



Rapid policy statement

Eltrombopag as bridging therapy to haematopoietic stem cell transplant in severe or very severe aplastic anaemia during the COVID-19 pandemic (in adults) (RPS 2006)

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[updates since version 2 (published 18 March 2021) are highlighted in **yellow**.]

Summary

In response to the public health emergency posed by coronavirus disease 2019 (COVID-19), NHS England has established a rapid policy development process to aid clinicians in offering best care and advice to patients with or at risk of COVID-19. This document sets out the recommendations for the use of eltrombopag as bridging therapy to haematopoietic stem cell transplant (HSCT) in patients with severe or very severe aplastic anaemia. The European Society for Blood and Marrow Transplantation (EBMT Statement, March 2020) and the American Society of Hematology (ASH Statement, March 2020) have both released statements recommending the use of eltrombopag as bridging treatment for patients with severe or very severe aplastic anaemia during the COVID-19 pandemic.

Commissioning position

Eltrombopag is recommended to be available as a treatment option through routine commissioning as bridging therapy to HSCT or to immunosuppressive therapy with antithymocyte globulin for patients with severe or very severe aplastic anaemia within the criteria set out in this document.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England and NHS Improvement's values. Throughout the development of the policies and processes cited in this document, we have:

- given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

Aplastic anaemia is a rare and serious bone marrow failure disorder causing a high risk of life-threatening bleeding and infections, and requiring frequent hospital admissions. Current definitive treatments for aplastic anaemia are stem cell transplant or immunosuppressive therapy with antithymocyte globulin and/or ciclosporin. Stem cell transplant is a procedure in which a patient receives healthy stem cells to replace damaged stem cells.

Immunosuppressive treatment is where drugs are given to lower the body's immune response. Stem cell transplant and antithymocyte globulin treatment require hospital admission.

The proposed treatment is a drug called eltrombopag with or without ciclosporin.

Eltrombopag helps to improve blood counts, is given as a tablet and can reduce the requirement for stem cell transplant or immunosuppressive therapy, and so reduces the requirement for admission to hospital until patients can receive definitive treatment.

Overview

The condition

Aplastic anaemia is a rare and serious bone marrow failure disorder causing a very high risk of life-threatening bleeding and infections, and requiring frequent hospital admission to treat dangerous infections with prolonged courses of antibiotics and antifungal drugs.

Aplastic anaemia has an incidence of 2.4/million/annum (Montané et al, 2008), accounting for around 158 new cases per annum in the UK. Of these, 62% will have severe or very

severe disease (Vaht et al, 2017), representing around 98 new cases per annum. No prevalence data exists.

Treatment options for severe or very severe aplastic anaemia are:

1. Haematopoietic stem cell transplant (HSCT), which leads to a long-term cure in around 80% of patients.
2. Immunosuppressive therapy with antithymocyte globulin and ciclosporin, which is successful in around 67% of patients, though response to treatment takes around three months.
3. Alternative treatments include some less effective drugs such as anabolic steroids (25% response rate with high risk of liver toxicity) and alemtuzumab (35% response rate with high risk of viral infections).

Intervention

Eltrombopag is a thrombopoietin receptor agonist that binds to and activates the thrombopoietin (TPO) receptor, increasing platelet production. It is given orally, once daily, without the need for admission to hospital, and can be given either alone or in combination with ciclosporin. Eltrombopag is licensed for use in patients with acquired severe aplastic anaemia refractory to immunosuppressive therapy and who are unsuitable for HSCT.

Clinical problem

Due to COVID-19 there is an urgent need to avoid hospitalisation in high-risk patients. Patients with severe or very severe aplastic anaemia would be considered as in a high-risk category. Ideally, patients with severe or very severe aplastic anaemia who do not require urgent HSCT (which requires hospital admission for around four weeks) or immunosuppressive therapy with antithymocyte globulin (which requires hospital admission for around one to two weeks) should be managed at home where possible. The off-label use of eltrombopag with or without ciclosporin could be used as bridging therapy until such time as HSCT or antithymocyte globulin therapy can be more safely undertaken or until determined by the haematology multidisciplinary team (MDT) (as per NG47; NICE, 2016).

Evidence summary

Three papers were presented for review by NHS England:

- Paper 1: a prospective case series of 43 patients who received eltrombopag for refractory severe aplastic anaemia.
- Paper 2: a prospective cohort study of 92 patients who received eltrombopag for previously untreated severe aplastic anaemia.

- Paper 3: a prospective case series of 40 patients who received eltrombopag for refractory severe aplastic anaemia.

Paper 2 states that all patients were evaluated at one centre in the US. None of the three papers specifies the country or setting where patients were treated.

Paper 1 (Desmond et al, 2014): Eltrombopag restores tri-lineage haematopoiesis in refractory severe aplastic anaemia which can be sustained on discontinuation of drug

This paper reports a prospective case series of 43 patients consecutively recruited between July 2009 and February 2013. Number of treatment centres and country were not reported. Patients were aged ≥ 12 years and had severe aplastic anaemia refractory to at least one course of antithymocyte-globulin-based immunosuppressive therapy initiated at least six months previously, and with platelet counts $< 30 \times 10^3/\mu\text{L}$. Patients initially received 50mg eltrombopag daily, which was increased by 25mg every two weeks to a maximum dose of 150mg, if the platelet count had not increased by $20 \times 10^3/\mu\text{L}$. Patients received eltrombopag for three to four months, with those who responded offered the option of continuing eltrombopag. Patients were followed up for a median of 13 months (range 3 to 51 months). Patients continued supportive care with platelet and red blood cell transfusions as required and continuation of ciclosporin was permitted. The authors stated that three patients were on stable doses of ciclosporin throughout the study. However, it is not clear if these were the only patients who received ciclosporin during the study period.

Paper 2 (Townesley et al, 2017): Eltrombopag added to standard immunosuppression for aplastic anaemia

This paper reports a prospective cohort study of 92 patients consecutively recruited between June 2012 and November 2015. Evaluations were performed at one US centre. It is not clear if all patients were treated at this centre. Patients were aged ≥ 2 years and had previously untreated severe aplastic anaemia. Patients received a daily dose of eltrombopag with those aged ≥ 12 years receiving 150mg, those aged six to 11 years receiving 75mg, and those aged two to five years receiving 2.5mg/kg of body weight. Patients of East or Southeast Asian ethnicity received 50% of the eltrombopag dose. Patients were consecutively enrolled to one of three cohorts with the results from the earlier cohorts informing the treatment regimen of subsequent cohorts:

- Cohort 1: antithymocyte globulin from days 1 to 4, followed by eltrombopag from day 14 to six months (n=30).
- Cohort 2: antithymocyte globulin from days 1 to 4, followed by eltrombopag from day 14 to three months (n=31).
- Cohort 3: antithymocyte globulin from days 1 to 4 concurrently with eltrombopag from day 1 to six months (n=31).

All patients received concurrent ciclosporin for six months. Patients were followed up for a median of 703 days (range 84 to 1,422).

Paper 3 (Winkler et al, 2019): Treatment optimisation and genomic outcomes in refractory severe aplastic anaemia treated with eltrombopag

This paper reports a prospective case series of 40 patients. Recruitment details, number of treatment centres and country were not reported. Patients were aged ≥ 2 years and had severe aplastic anaemia refractory to at least one cycle of antithymocyte-globulin with ciclosporin (ATG/CSA), with persistence of multi- or uni-lineage cytopenias¹ for at least six months after initiation of ATG/CSA. Patients received a daily dose of eltrombopag for six months with responders given the option of continuing on eltrombopag. Patients aged ≥ 12 years received 150mg, those aged six to 11 years received 75mg, and those aged two to five years received 2.5mg/kg of body weight. Patients of East or Southeast Asian ethnicity received 50% of the eltrombopag dose. Patients were followed up for a median of 27.5 months (range 3.0 to 46.7). No statement regarding concurrent treatments was provided. It is therefore unclear whether patients received any concurrent treatments. The authors also reported some results for a pooled population that combined the patients from this case series with the 43 patients from the Desmond et al (2014) case series (Paper 1).

Effectiveness

Haematological response

Desmond et al (2014) reported that 17 of 43 patients (40%) had a haematological response² at three to four months. Median time to initial response was 12 weeks (range 8 to 14 weeks). Absolute reticulocyte count was the only statistically significant pre-treatment predictor for response (responders 41.8³ vs non-responders 24.2, $p=0.023$). Fourteen of 17 responders continued to receive eltrombopag for a median of 12 months (range 6 to 37).

Nine of the 17 responders no longer met the criteria for severe aplastic anaemia after receiving eltrombopag for a median of six months (range 3 to 21). The authors also reported that two patients who were non-responders during the initial three to four months continued

¹ Platelet count $<30 \times 10^9/L$ or platelet transfusion dependence, absolute neutrophil count $<0.5 \times 10^9/L$, and/or haemoglobin $<9.0g/dL$ or red blood cell transfusion dependence.

² Defined as uni- or multi-lineage recovery by one or more of the following criteria: (1) platelet response (increase to $20 \times 10^3/\mu L$ above baseline or stable platelet counts with transfusion independence for a minimum of eight weeks in those who were transfusion dependent at study entry); (2) erythroid response (when pre-treatment haemoglobin was $<9g/dL$, defined as a 1.5g/dL increase in haemoglobin or, in transfused patients, a reduction in the units of packed red blood cell transfusions by an absolute number of ≥ 4 transfusions for eight consecutive weeks, compared with the pre-treatment transfusion number in the previous eight weeks); and (3) neutrophil response (when pre-treatment absolute neutrophil count (ANC) of $<0.5 \times 10^3/\mu L$ was at least a 100% increase in ANC, or an ANC increase $>0.5 \times 10^3/\mu L$, and the toxicity profile as measured using Common Terminology Criteria for Adverse Events).

³ Unit of measurement not stated.

to show clinical improvement after discontinuing eltrombopag. Nine of 15 patients who were receiving platelet transfusions became transfusion independent.

Townsley et al (2017) reported the haematological response as complete response⁴ and partial response⁵ at three months and six months for the whole study population (n=92) and the individual cohorts. The authors also combined the number of patients achieving a complete and partial response to give an overall response.

28 of 92 patients (30%, 95%CI 21–40) had a complete response at three months and 36 (39%, 95%CI 29–49) at six months. A partial response was seen for 46 of 92 patients (50%, 95%CI 40 to 60) at three months and 44 (48%, 95%CI 37 to 58) at six months. Combined, this gave an overall response for 74 patients (80%, 95%CI 72–89) at three months and 80 patients (87%, 95%CI 80–94) at six months.

In exploratory analysis, the authors reported that the overall response for patients in this study was statistically significantly higher than the overall response of 66% in a historical cohort of 102 patients who had received ATG/CSA during previous clinical trials (Scheinberg et al, 2009; 2011) conducted by the authors (p<0.001). The authors stated that the demographic and clinical characteristics of the patients in this study were similar to those of the historical cohort.

Haematological responses by cohort are summarised below.

Table 1: Haematological response by cohort (Townsley et al, 2017)

		Cohort 1 (n=30) n (%), 95%CI)	Cohort 2 (n=31) n (%), 95%CI)	Cohort 3 (n=31) n (%), 95%CI)
Complete response	3 months	5 (17%, 3–31)	8 (26%, 9–42)	15 (48%, 30–67)
	6 months	10 (33%, 15–31)	8 (26%, 9–42)	18 (58%, 40–76)
Partial response	3 months	18 (60%, 41–79)	16 (52%, 33–70)	12 (39%, 21–57)
	6 months	14 (47%, 28–66)	19 (61%, 43–79)	11 (35%, 18–53)
Overall response	3 months	23 (77%, 61–93)	24 (77%, 62–93)	27 (87%, 75–100)
	6 months	24 (80%, 65–95)	27 (87%, 75–100)	29 (94%, 84–100)

Among patients who had a response, median time to transfusion independence was 32 days (interquartile range (IQR) 12 to 38) for platelets and 39 days (IQR 10 to 73) for red cells. Eltrombopag was discontinued in 17 patients who reached a platelet count of >200,000/mm³.

⁴ Defined as an absolute neutrophil count of ≥1,000/mm³, a haemoglobin level of ≥10g/dL and a platelet count of ≥100,000/mm³.

⁵ Defined as blood counts that no longer met the criteria for severe aplastic anaemia but did not meet the criteria for complete response.

The authors stated that a longer telomere length of leukocytes at baseline and younger age were the only significant predictors of response.

Winkler et al (2019) reported that 20 of 40 patients (50%) had a haematological response⁶ after 24 weeks of eltrombopag. The authors reported that all responding patients were fully transfusion independent at 24 weeks or soon afterwards. Nineteen of 20 responders continued to receive eltrombopag beyond 24 weeks. Eltrombopag was discontinued in 13 patients who reached robust or stable tri-lineage response criteria⁷ after a median of 11.6 months (range 6.2 to 27.5).

No significant predictors of response at 24 weeks were identified.⁸ The authors also reported a pooled analysis for 40 patients from Winkler et al (2019) and 43 patients from Desmond et al (2014). The pooled analysis identified higher absolute reticulocyte count ($p < 0.022$) and shorter duration from first immunosuppressive therapy to start of eltrombopag ($p < 0.009$) as statistically significant predictors of response at 12 weeks.

Survival

Townsley et al (2017) reported an overall survival rate of 97% (95%CI 94–100) at two years. This was 99% (95%CI 97–100) when data was censored to account for patients who had received a HSCT.

Winkler et al (2019) reported that one patient died from acute myeloid leukaemia during the study period.

Relapse

Townsley et al (2017) reported that 25 of 78 patients who had responded after six months of eltrombopag and ciclosporin later relapsed. Relapse was defined as declining blood counts that warranted the re-introduction of full-dose ciclosporin. The re-institution of full-dose ciclosporin reversed the relapse in 13 of the 25 patients. The addition of eltrombopag in combination with ciclosporin reversed the relapse in an additional 10 patients.

⁶ Defined as improvements in ≥ 1 blood lineages: (1) platelet count increase of $\geq 20 \times 10^9/L$ above baseline, or stable platelet counts with transfusion independence for ≥ 8 consecutive weeks before response assessment in platelet transfusion-dependent patients; (2) haemoglobin increase of $\geq 1.5g/dL$, or for transfusion-dependent patients, a reduction in the units of packed red blood cells transfused by at least 50% during the eight consecutive weeks before response assessment compared with the eight weeks before study entry; and/or (3) $\geq 100\%$ increase in ANC or an ANC $> 0.5 \times 10^9/L$.

⁷ Robust ANC $> 1 \times 10^9/L$, haemoglobin $> 10g/dL$ and platelets $> 50 \times 10^9/L$ for > 8 weeks or stable counts with transfusion independence for > 6 months

⁸ The authors stated the following factors as not predictive of response at 24 weeks: absolute reticulocyte count, absolute neutrophil count, age-adjusted telomere length, time from first and last immunosuppressive therapy, number of rounds of immunosuppressive therapy or presence of $> 1\%$ glycosylphosphatidylinositol-deficient neutrophils.

Winkler et al (2019) (n=40) reported that of 13 responders who had discontinued eltrombopag, five restarted eltrombopag due to falling blood counts a median of 172 days (range 64 to 279) after discontinuation. All five achieved a second response. The authors also reported that an additional patient who had initially responded lost haematological response while still receiving eltrombopag.

Health-related quality of life

Desmond et al (2014) narratively reported no significant difference between baseline and post-treatment physical and mental health scores for 27 patients who completed the SF-36 at three to four months (scores not reported).

Townsley et al (2017) reported that five quality of life assessment scales⁹ were completed by 69 adults. There was a statistically significant improvement from baseline to six months for two of the measures: FACT-N (124.2 ± 20.2 vs 141.8 ± 23.3 , $p=0.0005$) and GPH (43.9 ± 8.1 vs 47.6 ± 7.4 , $p=0.004$). Treatment responders were reported to have significantly higher levels of physical overall health-related quality of life than non-responders at six months (scores not reported).

Clonal evolution¹⁰

Desmond et al (2014) reported that eight of 43 patients developed clonal cytogenetic abnormalities while receiving eltrombopag. Clonal evolution events (not further defined) occurred in six non-responding patients and two responders. Five of these eight patients developed chromosome 7 abnormalities. The authors reported that five of the patients who experienced clonal evolution proceeded immediately to transplant. No predicative factors for clonal evolution were identified.

Townsley et al (2017) reported clonal cytogenetic evolution in seven of 92 patients, defined as a new clonal cytogenetic abnormality or characteristic changes in bone marrow consistent with the myelodysplastic syndrome or acute myeloid leukaemia. This occurred three to six months after treatment in five patients and at 30 months in two patients. Five of the seven patients had lost chromosome 7 and one patient had progressed to acute myeloid leukaemia.

Haemolytic paroxysmal nocturnal haemoglobinuria (PNH) developed in two patients during long-term follow-up. In nine patients, pre-existing PNH clones became undetectable after treatment.

⁹ PROMIS Global Physical (GPH) and Mental (GMH) Health, Functional Assessment of Cancer Therapy-Neutropenia (FACT-N), PROMIS sleep disturbance and applied cognitive abilities.

¹⁰ Clonal evolution is the development of clonal cytogenetic abnormalities with loss of all or part of the long arm of chromosome 7, described as the most frequent and most prognostically ominous abnormality (Winkler et al, 2019).

Winkler et al (2019) reported clonal evolution in seven patients (18%), defined as abnormalities on standard metaphase analysis of bone marrow or overt clinical transformation to myelodysplastic syndromes/acute myeloid leukaemia. All seven patients had complete or partial loss of chromosome 7, detected at 12 weeks in six cases and 24 weeks in one case. Six of these patients were non-responders to eltrombopag. The authors stated that transformation to leukaemia did not occur in any of the patients with cytogenetic evolution. However, one patient (without available cytogenetics) was diagnosed with acute myeloid leukaemia at an outside hospital after receiving eltrombopag for 10 weeks. No predicative factors for clonal evolution were identified.

One patient developed PNH¹¹ at 24 weeks. For eight patients with pre-existing PNH, four had a >20% increase in PNH clone size after six months of eltrombopag, with this plateauing or slightly increasing in the other four.

Safety

Desmond et al (2014) reported that two of 43 patients experienced reversible transaminitis related to treatment. Both patients required treatment interruption after which eltrombopag use continued. The authors reported no significant increase in fibrosis after a median follow-up of 13 months (range 3 to 51 months). The authors also reported no thrombotic events while patients received eltrombopag. However, one patient experienced a lower extremity deep venous thrombosis 14 months after ceasing eltrombopag treatment.

Townsley et al (2017) reported treatment interruption in seven of 92 patients due to transient elevations in liver enzyme levels. Two patients discontinued eltrombopag due to cutaneous eruptions. Adverse events of grade 3 (severe) or higher that were attributed to eltrombopag included liver test abnormality (18%), increased alanine aminotransferase level (10%), increased aspartate aminotransferase level (3%), blood bilirubin increase (13%), abdominal pain (2%), maculopapular rash (2%) and pruritus (1%). The authors reported no increase in the incidence of fibrosis.

Winkler et al (2019) reported that four of 40 patients experienced temporary grade 3 elevations in liver enzyme levels (no further details provided).

¹¹ A PNH clone was considered present if glycosylphosphatidylinositol negative neutrophils exceeded 1% according to flow cytometry.

Implementation

Criteria

Eltrombopag is being suggested as 'bridging' treatment during the COVID-19 pandemic. It should be discontinued when HSCT programmes are recovered following the COVID-19 pandemic.

Use of eltrombopag should be in line with the Summary of Product Characteristics (SPC) where possible (EMC, 2019).

Inclusion criteria

Patients should have a diagnosis of severe or very severe aplastic anaemia and one of the following:

- identified as suitable for HSCT but transplantation should be deferred until the risk associated with COVID-19 has reduced (ie eltrombopag as bridging treatment)¹²
- failed to respond to previous treatment with immunosuppressive drugs (antithymocyte globulin and ciclosporin) and awaiting further treatment with either HSCT or additional immunosuppressive drugs (ie eltrombopag as bridging treatment).¹³

The suitability and use of eltrombopag alone or in combination with ciclosporin should be made by a MDT, including regular review and decisions about continuing planned definitive treatments.

Exclusion criteria

Patients who meet **both** the following criteria are not suitable for bridging treatment with eltrombopag with or without ciclosporin:

- patients for whom HSCT is urgently indicated
- patients for whom immunosuppressive therapy (with antithymocyte globulin) is urgently indicated.

Furthermore, patients who meet any of the following criteria are not suitable for bridging treatment with eltrombopag with or without ciclosporin:

- patients with liver impairment as defined in the SPC
- patients with cytogenetic abnormalities which are recurrent in myelodysplastic syndrome (according to revised WHO 2008 criteria)

¹² Some patients may still require urgent HSCT or immunosuppressive therapy (with antithymocyte globulin) during the COVID-19 pandemic, based on clinical risk assessment (BSBMT&CT Statement, May 2020).

- patients with history or clinical suspicion of constitutional aplastic anaemia
- patients with history of malignant tumour with active disease within five years.

Stopping criteria

If a patient becomes ineligible for HSCT or immunosuppressive therapy with antithymocyte globulin at any time, then bridging treatment with eltrombopag must be tapered and then withdrawn in accordance with standard practice.

Eltrombopag should be tapered and then discontinued if the patient reaches a robust or stable tri-lineage response, including:

- absolute neutrophil count $>1 \times 10^9/L$
- haemoglobin $>10g/dL$
- platelets $>50 \times 10^9/L$
- or stable counts of the above with transfusion independence for >6 months.

Eltrombopag should be tapered and then discontinued if there is no response after six months following MDT discussion.

Patient pathway

Patients may be identified as having aplastic anaemia following blood tests and bone marrow examination after presentation with infection. Definitive, first-line treatment for severe or very severe aplastic anaemia would be HSCT or immunosuppressive therapy; the choice is determined by the MDT (as per NG47; NICE, 2016) and the patient. However, due to the COVID-19 pandemic, admission to hospital is associated with increased risk. Patients can be considered for treatment with eltrombopag with or without ciclosporin as a bridging treatment to HSCT or antithymocyte globulin immunosuppressive therapy if they meet the inclusion and exclusion criteria as described in this policy. Patients may still need to be admitted to hospital to receive blood products or treatment for serious infections, or may still require definitive treatment despite the use of eltrombopag. Continuation of eltrombopag should be subject to periodic review by the haematology MDT. Eltrombopag will be available until HSCT programmes are recovered following the COVID-19 pandemic.

Governance

The MDT will inform the operational delivery networks for blood and marrow transplantation of the decision to defer HSCT and use eltrombopag as bridging treatment to transplantation or immunosuppressive therapy with antithymocyte globulin. This policy is in line with the rapid NICE guideline (NG164, NICE 2020) relating to HSCT during the COVID-19 pandemic.

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Effective from:

This policy will be in effect from the date of publication.

Policy review date

This is a rapid policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. It is the intention that this policy will be reviewed as the context of the COVID-19 pandemic evolves. **This document will be reviewed prior to April 2022.**

Links to other policies

A NICE technology appraisal for eltrombopag for use in severe aplastic anaemia (TA382; NICE, 2016) was terminated as the manufacturer did not submit the required evidence.

A rapid NICE guideline has been developed for the use of HSCT during the COVID-19 pandemic (NG164; NICE, 2020).

The SPC for eltrombopag is available on the Electronic Medicines Compendium (EMC 2019).

Definitions

Bone marrow failure	Failure of the bone marrow (the soft, spongy centre of specific bones) to produce enough healthy blood cells.
Haematopoietic stem cell transplant (HSCT)	A procedure that replaces the patient's own blood stem cells and immune system with those from a healthy donor.
Immunosuppressive therapy	Drugs that weaken the patient's immune system, often because it is not working properly and can attack the body's own tissues.

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