Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Eltrombopag

Nonsponsored Review

Therapeutic area: Severe Aplastic Anemia

Clinical Review

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Abbreviations

AE	adverse event
allo-HSCT	allogeneic hematopoietic stem cell transplant
AML	acute myeloid leukemia
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATG	anti-thymocyte globulin
CBC	complete blood count
CI	confidence interval
GVHD	graft versus host disease
hATG	horse anti-thymocyte globulin
HR	hazard ratio
HRQoL	health-related quality of life
IQR	interquartile range
IST	immunosuppressive therapy
ITT	intention-to-treat
MDS	myelodysplastic syndrome
OR	odds ratio
RR	risk ratio
RCT	randomized controlled trial
SAA	severe aplastic anemia
SAE	serious adverse event
vSAA	very severe aplastic anemia

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Eltrombopag, 25 mg, 50 mg film-coated tablets for oral use
Health Canada indication	For patients with severe aplastic anemia who have had insufficient response to immunosuppressive therapy
Indication under consideration for reimbursement	In combination with immunosuppressive therapy in previously untreated patients with severe aplastic anemia
Health Canada approval status	Not approved
NOC date	Not applicable
Requester	FWG

FWG = Formulary Working Group; NOC = Notice of Compliance.

Introduction

Severe aplastic anemia (SAA) is a rare cause of bone marrow failure mediated by cytotoxic T lymphocytes targeting patients' own hematopoietic stem cells.[1] Common symptoms include weakness and fatigue, frequent infections, unexplained or easy bruising, and shortness of breath, but some patients are asymptomatic and their disease is detected incidentally from routine blood tests. The initial diagnosis work-up includes blood tests (complete blood count [CBC] and reticulocyte count), and bone marrow examination with cytogenic and molecular testing. Severity is classified by platelet, neutrophil, and reticulocyte count.[2] If left untreated, SAA can rapidly result in end-organ complications from pancytopenia and may eventually be fatal. Treatment options include either allogeneic hematopoietic cell transplant (allo-HSCT) or immunosuppressive therapy (IST) with horse antithymocyte globulin (hATG) and cyclosporine.[1] The choice of 1 of these treatments is usually based on the availability of a matched sibling donor and the patient's age. However, despite good survival rates for both treatments, there are differences with respect to eligibility as well as long-term outcomes. Front-line allo-HSCT is generally limited to patients younger than 40 years with a human leukocyte antigen–matched sibling donor. Patients undergoing allo-HSCT are at risk of early complications related to the toxicity of the preparative regimen, infections, and acute graft versus host disease (GVHD), and in the long term may develop chronic GVHD (cGVHD), which is associated with treatment-related mortality rates of at least 20%. Patients treated with IST often do not have a complete recovery of blood counts and are prone to complications from the lingering cytopenias, as well as relapse of their disease.[3,4]

The Provincial Advisory Group (PAG), Formulary Working Group (FWG), and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice to add eltrombopag to front-line IST for patients with SAA. The FWG requested that CADTH review eltrombopag in combination with IST for previously untreated patients with SAA and provide a reimbursement recommendation.

The clinical and pharmacoeconomic evidence for the review were provided through the CADTH Nonsponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with eltrombopag in combination with IST and comparators deemed to be appropriate based on feedback from clinical experts and public drug programs for previously untreated SAA.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review. No input was received from clinician groups.

Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups.

One patient advocacy group, the Aplastic Anemia and Myelodysplasia Association of Canada (AAMAC), submitted the patient input for this review. AAMAC is a federally incorporated, registered national charity with the goal of providing a seamless support network for every patient, family member, friend, and concerned health care provider in Canada dealing with aplastic anemia, myelodysplasia, or paroxysmal nocturnal hemoglobinuria. The submission was based on perspectives gathered through an online patient survey combined with telephone interviews with patients who had experience with eltrombopag, between May 2, 2023, and June 20, 2023. Eleven patients responded to the survey. Nine out of the 11 respondents who completed the survey had prior experience with eltrombopag treatment, and among them, 5 participants participated in a telephone interview.

Respondents noted several side effects of SAA that negatively impact their quality of life, including "constant stress," "brain fog," fear and uncertainty due to limited treatment options, and feelings of dependence. Limiting long-term disease consequences and preventing relapse were among the most valued treatment outcomes. Respondents noted several side effects of treatments like cyclosporine, anti-thymocyte globulin (ATG), and blood transfusions, with nausea and headaches being cited as the most difficult to tolerate. Cost of treatment, travel distance to access treatment, and the unavailability of treatment in Canada were cited as barriers to access.

Patients who had experience with eltrombopag indicated positive effects across all aspects, particularly in improving complete blood count (CBC) and reticulocyte counts, aligning with patients' prioritized health outcomes. Respondents described the side effects as tolerable. Overall, 89% of respondents who received eltrombopag said that they would recommend it to other patients with SAA.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Two clinical experts provided expert knowledge regarding treatment strategies in Canada. The clinical experts reported that treatment goals for SAA are to achieve transfusion independence for both platelets and red cells, achieve neutrophil recovery, avoid infection-related complications, and improve symptoms related

to cytopenias, allowing patients to return to their prior functional status. Clinical experts noted that treatment with front-line cyclosporine and hATG is associated with a longer time to first response (up to 6 months) leading to prolonged transfusion dependence and elevated risk of infectious complications during this time. Further, the clinical experts noted that many patients must relocate for prolonged periods to be closer to centres that administer IST, and most are unable to work while they are severely cytopenic. Allo-HSCT, while recommended by some experts for patients younger than 40 years as front-line treatment, is not always a viable option due to lack of available donors or logistical challenges. Further, many patients may not tolerate allo-HSCT due to age or comorbidities, and it is associated with many complications including GVHD and treatment-related mortality of at least 20%.

Clinical experts suggested that eltrombopag should be considered as front-line therapy in combination with cyclosporine and hATG. Clinical experts suggested that patients likely to benefit from treatment with eltrombopag and IST include those with a pathologically confirmed diagnosis of SAA with exclusion of other causes of marrow aplasia; those who have not previously received treatment for SAA, except for prior supportive treatments; and those who are not planned to undergo front-line allo-HSCT. Red cell transfusion independence, platelet transfusion independence, and an absolute neutrophil count (ANC) greater than 0.5×10^9/L were noted to be associated with improvement in survival and quality of life, and experiencing at least a partial response in these outcomes would be considered clinically meaningful. Reasons to consider treatment discontinuation include: not experiencing at least a partial response at 6 months, development of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), clonal evolution with new karyotypic or molecular abnormalities, or the development of reticulin fibrosis in the marrow. Occurrence of eltrombopag-specific adverse events (AEs) including elevated liver enzymes and bilirubin, the development of or coexisting liver cirrhosis or hepatitis C, progressive or worsening cataracts, or the presence of thromboembolism attributed to eltrombopag may also lead to discontinuation of eltrombopag. It was noted that treatment would take place at either an academic or community hospital that has hematology and oncology inpatient and outpatient services available and is experienced in the treatment of patients with SAA.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. For the CADTH review of eltrombopag in combination with IST for previously untreated patients with SAA, the drug plans provided questions pertaining to initiation, re-treatment, discontinuation, and duration of therapy, as well as a timeline for assessment of response. Public drug plans also noted that while this nonsponsored review is limited to an adult population, any funding decision would also impact the reimbursement status of this drug for a pediatric population.

Clinical Evidence

Protocol-Selected Studies

Description of Studies

One published, open-label, multicentre, phase III randomized controlled trial (RCT) was included in the systematic review. The RACE trial is an investigator-led trial conducted across 6 countries in Europe. In this trial, 197 newly diagnosed patients with SAA were randomized to either IST, consisting of hATG and cyclosporine (n = 101), or to 150 mg oral eltrombopag daily from day 14 to 6 months in addition to standard IST (n = 96). The primary end point was hematologic complete response at 3 months, and secondary end points included overall response, time to first response, best response, complete response, overall survival, event-free survival, and health-related quality of life (HRQoL). The median age of included patients was 53 years; 55% were male and 45% were female. Overall, 66% of patients had SAA and 34% had very severe aplastic anemia (vSAA). The median follow-up among patients in both treatment arms was 24 months.

Critical Appraisal

The RACE trial was powered to examine the superiority of IST plus eltrombopag over IST alone for the primary end point of hematologic complete response at 3 months in previously untreated patients with SAA. The trial was open-label, but the primary end point of hematologic complete response at 3 months and some other key end points including overall response, transfusion independence, and time to first response were lab-based objective measures, which were unlikely to be affected by the open-label design. The number of missing assessments for key outcomes was not reported in the trial publication; therefore, that risk of attrition bias cannot be ruled out. The statistical analysis of the primary end point was appropriate. However, several analyses that were planned were not performed or reported, and some between-group differences were also not reported.

The inclusion and exclusion criteria were deemed clinically relevant and reasonable by CADTH's clinical experts. However, the clinical experts noted that eligibility for sibling stem cell transplant as an exclusion criterion does not reflect clinical practice, especially for patients older than 30 to 40 years of age, as stem cell transplant is not a preferred front-line therapy for this age group. These patients would in fact be good candidates for IST in clinical practice. The clinical experts consulted by CADTH considered the trial outcomes clinically meaningful. However, some harms outcomes of special interest indicated by CADTH's clinical experts (e.g., presence and progression of cataracts and thrombocytosis or thromboembolism) were not reported.

Efficacy Results

The overall response rate at 3 months was 59% in the IST plus eltrombopag arm and 31% in the IST arm (adjusted risk ratio [RR] = 1.97; 95% confidence interval [CI], 1.44 to 2.69). At 6 months, the overall response was 68% in the IST plus eltrombopag arm, and 41% in the IST arm (adjusted RR = 1.71; 95% CI, 1.33 to 2.21). At 3 months, 22% of patients in the IST plus eltrombopag arm and 10% of patients in the IST arm had a complete response (odds ratio [OR] = 3.2; 95% CI, 1.3 to 7.8; P = 0.01). At 6 months, 32% of patients in the

IST plus eltrombopag arm and 20% of patients in the IST arm had a complete response (OR = 2.3; 95% CI, 1.1 to 4.7).

Among the patients who had a response, the median time to platelet transfusion independence was 68 days (interquartile range [IQR], 34 to 151) in the IST arm and 40 days (IQR, 20 to 80) in the IST plus eltrombopag arm. The median time to red cell transfusion independence was 140 days (IQR, 62 to 252) in the IST arm and 51 days (IQR, 23 to 122) in the IST plus eltrombopag arm.

The median time to first response was 8.8 months in the IST arm and 3.0 months in the IST plus eltrombopag arm. At 12 months, the complete response rate was 33% in the IST arm and 52% in the IST plus eltrombopag arm. The between-group difference and results of planned statistical tests were not reported.

Event-free survival at 2 years was 34% (95% CI, 24% to 44%) in the IST arm and 46% (95% CI, 36% to 57%) in the IST plus eltrombopag arm. The between-group difference and results of planned statistical tests were not reported.

At 6 months, the probability of overall survival was 93.1% (95% CI, 88.1% to 98.0%) in the IST arm and 96.9% (95% CI, 93.4% to 100.0%) in the IST plus eltrombopag arm. At 12 months, the probability of overall survival was 88.9% (95% CI, 82.8% to 95.1%), and 95.7% (95% CI, 91.6% to 99.8%) in the IST and IST plus eltrombopag arms, respectively. At both time points, the between-group difference and results of planned statistical tests were not reported.

Median scores for global health status (assessed using the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-30]) in the IST plus eltrombopag arm were 58.3 (IQR, 33.3 to 75.0) at baseline, 66.7 (IQR, 58.3 to 83.3) at 6 months, 75.0 (IQR, 58.3 to 83.3) at 12 months, and 83.3 (IQR, 66.7 to 91.7) at 24 months. In the IST group, the median scores for global health status were 50.0 (IQR, 33.3 to 66.7) at baseline, 66.7 (IQR, 50.0 to 83.3) at 6 months, 75.0 (IQR, 66.7 to 83.3) at 12 months, and 75.0 (IQR, 62.5 to 83.3) at 24 months. Between-group differences and results of statistical tests for each time point were not reported, but the authors reported “no difference” in the trend between arms.

Harms Results

A total of 1,819 AEs occurred in the IST arm and 1,480 in the IST plus eltrombopag arm. The most common system organ class AEs were gastrointestinal disorders (306 events in the IST arm; 273 events in the IST plus eltrombopag arm).

A total of 291 and 239 grade 3 or higher AEs were reported in the IST and IST plus eltrombopag arms, respectively. The most common grade 3 or higher AEs in both arms were infections and infestations (76 events in the IST arm; 63 events in the IST plus eltrombopag arm).

Twenty-two patients died during the trial (14 patients in the IST arm and 8 in the IST plus eltrombopag arm). A total of 13 patients died due to infections (9 in the IST arm and 4 in the IST plus eltrombopag arm). Two patients in the IST arm died due to bleeding. Other causes of death in the IST arm were lung cancer (n = 1), encephalopathy of unknown origin (n = 1), and transplant-related mortality (n = 1). Other causes of death

in the IST plus eltrombopag arm were acute respiratory distress syndrome of unknown origin (n = 1), aortic valve disease (n = 1), cardiac tamponade (n = 1), and thrombosis (n = 1).

Cost Information

As CADTH does not have access to an economic model to address the specified research question, the economic review included a comparison of the treatment costs of IST plus eltrombopag and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.

Based on publicly available list prices, and assuming a 6-month course of eltrombopag, the cost of treatment with IST plus eltrombopag is $89,543 or $102,674 per patient when the originator brand of eltrombopag is considered, depending on the hATG regimen used. The cost of treatment for the same regimen assuming the use of generic eltrombopag is $78,866 or $91,998 per patient. The cost of IST alone is $18,368 or $31,499 per patient, depending on the hATG regimen used. As such, the incremental cost of IST plus eltrombopag compared to IST alone is $71,175 if the originator brand is used, or $60,499 if generic eltrombopag is used. These incremental costs are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug payers.

Table 2: Summary of Key Results From the RACE Trial

Outcome	IST N = 101 (efficacy)	IST + EPAG N = 96 (efficacy)
Efficacy		
Hematologic response at 3 months		
Complete response, n (%)	10 (10)	21 (22)
OR (95% CI); P value[a]	3.2 (1.3 to 7.8); P = 0.01	
Partial response, n (%)	21 (21)	36 (38)
No response, n (%)	70 (69)	39 (41)
Overall response,[b] n (%)	31 (31)	57 (59)
Adjusted RR (95% CI)	1.97 (1.44 to 2.69)	
Time to transfusion independence, days		
Platelet transfusion, median (IQR)	68 (34 to 151)	40 (20 to 80)
Red cell transfusion, median (IQR)	140 (62 to 252)	51 (23 to 122)
Time to first response		
Median, months	8.8	3.0
Event-free survival		
Median % (95% CI)	34% (24 to 44)	46% (36 to 57)
Overall survival		
At 6 months, probability (95% CI)	93.1 (88.1 to 98.0)	96.9 (93.4 to 100.0)
At 12 months, probability (95% CI)	88.9 (82.8 to 95.1)	95.7 (91.6 to 99.8)

Outcome	IST N = 101 (efficacy)	IST + EPAG N = 96 (efficacy)
At 24 months, probability (95% CI)	85.0 (77.7 to 92.4)	89.5 (82.4 to 96.6)
HRQoL, EORTC QLQ-30 global health status		
Baseline, median (IQR)	50.0 (33.3 to 66.6)	58.3 (33.3 to 75.0)
6 months, median (IQR)	66.6 (50.0 to 83.3)	66.7 (58.3 to 83.3)
12 months, median (IQR)	75.0 (66.6 to 83.3)	75.0 (58.3 to 83.3)
24 months, median (IQR)	75.0 (62.5 to 83.3)	83.3 (66.6 to 91.6)
Harms		
Number of AEs	1,819	1,480
Number of AEs (grades 3 to 5)	291	239
Deaths, n (%)	14 (13.8)	8 (8.3)

AE = adverse event; CI = confidence interval; EORTC QLQ-30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; EPAG = eltrombopag; IQR = interquartile range; IST = immunosuppressive therapy; RR = risk ratio.

[a]The pooled odds ratios for the IST + EPAG arm compared with IST arm and 95% CIs were obtained using the Mantel-Haenszel test, stratified according to the factors used at randomization (age, severity of aplastic anemia, and study centre).

[b]The overall response corresponded to the percentage of patients who had a partial or complete response.

Source: Peffault de Latour et al. (2022).[5]

Conclusions

The results of a single open-label trial (the RACE trial; n = 197) suggest that the addition of eltrombopag to IST with hATG and cyclosporine, as compared with IST alone, resulted in better short-term (3-month and 6-month) hematologic response in previously untreated patients with SAA. Despite important limitations related to the small sample size and limited number of events, as well as lack of comparative estimates for several end points, the gains made in terms of complete response, overall response, and time to first response with the addition of eltrombopag to IST are considered clinically important by the clinical experts. The benefit on important long-term outcomes, including maintenance of response and overall survival, is yet unknown. Although no excess toxicity appears to have been observed with the addition of eltrombopag to IST, a longer follow-up duration is needed to determine late-emerging toxicities, including myeloid malignant transformation, which usually appear 5 years to 10 years after diagnosis. The clinical experts indicated that adding eltrombopag to IST in the front-line setting for patients with SAA would fill an unmet treatment need, given the limited number of treatment options for these patients and the progressive course of the disease.

Results of the cost comparison of treatment costs demonstrate that, assuming a 6-month course of eltrombopag, the incremental cost of eltrombopag plus IST compared with IST alone would be $71,175 if the originator brand of eltrombopag is used, or $60,499 if generic eltrombopag is used. As such, the reimbursement of eltrombopag plus IST for the first-line treatment of patients with SAA is expected to increase overall treatment costs. Based on the clinical review conclusions, eltrombopag plus IST may provide a clinically important benefit compared to IST alone. As such, eltrombopag plus IST is associated with incremental costs and incremental benefit compared with IST alone. A cost-effectiveness analysis would therefore be required to determine the cost-effectiveness of eltrombopag plus IST compared with

IST alone. As a cost-effectiveness analysis was not available, the cost-effectiveness of eltrombopag plus IST in comparison with IST alone for the first-line treatment of patients with SAA could not be determined. According to clinical expert feedback elicited by CADTH for this review, based on the differences in time to transfusion independence differences reported in the RACE trial, there may be some savings in blood product resource use with eltrombopag plus IST compared to IST alone. While there is uncertainty in the unit costs of these blood products, the resource use differences are unlikely to fully offset the cost of eltrombopag even at the highest blood product costs identified. To consider this alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of eltrombopag plus IST would be required.

Introduction

Disease Background

SAA is a hematological disorder characterized by bone marrow hypoplasia and pancytopenia. The main mechanism leading to bone marrow failure in most cases is immune-mediated destruction of hematopoietic stem and progenitor cells.[2] SAA is a rare disease with an annual incidence of approximately 2 cases per million people in Europe and North America, and a higher incidence in East Asian countries (4 to 5 cases per million).[6] There is no difference in incidence between males and females, and there are 2 peaks of incidence in children and young adults (aged 10 years to 25 years) and older adults (older than 60 years).[4]

Although drugs, viral infections, hepatitis, and pregnancy can trigger SAA, the onset in most cases is idiopathic.[2] Common symptoms include weakness and fatigue, frequent infections, unexplained or easy bruising, and shortness of breath. The initial diagnosis work-up includes blood tests (CBC and reticulocyte count), bone marrow examination with cytogenic and molecular testing, and further ancillary tests to rule out other causes of bone marrow failure. Although patients are usually symptomatic on presentation, some cases are detected incidentally when unexpected cytopenias are found on a routine blood count.[4] Aplastic anemia is characterized as severe according to the most common conventions with severity criteria, based on hypocellular bone marrow (< 25% [or < 50% if < 30% of bone marrow is hematopoietic cells]), and at least 2 of the following: peripheral blood neutrophil count less than 0.5×10^9/L, peripheral blood platelet count less than 20×10^9/L, and peripheral blood reticulocyte count less than 20×10^9/L.[1] If left untreated, SAA can rapidly result in end-organ complications from pancytopenia and may eventually be fatal.[4]

Standards of Therapy

The clinical experts consulted by CADTH indicated that the current treatment paradigm for patients with previously untreated SAA in Canada is IST with hATG and cyclosporine, or allo-HSCT. IST targets the underlying disease mechanism by suppressing this abnormal immunologic activity, allowing for stem cell expansion and marrow recovery. It is important to note that standard IST takes up to 6 months to be effective, and that patients are transfusion-dependent and at high risk of infectious complications during this time frame. Allo-HSCT also targets the underlying disease mechanism by replacing the immune system

entirely with a new donor immune system and donor stem cells. Symptoms generally improve after marrow recovery and transfusion independence are achieved.

According to the clinical experts consulted by CADTH for this review, goals of therapy include transfusion independence for both platelets and red cells, neutrophil recovery, avoiding infection-related complications, and improving symptoms related to cytopenias. In general, for patients older than 40 years, IST is used as a front-line treatment, with allo-HSCT reserved for use in the case of relapsed or refractory disease. In patients younger than 40 years with a human leukocyte antigen–identical sibling donor, allo-HSCT can be used as a front-line treatment — and this is recommended by some experts — but in practice, many centres in Canada cannot achieve the timelines needed to make this a feasible front-line treatment option for patients younger than 40 years. Consequently, several patients younger than 40 years will end up receiving a trial of IST. Allo-HSCT is also not a viable option for many patients, due to an inability to tolerate allo-HSCT because of age or comorbidities, lack of available sibling donors, or other factors that make this intensive treatment prohibitive. Further, allo-HSCT may be accompanied by many complications (such as GVHD and infection) and has a treatment-related mortality of at least 20%, even in otherwise healthy patients, and can significantly impair quality of life in the longer term due to cGVHD. As such, avoiding allo-HSCT unless it is an absolute necessity is important in reducing the risks of treatment-related morbidity and mortality, as well as the risks of impaired quality of life after treatment with allo-HSCT, for patients with SAA.

Drug

Eltrombopag is an oral, synthetic, small-molecule, thrombopoietin (TPO)-receptor agonist that interacts with the transmembrane domain of the human TPO receptor and initiates signalling cascades that induce proliferation and differentiation from bone marrow progenitor cells. Eltrombopag is indicated for the treatment of chronic immune thrombocytopenia to increase platelet counts in adult and pediatric patients aged 1 year and older who have had an insufficient response to corticosteroids or immunoglobulins, and to increase platelet counts in patients with thrombocytopenia who have chronic hepatitis C virus infection, to allow the initiation and maintenance of interferon-based therapy.[7] For patients with SAA, eltrombopag is indicated in combination with IST for the treatment of adult patients with SAA who have had an insufficient response to IST.[7] The current CADTH nonsponsored reimbursement request for eltrombopag in combination with IST for previously untreated SAA thus differs from the currently approved Health Canada indication.

Stakeholder Perspectives

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

One patient advocacy group, AAMAC, submitted patient input for this review. AAMAC is a federally incorporated, registered national charity with the goal of providing a seamless support network for every patient, family member, friend, and concerned health care provider in Canada dealing with aplastic anemia, myelodysplasia, or paroxysmal nocturnal hemoglobinuria.

The submission was based on perspectives gathered through an online patient survey combined with telephone interviews of patients with eltrombopag experience, between May 2, 2023, and June 20, 2023. The survey link was sent via email to people registered through the AAMAC database. The survey incorporated a combination of multiple-choice, rating, and open-ended questions to assess the impact of SAA on patients' lives and efficacy of current treatments, and to gather targeted feedback from patients with eltrombopag treatment experience. Eleven patients from British Columbia, Alberta, Manitoba, Ontario, and Quebec responded to the survey. Out of the 11 respondents who completed the survey, 9 had prior experience with eltrombopag treatment, and among them, 5 participants agreed to engage in telephone interviews with a consultant, providing further insights into their treatment experience and expanding upon their feedback.

Respondents indicated that the physical manifestation of SAA impacts various aspects of their lives, and fatigue (100%), unexplained or easy bleeding (82%), shortness of breath (64%), dizziness (46%), and rapid or irregular heart rate (46%) were the most common symptoms. Respondents indicated the “constant stress” from performing monthly blood tests and concern of getting other diseases, “brain fog,” fear and uncertainty due to limited treatment options, and a feeling of dependence deteriorated their quality of life.

All 11 respondents indicated that they had previously received cyclosporine, and the majority had received ATG (10 of 11; 91%) and blood transfusions (9 of 11; 82%). Respondents noted several side effects of these treatments (increased hair growth, hand or foot numbness, pain and discomfort, headache, hives, nausea, vomiting, and high blood pressure), with nausea and headaches being cited as the most difficult to tolerate. Cost of treatment was the most commonly cited barrier to access, with 55% of the respondents indicating that they needed financial assistance to deal with the costs associated with SAA or its treatment. Other barriers to access to treatment were travel distance to access treatment and the unavailability of treatment in Canada. In evaluating the importance of different outcomes for their SAA treatment, limiting long-term disease consequences and preventing relapse were both given the highest possible rating (5, or “very important”) by every respondent. Other outcomes (improving CBC and reticulocyte count, improving quality of life, reducing SAA symptoms, and managing treatment side effects) were rated 4.5 and higher.

Patients who had experience with eltrombopag rated the impact of eltrombopag on their quality of life, with average scores indicating positive effects across all aspects, particularly in improving CBC and reticulocyte counts, aligning with patients' prioritized health outcomes. Muscle aches were the most reported side effects of eltrombopag, followed by liver problems, diarrhea, and nausea, with all side effects described as tolerable. Some respondents indicated they were not always sure which side effects were due to eltrombopag and which were due to other drugs they were receiving concurrently. Overall, 89% of respondents who received eltrombopag said that they would recommend it to other patients with SAA. Caregivers who were interviewed also expressed satisfaction with eltrombopag due to its effectiveness and reduced side effects.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review

team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of SAA.

Unmet Needs

The clinical experts noted that the standard of care for patients with previously untreated SAA is IST with hATG and cyclosporine, as front-line treatment for patients older than 40 years. However, a significant number of patients do not show a response to IST with cyclosporine and hATG, with only 40% to 60% achieving a response at 6 months. Therefore, these patients require second-line therapy, such as allo-HSCT. Further, clinical experts noted that the prolonged time to response for IST with cyclosporine and hATG (6 months to 8 months) results in long periods of transfusion-dependent cytopenias and neutropenia, which are associated with downstream complications. Cirrhosis, heart failure, and diabetes due to iron overload resulting from repeated transfusions of red cells, and alloimmunization and severe bleeding complications due to repeated platelet transfusions, can occur. Additionally, prolonged neutropenia increases the risks of life-threatening infections, with mortality from infections in SAA reported to be as high as 5% to 10%. Clinical experts also noted that prolonged periods of severe cytopenias also result in significant reduction in quality of life and pose significant financial and emotional burden, as patients are unable to work and often have to be away from home to be near an appropriate treatment centre.

While allo-HSCT is recommended by some experts for patients aged 40 years and younger as front-line treatment, the clinical experts noted that many patients will not be eligible, either due to comorbidities or lack of donor options. The clinical experts emphasized that the determination of whether front-line allo-HSCT is appropriate depends entirely on the individual patient and involves numerous factors, and that there are no universally applicable guidelines that can definitively determine the eligibility of patients for front-line allo-HSCT. The clinical experts also noted that allo-HSCT is associated with many complications, including GVHD, and that the treatment-related mortality with allo-HSCT is at least 20%. The clinical experts indicated that treatment with allo-HSCT results in significant costs to the health care system. Highlighting equity issues, they noted that many patients who are unable to find allo-HSCT donors are from underserved communities, and that it is particularly difficult to find unrelated donors for Indigenous patients.

The clinical experts reported that goals of treatment for SAA are to attain transfusion independence for both platelets and red cells, neutrophil recovery, to avoid infection-related complications, and to improve symptoms related to cytopenias, allowing for patients to return to their prior functional status. Further, achieving marrow recovery as rapidly as possible and minimizing the cytopenic period were also noted to be important goals to avoid morbidity and mortality related to prolonged cytopenias, repeated transfusions, and infection, which are not currently met by standard treatment options such as IST. The clinical experts also noted that new treatments should also aim to avoid allo-HSCT, due to the risks of treatment-related morbidity and mortality and reduced quality of life associated with this procedure, and for the previously noted equity issues. Other quality of life–related treatment goals include avoidance of prolonged time away from home and work spent undergoing treatment by minimizing the cytopenic period of the disease.

Place in Therapy

The clinical experts suggested that eltrombopag should be considered as front-line therapy in combination with cyclosporine and hATG. They emphasized that the combination should not only be reserved for patients who do not show a response to other treatments. The experts noted that combination is considered the standard of care in many centres outside of Canada due to the higher overall response rates and more rapid time to response.

The clinical experts noted that eltrombopag would be the first treatment approved that has a unique mechanism of action (directly stimulating the hematopoietic stem cells within the bone marrow, expanding the stem cell compartment, and producing faster recovery of the peripheral blood counts), which complements the immunosuppressive effects of cyclosporine and hATG by directly stimulating marrow recovery while simultaneously suppressing the aberrant immune reaction observed in SAA. As such, this would result in a significant paradigm shift in the treatment of SAA. If funded, clinical experts anticipate a rapid uptake and routine use of IST and eltrombopag at most or all sites across Canada. The clinical experts also suggested that the use of eltrombopag in combination with cyclosporine and hATG has the potential to significantly reduce costs related to the transfusion medicine services needed by patients with SAA, given the more rapid transfusion independence observed over IST with cyclosporine and hATG alone.

Patient Population

The clinical experts suggested that patients most likely to benefit from treatment with eltrombopag in combination with cyclosporine and hATG, and most in need of intervention, include those with a pathologically confirmed diagnosis of SAA with exclusion of other causes of marrow aplasia, such as toxins, infections, and myeloid malignancies (e.g., MDS); those who have not previously received treatment for SAA, with the exception of prior supportive treatments, such as transfusions, antibiotics, and growth factors (erythropoiesis-stimulating agents and granulocyte colony-stimulating factor [G-CSFs]); and those who are not planned to undergo front-line allo-HSCT. Patients who have concomitant severe liver disease, cirrhosis, or uncontrolled hepatitis C infection, or who have MDS, other myeloid malignancies, or significant reticulin fibrosis in the marrow at baseline, would be least suitable to receive eltrombopag with cyclosporine and hATG.

The clinical experts noted that diagnosis of SAA Is ascertained with a bone marrow aspirate and biopsy, with ancillary tests to rule out secondary causes of marrow failure (e.g., toxins, infections). The clinical experts highlighted that a potential alternative diagnostic consideration is the hypoplastic variant of MDS, which has significant overlapping features with SAA, and hypoplastic MDS may also exhibit a response to IST. While hypoplastic MDS is not particularly common, differentiating it from SAA often requires evaluation by a skilled hematopathologist and the utilization of various diagnostic tools such as aspirate morphology, flow cytometry, karyotyping, and molecular diagnostics such as next-generation sequencing, as per the clinical experts. They also noted that there is no single test that can definitively differentiate between hypoplastic MDS and pure SAA.

Assessing Response to Treatment

Red cell transfusion independence, platelet transfusion independence, and an ANC greater than 0.5 were noted by the clinical experts to be the major goals of treatment for SAA. The clinical experts noted that these milestones are directly associated with improvement in survival and quality of life. As advised by the clinical experts, the response to treatment with IST should be routinely evaluated at 6 months, as this is typically the peak period by which most responses to IST will have occurred.

With regard to clinical outcomes studied in clinical trials, the clinical experts suggested that they align with clinical practice. While complete response is preferred, at least a partial response on the previously noted 3 outcomes would be considered clinically meaningful.

The clinical experts also indicated that AEs including elevated liver enzymes and bilirubin, presence of worsening or progressive cataracts, and uncontrolled thrombocytosis or thromboembolism related to eltrombopag use should be monitored. Other potential toxicities that need monitoring include development of MDS, AML, or other myeloid malignancies, including clonal evolution of cytogenetic or molecular abnormalities, and reticulin fibrosis in the marrow.

Discontinuing Treatment

The clinical experts suggested that treatment discontinuation with IST and/or eltrombopag would be considered when there has not been at least a partial response at 6 months or if the patient has developed MDS, AML, clonal evolution with new karyotypic abnormalities, or reticulin fibrosis in the marrow. Eltrombopag may be discontinued with the occurrence of eltrombopag-specific AEs, including elevated liver enzymes and bilirubin, the development of or coexisting liver cirrhosis or hepatitis C, progressive or worsening cataracts, or the presence of thromboembolism attributed to eltrombopag usage. A decision to treat a patient with allo-HSCT would also result in treatment discontinuation with IST with or without eltrombopag.

Prescribing Conditions

It was noted that treatment would take place at either an academic or community hospital that has hematology and oncology inpatient and outpatient services available, and under the care of hematologists and oncologists who are experienced in the treatment of patients with SAA. The hATG component is administered as an inpatient, with subsequent therapy usually managed in an outpatient setting, typically either through a medical day ward, infusion clinic, or other such service.

Additional Considerations

The clinical experts noted that while steroids are usually given along with hATG, their primary goal is to prevent serum sickness related to hATG administration, not to use them as an immunosuppressant. They also emphasized that pharmacoeconomic assessments of adding eltrombopag to current IST should consider the reduction in transfusion burden and associated cost reductions to transfusion medicine services, as well as the cost savings associated with the higher response rates leading to fewer patients needing allo-HSCT as a salvage therapy.

Clinician Group Input

No input from clinician groups was received.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's nonsponsored reimbursement review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 3.

The drug plans inquired about initiating therapy, addressing the possibility of re-treatment for relapsed patients, determining the criteria and duration for discontinuing therapy, and deciding whether to follow the 3-month or 6-month treatment duration of eltrombopag, and how to manage patients afterwards. It was also stated that public drug plans do not generally fund ATG. Public drug plans also noted that while this nonsponsored reimbursement review is limited to an adult population, any funding decision may also impact the reimbursement status of this drug for the pediatric population.

Table 3: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
Can the drug be given again to patients who relapse after a course of therapy? If so, what would be the appropriate timing of re-treatment and how would the drug be dosed?	The clinical experts do not expect any safety concerns in terms of re-treatment. However, there is a lack of efficacy data in the relapsed or refractory setting and no established guidance regarding the timing of re-treatment. The clinical experts noted that re-treatment in 6 months to 12 months would be reasonable timing, based on their experience and the protocol of the pivotal trial.[a]
Considerations for discontinuation of therapy	
How should clinically meaningful response be defined? What duration of treatment is appropriate for assessing response to therapy?	Clinically meaningful response includes: • red cell transfusion independence • platelet transfusion independence • ANC greater than 0.5. The clinical experts indicated that while CR is preferred, at least a PR on the previously noted 3 outcomes would be considered clinically meaningful, and a PR would result in minimizing the cytopenic period of the disease and infection-related complications. The clinical experts noted that there is no specific time point for assessment of response. However, blood CBC levels are monitored throughout the course of therapy, which is how response to therapy is assessed. The clinical experts stated that they consider 6 months to be the minimum duration of therapy at which to evaluate response. In this treatment setting, absence of a response before 6 months

Drug program implementation questions	Clinical expert response
	would not be interpreted as a definitive lack of response to treatment.
Considerations for prescribing of therapy	
Should treatment with eltrombopag only continue for 3 months or 6 months, as was the case in the pivotal trial? If so, how should patients be subsequently managed?	Three types of response can be expected: no response, PR, and CR. Guided by the evidence, study protocol of the pivotal trial,[a] and their clinical experience, the clinical experts suggested the following in terms of treatment continuation or discontinuation. **At 3 months:** • No response: Continue IST + eltrombopag. • PR: Continue IST + eltrombopag. • CR: Discontinue eltrombopag and continue IST with cyclosporine. **At 6 months:** • No response: Discontinue IST + eltrombopag. • PR: Consider continuing IST + eltrombopag for another 3 months to 6 months. • CR: Discontinue eltrombopag, continue IST and taper cyclosporine as per institutional practice. Some patients may be eligible for allo-HSCT if they have no response after 6 or more months of IST with eltrombopag. However, for the majority of patients, no alternative therapy is available. Referring to the product monograph, it was also noted that there is no definitive discontinuation timeline for partial responders to eltrombopag in combination with IST.

allo-HSCT = allogeneic hematopoietic stem cell transplant; ANC = absolute neutrophil count; CBC = complete blood count; CR = complete response; IST = immunosuppressive therapy; PR = partial response.

Industry Input

No industry input was provided to CADTH.

Clinical Evidence

The clinical evidence included in the review of eltrombopag in combination with IST is presented in 3 sections. The first section, the systematic review, includes studies that were selected according to an a priori protocol. The second section would include indirect evidence selected from the literature that met the selection criteria specified in the review; however, no indirect evidence was considered relevant for inclusion in the review. The third section would include long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review; however, none were considered relevant for inclusion in the review.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the efficacy and safety of eltrombopag in combination with IST for previously untreated adult patients with SAA.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 4. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 4: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Adult patients (aged 18 years and older) with previously untreated SAA
Intervention	Eltrombopag in combination with IST **Common regimen:** Intravenous hATG 40 mg/kg q.d. on days 1 to 4 Cyclosporine 2.5 mg/kg b.i.d. from day 1 onward Eltrombopag 150 mg p.o., q.d., starting either day 1 or day 14 onward
Comparators	• IST with combination of hATG and cyclosporine • allo-HSCT

Outcomes	**Efficacy outcomes:**
	• Overall response
	• Hematologic response (complete, partial), 3-month and 6-month
	• Transfusion independence
	• Time to first response
	• Event-free survival
	• Overall survival
	• Health-related quality of life
	Harms outcomes:
	• AEs, SAEs, WDAEs, mortality
	  ◦ Harms of special interest:
	  ▪ Elevated liver enzymes and bilirubin
	  ▪ Presence of or progressive cataracts
	  ▪ Uncontrolled thrombocytosis or thromboembolism
	  ▪ Myeloid malignancies including clonal evolution of cytogenetic abnormalities
	  ▪ Development of reticulin fibrosis in the marrow[1]

Study design	Published and unpublished phase II, III, and IV RCTs

AE = adverse effect; allo-HSCT = allogeneic hematopoietic stem cell transplant; hATG = horse antithymocyte globulin; IST = immunosuppressive therapy; p.o. = orally; q.d. = once daily; RCT = randomized controlled trial; SAA= severe aplastic anemia; SAE = severe adverse effect; WDAE = withdrawal due to adverse effect.

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist.[1]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the population, intervention, comparator, outcome, and setting (PICOS) framework and research questions. The main search concepts were eltrombopag and aplastic anemia. The following clinical trials registries were searched: the US National Institutes of Health's ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on June 5, 2023. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee (FMEC) on October 17, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature.[2] Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

A focused literature search for indirect treatment comparisons (ITCs) dealing with eltrombopag was run in MEDLINE and Embase on June 5, 2023. Retrieval was not limited by publication date or by language.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Characteristics of Included Studies

One study (the RACE trial) was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

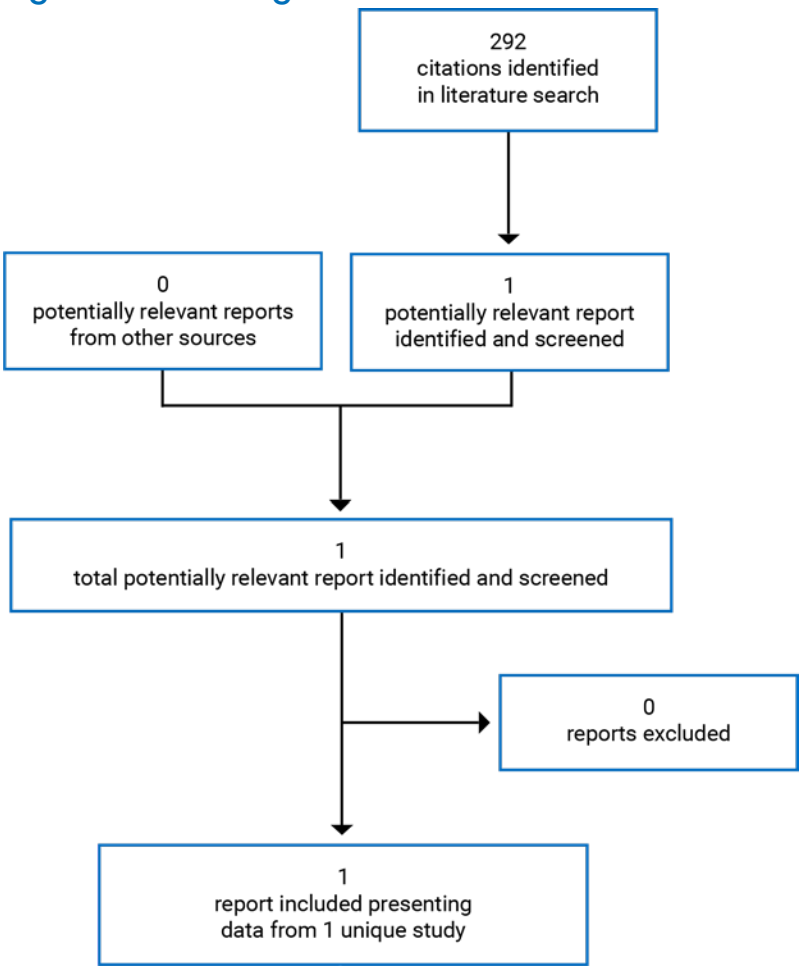

Table 5: Details of the Included Study

Detail	RACE trial
Designs and populations	
Study design	Phase III, open-label, multicentre, randomized controlled trial
Locations	24 sites in 6 European countries
Patient enrolment dates	July 2015 to April 2019
Randomized (N)	197 patients (IST arm, n = 101; IST + eltrombopag, n = 96)

Inclusion criteria	• Diagnosis of severe aplastic anemia or very severe aplastic anemia
	  ◦ At least 2 of the following:
	  ▪ Absolute neutrophil count < 0.5 × 10^9/L (severe) or < 0.2 × 10^9/L (very severe)
	  ▪ Platelet counts < 20 × 10^9/L
	  ▪ Reticulocyte counts < 60 × 10^9/L (using automated counter) or < 20 × 10^9/L (using manual count)

Detail	RACE trial
	◦ Associated with an hypocellular bone marrow (< 30% cellularity), without evidence of fibrosis or malignant cells • Male or female; age ≥ 15 years • Negative pregnancy test for people of childbearing potential
Exclusion criteria	• Prior immunosuppressive therapy with anti-thymocyte globulin (ATG) (horse or rabbit) or any other lymphocyte-depleting drug (i.e., alemtuzumab) • Eligibility for a sibling allogeneic stem cell transplant • Evidence of MDS, defined by the presence of myelodysplastic features, excess of blasts or karyotypic abnormalities typical of MDS (according to revised WHO 2008 criteria)[8] as well as other primitive marrow disease. Patients with diagnosis of AA with cytogenetic abnormalities that are recurrent in MDS (according to revised WHO 2008 criteria) were included in this category, and were not eligible for the study; patients with del(20q), + 8 and –Y were not included in this category, and thus were eligible for this study. • History or clinical suspicion of constitutional AA (i.e., Fanconi anemia with positive DEB/MMC test or dyskeratosis congenita) • History of malignant tumours with active disease within 5 years from enrolment, and/or previous chemoradiotherapy • Previous history of stem cell transplant • Treatment with CsA unless: ◦ < 4 weeks of CsA treatment before enrolment and ◦ Wash out period of 2 weeks before enrolment • CMV viremia, as defined by positive PCR (≥ 3.5 logarithm) or pp65 test (≥ 5 cells) • WHO performance status ≥ 3 • Pregnant or breastfeeding patients • Patients with end-stage hepatic, renal, or cardiac failure, or any other life-threatening concurrent disease • Patients with HIV infection • Patients without social health care assistance
Drugs	
Intervention	**Standard IST with hATG (ATGAM) and cyclosporine** hATG (ATGAM) for 4 consecutive days administered at a dose of 40 mg per kg of body weight per day, and oral cyclosporine at a dose of 5 mg per kg of body weight per day, from day 1 for at least 12 months (cyclosporine was discontinued after slow tapering in the next 6 months to 12 months) **plus** **Eltrombopag** at a dose of 150 mg daily, as 50 mg oral tablets, starting from day 14 (after starting ATGAM) through 6 months, or through 3 months in patients who had a complete response
Comparator(s)	**Standard IST with hATG (ATGAM) and cyclosporine** hATG (ATGAM) for 4 consecutive days administered at a dose of 40 mg per kg of body weight per day and oral cyclosporine at a dose of 5 mg per kg of body weight per day from day 1 for at least 12 months (cyclosporine was discontinued after slow tapering in the next 6 months to 12 months)
Concomitant medications and supportive care	• Corticosteroids at a dose of 1 mg/kg/day (intravenously or orally) for at least 7 days, and tapered and stopped within 2 weeks to 3 weeks post-treatment • Premedication with paracetamol (e.g., 1,000 mg) and/or antihistaminic medications (e.g., chlorpheniramine 10 mg)

Detail	RACE trial
	• Antimicrobial and antifungal prophylaxis • G-CSF if judged beneficial for patients (e.g., infectious complications in patients with severe neutropenia) • Red blood cell and platelet transfusions
Duration	
Follow-up	24 months (median)
Outcomes	
Primary end point	Hematologic complete response at 3 months
Secondary end points	• Overall response • Time to first response • Best response • Complete response • Overall survival • Event-free survival • Relapse • Clonal evolution • Hemolytic paroxysmal nocturnal hemoglobinuria • Discontinuation of immunosuppression • Health-related quality of life as reported by patient
Notes	
Publications included	Peffault de Latour et al. 2022
Sources of support	Funding provided by EBMT; eltrombopag was supplied by Novartis and hATG was supplied by Pfizer Inc.

EBMT = European Society for Blood and Marrow Transplantation; G-CSF = granulocyte colony stimulating factor; IST = immunosuppressive therapy.
Source: Peffault de Latour et al. (2022).[5]

Study Design

One published, open-label, multicentre, phase III RCT was included in the systematic review. The RACE trial was an investigator-led, multicentre, open-label RCT conducted by the European Society for Blood and Marrow Transplantation (EBMT) across 24 sites in 6 European countries. The trial compared hATG plus cyclosporine with or without eltrombopag in previously untreated patients with SAA or vSAA. Pfizer and Novartis provided the trial treatments, hATG, and eltrombopag, respectively, and provided research support to the EBMT under a Cooperative Research and Development agreement.

Patients were randomized 1:1 to receive either hATG plus cyclosporine or hATG plus cyclosporine and eltrombopag. Randomization was stratified according to age (≥ 15 years to < 40 years, or ≥ 40 years), disease severity (severe or very severe), and study centre. Administration of randomization was separated from the clinical investigators.

Patients were to remain in the trial for 2 years (for treatment and subsequent follow-up); the duration of the treatment with the investigational regimen was initially 3 months or 6 months (depending on hematological

response). However, given that re-introduction of the investigational regimen was allowed for 6 additional months, the treatment duration could be extended up to 18 months from enrolment. To study long-term effects of the investigational regimen, the follow-up of patients covered a minimum of 24 months from initial randomization. The long-term follow-up of the patients is to be conducted outside of the protocol and will be extended up to 10 years from treatment.

Inclusion and Exclusion Criteria

Patients aged 15 years and older were eligible for the trial if they had a new diagnosis of acquired SAA or vSAA and were not eligible for front-line allo-HSCT. Patients with prior IST with ATG (horse or rabbit) or any other lymphocyte-depleting drug, or those eligible for a sibling allo-HSCT, were ineligible. Patients with evidence of MDS or other primitive marrow disease, and those with a diagnosis of aplastic anemia with cytogenetic abnormalities that are recurrent in MDS, were also ineligible. Patients with a history or clinical suspicion of constitutional aplastic anemia, history of malignant tumours with active disease within 5 years from enrolment, and/or previous chemoradiotherapy or a history of stem cell transplant were also excluded from participation in the trial (Table 5).

Interventions

IST Arm

Horse antithymocyte globulin

hATG (ATGAM) was administered for 4 consecutive days (days 1 to 4), at a dose of 40 mg/kg/day, as an IV infusion lasting 12 hours to 18 hours. To prevent ATGAM-related side effects, such as serum sickness, corticosteroids were administered at a dose of 1 mg/kg/day (either intravenously or orally) for at least 7 days and then tapered and stopped within 2 weeks to 3 weeks post-treatment. Premedication with paracetamol and/or antihistaminic medications was also allowed. For patients with obesity, ATGAM was dosed approximately between 1.3 times ideal body weight [wording from original source] and actual weight.

Cyclosporine

Cyclosporine was administered starting on day 1 of treatment at a dose of 5 mg/kg orally, and then adjusted on blood levels (150 ng/mL to 250 ng/mL using the monoclonal assay; 200 ng/mL to 400 ng/mL using the polyclonal assay). Treatment was continued for at least 12 months. It could then be discontinued after slow tapering in the following 6 months to 12 months (approximately 10% per month). Therefore, patients remained on cyclosporine treatment for at least 18 months before withdrawal. In case of decrease in blood counts, cyclosporine could be resumed or re-escalated at the discretion of the study investigator.

IST Plus Eltrombopag Arm

hATG and cyclosporine were administered in the same manner as in the IST arm.

Eltrombopag

Eltrombopag was administered orally at a dose of 150 mg daily, as 50 mg tablets, starting from day 14 (after starting ATGAM). A 50% dose reduction (50 mg + 100 mg eltrombopag on alternating days) was recommended for patients of East Asian heritage (i.e., Japanese, Chinese, Taiwanese, and Korean).

Dietary adjustments were made to optimize eltrombopag absorption in the absence of calcium. Treatment was continued for at least 3 months (75 days of treatment) and then adjusted according to hematological response.

Treatment Interruption and Discontinuation

For patients who achieved complete response at 3 months, eltrombopag was discontinued. For patients achieving partial response at 3 months and for patients with no hematological response at 3 months, eltrombopag was continued up to 6 months at the same dose.

For patients achieving hematological response (complete or partial) who discontinued eltrombopag, the drug could be resumed in case of relapse or lack of robustness in the following scenarios:

- patients with complete response at 3 months who discontinued eltrombopag as per protocol, with subsequent relapse (i.e., no longer meeting the criteria of complete response)
- patients who discontinued eltrombopag at 6 months as per protocol, and
  - were in complete response at 6 months, with subsequent relapse (i.e., no longer meeting the criteria of complete response)
  - were in partial response at 6 months, with subsequent relapse (i.e., no longer meeting the criteria of partial response)
  - were in partial response at 6 months, with subsequent lack of robustness of their partial response, defined as a drop in hemoglobin greater than 2 g/dL (with hemoglobin < 10 g/dL), drop in ANC greater than 50% (with ANC < 1,000/μL), and drop in platelet count greater than 50% (with platelets < 50,000/μL).

In all such cases, the second course of eltrombopag treatment was reinitiated at the same dose of 150 mg per day, and was continued for 3 months in case of complete response at 3 months from re-introduction, or up to 6 months. After these additional 6 months of treatment, treatment could be continued outside the protocol by the treating physician but was no longer supplied by Novartis.

Patients with transient falls in blood counts secondary to infectious complication or any other medical conditions were not eligible for resuming eltrombopag treatment. Patients with late relapses (i.e., > 6 months from eltrombopag discontinuation) at time of cyclosporine tapering or discontinuation were also ineligible for re-introduction of eltrombopag in the trial.

Eltrombopag dose could be interrupted when clinically indicated at the discretion of the investigator. Interruptions were not reported as deviations; however, when the interruption was a consequence to a serious adverse event (SAE), the interruption was reported.

Supportive Care

All patients received antimicrobial and antifungal prophylaxis according to their institution's standard practice. Antibacterial and antifungal agents were administered throughout the study whenever ANC was less than 0.5×10^9/L. An antifungal drug active on mould infections (i.e., invasive fungal infections) was included (e.g., posaconazole or voriconazole). Prophylaxis against pneumocystis jirovecii was performed by

trimetoprim-sulphamethoxazole twice daily 3 times per week, until CD4+ lymphocytes exceeded 250/μL. All patients received antiviral prophylaxis by daily oral valacyclovir. Anti-cytomegalovirus (CMV) prophylaxis was not administered routinely. However, monitoring of CMV viremia and subsequent pre-emptive treatment by valganciclovir or other agents was allowed.

Although G-CSF was not used routinely in the patients during the trial, its use was permitted in particular clinical conditions such as infectious complications in patients with severe neutropenia, when at the judgment of the investigator G-CSF would be considered beneficial. Red blood cell and platelet transfusions were given according to standard practice at the investigator's discretion. Generally, red cell transfusions were given to maintain hemoglobin levels greater than 8 g/dL, or in case of clinically significant symptoms; platelet transfusions were given when platelets were less than 10×10^9/L, or regardless of platelet count in case of bleeding episodes.

Subsequent Therapy

Treatment was considered to have failed if patients did not have complete or partial response at 6 months from randomization, and these patients were eligible for additional treatments. Second-line treatment including bone marrow transplant was chosen at the discretion of the investigator and was not prescribed as per protocol.

Outcomes

The efficacy end points identified in the CADTH review protocol that were assessed in the RACE trial are summarized as follows.

The primary end point of the RACE trial was hematologic complete response at 3 months. The key secondary end points were overall response, time to first response, best response and complete response, overall survival, event-free survival, relapse, clonal evolution, hemolytic paroxysmal nocturnal hemoglobinuria, discontinuation of immunosuppression, and HRQoL.

Hematological response was assessed at 3, 6, 12, 18, and 24 months from treatment initiation; hematological response had to be demonstrated by a minimum of 3 determinations over a period of at least 2 weeks, starting at least 2 weeks after last transfusion. Hematological response was classified as complete, partial, or no response.

- Complete response was defined by a hemoglobin level greater than 10 g/dL, ANC greater than 1.0 G/L, and platelet count greater than 100 G/L.
- Partial response was defined as no longer meeting the criteria for SAA and transfusion independency, with hemoglobin levels greater than 8 g/dL, ANC greater than 0.5 G/L, and a platelet count greater than 20 G/L.
- Overall response was defined as the proportion of patients who had a partial or complete response.
- Patients who died without complete response were considered to be nonresponders at 3 months. At 6 months, cases who had experienced HSCT, clonal evolution, or death were considered nonresponders.

Time to first response was defined as time from treatment initiation (day 1) until the first assessment of partial or complete response confirmed in at least 3 consecutive determinations.

Event-free survival was defined as time from treatment initiation to either relapse (i.e., decreased blood counts resulting in a need for transfusion or to reinstate IST or HSCT), death, treatment failure, or clonal evolution (i.e., acute leukemia, MDS, and/or new karyotypic abnormality indicative of myeloid malignancy), whichever occurs first, censoring observations at last follow-up for patients who were alive and event-free.

Overall survival was defined as the time from treatment initiation (day 1) until death; observations were censored for patients alive at last follow-up.

HRQoL was assessed via patient self-report using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-30) questionnaire. The 30 questions cover: global health status or quality of life (QoL), 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea or vomiting, and pain) and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties due to treatment or illness). QoL assessment in the RACE trial focused on the following 9 scales: global health status or QoL, all 5 functional scales, 2 symptom scales (fatigue and pain), and 1 single item (financial difficulties). Total scores range from 0 to 100, with higher scores corresponding to better HRQoL. HRQoL was assessed at baseline and at 6, 12, and 24 months after randomization.

All AEs and SAEs that occurred between the first trial-related procedure (i.e., screening) until the last follow-up visit (or after this date, if the investigator considered the event to be related to the trial treatment) were recorded. SAEs were defined as any untoward medical occurrences or effects in a patient treated on a trial protocol, which do not necessarily have a causal relationship with the trial treatment (or medication error, or misuse or abuse of medicinal product), and which also — at any dose — result in death, are life-threatening, are a cancer, result in persistent or significant disability or incapacity, require inpatient hospitalization or prolong existing hospitalization, result in congenital anomaly or birth defect, or are otherwise medically significant (i.e., all accidental or intentional overdoses whether they result in an AE or not, or any events that the investigator considers significant but are not included in the preceding list). Severe infectious complications and liver abnormalities (liver enzyme values) were of special interest in the trial and were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria version 4[9] for severity grading. According to the protocol, serum alanine transaminase (ALT), aspartate aminotransferase (AST), and bilirubin were to be measured before initiation of eltrombopag, every 2 weeks during the dose adjustment phase, and monthly following establishment of a stable dose.

Statistical Analysis

The study was designed to test the superiority of eltrombopag in combination with IST relative to IST alone. Complete response rate after standard IST was estimated to be below 10%. The sample size was calculated on the hypothesis that the experimental arm would increase the 3-month response rate up to 21% (or 3-fold, based on the 7% reported in a previous study).[10] The estimated sample size was calculated to be 192 patients (96 per treatment arm) to achieve 80% power to reject the null hypothesis at an alpha of 5%. The

sample size was increased by 4% to a total number of 200 patients (100 per treatment arm) to compensate for patients that could not be evaluated.

All efficacy end point analyses were based on the intent-to-treat (ITT) population comparing randomized groups, regardless of actual treatment administered and adherence. The cut-off date for analysis was March 1, 2020. There was no control for multiple testing. The primary end point of the study, which was the proportion of patients who achieved complete response in the first 3 months, was assessed by the Mantel-Haenszel pooled OR (95% CI) with continuity correction, stratified according to the factors used for randomization (age, disease severity, and study centre). Patients who withdrew or were not evaluable at this time point were excluded from the analysis. The following sensitivity analyses were planned to assess the impact of these exclusions: all missing cases imputed as failures, all missing cases imputed as complete responses, all missing experimental group cases imputed as failures, and all missing comparator group cases imputed as complete responses. Complete response at 6 months was assessed with the same method. Overall response was assessed at 3 months and 6 months using generalized linear models with log link, adjusted for age and disease severity, and presented as an RR with 95% CI.

Overall survival and event-free survival were summarized using the Kaplan-Meier curves, with the difference between groups tested using a stratified log-rank test. Patients with missing data for EFS were excluded from the analysis. Sensitivity analyses were planned to assess the impact of these exclusions.

Time-to-event end points with competing risks (i.e., time to first response) were summarized using crude cumulative incidence curves, with the difference between groups tested using Gray's test. Competing events for time to first response were HSCT, additional treatments, malignant clonal evolution, and death. Patients with missing data were excluded and no sensitivity analyses were planned.

Transfusion independence was reported using descriptive statistics. Patients with missing data were excluded from the analysis.

HRQoL data were analyzed by linear mixed models using maximum likelihood estimation to assess changes over time and differences between treatment arms. The models included the fixed effects of the timing and interaction between timing and treatment group, and the random effect of the individual patient (to account for the association between repeated measurements in the same patient). The analysis included the assumption that patients with missing data are missing at random.

The population for safety end points included all cases except one, who did not start the assigned protocol treatment. Safety end points were reported using descriptive statistics. Formal statistical comparison was performed for severe infectious complications and liver abnormalities, considering grade 3 to 5 events occurring during the first 6 months or until the occurrence of stem cell transplant, clonal evolution, relapse, or death, testing the rate ratios by Poisson-based exact methods.

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparators

The RACE trial was powered to examine the superiority of IST and eltrombopag over IST alone for the primary end point of hematologic complete response at 3 months in previously untreated patients with SAA. The trial was open-label, although patient blinding would not have been feasible given the differences in the 2 study treatment regimens. Nonetheless, bias resulting from lack of blinding of patients and investigators to assigned study treatments cannot be ruled out. For example, knowledge of treatments by study investigators could have resulted in different concomitant supportive care being offered to patients in the 2 treatment arms. Patients who did not have complete or partial response at 6 months were eligible for additional treatment at the discretion of the investigator. Approximately 40% of patients in the IST arm went on to receive eltrombopag. Other treatment regimens including HSCT were balanced between treatment arms. The additional line of treatment, particularly with eltrombopag could affect long-term outcomes including event-free survival and overall survival, and minimize observed differences between treatment arms.

The open-label design may have introduced bias in measurement of some outcomes. For example, a patient's knowledge of their assigned treatment may have affected some safety end points and subjective patient-reported outcomes (e.g., HRQoL). The primary end point of hematologic complete response at 3 months and some other key end points — including overall response, transfusion independence, and time to first response — were lab-based objective measures, which were unlikely to be affected by the open-label design.

Selection, Allocation, and Disposition of Patients

Patients were randomized 1:1 using appropriate methods to achieve prognostic balance and conceal allocation until group assignment. Reported baseline characteristics were balanced between treatment arms, suggesting that the randomization was successful.

Details of patient disposition were not reported in the trial publication, including number of patients that discontinued treatment but remained in the study. Reasons for discontinuation of eltrombopag in the IST plus eltrombopag arm were provided.

Outcome Measures

The measurement of hematologic response at 3 months and 6 months are reasonable in this setting. All important outcomes identified in the CADTH protocol were included in the trial. Results for all outcomes outlined in the trial protocol were reported, which minimizes concern regarding selective reporting of outcomes. Harms outcomes were reported only as number of occurrences rather than as numbers and proportions of patients with AEs, which does not allow a full comparison of harms results between treatment arms. Although the EORTC QLQ-30 is a widely used instrument to measure HRQoL, it was designed for use in cancer patients, and its validity, reliability, and responsiveness to change in patients with SAA are uncertain. Of note, attrition and sample size for HRQoL assessment at different time points were not reported; it is not clear whether the missing at random assumption would be reasonable.

Statistical Analysis

Several analyses that were planned were not performed or presented, and some between-group differences were not reported. This is an important limitation, as without confidence intervals it is difficult to understand the potential precision of between-group differences and draw well-informed conclusions. In addition, missing data and attrition in the trial may impact the internal validity of the evidence. The robustness of results cannot be confirmed because results of all of the sensitivity analyses to explore the robustness of the missing data assumptions were not presented. The number of missing assessments for key outcomes was not reported in the trial publication; therefore, that risk of attrition bias cannot be ruled out. The statistical analysis of the primary end point was appropriate. However, there was a lack of comparative effect estimates for secondary efficacy outcomes. The analysis of HRQoL using mixed effects models assessing changes over time was appropriate.

External Validity

Patient Selection

The inclusion and exclusion criteria were deemed clinically relevant and reasonable by CADTH's clinical experts. However, the clinical experts noted that eligibility for sibling stem cell transplant as an exclusion criterion does not reflect clinical practice, especially for patients older than 30 to 40 years, as stem cell transplant is not a preferred front-line therapy for this age group. These patients would in fact be good candidates for IST in clinical practice. In addition, patients with prior malignancies (who were excluded from the trial) might be considered for treatment with IST and eltrombopag on a case-by-case basis.

Treatment Regimen and Length of Follow-Up

The administration of IST and eltrombopag in the RACE trial was consistent with common practice. The clinical experts noted that eltrombopag may be started on day 1 at some centres instead of day 14, which was the case in the RACE trial. In addition, it was noted that some centres may use hATG at 15 mg/kg of body weight over 5 days.

The duration of treatment in the trial was consistent with experience from clinical practice, based on the input from clinical experts. The supportive care and co-interventions (infection prophylaxis and G-CSF) were consistent with common clinical practice. Length of follow-up as related to assessment of outcomes was also consistent with clinical practice. Follow-up may not have been sufficiently long to determine long-term efficacy (e.g., duration of response and overall survival), and harms (e.g., malignancy). Follow-up of patients in the RACE trial outside of protocol is currently ongoing, which mirrors regular follow-up in clinical practice.

Outcome Measures

The clinical experts consulted by CADTH considered the trial outcomes clinically meaningful. Hematologic response in clinical practice is measured at similar time points to the trial (i.e., 3 months and 6 months, and longer). Outcomes that are important to patients were also included (e.g., HRQoL).

Some harms outcomes of special interest indicated by CADTH's clinical experts (e.g., presence and progression of cataracts and thrombocytosis or thromboembolism) were not reported.

Results of the Included Study

Baseline Characteristics

Baseline characteristics were balanced between treatment arms. The median age was 53 years (52 years in the IST arm and 55 years in the IST plus eltrombopag arm), and 55% of the patients were male while 45% were female. Overall, 66% of patients had SAA, and 34% had vSAA. The median follow-up among patients in both treatment arms was 24 months (95% CI, 23 to 24).

Patient Disposition

A total of 285 patients were assessed for eligibility; 202 met eligibility criteria and were randomized. Five patients were found to be misdiagnosed (2 had moderate aplastic anemia, 1 had AML, and 2 had MDS). The analysis set consisted of 197 patients; 101 patients were randomized to the IST arm, and 96 were randomized to the eltrombopag arm.

One patient in the IST arm who died prematurely did not begin to receive hATG according to the protocol; all other patients received hATG. Six patients (3 per arm) had an interrupted course of hATG because of safety reasons or the physician's decision. Cyclosporine was permanently discontinued within the first 6 months in 18 patients (11 in the IST arm and 7 in the IST plus eltrombopag arm), mainly because of renal toxicity. All patients who were randomly assigned to the IST plus eltrombopag arm received eltrombopag, which was discontinued before 6 months in 10 patients.

Subsequent Therapy

Some patients received additional treatment after first-line treatment during the trial. In the second line, additional treatments included eltrombopag (42 patients in the IST arm and 22 patients in the IST plus eltrombopag arm), androgens (1 patient in the IST plus eltrombopag arm), transplant (8 patients in the IST arm and 11 patients in the IST plus eltrombopag arm), and other immunosuppressive regimens (2 patients in the IST plus eltrombopag arm). Third-line treatments included eltrombopag (10 patients in the IST arm and 3 patients in the IST plus eltrombopag arm), ATG (1 patient in the IST plus eltrombopag arm), androgens (3 patient in the IST arm and 1 patient in the IST plus eltrombopag arm), and transplant (2 patients in the IST arm). In the fourth line and beyond, in the IST arm, 1 patient received eltrombopag, 3 patients received androgens, and 2 patients underwent transplant. In the IST plus eltrombopag arm, 1 patient received androgens.

A total of 23 patients underwent allo-HSCT (12 in the IST arm and 11 in the IST plus eltrombopag arm). The median age of patients who went on to HSCT was 36 years in the IST arm and 47 years in the IST plus eltrombopag arm. The median time from randomization to HSCT was 7.2 months in the IST arm and 9.0 months in the IST plus eltrombopag arm.

Table 6: Baseline Patient Characteristics – RACE Trial

Characteristic	IST (N = 101)	IST + EPAG (N = 96)	All patients (N = 197)
Follow-up (months)			
Median (95% CI)	24 (23 to 24)	23 (19 to 24)	24 (23 to 24)
Age (years)			
Median (range)	52 (18 to 81)	55 (16 to 77)	53 (15 to 81)
Age category, n (%)			
≥ 15 years to < 18 years	7 (7)	2 (2)	9 (5)
≥ 18 years to < 40 years	29 (29)	27 (28)	56 (28)
≥ 40 years to < 65 years	43 (43)	43 (45)	86 (44)
≥ 65 years	22 (22)	24 (25)	46 (23)
Sex, n (%)			
Male	52 (52)	56 (58)	108 (55)
Female	49 (48)	40 (42)	89 (45)
Severity of aplastic anemia, n (%)			
Severe	67 (66)	62 (65)	129 (66)
Very severe	34 (34)	34 (35)	68 (34)
Laboratory values			
GPI-deficient neutrophils ≥ 1.0%, n of total n (%)	44 of 100 (44)	33 of 93 (36)	77 of 193 (40)
Reticulocyte count per mm^3			
Median (IQR)	20,000 (8,900 to 36,000)	23,300 (12,000 to 46,800)	21,000 (10,000 to 38,000)
Neutrophil count per mm^3			
Median (IQR)	300 (100 to 700)	500 (100 to 1,000)	400 (100 to 800)
Lymphocyte count per mm^3			
Median (IQR)	1,400 (1,000 to 1,800)	1,400 (1,000 to 1,700)	1,400 (1,000 to 1,800)
Platelet count per mm^3			
Median (IQR)	18,000 (10,000 to 32,000)	15,000 (10,000 to 29,000)	17,000 (10,000 to 30,000)
Cytogenetic abnormalities, n of total n (%)			
Normal	64 of 86 (74)	61 of 84 (73)	125 of 170 (74)
Abnormal karyotype[1]	7 of 86 (8)	6 of 84 (7)	13 of 170 (8)
Karyotype analysis failed	15 of 86 (17)	17 of 84 (20)	32 of 170 (19)

Characteristic	IST (N = 101)	IST + EPAG (N = 96)	All patients (N = 197)
Somatic myeloid mutations, n of patients out of total n evaluated (%)	23 of 78 (29)	24 of 78 (31)	47 of 156 (30)

CI = confidence interval; EPAG = eltrombopag; GPI = glycophosphatidylinositol; IQR = interquartile range; IST = immunosuppressive therapy.

[1]The category of abnormal karyotype included 7 patients with deletion Y (3 in group A and 4 in group B), 2 patients with trisomy 8 in group A, 1 patient with deletion 20q in group B, and 3 patients (1 in group A and 2 in group B) with other abnormalities.

[2]In 41 patients, mutations were missing at baseline for the following reasons: 9 minors (< 18 years) could not be included according to the King's College London Haemato-Oncology Tissue Bank policy, 8 patients did not consent to biosampling, 2 samples were lost during transit to the central laboratory, and 22 samples were not included for other reasons, mainly because the analysis had not been performed at the time of data lock.

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Efficacy Results

Only those efficacy outcomes identified as relevant in the review protocol are reported below.

Overall Response

The overall response rate at 3 months was 59% in the IST plus eltrombopag arm and 31% in the IST arm (adjusted RR = 1.97; 95% CI, 1.44 to 2.69). At 6 months, the overall response was 41% in the IST arm (adjusted RR = 1.71; 95% CI, 1.33 to 2.21) (Table 7).

Of the 70 patients in the IST arm who did not have a response at 3 months, 14 patients (20%) had an overall response at 6 months (4 had a complete response, and 10 had a partial response). Of the 39 patients in the IST plus eltrombopag arm who did not have a response at 3 months, 11 patients (28%) had an overall response at 6 months (4 had a complete response, and 7 had a partial response). Between-group differences were not reported.

Hematologic Response at 3 Months and at 6 Months

At 3 months, 10% of patients in the IST arm and 22% of patients in the IST plus eltrombopag arm had a complete response (OR = 3.2; 95% CI, 1.3 to 7.8; P = 0.01) (Table 7). The results of prespecified sensitivity analyses were not presented; however, additional analyses using alternative models were used to verify the robustness of the findings given sparse strata. The findings of these analyses generally aligned with the main analysis. At 6 months, 20% of patients in the IST arm and 32% of patients in the IST plus eltrombopag arm had a complete response. At 12 months, the complete response rate was 33% in the IST arm and 52% in the IST plus eltrombopag arm (Figure 2).

Table 7: Hematologic Response

Cohort and response	Response at 3 months		Response at 6 months	
	IST (N = 101)	IST + EPAG (N = 96)	IST (N = 101)	IST + EPAG (N = 95)[1]
All patients, n (%)				
Complete response[2]	10 (10)	21 (22)	20 (20)	30 (32)
OR (95% CI), P value[3]	3.2 (1.3 to 7.8),[1] P = 0.01		—	—
RR (95% CI)[4]	2.21 (1.11 to 4.37)		1.68 (1.05 to 2.68)	
Partial response	21 (21)	36 (38)	21 (21)	35 (37)
No response	70 (69)	39 (41)	60 (59)	30 (32)
Overall response[5]	31 (31)	57 (59)	41 (41)	65 (68)
RR (95% CI)[4]	1.97 (1.44 to 2.69)		1.71 (1.33 to 2.21)	

CI = confidence interval; EPAG = eltrombopag; IST = immunosuppressive therapy; OR = odds ratio; RR = risk ratio; vs. = versus.

[1]One patient in the IST + EPAG arm did not have follow-up to the 6-month evaluation and did not have a competing event at the last follow-up.

[2]At 6 months, 4 of the patients who had had a complete response at 3 months (1 patient in the IST arm and 3 patients in the IST + EPAG arm) had loss of response (i.e., they moved from complete response to no response) and 7 patients (all in the IST + EPAG arm) had a downgrade in response from complete response to partial response.

[3]The ORs for the IST + EPAG arm compared with IST arm and 95% CIs were obtained using a Mantel-Haenszel test, stratified according to the factors used at randomization (age, severity of aplastic anemia, and centre).

[4]Adjusted rates were computed using generalized linear models with log link; adjustment factors were age (15 years to 40 years vs. 40 years and older) and disease severity (severe vs. very severe).

[5]The overall response corresponded to the percentage of patients who had a partial or complete response.

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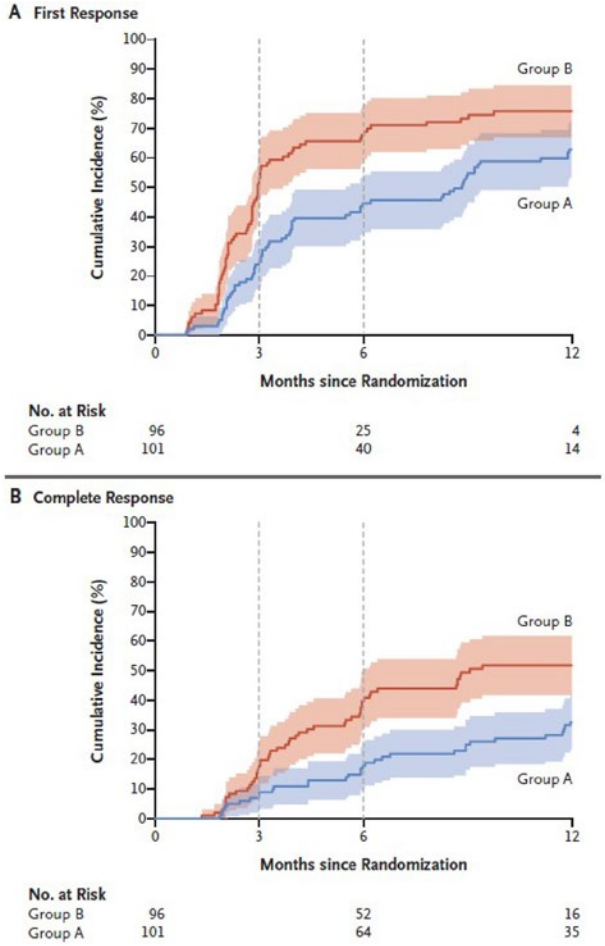
Transfusion Independence

Among the patients who had a response (n = 106), the median time to platelet transfusion independence was 68 days (IQR, 34 to 151) in the IST arm and 40 days (IQR, 20 to 80) in the IST plus eltrombopag arm. The median time to red cell transfusion independence was 140 days (IQR, 62 to 252) in the IST arm and 51 days (IQR, 23 to 122) in the IST plus eltrombopag arm.

Time to First Response

The median time to first response was 8.8 months in the IST arm and 3.0 months in the IST plus eltrombopag arm. The between-group difference and results of planned statistical tests were not reported.

Figure 2: Kinetics of Hematologic Response



EPAG = eltrombopag; IST = immunosuppressive therapy; No. = number.

Note: Group A = IST; group B = IST + EPAG.

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Event-Free Survival

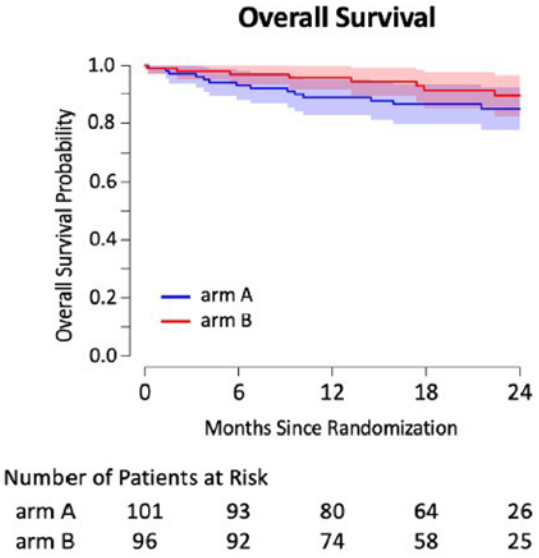
Event-free survival at 2 years was 34% (95% CI, 24 to 44) in the IST arm and 46% (95% CI, 36 to 57) in the IST plus eltrombopag arm. The most common treatment failure event was no response in the IST arm, and no response and use of additional treatment in the IST plus eltrombopag arm. The between-group difference and results of planned statistical tests were not reported. The results of preplanned sensitivity analyses to assess the impact of missing data were not reported.

Overall Survival

At 6 months, the probability of overall survival was 93.1% (95% CI, 88.1% to 98.0%) in the IST arm and 96.9% (95% CI, 93.4% to 100.0%) in the IST plus eltrombopag arm. At 12 months, the probability of overall survival was 88.9% (95% CI, 82.8% to 95.1%) in the IST arm and 95.7% (95% CI, 91.6% to 99.8%) in the IST plus

eltrombopag arm. At 24 months, the probability of overall survival was 85.0% (95% CI, 77.7% to 92.4%) in the IST arm and 89.5% (95% CI, 82.4% to 96.6%) in the IST plus eltrombopag arm (Figure 3). Between-group differences and planned statistical tests for each time point were not reported. The results of preplanned sensitivity analyses to assess the impact of missing data were not reported.

Figure 3: Overall Survival



EPAG = eltrombopag; IST = immunosuppressive therapy.

Note: Arm A = IST, arm B = IST + EPAG.

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Health-Related Quality of Life

Median scores for global health status in the IST plus eltrombopag arm were 58.3 (IRQ, 33.3 to 75.0) at baseline, 66.7 (IQR, 58.3 to 83.3) at 6 months, 75.0 (IQR, 58.3 to 83.3) at 12 months, and 83.3 (IQR, 66.7 to 91.7) at 24 months. In the IST group, the median scores for global health status were 50.0 (IQR, 33.3 to 66.7) at baseline, 66.7 (IQR, 50.0 to 83.3) at 6 months, 75.0 (IQR, 66.7 to 83.3) at 12 months, and 75.0 (IQR, 62.5 to 83.3) at 24 months. Between-group differences and results of statistical tests for each time point were not reported, but the authors reported “no difference” in the trend between arms.

Harms Results

Only those harms identified in the review protocol are reported subsequently.

Adverse Events

A total of 1,819 events occurred in the IST arm and 1,480 events occurred in the IST plus eltrombopag arm. The most common AEs reported as system organ class AEs were gastrointestinal disorders (306 events in the IST arm and 273 events in the IST plus eltrombopag arm), general disorders and administration site

conditions (194 events in the IST arm and 161 events in the IST plus eltrombopag arm), and infections and infestations (215 events in the IST arm and 177 events in the IST plus eltrombopag arm) (Table 8).

Serious Adverse Events

A total of 291 and 239 grade 3 or higher AEs were reported in the IST and IST plus eltrombopag arms, respectively. The most common grade 3 or higher AE in both arms was infections and infestations (76 events in the IST arm and 63 events in the IST plus eltrombopag arm) (Table 9).

Withdrawals Due to Adverse Events

Reasons for eltrombopag discontinuation in the first 6 months among patients in the IST plus eltrombopag arm included pulmonary embolism (1 patient, 1.0%), increase in reticulin deposition in the bone marrow (2 patients, 2.1%), elevated liver enzyme levels (4 patients, 4.1%), rhabdomyolysis (1 patient, 1.0%), skin toxidermia (1 patient, 1.0%) and cytomegalovirus infection (1 patient, 1.0%).

Mortality

Twenty-two patients died during the trial (14 patients in the IST arm and 8 in the IST plus eltrombopag arm). A total of 13 patients died due to infections (9 in the IST arm and 4 in the IST plus eltrombopag arm). Two patients in the IST arm died due to bleeding. Other causes of death in the IST arm were lung cancer (n = 1), encephalopathy of unknown origin (n = 1), and transplant-related mortality (n = 1). Other causes of death in the IST plus eltrombopag arm were acute respiratory distress syndrome of unknown origin (n = 1), aortic valve disease (n = 1), cardiac tamponade (n = 1), and thrombosis (n = 1).

Table 8: Any AEs

System organ class AE	IST	IST + EPAG	Total
Blood and lymphatic system disorders	68	64	132
Cardiac disorders	30	21	51
Ear and labyrinth disorders	25	9	34
Endocrine disorders	20	8	28
Eye disorders	43	36	79
Gastrointestinal disorders	306	273	579
General disorders and administration site conditions	194	161	355
Hepatobiliary disorders	42	34	76
Immune system disorders	27	17	44
Infections and infestations	215	177	392
Injury, poisoning, and procedural complications	12	15	27
Investigations	127	112	239
Metabolism and nutrition disorders	63	47	110

System organ class AE	IST	IST + EPAG	Total
Musculoskeletal and connective tissue disorders	116	100	216
Neoplasms benign, malignant and unspecified (including cysts and polyps)	9	3	12
Nervous system disorders	142	82	224
Psychiatric disorders	27	20	47
Renal and urinary disorders	68	64	132
Reproductive system and breast disorders	18	13	31
Respiratory, thoracic, and mediastinal disorders	101	64	165
Skin and subcutaneous tissue disorders	108	105	213
Social circumstances	1	0	1
Surgical and medical procedures	8	8	16
Vascular disorders	49	47	96
Total	1,819	1,480	3,299

AE = adverse event; EPAG = eltrombopag; IST = immunosuppressive therapy.

Note: All safety data are from date of randomization to the cut-off date of March 1, 2020. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4).

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Table 9: Grade 3 or Higher AEs

System organ class AE	IST	IST + EPAG	Total
Blood and lymphatic system disorders	38	33	71
Cardiac disorders	7	6	13
Ear and labyrinth disorders	2	0	2
Endocrine disorders	0	1	1
Eye disorders	1	2	3
Gastrointestinal disorders	8	24	32
General disorders and administration site conditions	19	20	39
Hepatobiliary disorders	17	7	24
Immune system disorders	10	4	14
Infections and infestations	76	63	139
Investigations	29	20	49
Metabolism and nutrition disorders	14	6	20
Musculoskeletal and connective tissue disorders	8	7	15

System organ class AE	IST	IST + EPAG	Total
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5	1	6
Nervous system disorders	8	9	17
Psychiatric disorders	3	1	4
Renal and urinary disorders	10	6	16
Respiratory, thoracic, and mediastinal disorders	8	9	17
Skin and subcutaneous tissue disorders	9	5	14
Social circumstances	1	0	1
Surgical and medical procedures	4	5	9
Vascular disorders	14	10	24
Total	291	239	530

AE = adverse event; EPAG = eltrombopag; IST = immunosuppressive therapy.

Note: Grade 3 or higher AEs from date of randomization to the cut-off date of March 1, 2020. Events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4).

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Harms of Special Interest

Elevated Liver Enzymes and Bilirubin

The study reported the occurrence of "liver issues." The proportion of patients with elevated liver enzymes was not reported in the study publication. Twelve patients (12.0%) in the IST arm and 11 patients (11.5%) in the IST plus eltrombopag arm had 1 grade 3 or higher occurrence of liver issues from treatment initiation. Five patients (5.0%) in the IST arm and 2 patients (2.1%) in the IST plus eltrombopag arm had 2 liver issues. One patient (0.5%) in the IST plus eltrombopag arm had 4 liver issues and 1 patient (1.0%) in the IST arm had 5 liver issues. The incidence rates of grade 3 to 5 liver issues in the first 6 months from treatment initiation or until the occurrence of relapse, transplant, malignant clonal evolution, or death were 0.41 in the IST plus eltrombopag arm versus 0.57 in the IST arm (rates in person-years) (RR = 0.71; 95% CI, 0.37 to 1.33).

Presence of Cataracts or Progressive Cataracts

Overall, 79 occurrences of eye disorders were reported in the trial (43 in the IST arm and 36 in the IST plus eltrombopag arm). The number of patients with cataracts specifically was not reported.

Uncontrolled Thrombocytosis or Thromboembolism

The number of thrombocytosis or thromboembolism events was not reported.

Myeloid Malignancies Including Clonal Evolution of Cytogenetic Abnormalities

During the disease course, the frequency of mutations in patients increased from approximately 30% in both treatment arms at baseline to 66% in the IST arm and 55% in the IST plus eltrombopag arm at 6 months, and to 77% and 52%, respectively, at 24 months. Irrespective of baseline mutations, at 6 months, new or additional mutations were acquired in 30 patients (53%) in the IST arm and in 22 patients (39%) in the IST

plus eltrombopag arm. At 24 months, new or additional mutations were acquired in 16 patients (62%) in the IST arm and in 6 patients (27%) in the IST plus eltrombopag arm.

Development of Reticulin Fibrosis in the Marrow

At 6 months, 2 out of 70 evaluable patients in the IST arm and 8 out of 73 evaluable patients in the IST plus eltrombopag arm had reticulin fibrosis. At 24 months, 6 out of 43 evaluable patients in the IST arm and 4 out of 42 evaluable patients in the IST plus eltrombopag arm had reticulin fibrosis.

Table 10: Summary of Harms Outcomes in the RACE Trial

Outcome	IST	IST + EPAG
Number of AEs	1,819	1,480
Number of AEs – grade 3 to 5	291	239
Deaths, n	14	8
Causes of death, n		
Infection	9	4
Bleeding	2	0
Other	3	4
Lung cancer	1	0
Encephalopathy of unknown origin	1	0
Acute respiratory distress syndrome of unknown origin	0	1
Aortic valve disease	0	1
Cardiac tamponade	0	1
Thrombosis	0	1
Transplant-related mortality	1	0

AE = adverse event; EPAG = eltrombopag; IST = immunosuppressive therapy.

From New England Journal of Medicine, Peffault de Latour et al., Eltrombopag Added to Immunosuppression in Severe Aplastic Anemia, 386., 11 to 23. Copyright (2022) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[5]

Indirect Evidence

A total of 23 references were identified from the ITC search. After title and abstract screening, none met the selection criteria to be included for full-text review. No ITCs were included in this review.

Other Relevant Evidence

No other evidence relevant to this review was identified.

Economic Evidence

As this review is part of the CADTH Nonsponsored Reimbursement Review program, in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for eltrombopag in

combination with IST in SAA. As a result, the economic review consists only of a cost comparison for eltrombopag plus IST compared with IST alone.

CADTH Analyses

The comparators presented in Table 11 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on clinical study dosing and treatment centre practice guidelines, and were validated by clinical experts. If discrepancies in dosing between the clinical study dosing and Canadian clinical practice were noted, the dose specified by clinical experts was used. Eltrombopag is indicated for adult patients with SAA who have had an insufficient response to IST; first-line therapy is therefore not part of the Health Canada indication.[11,12] Based on Ontario Drug Benefit (ODB) Exceptional Access Program (EAP) and Saskatchewan Formulary list prices accessed in August 2023, 25 mg and 50 mg tablets of eltrombopag (Revolade) are priced at $65 and $130, respectively,[13,14] although the programs' reimbursement criteria for exceptional status drugs did not include reimbursement of eltrombopag for the treatment of SAA at any line of therapy at the time of this review.[15,16] Also in August 2023, a newly marketed generic form of eltrombopag was listed on the ODB formulary as an off-formulary product interchangeable with Revolade, at list prices of $55 and $110 for 25 mg and 50 mg tablets, respectively.[17,18] Pricing for other products was based on publicly available list prices or estimates from the literature.

When used at a dose of 150 mg daily, the cost of eltrombopag plus IST where eltrombopag is used for 6 months and cyclosporine is used for 12 months plus a taper of approximately 10 months, the cost of treatment with the Revolade brand of eltrombopag was $89,543 or $102,674, depending on the hATG regimen used. The cost of treatment for the same regimen, assuming the use of generic eltrombopag was $78,866 or $91,998. The cost of IST alone was $18,368 or $31,499, depending on the hATG regimen used. Note that results may differ by jurisdiction should prices differ from those presented in Table 11.

Table 11: CADTH Cost Comparison Table for SAA

Treatment	Strength or concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Cost per course ($)
Eltrombopag plus IST						
Eltrombopag (Revolade)	25 mg 50 mg	Tablet	65.0000[13,18] 130.0000[13,18]	150 mg daily starting either day 1 or 14, for 3 to 6 months[ab]	390.00	Three months: 35,588 Six months: 71,175
Eltrombopag (generic)	25 mg 50 mg	Tablet	55.2500[c] 110.5000[c]		331.50	Three months: 30,249 Six months: 60,499
hATG (ATGAM)	50 mg/mL	5 mL ampoules	486.3600[d]	15 mg/kg/day for 5 days[19] OR	2,431.80 per day for 5 days OR	12,159 per 5-day course OR

Treatment	Strength or concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Cost per course ($)
				40 mg/kg/day for 4 days.[5,20]	6,322.68 per day for 4 days	25,291 per 4-day course
Cyclosporine (Neoral, generics)	10 mg 25 mg 50 mg 100 mg	Capsules	0.7115[18] 0.7870[18] 1.5350[18] 3.0720[18]	5 mg/kg/day (rounded to nearest 25 mg) for at least 12 months, then tapered and discontinued by 24 months[5,20]	12.29 during initial 12 months	12 months + 10% taper per month thereafter: 6,209
Eltrombopag (Revolade) plus IST regimen cost per course					3 months of eltrombopag: 53,955 or 67,087 6 months of eltrombopag: 89,543 or 102,674	
Eltrombopag (generic) plus IST regimen cost per course					3 months of eltrombopag: 48,617 or 61,749 6 months of eltrombopag: 78,866 or 91,998	
Immunosuppressive therapy						
hATG (ATGAM)	50 mg/mL	5 mL ampoules	486.3600[d]	15 mg/kg over 6 to 8 hours for 5 days[19] or 40 mg/kg over 12 to 18 hours for 4 days[5,20]	2,431.80 per day for 5 days or 6,322.68 per day for 4 days	12,159 or 25,291
Cyclosporine (Neoral, generics)	10 mg 25 mg 50 mg 100 mg	Capsules	0.7115[18] 0.7870[18] 1.5350[18] 3.0720[18]	5 mg/kg/day (rounded to nearest 25 mg) for at least 12 months, then tapered and discontinued by 24 months[5,20]	12.29 during initial 12 months	12 months + 10% taper per month thereafter: 6,209
Immunosuppressive therapy					18,368 or 31,499	
Transfusions and transplants						
Allogeneic hematopoietic stem cell transplant	Not applicable	Procedure	100,613[e]	Surgical procedure, bone marrow or stem cell transplant	Not applicable	100,613
Packed red blood cells	Not applicable	285 mL unit[21]	801.36[f]	Individualized; 1 to 2 units assumed to be received 2.00 times per month[22,23]	52.69 to 105.38	Three months: 4,808 to 9,616 Six months: 9,616 to 19,232

Treatment	Strength or concentration	Form	Price ($)	Recommended dosage	Daily cost ($)	Cost per course ($)
Platelets	Not applicable	220 mL unit[21]	75 to 450[24]	Individualized; 1 to 2 units assumed to be received 2.64 times per month[22,23]	6.51 to 78.12	Three months: 594 to 7,128 Six months: 1,188 to 14,256

CIHI = Canadian Institute for Health Information; hATG = horse antithymocyte globulin; IST = immunosuppressive therapy; SAA = severe aplastic anemia.

Notes: Costs are drug acquisition costs and do not include dispensing fees, markups, or administration. Calculated costs assume a 365-day year, an 80 kg patient, and wastage of excess medication in vials if applicable. hATG, stem cell transplant, packed red blood cells, and platelets are not funded by Canadian drug plan payers.

ISTs also consist of supportive medications such as corticosteroids, antiemetics, antipyretics, antifungals, antivirals, antimicrobials, granulocyte colony-stimulating factor, etc.[5,19,20] These regimens are not expected to change due to the use of eltrombopag and have thus not been detailed or costed here.

[a]Dosing as per Peffault de Latour et al., 2022.[5] Complete responders received 3 months of eltrombopag, while others received 6 months. This dosing differs from the dosing recommended in the product monograph, which suggests initiation at 50 mg daily for most patients, increasing in 50 mg increments every 2 weeks as necessary to achieve target platelet count ≥ 50 × 10^9/L, maximum 150 mg daily.[11,12] While the Peffault de Latour et al. (2022) trial initiated eltrombopag on day 14 after hATG and cyclosporine treatment began, clinical expert opinion elicited by CADTH indicated that starting eltrombopag as quickly as access can be obtained is ideal (i.e., on day 1). Costing is therefore reflective of eltrombopag initiation on day 1.

[b]According to clinical expert opinion elicited by CADTH, some clinicians initiate eltrombopag at 75 mg daily for patients of Southeast or East Asian descent or those with hepatic impairment, similar to the halving of the dose regimen recommended in the product monograph for such patients.[11,12] Alternatively, also according to clinical expert opinion, all patients may be initiated on 150 mg daily, but monitored for signs of hepatic impairment and reduced 75 mg daily as needed. The cost of eltrombopag 75 mg daily is $17,550 to $35,100 for a 3-month to 6-month supply.

[c]Ontario Drug Benefit formulary off-formulary interchangeable list price (August 2023).[13,18]

[d]Association québécoise des pharmaciens propriétaires (AQPP) list price as reported by IQVIA DeltaPA (August 2023).[17]

[e]Estimate is from CIHI Patient Cost Estimator for Case Mix 610 Bone Marrow/Stem Cell Transplant for adults aged 18 to 59 years, chosen jurisdiction "Canada" from fiscal year 2019 to 2020, accessed June 2023.[25] Originally reported as $87,219, which was then inflated from 2020 to 2023 dollars using the Bank of Canada Inflation Calculator.[26]

[f]Reported as $666.10 in Lagerquist et al. (2017),[27] of which $243.10 was for in-hospital transfusion costs and $423 was for acquisition costs for the blood supplier. Inflated to 2023 dollars using the Bank of Canada Inflation Calculator.[26]

Patients receiving IST also require regular transfusions with packed red blood cells and platelets. Due to uncertainty in the unit cost of these blood products (refer to Table 12), as well as additional uncertainty regarding which aspects of blood product acquisition, delivery, storage, and administration were included within these unit costs; and a lack of information on blood product utilization and duration of use among patients who were not complete or partial responders within the RACE trial,[5] CADTH was unable to undertake a full cost-minimization analysis considering the potential cost offsets associated with the reimbursement of eltrombopag for the first-line treatment of SAA. Evidence from the RACE trial indicated higher rates of complete and partial response among patients receiving eltrombopag plus IST versus IST alone. Further, patients in the RACE trial who were partial or complete responders to eltrombopag plus IST had a shorter time to transfusion independence compared to IST alone (i.e., 89 fewer days and 28 fewer days to independence for red blood cells and platelets, respectively) (Table 12). Therefore, compared to IST alone, the use of eltrombopag may be associated with an estimated median reduction of 5.9 units to 11.7 units of packed red blood cells and 2.4 units to 4.9 units of platelets per responding patient (Table 12). However, even at the highest estimated unit costs found (Table 11), savings to public health care payers associated with reduced blood product use are unlikely to fully offset the cost of eltrombopag.

Table 12: Estimated Blood Product Resource Use Among Patients With SAA Who Had a Complete or Partial Response to Treatment

Treatment	RBC transfusions per month[a]	Time to RBC transfusion independence (days)[b]	Total RBC units per responder[c]	Platelet transfusions per month[a]	Time to platelet transfusion independence (days)[b]	Total platelet units per responder[c]
Eltrombopag plus IST	2.00	51	3.4 to 6.7	2.64	40	3.5 to 6.9
IST alone	2.00	140	9.2 to 18.4	2.64	68	5.9 to 11.8
Incremental	**0**	**−89**	**−5.9 to −11.7**	**0**	**−28**	**−2.4 to −4.9**

IST = immunosuppressive therapy; SAA = severe aplastic anemia; RBC = red blood cell.

[a]Based on the monthly utilization of red blood cells and platelets reported in a budget impact analysis[22] for the IST group. While this publication reported a reduced monthly utilization of blood products for patients using eltrombopag plus IST compared to IST alone, the estimate assumed that blood product utilization with and without eltrombopag would be equivalent to utilization rates reported before and after eltrombopag was introduced to patients with an insufficient response to IST alone.[28] CADTH considered it to be more appropriate and conservative to assume equal monthly utilization between treatment groups when considering eltrombopag as part of first-line therapy for SAA.

[b]Median time to transfusion independence among responders as reported in the RACE trial.[5]

[c]Calculated units assume a 365-day year, where each month is 1/12 of a year. Patients are assumed to receive 1 to 2 units of RBC or platelets with each transfusion, based on clinical expert opinion elicited by CADTH as well as guidance from Using Blood Wisely.[23]

Issues for Consideration

- **Different budget holders:** While the use of eltrombopag would be associated with additional costs from the Canadian drug plan payer perspective (Table 11), the reimbursement of eltrombopag for SAA may reduce the use of blood products (Table 12) as well as associated transfusion time, which, if realized, would result in savings to other budget holders. A reduction in the use of blood products is also relevant given ongoing reports of blood and plasma shortages in Canada.[29] A cost-effectiveness analysis would be required to incorporate the costs and benefits associated with reductions in blood product use. hATG is also not typically funded by Canadian drug payers; however, the reimbursement of eltrombopag is not expected to alter ATG usage.
- **Potential for reduced costs to patients:** According to clinical expert opinion elicited by CADTH, due to the requirement for regular transfusions of packed red blood cell and platelets, patients with SAA who do not live in major centres have to travel (either alone or with a caregiver or family member) to a treatment centre and remain nearby for the duration of their transfusion treatments. This duration may be as long as 6 months, and travel, lodging, and parking expenses are typically at patients' own cost. A reduction in the duration of transfusion therapy could alleviate financial burdens for patients.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on September 5, 2023.

Discussion

Summary of Available Evidence

The RACE trial that forms the evidence base for this review was an investigator-led, open-label, multicentre, phase III RCT conducted across 6 countries in Europe. In this trial, 197 newly diagnosed patients with SAA who were ineligible for upfront allo-HSCT were recruited and randomized 1:1 to either standard IST with hATG and cyclosporine (N = 101), or oral eltrombopag (n = 96) 150 mg daily from day 14 to 6 months in addition to standard IST. The primary end point was hematologic complete response at 3 months and secondary end points included overall response, time to first response, best response and complete response, overall survival, event-free survival, relapse, and HRQoL. The median age of included patients was 53 years, and 55% of the patients were male while 45% were female. Overall, 66% of patients had SAA, and 34% had vSAA. The median follow-up among patients in both treatment arms was 24 months. The long-term follow-up of the patients will be conducted outside of the protocol and is intended to extend up to 10 years from treatment.

Interpretation of Results

Efficacy

In the RACE trial, the addition of eltrombopag to standard IST (hATG and cyclosporine) resulted in improved hematologic complete response and overall responses at 3 months compared to IST alone. At 3 months, 22% of patients who received IST plus eltrombopag had a complete response, compared to 10% of patients who received IST alone. Overall response was 59% and 31% in the IST plus eltrombopag and IST arms, respectively. These results were maintained at 6 months; overall response rate increased to 41% in the IST arm and 68% in the IST plus eltrombopag arm. The small sample size and the fact that some outcomes (e.g., hematologic response) were based on a small number of events somewhat reduce our confidence in the findings. However, this is a common limitation with clinical trials involving rare diseases such as SAA. The clinical experts consulted by CADTH considered these differences in response rates clinically meaningful. They indicated that, in the SAA setting, the response rates observed with eltrombopag addition to IST are compelling because no therapy other than IST, to date, has resulted in such magnitude of response.

The results of other secondary end points appear to be supportive of the primary end point, but without comparative estimates and confidence intervals to assess precision for several of the outcomes, any conclusions based on these end points are uncertain. The median time to first response was shorter for patients treated with combination of IST and eltrombopag than for those treated with IST alone. The faster response rate was accompanied by the achievement of earlier red cell and platelet transfusion independence in the IST plus eltrombopag arm. The clinical experts indicated that these results are considered clinically meaningful by reducing burden of transfusion on patients and the health care system. Event-free survival at 2 years was also better for patients treated with eltrombopag in addition to IST compared to the IST alone (46% versus 34%). However, the addition of eltrombopag to IST did not result in significantly improved overall survival, which may be partly explained by the additional effect of rescue treatment. For example, 42% of patients in the IST arm went on receive eltrombopag during the trial as second-line therapy. Patient-reported HRQoL showed overall improvement in both treatment arms, with no considerable differences between them

suggesting that the addition of eltrombopag to IST is not detrimental to quality of life. However, follow-up duration is not currently sufficiently long to measure long-term efficacy including duration of response, and overall survival.

Harms

AEs and SAEs (grade 3 or higher AEs) were reported as numbers of events for each system organ class. The proportion of patients who experienced at least 1 AE or SAE was not reported. Therefore, although the number of AEs between the 2 treatment arms were largely similar, no comparison of the proportion of patients experiencing AEs can be made. In terms of discontinuation of treatment, 2 patients discontinued eltrombopag because of focal grade 1 reticulin deposition in the trephine biopsy that reversed on discontinuation of eltrombopag which the study investigators considered consistent with the long-term follow-up of the use of a thrombopoietin receptor agonist in immune thrombocytopenia.[5,30]

The clinical experts consulted for this review indicated that the most common AE related to eltrombopag in combination with IST is abnormal liver function; increases in ALT, AST, and bilirubin were observed in previous clinical studies with eltrombopag.[31] The risk of hepatotoxicity was discussed in the trial protocol, and liver function tests were planned at regular intervals during the trial (i.e., every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose). The proportion of patients with liver issues was similar in the 2 treatment arms. Four patients discontinued eltrombopag before 6 months because of elevated liver enzymes. However, it is unclear what these abnormalities were. As with some efficacy outcomes, the current follow-up duration is not sufficiently long to determine long-term harms, such as occurrence of secondary malignancies.

The frequency of mutations was similar in the 2 treatment arms, increasing from approximately 30% at baseline to 66% in the IST arm, and 55% in the IST plus eltrombopag arm at 6 months, and further to 77% and 52%, respectively, at 24 months. The trial reported that baseline or acquired mutations did not correlate with hematologic response or with overall survival, suggesting the emergence of clonal hematopoiesis rather than secondary malignancy. However, the authors noted that, given that time to malignancy is usually 5 years to 10 years after diagnosis and treatment of SAA, the median follow-up of 24 months remains too short to observe potential secondary malignancies. A long-term follow-up of the trial is planned to explore the clinical relevance of oligoclonal hematopoiesis and to evaluate the risk of myeloid malignant transformation, which is expected to appear in 10% to 15% of patients, 5 years to 10 years after diagnosis.[5]

The other 2 AEs of interest specified in this review's protocol (presence of cataracts or progressive cataracts, and uncontrolled thrombocytosis or thromboembolism) were not reported. Some of the cataract events may have been captured in the system organ class of eye disorders, and there were similar number of occurrences in the 2 treatment arms. The clinical experts indicated that presence of cataracts or progressive cataracts, and thrombocytosis and thromboembolism events, are expected to be rare events with the study regimens.

Cost

Based on publicly available list prices and assuming a six-month course of eltrombopag, treatment with eltrombopag plus IST would cost $89,543 or $102,674 per patient when the originator brand of eltrombopag is considered, depending on the hATG regimen used. The cost of treatment for the same regimen, assuming the use of generic eltrombopag was $78,866 or $91,998 per patient. The cost of IST alone was $18,368 or $31,499 per patient, depending on the hATG regimen used. As such, the incremental cost of eltrombopag plus IST compared to IST alone is $71,175 if the originator brand is used, or $60,499 if generic eltrombopag is used. These incremental costs are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug payers.

Conclusions

The results of a single open-label trial (the RACE trial; N = 197) suggest that the addition of eltrombopag to IST with hATG and cyclosporine, as compared with IST alone, resulted in better short-term (3-month and 6-month) hematologic response in previously untreated patients with SAA. Despite important limitations related to the small sample size and limited number of events, as well as lack of comparative estimates for several end points, the gains made in terms of complete response, overall response, and time to first response with the addition of eltrombopag to IST are considered clinically important by the clinical experts. The benefit on important long-term outcomes, including maintenance of response and overall survival, is yet unknown. Although no excess toxicity appears to have been observed with the addition of eltrombopag to IST, a longer follow-up duration is needed to determine late-emerging toxicities, including myeloid malignant transformation, which usually appear 5 years to 10 years after diagnosis. The clinical experts indicated that adding eltrombopag to IST in the front-line setting for patients with SAA would fill an unmet treatment need, given the limited number of treatment options for these patients and the progressive course of the disease.

Results of the cost comparison of treatment costs demonstrate that, assuming a 6-month course of eltrombopag, the incremental cost of eltrombopag plus IST compared with IST alone would be $71,175 if the originator brand of eltrombopag is used, or $60,499 if generic eltrombopag is used. As such, the reimbursement of eltrombopag plus IST for the treatment of first-line treatment of patients with SAA is expected to increase overall treatment costs. Based on the clinical review conclusions, eltrombopag plus IST may provide a clinically important benefit compared to IST alone. As such, eltrombopag plus IST is associated with incremental costs and incremental benefits compared with IST alone. A cost-effectiveness analysis would therefore be required to determine the cost-effectiveness of eltrombopag plus IST compared with IST alone. As a cost-effectiveness analysis was not submitted, the cost-effectiveness of eltrombopag plus IST in comparison with IST alone for the first-line treatment of patients with SAA could not be determined. According to clinical expert feedback elicited by CADTH for this review, based on the differences in time to transfusion independence differences reported in the RACE trial, there may be some savings in blood product resource use with eltrombopag plus IST compared to IST alone. While there is uncertainty in the unit costs of these blood products, the resource use differences are unlikely to fully offset the cost of eltrombopag even at the highest blood product costs identified. To consider this alongside the health care

resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of eltrombopag plus IST would be required.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: June 5, 2023

Alerts: Monthly search updates until project completion

Search filters applied: None

Limits:

- Conference abstracts: Excluded

Table 13: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary

Syntax	Description
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq = #	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multidatabase Strategy

1. (eltrombopag* or revolade* or promacta* or alvaiz* or DDL701 or DDL 701 or SB497 115 or SB 497 115 or SB497115 or SB 497115 or SSS20 or SSS 20 or ETB115 or ETB 115 or S56D65XJ9G).ti,ab,kf,rn,nm,hw,ot.
2. exp Anemia, aplastic/
3. ((aplast* or hypoplast* or hypo plast* or aregenerative) adj2 (anem* or anaem*)).ti,ab,kf.
4. (blood aplasia* or erythroblastopenia* or erythroid hypoplasia* or hypothycemia* or pancytopenia* or paralytic anaemia* or paralytic anemia*).ti,ab,kf.
5. or/2-4
6. and/1,5
7. 6 use medall
8. *Eltrombopag/
9. (eltrombopag* or revolade* or promacta* or alvaiz* or DDL701 or DDL 701 or SB497 115 or SB 497 115 or SB497115 or SB 497115 or SSS20 or SSS 20 or ETB115 or ETB 115).ti,ab,kf,dq,ot.
10. or/8-9
11. exp Aplastic anemia/
12. ((aplast* or hypoplast* or hypo plast* or aregenerative or fanconi) adj2 (anem* or anaem*)).ti,ab,kf,dq.
13. (blood aplasia* or erythroblastopenia* or erythroid hypoplasia* or hypothycemia* or pancytopenia* or paralytic anaemia* or paralytic anemia*).ti,ab,kf,dq.
14. or/11-13

15. and/10,14
16. 15 use oemezd
17. conference abstract.pt.
18. 16 not 17
19. or/7,18
20. remove duplicates from 19

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results eltrombopag, aplastic anemia]

WHO ICTRP

International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials.

[Search terms -- eltrombopag, aplastic anemia]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- eltrombopag, aplastic anemia]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- eltrombopag, aplastic anemia]

EU Clinical Trials Information System

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- eltrombopag, aplastic anemia]

Grey Literature

Search dates: May 23, 2023, to May 31, 2023

Keywords: eltrombopag, aplastic anemia

Limits: None

Updated: Search updated before the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

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