopoietin receptor on megakaryocytes. Recently, thrombopoietin mimetic drugs have been introduced; these stimulate platelet production *via* activation of the thrombopoietin receptor. Two thrombopoietin mimetics are currently approved in the US and Europe: romiplostim and eltrombopag. Romiplostim is a peptibody (Fc-peptide fusion protein) thrombopoietin mimetic, while eltrombopag is a small-molecule thrombopoietin mimetic; both increase platelet counts. The major goal of ITP therapy is a sustained increase in platelet count that is considered safe for the individual patient (21;22). Correspondingly, the outcomes assessed in this analysis are platelet response rates, generally defined as the percentage of patients achieving a platelet count above

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a certain threshold (21). The specific definitions of platelet response in the included trials are described in the Results section.

There are no head-to-head randomized controlled trials (RCTs) comparing romiplostim versus eltrombopag; however, recent trials have compared each against placebo. Indirect comparisons are recommended in the UK National Institute for Health and Clinical Excellence (NICE) methods guide where no head-to-head RCTs exist (18). An indirect comparison for romiplostim and eltrombopag was previously conducted within the eltrombopag Single Technology Appraisal (STA) submission to NICE (10). This analysis included two trials of romiplostim (one in splenectomized and one in nonsplenectomized participants) and one trial of eltrombopag (36 percent of participants splenectomized). The romiplostim data were pooled by simply summing the frequencies of platelet response across the romiplostim arms of the two trials, and similarly summing the data across the two placebo arms. This method of pooling was questioned within the corresponding NICE Evidence Review Group (ERG) review of the submission, as it breaks within-trial randomization (8). The ERG report for eltrombopag (8) presented an alternative analysis in which the romiplostim data were pooled using logistic regression. This method may result in underestimated standard errors for treatment effects, as it includes a fixed treatment effect and effectively treats the results of the two trials as arising from a single trial with a common study effect (12).

The objectives of this analysis were to explore additional methods for undertaking the indirect comparison of romiplostim and eltrombopag, particularly methods allowing robust consideration of parameter uncertainty, and to compare the results with those previously presented. First, we explored alternative methods of pooling the romiplostim data. Second, while the above analyses pooled the data on each intervention followed by indirect comparison of pooled values, we planned to undertake a Bayesian metaregression analysis combining results of all trials for both interventions within a single model. Bayesian analysis estimates a parameter by combining two components: the "likelihood function" or observed data model (e.g., trial data), and the "prior distribution" based on prior assumptions about parameters in the model. The resulting distribution is known as the "posterior distribution." In this way, Bayesian analyses take account of uncertainty when estimating the value of a parameter in the general population (19). Indirect comparisons preserve within-trial randomization by comparing relative treatment effects (e.g., odds ratios, ORs) from each trial, rather than comparing individual treatment arms from different trials (13). The power to detect significant effects is usually lower for an indirect comparison, resulting in larger standard errors. In addition, it is important to account properly for heterogeneity between studies, so the variability of relative effects is not underestimated. This report presents an indirect comparison of romiplostim and eltrombopag using Bayesian metaregression, and contrasts the results with those of previous indirect comparisons using non-Bayesian approaches.

METHODS

Systematic Identification of Trials

A systematic review was undertaken to identify relevant RCTs of romiplostim and eltrombopag for ITP. The following databases were searched in February 2010: MEDLINE, MEDLINE in Process, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, NHS EED and NHS HTA, Science Citation Index, and BIOSIS Previews. Additional focused searches were undertaken in October 2010. Abstracts of the American Society of Hematology (ASH) and the European Hematology Association were searched for 2007–09. The Medline search strategy is shown in Supplementary Appendix 1, which can be viewed online at www.journals.cambridge.org/thc2012029. Following identification of a relevant eltrombopag trial from conference abstracts, the main journal publication was sought after the main literature searches.

Trials were included if they were RCTs comparing romiplostim or eltrombopag versus placebo for management of ITP, had a treatment duration of at least 24 weeks, were double-blind (patients and investigators blinded) and reported data on platelet response. Trial quality was assessed using criteria from the Cochrane Collaboration (6). Three trials, two of romiplostim and one of eltrombopag, met the inclusion criteria (the same trials were included in previous analyses reported within the eltrombopag STA submission and ERG review).

Indirect Comparison Methods

Previous indirect comparisons of romiplostim and eltrombopag, undertaken within the eltrombopag STA submission and ERG review, were replicated. Further analyses were undertaken using alternative methods for pooling the romiplostim data. Finally, the indirect comparison was undertaken using a Bayesian metaregression model which includes data from all three trials (romiplostim and eltrombopag) in a single model.

Previous Methods of Indirect Comparison

Analysis 1: Summing of Romiplostim Data Then Bucher Indirect Comparison. The analyses within the eltrombopag STA submission (10) pooled the romiplostim data by summing frequencies of platelet response across the romiplostim arms of the two trials, and similarly summing the data across the placebo arms of the two trials. This method of pooling was questioned within the ERG review as it breaks within-trial randomization (8). The method proposed by Bucher et al. (1997) (1) was then used to indirectly compare eltrombopag and romiplostim. This method is essentially a comparison between two relative effects, and can compare two treatments (A and C) which have not been compared directly, but have each been compared with a common comparator (B).

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The relative treatment effect (OR) for A versus C can be estimated as: indirect $OR_{AC} = OR_{AB} / OR_{CB}$. This can be written on a log scale as: $\log(OR_{AC}) = \log(OR_{AB}) - \log(OR_{CB})$. This method assumes that the underlying treatment effect for each comparison is fixed (12).

Analysis 2: Logistic Regression (Fixed Treatment Effects) to Pool Romiplostim Data Then Bucher Indirect Comparison. The analyses undertaken within the ERG review (8) again used two steps. Romiplostim data were pooled using logistic regression; data from all trial participants were used to model the relationship between platelet response and two binary variables: treatment with romiplostim or placebo, and splenectomy status (no interaction between these was assumed). It was assumed that the treatment effect was fixed; that is, that the effect of romiplostim in the general population was a fixed value and the ORs only varied between trials due to sampling of trial populations. The indirect comparison was then conducted using the Bucher method (1).

Alternative Methods for Indirect Comparison

Analysis 3: Meta-analysis to Pool Romiplostim Data Then Bucher Indirect Comparison. As an alternative to Analysis 1, we pooled the romiplostim trial data using standard meta-analysis. The fixed-effect Mantel-Haenszel approach was used to calculate study weights because the placebo groups all had small event rates (this approach does not allow random effects to be introduced) (6). A Bucher indirect comparison was then conducted (1).

Analysis 4: Logistic Regression (Random Treatment Effects) to Pool Romiplostim Data Then Bucher Indirect Comparison. As an alternative to Analysis 2, we used logistic regression to combine data from the romiplostim trials. A random effects model was used for the treatment effect, whereby the effect of romiplostim in the general population was assumed to follow an underlying distribution and the ORs in each trial were assumed random samples from this distribution. A logistic regression analysis was conducted assuming a prior distribution for the between-trials standard deviation. A Bucher indirect comparison was then conducted (1).

Analysis 5: Bayesian Metaregression. Bayesian metaregression analyses using a logit model were conducted to indirectly compare eltrombopag and romiplostim (detailed in Supplementary Appendix 2, which can be viewed online at www.journals.cambridge.org/thc2012029; contained therein is Supplementary Table 1, which also can be viewed online at www.journals.cambridge.org/thc2012029). Whereas Analyses 2 and 4 used logistic regression to pool the romiplostim data, the Bayesian analysis used logistic regression to pool data from all trials (romiplostim and eltrombopag), according to standard practice (12;16;25). The model estimated probability of platelet response per treatment group per trial, based on three parameters: study effect (log-odds of response for placebo group in that trial); treatment effect (log OR for romiplostim or eltrombopag versus placebo); and effect of splenectomy (log OR for splenectomized versus nonsplenectomized groups). The study effect and splenectomy effect were allocated noninformative Normal prior distributions with mean = 0 and SD = 1,000, again according to standard practice (25). Each study effect was allocated a separate parameter (16). A random effects model was assumed for treatment effects, based on a Normal distribution. The model estimated a treatment effect (log OR) for romiplostim versus placebo and eltrombopag versus placebo. The indirect log OR for eltrombopag versus romiplostim was estimated from the posterior distribution for the difference between the two treatment effects (16). The between-trial variance for treatment effect was assumed to be common across all trials (according to standard practice) because there was little data from which to estimate a separate variance for each treatment. The prior distribution for treatment effect standard deviation (uniform distribution between 0 and 0.6) reflected a general suggestion from Sutton et al., so that any observed OR may vary by up to 4.6 times greater (or 0.22 times smaller) than the true OR with equal probability (25). Analyses were conducted using Markov chain Monte Carlo (MCMC) sampling within OpenBUGS, the open software license equivalent of WinBUGS (OpenBUGS, v 3.0) (24).

Compared with Analysis 5, Analyses 3 and 4 are limited by two factors. First, the likelihood function in Analysis 5 samples from the binomial, that is, true, distribution, whereas Analyses 3 and 4 rely on a Normal approximation assumption. Such approximations perform poorly when event rates are small, as in the placebo groups discussed here, as the binomial likelihood function is highly skewed. Also, Analysis 5 allows more precise modeling of uncertainty, which is especially important when the number of studies is small.

RESULTS

Characteristics and Quality of Included Trials

The literature search identified four RCTs of romiplostim and four RCTs of eltrombopag. Of these, one romiplostim trial (3) and three eltrombopag trials (2;4;26) were excluded due to short treatment duration of 6 weeks. An additional romiplostim trial (15) was excluded as it was an open-label trial designed to assess requirement for splenectomy rather than platelet response; it also differed from the included romiplostim trials on inclusion criteria (platelet count $<50 \times 10^9$/L rather than $<30 \times 10^9$/L) romiplostim starting dose (3 μg/kg rather than 1 μg/kg), and comparator arm (standard-of-care alone rather than placebo).

Therefore, two RCTs of romiplostim (Kuter 2008a and Kuter 2008b) (14) and one RCT of eltrombopag (Cheng 2011; RAISE trial) (5) were considered relevant for inclusion in the indirect comparison (Table 1). All three were double-blind phase III RCTs comparing either romiplostim or eltrombopag against placebo in adults with ITP (platelet count $<30 \times 10^9$/L and failed $\geq$ 1 prior ITP therapy); with treatment duration $\geq$ 24 weeks; and reporting platelet response. Romiplostim was administered at a starting dose of 1 μg/kg/week and eltrombopag

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Table 1. Characteristics and Quality of Included Trials

Trial	Trial design and quality	Treatment duration	*N*	Treatment	Comparator	Concomitant therapies	Population
Romiplostim							
Kuter 2008a (14) (trial 20030105) Splenectomized	• Phase III • Randomised (stratified by concurrent ITP medications) • Double-blind (subjects and study site personnel) • Allocation concealed (automated telephone system) • Sample size calculation; adequate power • Intention-to-treat analysis	24 weeks	63	Romiplostim 1μg/kg/week (adjusted to maximum 15 μg/kg). Median weekly dose 3 μg/kg. $N = 42$	Placebo $N = 21$	Both groups could receive concomitant and rescue therapies as required	Adults with chronic ITP, platelets $< 30 \times 10^9$/L, completed ≥ 1 prior therapy All splenectomized
Kuter 2008b (14) (trial 20030212) Non-splenectomized	• Phase III • Randomised (stratified by concurrent ITP medications) • Double-blind (subjects and study site personnel) • Allocation concealed (automated telephone system) • Sample size calculation; adequate power • Intention-to-treat analysis	24 weeks	62	Romiplostim 1μg/kg/week (adjusted to maximum 15 μg/kg). Median weekly dose 2 μg/kg. $N = 41$	Placebo $N = 21$	Both groups could receive concomitant and rescue therapies as required	Adults with chronic ITP, platelets $< 30 \times 10^9$/L, completed ≥ 1 prior therapy All non-splenectomized
Eltrombopag							
RAISE trial (TRA102537) Cheng 2011 (5); eltrombopag STA report (10) 36% splenectomized	• Phase III • Randomized (stratified by splenectomy status; concurrent ITP medications; platelet count) • Double-blind (patients, investigators, and those assessing data) • Allocation concealed (automated telephone system) • Sample size calculation; adequate power • Intention-to-treat analysis	26 weeks	197	Eltrombopag 50 mg/day (adjusted to maximum 75 mg/day) $N = 135$	Placebo $N = 62$	Both groups could receive concomitant and rescue therapies as required	Adults with chronic ITP of >6 months' duration, platelets $< 30 \times 10^9$/L, relapsed or refractory to ≥ 1 prior therapies 71/197 (36%) splenectomized

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at 50 mg/day; doses were adjusted based on platelet count; and patients could receive concomitant and rescue therapies as required. Platelet counts were assessed weekly in the romiplostim RCTs (14), while for eltrombopag they were assessed weekly for the first 6 weeks and at least once every 4 weeks thereafter (5). All three RCTs were of high quality, with adequate randomization and allocation concealment, double-blinding, adequate power, and baseline comparability between groups (Tables 1 and 2). Baseline patient characteristics were similar across trials, with a few differences as follows (Table 2). For romiplostim, one RCT enrolled splenectomized patients and one nonsplenectomized patients (50 percent splenectomized across the two trials) (14), while in the eltrombopag RCT 36 percent of patients were splenectomized (and randomization stratified by splenectomy status) (5). The percentage of patients receiving concomitant ITP medication at baseline was slightly higher for eltrombopag. The percentage of patients having received ≥ 3 prior therapies was slightly higher for romiplostim.

Platelet Response Rate Definitions

Platelet response rates were defined as *a priori* outcome measures in the romiplostim RCTs. For the eltrombopag RCT, response rates were reported as *post hoc* analyses within the eltrombopag STA submission (10); updated data were later reported in the manufacturer's response to the NICE Appraisal Consultation Document (ACD) (11) and in the ERG comment on this response (9). Definitions of overall and durable response differed slightly for romiplostim and eltrombopag. Overall platelet response was defined in the romiplostim trials as the percentage of patients with a platelet count $\geq 50 \times 10^9$/L on at least 4 weeks during the trial, excluding responses within 8 weeks after rescue medications (14). For eltrombopag, overall response was defined as the percentage of patients with platelet count ≥ 50 and $\leq 400 \times 10^9$/L for at least 4 consecutive weeks, excluding those receiving rescue medication during the assessment following a platelet response (11). Durable platelet response was defined for romiplostim as the percentage of patients with platelet count $\geq 50 \times 10^9$/L on at least 6 of the last 8 weeks of treatment, with no rescue medications at any time during the trial (14). For eltrombopag, durable response was defined as the percentage of patients with platelet count ≥ 50 and $\leq 400 \times 10^9$/L on at least 6 of the last 8 weeks of treatment, excluding subjects who received rescue medication (10).

Platelet Response Rates With Romiplostim and Eltrombopag

Overall and durable platelet response rates for the three trials are shown in Table 3. Overall platelet response rates for romiplostim were 33/42 (79 percent) for splenectomized patients (0/21; 0 percent for placebo) and 36/41 (88 percent) for nonsplenectomized patients (3/21; 14 percent for placebo) (14). Overall platelet response rates for eltrombopag were 26/50 (52 percent) for splenectomized patients (2/21; 10 percent for placebo) and 51/85 (60 percent) for nonsplenectomized patients (5/41; 12 percent for placebo) (5;9–11).

Durable platelet response rates for romiplostim were 16/42 (38 percent) for splenectomized patients (0/21; 0 percent for placebo) and 25/41 (61 percent) for nonsplenectomized patients (1/21; 5 percent for placebo) (14). Durable platelet response rates for eltrombopag were 19/50 (38 percent) for splenectomized patients (1/21; 5 percent for placebo) and 38/85 (45 percent) for nonsplenectomized patients (3/41; 7 percent for placebo) (5;9–11).

Results of Indirect Comparison

The results of the indirect comparison using various methods are summarized in Table 4. In terms of overall platelet response, Bayesian metaregression (Analysis 5) gave an OR for eltrombopag versus romiplostim of 0.11 (95 percent credible interval 0.02 to 0.66). Results were consistent across analyses, all of which gave indirect ORs ranging from 0.10 to 0.16). The *p* values for non-Bayesian analyses, and Bayesian posterior probabilities that the indirect OR did not favor romiplostim, ranged from 0.01 to 0.05 across all analyses of overall response. The probability density functions for the posterior distribution of the log indirect odds ratios for platelet response are shown in Supplementary Figure 1, which can be viewed online at www.journals.cambridge.org/thc2012029. The indirect evidence suggests romiplostim significantly improves overall platelet response rates compared with eltrombopag.

In terms of durable platelet response, the Bayesian metaregression analyses gave an OR of 0.15 (95 percent credible interval 0.01 to 1.88). Results were relatively consistent across analyses, with ORs ranging from 0.13 to 0.36. The lower event rates for the durable response outcome corresponded to wider confidence (and credible) intervals and a lack of a significant difference between groups. *P* values for non-Bayesian analyses, and Bayesian posterior probabilities that the indirect OR did not favor romiplostim, ranged from 0.08 to 0.40 for all analyses of durable response. There was no significant difference in durable platelet response in any analysis, although the direction of effect favored romiplostim. Regarding heterogeneity between trials, the fixed-effect analyses (Analyses 2 and 3) both gave I-squared values of 0 for both overall and durable platelet response.

DISCUSSION

Comparison of Results of Indirect Comparison Using Different Approaches

The Bayesian metaregression results were consistent with the non-Bayesian approaches to indirect comparison. All analyses suggested romiplostim significantly improves overall platelet response rates compared with eltrombopag, while all analyses of durable platelet response favored romiplostim but were not significant. This difference between outcomes was robust to changes in analysis method. Increases in platelet count represent

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Table 2. Baseline Patient Characteristics

Trial	Trial arm	Age (median, range)	Female	Splenectomized	Platelet count (median)	Concomitant ITP medication	Duration of ITP, years (median, range)	Prior ITP therapies	Bleeding symptoms at baseline
Romiplostim									
Kuter 2008a (14) (trial 20030105)	Romiplostim ($N = 42$)	51 (27–88)	27 (64%)	42 (100%)	14×10^9/L	12 (29%)	7.8 (0.6 - 44.8)	$\geq$ 3 therapies: 39 (93%)	78%*
Splenectomized	Placebo (N = 21)	56 (26–72)	11 (52%)	21 (100%)	15×10^9/L	6 (29%)	8.5 (1.1 - 31.4)	$\geq$ 3 therapies: 20 (95%)	
Kuter 2008b (14) (trial 20030212)	Romiplostim ($N = 41$)	52 (21–80)	27 (66%)	0 (0%)	19×10^9/L	11 (27%)	2.2 (0.1 – 31.6)	$\geq$ 3 therapies: 15 (37%)	79%*
Non-splenectomized	Placebo ($N = 21$)	46 (23–88)	16 (76%)	0 (0%)	19×10^9/L	10 (48%)	1.6 (0.1 – 16.2)	$\geq$ 3 therapies: 5 (24%)	
All patients from two trials	Romiplostim ($N = 83$)	52 (21–88)	54 (65%)	42 (51%)	16×10^9/L	23 (28%)	Not reported	$\geq$ 3 therapies: 54 (65%)	78%*
	Placebo ($N = 42$)	52 (23–88)	27 (64%)	21 (50%)	18×10^9/L	16 (38%)	Not reported	$\geq$ 3 therapies: 25 (60%)	
Eltrombopag									
RAISE trial (TRA102537)	Eltrombopag ($N = 135$)	47 (18–85)	93 (69%)	50 (37%)	16×10^9/L	63 (47%)	Not reported	$\geq$ 2 therapies: 105 (78%) $\geq$ 3 therapies: 75 (56%) $\geq$ 4 therapies: 51 (38%) $\geq$ 5 therapies: 35 (26%)	73%
Cheng 2011 (5); eltrombopag STA report (10) 36% splenectomized	Placebo ($N = 62$)	53 (18–77)	43 (69%)	21 (34%)	16×10^9/L	31 (50%)	Not reported	$\geq$ 2 therapies: 50 (81%) $\geq$ 3 therapies: 32 (52%) $\geq$ 4 therapies: 20 (32%) $\geq$ 5 therapies: 11 (18%)	77%

* Amgen data on file (bleeding at baseline for romiplostim).

Table 3. Overall and Durable Platelet Response Rates for Romiplostim and Eltrombopag

Eltrombopag (1 trial) (5;10;11)	Eltrombopag	Placebo	Romiplostim (2 trials) (14)	Romiplostim	Placebo
Overall response			**Overall response**		
Splenectomy	26 / 50 (52%)	2 / 21 (10%)	Splenectomy (Kuter 2008a (14))	33 / 42 (79%)	0 / 21 (0%)
No splenectomy	51 / 85 (60%)	5 / 41 (12%)	No splenectomy (Kuter 2008b (14))	36 / 41 (88%)	3 / 21 (14%)
All patients (single trial; Cheng 2011 (5))	77 / 135 (57%)	7 / 62 (11%)	All patients (across 2 trials)	69 / 83 (83%)	3 / 42 (7%)
Durable response			**Durable response**		
Splenectomy	19 / 50 (38%)	1 / 21 (5%)	Splenectomy (Kuter 2008a (14))	16 / 42 (38%)	0 / 21 (0%)
No splenectomy	38 / 85 (45%)	3 / 41 (7%)	No splenectomy (Kuter 2008b (14))	25 / 41 (61%)	1 / 21 (5%)
All patients (single trial; Cheng 2011 (5))	57 / 135 (42%)	4 / 62 (6%)	All patients (across 2 trials)	41 / 83 (49%)	1 / 42 (2%)

Note. Eltrombopag data are based on a single RCT (RAISE; Cheng 2011) (5) and patients are subgrouped according to splenectomy status. Eltrombopag data were initially reported as post-hoc analyses within the eltrombopag STA submission to NICE (10) (p80–82); updated data were later reported in the manufacturer's response to the NICE Appraisal Consultation Document (ACD) (11) (p7–9) and in the ERG comment on this response (9) (p4). Romiplostim data are based on two RCTs, one in splenectomized patients and one in non-splenectomized patients (Kuter et al 2008) (14). Definitions of overall and durable platelet response differ slightly for romiplostim and eltrombopag and are described in the main text.

decreased risk of bleeding in ITP patients, with treatment rarely indicated in patients with counts above 50×10^9/L (21).

Comparability of Included Trials

Indirect comparisons allow comparison of two or more interventions where no head-to-head trials exist, and are consistent with the NICE Guide to the Methods of Technology Appraisal (18). A limitation is that included trials may differ in patient population and trial design. Regarding patient population, the romiplostim and eltrombopag trials were reasonably similar for age, gender, baseline platelet count and bleeding symptoms. Differences included percentage of splenectomized patients (50 percent across romiplostim trials, 36 percent for eltrombopag); percentage receiving concomitant ITP medication at baseline (slightly higher for eltrombopag); and percentage having received $\geq$ 3 prior therapies (slightly higher for romiplostim). Included trials were similar in design, with treatment duration $\geq$ 24 weeks. Overall and durable platelet response were prespecified outcomes for romiplostim, but were *post hoc* analyses with slightly different definitions for eltrombopag. Platelet counts were assessed weekly for romiplostim, while for eltrombopag they were assessed weekly for 6 weeks then $\geq$ once every 4 weeks. In summary, the included trials appeared sufficiently similar, with the slight differences not clearly favoring either treatment.

Consistency and Appropriateness of Methods

The analyses varied regarding assumptions about uncertainty in treatment effects of romiplostim and eltrombopag. Results of the different analyses were reasonably consistent. The appropriateness of each method in this case is discussed below.

Analyses Involving Pooling Romiplostim Data Followed by Bucher Indirect Comparison

Four analyses used various methods to pool the romiplostim data, followed by indirect comparison using the Bucher method (1). The analysis within the eltrombopag STA submission (Analysis 1) (10) pooled the romiplostim data by summing platelet response frequencies across the romiplostim arms of the two trials, and similarly summing the data across the two placebo arms. This method of pooling was questioned by the ERG as it breaks within-trial randomization (8). In contrast, our Analysis 3 used meta-analysis to pool the romiplostim data; this approach does not break randomization and accounts for romiplostim data coming from two separate trials. Results of Analyses 1 and 3 were similar for overall response. For durable response, results were again similar, though Analysis 3 (meta-analysis) gave a slightly lower OR for romiplostim versus placebo and therefore slightly higher OR for eltrombopag versus romiplostim, possibly due to small event rates in the placebo arms of the romiplostim trials and the 0.5 correction for values of zero.

The ERG report for eltrombopag (8) pooled the romiplostim data using logistic regression (Analysis 2). This method may result in underestimated standard errors for treatment effects, as it includes a fixed treatment effect and effectively treats the results as arising from a single trial with a common study effect (12). Our Analysis 4 was similar to the ERG analysis, using logistic regression to combine the romiplostim data; however, we used a random effects model for treatment effect, providing more robust consideration of uncertainty. It is worth noting that the logistic regression approach (Analysis 4) is based on a binomial likelihood, whereas the Mantel-Haenszel meta-analysis (Analysis 3) assumes a Normal approximation. All four methods used the Bucher method of indirect comparison, and gave relatively consistent results (12).

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Table 4. Indirect Comparison of Eltrombopag and Romiplostim

Analysis method	OR eltrombopag vs. placebo (95% CI)	OR romiplostim vs. placebo (95% CI)	Indirect OR eltrombopag vs. romiplostim (95% CI)	SE of log indirect OR	*p* value or probability indirect OR does not favor romiplostim[a]
Overall platelet response					
Previous analyses in STA submission and ERG report					
Analysis 1 (eltrombopag STA): Summing of romiplostim data across trial arms then Bucher indirect comparison	10.4 (4.4, 24.6)	64.1 (17.3, 236.8)	0.16 (0.03, 0.78)	0.798	.02
Analysis 2 (ERG report): Pooling of romiplostim data via logistic regression (fixed treatment effects) then Bucher indirect comparison	10.4 (4.4, 24.6)	77.7 (19.5, 309.9)	0.13 (0.03, 0.68)	0.830	.02
Alternative methods for indirect comparison					
Analysis 3: Meta-analysis of romiplostim data (Mantel-Haenszel weighting) then Bucher indirect comparison	10.4 (4.4, 24.6)	68.4 (12.8, 365.6)	0.15 (0.02, 1.00)	0.961	.05
Analysis 4: Pooling of romiplostim data via logistic regression (random treatment effects) then Bucher indirect comparison*	10.4 (4.4, 24.6)	105.8 (24.6, 598.8)	0.10 (0.02, 0.57)	0.899	.01
Analysis 5: Bayesian metaregression of romiplostim and eltrombopag data (random treatment effects)*	11.6 (4.4, 33.8)	106.1 (25.0, 593.5)	0.11 (0.02, 0.66)	0.957	.01
Durable platelet response					
Previous analyses in STA submission and ERG report					
Analysis 1 (eltrombopag STA): Summing of romiplostim data across trial arms then Bucher indirect comparison	10.6 (3.6, 30.9)	40.0 (5.3, 304.7)	0.26 (0.03, 2.62)	1.171	.26
Analysis 2 (ERG report): Pooling of romiplostim data via logistic regression (fixed treatment effects) then Bucher indirect comparison	10.6 (3.6, 30.9)	45.0 (5.8, 348.4)	0.24 (0.02, 2.37)	1.178	.22
Alternative methods for indirect comparison					
Analysis 3: Meta-analysis of romiplostim data (Mantel-Haenszel weighting) then Bucher indirect comparison	10.6 (3.6, 30.9)	29.3 (3.6, 236.9)	0.36 (0.03, 3.79)	1.198	.40
Analysis 4: Pooling of romiplostim data via logistic regression (random treatment effects) then Bucher indirect comparison*	10.6 (3.6, 30.9)	84.2 (10.5, 2000.2)	0.13 (0.01, 2.09)	1.433	.15
Analysis 5: Bayesian metaregression of romiplostim and eltrombopag data (random treatment effects)*	12.5 (4.0, 47.8)	84.3 (10.3, 2036.5)	0.15 (0.01, 1.88)	1.499	.08

[a] The *p* value (non-Bayesian analyses) or probability indirect OR does not favor romiplostim (Bayesian analyses in WinBUGS, marked*).

ERG, Evidence Review Group; CI, confidence interval (for non-Bayesian analyses) or credible interval (Bayesian analyses in WinBUGS, marked*); OR, odds ratio; SE, standard error; STA, single technology assessment.

Bayesian Metaregression

Whereas Analyses 2 and 4 used logistic regression to pool the romiplostim data only, the Bayesian indirect comparison (Analysis 5) used logistic regression to pool data from all three trials (romiplostim and eltrombopag). The Bayesian indirect comparison may perhaps be considered the most robust analysis described here, as it follows current best practice for indirect comparisons (16), incorporating all trial data in a single model and accounting appropriately for parameter uncertainty. Results of this analysis were consistent with the other analyses.

CONCLUSIONS

The Bayesian metaregression for overall platelet response gave an OR for eltrombopag versus romiplostim of 0.11 (95 percent credible interval 0.02 to 0.66). Results were consistent across the different analyses, all of which gave indirect OR estimates ranging from 0.10 to 0.16, while *p* values and Bayesian posterior probabilities ranged from 0.01 to 0.05 for all analyses of overall response. The indirect evidence suggests romiplostim significantly improves overall platelet response rates compared with eltrombopag.

The Bayesian metaregression for durable platelet response gave an OR of 0.15 (95 percent credible interval 0.01 to 1.88). Results were again relatively consistent across analyses, with ORs ranging from 0.13 to 0.36 and *p* values and Bayesian posterior probabilities ranging from 0.08 to 0.40. The indirect evidence does not suggest romiplostim significantly improves durable platelet response compared with eltrombopag, though ORs favored romiplostim.

The analyses presented here, first, explored different methods for combining data from the two romiplostim trials, and, second, reported a Bayesian metaregression which included data from all three trials (romiplostim and eltrombopag) in a single model. Results of the different analyses were consistent for both overall and durable platelet response. The Bayesian metaregression approach generated similar results to other indirect comparison methods, and may be considered the most robust of the analyses described here, as it incorporates all trial data in a single model and accounts appropriately for parameter uncertainty.

SUPPLEMENTARY MATERIAL

Supplementary Appendix 1
Supplementary Appendix 2
Supplementary Table 1
Supplementary Figure 1
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CONFLICTS OF INTEREST

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