

Avatrombopag and lusutrombopag for thrombocytopenia in people with chronic liver disease needing an elective procedure: a systematic review and cost-effectiveness analysis

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Scientific summary

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Scientific summary

Background

Platelets play a critical role in haemostasis, a process that causes bleeding to stop. A reduction in platelets circulating in the blood is referred to as thrombocytopenia. It is usually defined as a platelet count of < 150,000 per microlitre of blood.

Thrombocytopenia occurs frequently in chronic liver disease, either directly or as a result of interferon-based antiviral treatment of liver infection. Severe thrombocytopenia arising from the risk of excessive bleeding during and after surgery can significantly affect the clinical management of chronic liver disease, leading to delay and, potentially, to increased morbidity and mortality.

Until this assessment, to our knowledge there were no licensed treatment options in the UK for treating thrombocytopenia in people with chronic liver disease requiring surgery. Treatment for severe thrombocytopenia can include platelet transfusion, splenic artery embolisation and surgical splenectomy.

The interventions studied are small-molecule thrombopoietin receptor agonists avatrombopag (Doptelet®; Dova Pharmaceuticals, Durham, NC, USA) and lusutrombopag (Mulpleta®; Shionogi Inc., London, UK). The licensed dose of avatrombopag will be dependent on baseline platelet count (i.e. 60 mg if the baseline platelet count is < 40,000/ μ l and 40 mg if it is 40,000–< 50,000/ μ l). The recommended dose of lusutrombopag is 3 mg once per day for 7 days, and the elective procedure should be performed from day 9 after treatment initiation.

Objectives

- To determine the clinical effectiveness and cost-effectiveness of avatrombopag and lusutrombopag within their marketing authorisations in comparison with no thrombopoietin receptor agonist (established clinical management without either thrombopoietin receptor agonist, including, but not limited to, platelet transfusion) for treating thrombocytopenia in people with chronic liver disease needing an elective procedure.
- Because the licensed dose for avatrombopag is dependent on baseline platelet count (i.e. 60 mg if the baseline platelet count is < 40,000/ μ l and 40 mg if it is 40,000–< 50,000/ μ l), both clinical effectiveness and cost-effectiveness analyses were conducted in each of these two subgroups.

Methods

Throughout the review, the methods recommended by the Cochrane Collaboration Handbook and the Centre for Reviews and Dissemination, York, were applied to reduce the risk of bias and error. Literature searches were conducted to identify relevant information about the clinical effectiveness, safety and cost-effectiveness of avatrombopag and lusutrombopag. The searches also identified studies of the clinical effectiveness, safety and cost-effectiveness of established clinical management of thrombocytopenia in people with chronic liver disease. English-language and non-English-language articles were obtained from several databases, including MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials, all of which were searched from inception. Grey literature was also searched, and reference checking of included studies was carried out. The following inclusion criteria were applied for screening: adults with thrombocytopenia associated with chronic liver disease needing an elective procedure, avatrombopag or lusutrombopag as intervention and any one of a range of

clinical effectiveness outcomes. Titles and abstracts identified through electronic database and other searches were independently screened by two reviewers. During this initial phase of the screening process, any references that it could be determined from the title or abstract did not meet the inclusion criteria were excluded. Full-paper copies were obtained of all of the remaining references. These were then independently examined in detail by two reviewers to determine whether or not they met the criteria for inclusion in the review. Data extraction and quality assessment using the Cochrane Collaboration Quality Assessment Tool for randomised controlled trials was carried out by two reviewers. Meta-analysis was conducted using both fixed-effects and random-effects models, and forest plots of effect sizes were presented for each of the main outcomes, which were the proportion of patients receiving no platelet transfusion prior to the elective procedure or rescue therapy for bleeding, and the proportion of patients receiving no platelet transfusion prior to the elective procedure. These outcomes were determined on the basis that they were the primary outcomes in all but one of the trials. Another outcome of interest was the proportion of patients receiving no rescue therapy for bleeding (referred to as 'rescue therapy'). Neither quality of life nor survival was an outcome in any study, although mortality was reported. Subgroup analysis according to degree of thrombocytopenia ($< 40,000/\mu\text{l}$ or $40,000 - < 50,000/\mu\text{l}$) was performed in order to match the expected licensed doses of avatrombopag. Sensitivity analysis according to clinical and statistical heterogeneity (I^2) was conducted.

The cost-effectiveness analysis was conducted for the subgroups separately (patients with a platelet count of $< 40,000/\mu\text{l}$ and patients with a platelet count of $40,000 - < 50,000/\mu\text{l}$), using a decision-analytic model, which included a short-term decision tree to model the clinical trial period (35 days) and an appended Markov model to model the life expectancy of a person with chronic liver disease over the long term (50 years). The short-term decision tree model has the following chance nodes: (1) receiving/not receiving platelet transfusion, (2) rescue therapy/no rescue therapy, (3) receiving/not receiving the elective invasive procedure within the 35-day study period and (4) death/no death due to platelet transfusion, surgery or rescue therapy. In addition, adverse events resulting from treatment, platelet transfusion and surgery were included in the model. The primary efficacy and safety inputs for the no thrombopoietin receptor agonist, lusutrombopag and avatrombopag treatment arms were obtained from an indirect treatment comparison that was performed using Bayesian meta-analysis. The utility, cost and mortality inputs were sourced from the literature and detailed data from the trials. The deterministic base-case results from the cost-effectiveness analysis were presented together with the probabilistic sensitivity analysis. This incorporates the parametric uncertainty surrounding the input parameters utilised in the economic model as well as the results from scenario analyses, which focused on the economic model's structural uncertainty.

Study results

From a comprehensive search that retrieved 11,305 records, 35 references pertaining to six studies were included after screening. All six studies were rated as being at low risk of bias in both sets of the trials for each of the thrombopoietin receptor agonists: ADAPT-1, ADAPT-2 and Study 202 for avatrombopag, and L-PLUS (Lusutrombopag for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Invasive Procedures), L-PLUS 2 (Lusutrombopag for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Invasive Procedures 2) and the JapicCTI-121944 study for lusutrombopag.

The main finding was that both avatrombopag (for both platelet subgroups) and lusutrombopag were clearly clinically effective in comparison with no thrombopoietin receptor agonist in terms of primary outcomes, including that for three of the main trials, ADAPT-1, ADAPT-2 and L-PLUS 2, that is avoidance of platelet transfusion or rescue procedure for bleeding. Neither avatrombopag nor lusutrombopag was unequivocally better than no thrombopoietin receptor agonist in terms of adverse events, and a small amount of evidence showed a higher percentage of deaths with both thrombopoietin receptor agonists.

The main outcomes of avoidance of the composite outcome no platelet transfusion before the elective procedure or rescue therapy, or avoidance of platelet transfusion only, were analysed according to the subgroups that matched the expected licensed doses of avatrombopag (< 40,000/ μ l for 60 mg or 40,000–< 50,000/ μ l for 40 mg). Both avatrombopag and lusutrombopag were superior to placebo and mostly with a statistically significant difference (i.e. 95% confidence intervals did not overlap the point of no difference). However, when the outcome of avoidance of rescue therapy was considered alone, albeit only in those who did not receive platelet transfusion before the elective procedure, the lusutrombopag trials were revealed to have a much lower frequency than the avatrombopag trials regardless of treatment arm, the explanation for which is not obvious. They also show that there was no statistically significant difference between lusutrombopag and placebo. However, there was a statistically significant difference for avatrombopag in the < 40,000/ μ l subgroup of ADAPT-1 and the 40,000–< 50,000/ μ l subgroup of ADAPT-2. This did imply an advantage of avatrombopag over lusutrombopag in the risk of avoiding rescue therapy from meta-analysis using an indirect comparison, but this was statistically significant only in the fixed-effects analysis on the relative risk scale of the < 40,000/ μ l subgroup (Table a).

Clinical heterogeneity was found between the lusutrombopag trials as well as between the lusutrombopag and avatrombopag sets of trials. However, statistical heterogeneity was no more than moderate, and the robustness of outcomes in terms of the extent of difference between thrombopoietin receptor agonist and no thrombopoietin receptor agonist and between both thrombopoietin receptor agonists was demonstrated in sensitivity analyses. Survival was not an efficacy outcome, and mortality data were provided for only very short-term follow-up, although there appeared to be little difference between treatments. No quality-of-life data were provided, although it is plausible that thrombopoietin receptor agonists have little clinical impact other than reducing the need for platelet transfusion.

When the cost-effectiveness of both thrombopoietin receptor agonists compared with no thrombopoietin receptor agonist was assessed, it was clear that, in terms of quality-adjusted life-years, thrombopoietin receptor agonists has only a marginal benefit over care as usual (Table b). When uncertainty is taken into account, both lusutrombopag and avatrombopag have about 50% chance of being more effective than no thrombopoietin receptor agonist. This essentially reduces the cost-effectiveness analysis to a cost-minimisation analysis. For both subgroups, no thrombopoietin receptor agonist clearly has the lowest costs, even uncertainties are taken into account.

In the probabilistic sensitivity analysis, it was shown that, for all thresholds below £100,000, no thrombopoietin receptor agonist had 100% probability of being cost-effective.

Various scenario analyses showed that the results are most sensitive to the (currently unknown) price of avatrombopag.

TABLE a Relative risks (95% confidence intervals) for lusutrombopag vs. avatrombopag for three main outcomes from indirect comparison

Type of effect	No platelet transfusion prior to the elective procedure nor rescue therapy	No platelet transfusion	No rescue therapy
<i>Subgroup with a baseline platelet count of < 40,000/μl</i>			
Fixed	1.29 (0.72 to 2.31)	1.93 (1.15 to 3.22)	0.71 (0.54 to 0.93)
Random	1.63 (0.61 to 4.37)	2.43 (0.95 to 6.27)	0.67 (0.41 to 1.08)
<i>Subgroup with a baseline platelet count of 40,000–< 50,000/μl</i>			
Fixed	1.02 (0.62 to 1.66)	1.31 (0.86 to 2.01)	0.81 (0.62 to 1.05)
Random	1.13 (0.61 to 2.11)	1.62 (0.63 to 4.18)	0.81 (0.62 to 1.05)

TABLE b Deterministic base-case discounted assessment group model results

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Platelet count of < 40,000/μl subgroup							
No thrombopoietin receptor agonist	Confidential information has been removed	7.3961	3.3626				
Lusutrombopag	Confidential information has been removed	7.3961	3.3627	592	0.00002	0.00017	3,422,801
Avatrombopag 60 mg	Confidential information has been removed	7.3961	3.3627	49	-0.000006	-0.000079	Dominated
Platelet count of 40,000-< 50,000/μl subgroup							
No thrombopoietin receptor agonist	Confidential information has been removed	7.3961	3.3625				
Lusutrombopag	Confidential information has been removed	7.3961	3.3625	624	0.00002	0.00000	84,890,361,589
Avatrombopag 40 mg	Confidential information has been removed	7.3961	3.3629	9	0.00000	0.00041	21,947
ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year.							

In 3 of the 15 other scenarios, 'number of adult therapeutic doses per platelet transfusion', 'cost of platelet transfusion' and 'under-reporting factor for serious hazards of transfusion data platelet transfusion-specific mortality', the avatrombopag costs would decrease in the 40,000–< 50,000/ μ l subgroup to values around 10% more than no thrombopoietin receptor agonist in the most extreme scenarios. However, even then, the incremental cost-effectiveness ratios would remain very high and clearly out of the range of acceptable incremental cost-effectiveness ratios.

Conclusions

If the aim of service provision is to reduce platelet transfusion prior to elective procedures in patients with chronic liver disease, then both lusutrombopag 3 mg and avatrombopag, 60 mg or 40 mg for the < 40,000/ μ l or 40,000–< 50,000/ μ l subgroups, respectively, would seem to be able to do that safely. The evidence suggests that avatrombopag might also be able to reduce the need for rescue therapy for bleeding. However, given the large difference between the rates of rescue therapy in the lusutrombopag and avatrombopag trials, it is uncertain what the circumstances are under which this might be observed in clinical practice. The assessment of the cost-effectiveness of lusutrombopag and avatrombopag confirmed that, although both were successful in avoiding platelet transfusions prior to surgery, this did not translate into additional long-term health benefits over placebo in terms of quality-adjusted life-years. Therefore, cost minimisation becomes the focus. For both platelet count subgroups, no thrombopoietin receptor agonist was clearly cheaper than both lusutrombopag and avatrombopag, as the cost savings from avoiding platelet transfusions were more than offset by the cost of the drugs. The probabilistic sensitivity analysis showed that, for all thresholds below £100,000, no thrombopoietin receptor agonist had a 100% probability of being cost-effective. Uncertainty surrounding the price of avatrombopag, the content and costs of platelet transfusions and the potential under-reporting in the data used to estimate platelet transfusion specific mortality had most impact on results. However, even when extreme values were tested, incremental cost-effectiveness ratios comparing lusutrombopag and avatrombopag with no thrombopoietin receptor agonist remained substantially higher than National Institute for Health and Care Excellence thresholds.

Given the need to compare the two thrombopoietin receptor agonists and the potential lack of comparability of the extant trials, a head-to-head trial is warranted. Ideally, this should measure all relevant outcomes, including risk of platelet transfusion separate from rescue therapy and with a longer follow-up, at least of mortality and quality of life. The trial should be of a size that permits subgroup analysis according to baseline platelet count as well as in terms of type of chronic liver disease and elective procedure. Any future trials in this area should focus on the consistent collection of data on the content of platelet transfusions in terms of the number of platelets transfused or consistently and clearly defining terms such as units or doses so that accurate costs can be calculated. This is particularly important given that the avoidance of platelet transfusion does not seem to translate into differences in quality-adjusted life-years. Therefore, accurate costing is crucial for decision-making.

Study registration

This study is registered as PROSPERO CRD42019125311.

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