Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura: a single technology appraisal

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical and cost-effectiveness of romiplostim for the treatment of adults with chronic immune or idiopathic thrombocytopenic purpura (ITP) based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's evidence came from two relatively high-quality randomised controlled trials (RCTs). The ERG found no evidence that any important data were missed or that data extraction was inaccurate. In both RCTs more patients in the romiplostim than in the placebo group achieved a durable platelet response [non-splenectomised patients: romiplostim 25/41 (61%), placebo 1/21 (5%), odds ratio (OR) 24.45, 95% confidence interval (CI) 3.34 to 179.18; splenectomised patients: romiplostim 16/42 (38%), placebo 0/21 (0%), OR 8.5 (95% CI 1.15 to 372)] and an overall platelet response [non-splenectomised patients: romiplostim 36/41 (88%), placebo 3/21 (14%), OR 34.74, 95% CI 7.77 to 155.38; splenectomised patients: romiplostim 33/42 (79%), placebo 0/21 (0%), OR 16.6 (95% CI 2.37 to 706]. The difference in mean period with a platelet response was 13.9 weeks (95% CI 10.5 to 17.4) in favour of romiplostim in the RCT of non-splectomised patients and 12.1 weeks (95% CI 8.7 to 15.6) in favour of romiplostim in the RCT of splectomised patients. The manufacturer's economic model evaluated the cost-effectiveness of romiplostim compared with standard care. The

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

ERG had concerns about the way the decision problem was addressed in the economic model and about the non-adjustment of findings for confounding factors. In non-splenectomised patients, using romiplostim as a first option treatment, the base-case incremental cost-effectiveness ratio (ICER) was £14,840 per quality-adjusted life-year (QALY). In splenectomised patients the ICER was £14,655 per QALY. Additional sensitivity analyses performed by the ERG identified two issues of importance: whether individuals entered the model on watch and rescue or on active therapy in the comparator arm (ICER £21,674 per QALY for non-splenectomised patients, £29,771 per QALY for splenectomised patients); whether it was assumed that any unused medicine would be wasted. Combining all of the separate sensitivity analyses, and assuming that watch and rescue was not the first-line treatment, increased the ICERs further (non-splenectomised £37,290 per QALY; splenectomised £131,017 per QALY). In conclusion, the manufacturer's submission and additional work conducted by the ERG suggest that romiplostim has short-term efficacy for the treatment of ITP, but there is no robust evidence on long-term effectiveness or cost-effectiveness of romiplostim compared with relevant comparators.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP).

Description of the underlying health problem

Immune thrombocytopenic purpura is a condition in which autoantibodies are formed against platelets. ITP may present as bleeding and/or bruising or may be asymptomatic and picked up on blood counts taken for other reasons. The incidence rates quoted for adult ITP in the UK/USA range from 1.13[2] to 6.6[3] per 100,000 per year. Licensed treatments for ITP are steroids, intravenous immunoglobulin and anti-D immunoglobulin. Other treatments include splenectomy (a surgical treatment), cyclophosphamide, vinca alkaloids, danazol, azathioprine, ciclosporin, rituximab, mycophenolate mofetil, dapsone, alemtuzumab, autologous stem cell transplantation, interferon and combination chemotherapy. More recent novel treatments include the thrombopoietin analogues (romiplostim and eltrombopag), which appear to increase platelet production.

Scope of the ERG report

The manufacturer's submission assessed the efficacy, safety and cost-effectiveness of romiplostim for the treatment of chronic ITP in adult patients with platelet counts of less than 30×10^9/l. Two subgroups were assessed: non-splenectomised patients with inadequate response to initial corticosteroid treatment, in whom splenectomy was medically contraindicated, and ITP patients refractory to splenectomy. The primary outcome was the incidence of durable response, defined as achieving at least six weekly platelet responses (platelets $\geq 50 \times 10^9$/l) during the last 8 weeks of treatment with no rescue medications administered at any time during the 24-week treatment period.

The data used to assess the efficacy and safety of romiplostim came from two small randomised controlled trials (RCTs) by Kuter and colleagues[4] comparing romiplostim with placebo in (1) non-splenectomised patients and (2) splenectomised patients. In addition, data were also reported for an 'ITP safety set' consisting of a number of other non-randomised phase II studies.

The manufacturer submitted an economic evaluation. The economic model was a cohort-type model constructed in Microsoft EXCEL in which the two patient populations were modelled. The model evaluated the cost-effectiveness of romiplostim compared with standard care, defined by reference to international guidelines in the treatment of

ITP and the manufacturer's own commissioned survey. In the model, patients initially enter a watch and rescue state or are treated first with romiplostim. The model was populated with a variety of observational data for the effectiveness of alternative treatments from a number of small studies. The RCT data on romiplostim were also treated as observational data within the economic model.

Romiplostim is designed to increase the production of platelets at a rate that outpaces their destruction by the immune system. The European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) positive opinion for romiplostim (Nplate™, Amgen) stated that Nplate was indicated for adult chronic ITP splenectomised patients who were refractory to other treatments, and that Nplate could also be considered as second-line treatment for adult non-splenectomised patients in whom surgery was contraindicated.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

Following submission of the manufacturer's report the ERG:

- requested clarification from the manufacturer on a number of points, mainly relating to the clinical effectiveness and cost-effectiveness aspects of the submission
- assessed the clinical effectiveness part of the manufacturer's submission for its quality as a systematic review using the questions in the Centre for Reviews and Dissemination (CRD) Report No. 4[5]
- replicated the manufacturer's MEDLINE search strategy with the inclusion of the term 'nplate.tw,rn' and adapted the searches for the other databases using the appropriate subject heading terms
- undertook complementary searches for additional evidence on each comparator
- requested the manufacturer to rerun the economic model for a number of additional analyses, and
- performed additional sensitivity analyses on the economic model.

Results

Summary of submitted clinical evidence

Evidence on the efficacy of romiplostim came from two RCTs by Kuter and colleagues with a 24-week follow-up.[4] In the RCT of non-splenectomised patients, 25/41 (61%) patients in the romiplostim group and 1/21 (5%) in the placebo group achieved a durable platelet response [odds ratio (OR) 24.45, 95% confidence interval (CI) 3.34 to 179.18]. An overall platelet response was achieved by 36/41 (88%) patients in the romiplostim group and 3/21 (14%) in the placebo group (OR 34.74, 95% CI 7.77 to 155.38). The Kaplan–Meier estimated median time to the first platelet response was 2.0 weeks and the mean period with a platelet response was 15.2 weeks for romiplostim and 1.3 weeks for placebo (difference 13.9 weeks, 95% CI 10.5 to 17.4 weeks).

In the RCT of splenectomised patients, 16/42 (38%) patients in the romiplostim group and 0/21 (0%) in the placebo group achieved a durable platelet response. The OR estimated by the ERG using an assumption of one event in the placebo group was 8.5 (95% CI 1.15 to 372). An overall platelet response was achieved by 33/42 (79%) patients in the romiplostim group and 0/21 (0%) in the placebo group. The OR estimated by the ERG using the same assumption above was 16.6 (95% CI 2.37 to 706). The Kaplan–Meier estimated median time to the first platelet response was 3.0 weeks and the mean period with a platelet response was 12.3 weeks for romiplostim and 0.2 weeks for placebo (difference 12.1 weeks, 95% CI 8.7 to 15.6 weeks).

The efficacy of 24-week administration of romiplostim was significantly better than that of placebo in the above outcomes and also in reduction of concurrent ITP therapy. Across both studies headache (29/84, 35%) was the most common adverse drug reaction amongst romiplostim patients, followed by arthralgia (22/84, 26%), dizziness (14/84, 17%) and insomnia (13/84, 15%). In the RCT of splenectomised patients three patients in the placebo group died, with causes of death pneumonia, pulmonary embolism and cerebral haemorrhage. In the RCT of non-splenectomised patients one patient in the romiplostim group died, the cause of death being an intracranial haemorrhage.

The manufacturer used evidence from existing reviews and primary studies from complementary searches to report the efficacy and safety of

comparator drugs. The majority of the efficacy and safety data came from non-randomised studies or case series.

Summary of submitted cost-effectiveness evidence

The manufacturer's economic model evaluated the cost-effectiveness of romiplostim compared with standard care, defined by reference to international guidelines on the treatment of ITP and the manufacturer's own commissioned survey. In the model, patients initially entered a watch and rescue state or were treated first with romiplostim.

The results from the manufacturer's revised base-case analysis showed that, in non-splenectomised patients, using romiplostim as a first option treatment resulted in an incremental cost-effectiveness ratio (ICER) of £14,840 per quality-adjusted life-year (QALY). In splenectomised patients the ICER was £14,655 per QALY. Additional sensitivity analyses were performed by the ERG (*Tables 1* and *2*). The combined sensitivity analysis provided far larger changes in the ICER than were reflected in one-way sensitivity analysis. The two issues of most importance were (1) whether individuals entered the model on watch and rescue or on an active therapy in the comparator arm (ICER £21,674 per QALY for non-splenectomised patients, £29,771 per QALY for splenectomised patients) and (2) as vials of the drug came in a fixed size, whether it was assumed that any unused medicine would be wasted. Combining all of the separate sensitivity analyses, with the additional assumption that watch and rescue was not the first-line treatment, increased the ICERs further (non-splenectomised £37,290 per QALY; splenectomised £131,017 per QALY).

Commentary on the robustness of submitted evidence

Overall the quality of the RCTs reporting romiplostim was relatively high and the ERG found no evidence that any data of consequence were missed in the reviews or that data extraction was inaccurate. The evidence base for both romiplostim and the comparator treatments was limited.

Although the decision problem, description of alternatives and perspective were all well outlined

TABLE 1 *ERG's exploratory sensitivity analyses (non-splenectomised patients)*

Scenario	ICER (£ per QALY gained)	
	Watch and rescue is initial comparator intervention (as adopted by manufacturer)	**Rituximab is initial comparator intervention (ERG analysis using manufacturer's model)**
Base case	14,633	21,674
1. Use of EQ-5D data from RCTs	16,503	24,426
2. Change in number of vials (from 0.93 to 1.0)	21,214	28,556
3. Serious adverse events +50%	14,623	21,658
4. Serious adverse events –50%	14,641	29,741
5. Cost of bone marrow test included	14,663	21,706
6. Cost of blood assessment included	19,230	36,131
7. Reducing frequency of physician visits	14,669	21,701
8. Combining 1 and 2 and 4–7	29,179	37,290
9. Response rate for romiplostim (worst case for censoring)	16,258	57,593
10. Response rate for romiplostim (best case for censoring)	14,152	18,776
11. Combining 8 and 9	29,934	76,728
12. Romiplostim effectiveness reduced to 0.25 of base case	16,354	165,129
13. Romiplostim effectiveness reduced to 0.75 of base case	14,884	26,439

EQ-5D, EuroQol 5 dimensions questionnaire; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RCTs, randomised controlled trials.

TABLE 2 *ERG's exploratory sensitivity analyses (splenectomised patients)*

Scenario	ICER (£ per QALY gained)	
	Watch and rescue is initial comparator intervention (as adopted by manufacturer)	**Rituximab is initial comparator intervention (ERG analysis using manufacturer's model)**
Base case	15,595	29,771
1. Use of EQ-5D data from RCTs	17,580	33,558
2. Change in number of vials (from 1.38 to 2.0)	91,406	109,802
3. Serious adverse events +50%	15,580	21,687
4. Serious adverse events –50%	15,608	29,796
5. Cost of bone marrow test included	15,639	29,817
6. Cost of blood assessment included	22,068	26,154
7. Reducing frequency of physician visits	15,642	29,803
8. Combining 1 and 2 and 4–7	110,352	131,017
9. Response rate for romiplostim (worst case for censoring)	17,501	106,703
10. Response rate for romiplostim (best case for censoring)	15,367	24,669
11. Combining 8 and 9	106,515	233,106
12. Romiplostim effectiveness reduced to 0.25 of base case	17,245	446,204
13. Romiplostim effectiveness reduced to 0.75 of base case	15,808	39,268

EQ-5D, EuroQol-5 dimensions questionnaire; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RCTs, randomised controlled trials.

in the submission, there were some concerns about the way that the decision problem was addressed in the economic model, which related to the structure of the model and whether patients entered the model on watch and rescue or on an active treatment.

The ERG raised a number of concerns about the pre-model data analyses and the statistical and epidemiological techniques employed. These concerns related to the manufacturer not adjusting the findings for confounding factors (e.g. severity of ITP, age, number of previous treatments, concurrent treatments, and withdrawal rates), which might affect the reliability and size of the treatment effect.

Conclusions

Based on the manufacturer's submission and the additional work conducted by the ERG the evidence available for romiplostim for both non-splenectomised and splenectomised patient groups suggests that:

- romiplostim appears to be a safe treatment for ITP, although no long-term data exist
- romiplostim has short-term efficacy for the treatment of ITP
- there is no robust evidence on long-term efficacy of romiplostim
- there is no robust evidence on long-term effectiveness of romiplostim compared with relevant comparators
- there is no robust evidence on long-term cost-effectiveness of romiplostim compared with relevant comparators.

Key issues for the decision-making process are:

- Will the use of romiplostim lead to wastage of the drug? Within the base-case industry submission it was assumed that there would be no wastage, but if there is then the cost-effectiveness of romiplostim will be reduced.
- Is the appropriate comparison for romiplostim an active treatment rather than watch and rescue? If so then the use of romiplostim is far less likely to be considered cost-effective.
- Can the results of an international study be extrapolated to the UK population? There appeared to be differences between the study population and the average UK patient.
- Is it plausible that patients in the romiplostim trial who were censored were more likely to

cease to respond to romiplostim? If so then the use of romiplostim is far less likely to be considered cost-effective.
- What is the extent and direction of bias caused by the use of indirect comparisons of non-comparative observational data? If the current data, as used in the manufacturer's submission, overestimate the relative effectiveness of romiplostim then it is far less likely to be considered cost-effective.

Summary of NICE guidance issued as a result of the STA

At the time of writing, the guidance had not been issued by NICE .

Key references

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