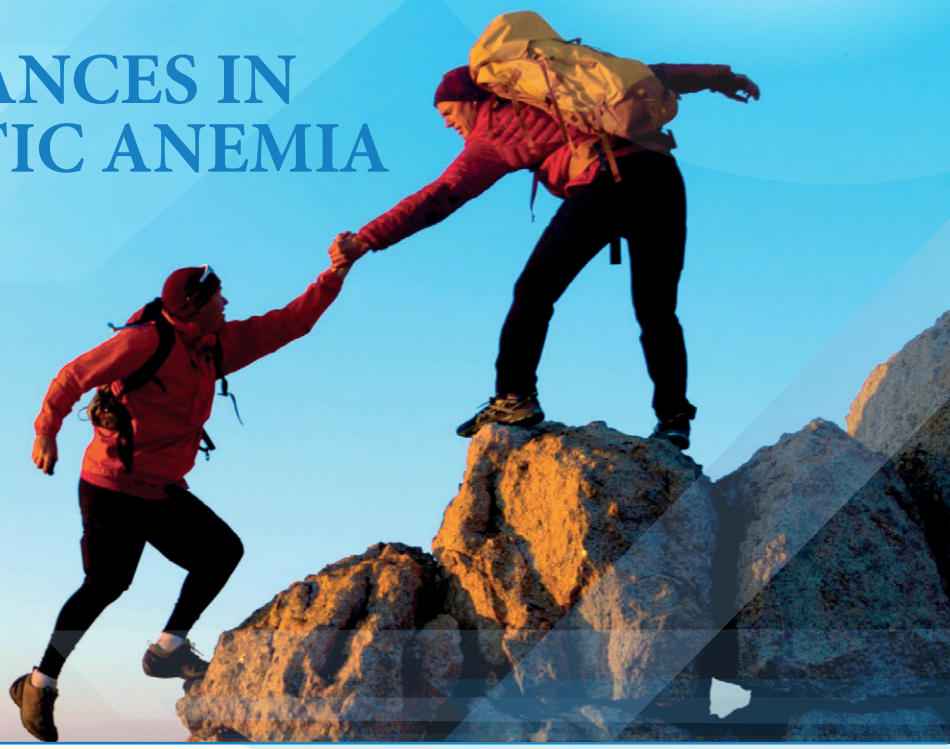
CURRENT ADVANCES IN SEVERE APLASTIC ANEMIA

VIRTUAL WEBINAR

8th October 2020



Speakers

Professor Phillip Scheinberg
Chief of Clinical Hematology,
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de Sao Paulo

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Welcome and Introduction

"Current Advances in Severe Aplastic Anemia (SAA)" was organized on October 8, 2020.

Session 1: Advances in SAA treatment landscape

Speaker: Professor Phillip Scheinberg
Chief of Clinical Hematology,
Hospital A Beneficencia Portuguesa de
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The characteristics of aplastic anemia, evolution in treatment modalities, and advances in non-transplant treatment modalities in SAA, were discussed by Prof. Scheinberg in the first session.

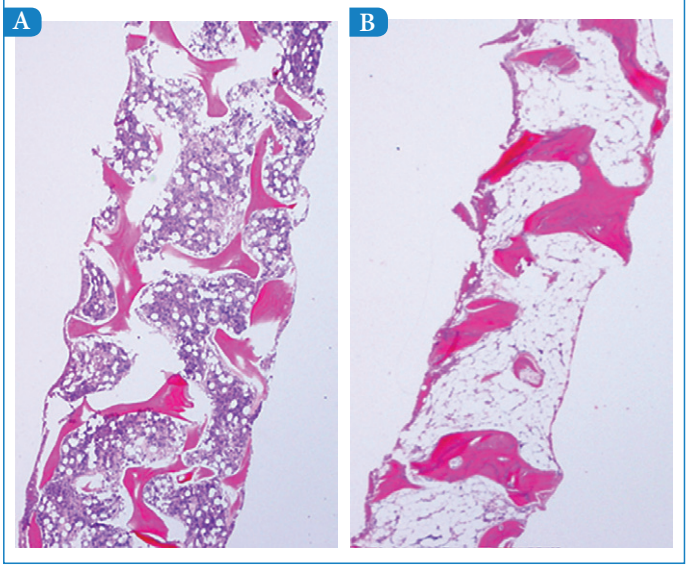
Overview of aplastic anemia

Aplastic anemia is characterized by the destruction of bone marrow:

Hypocellular bone marrow is a typical characteristic feature of SAA and this condition can arise in other diseases, including Fanconi anemia, immune-acquired aplastic anemia, dyskeratosis congenital, or drug-induced

hypocellularity where patients are undergoing chemotherapy.[1] The non-hereditary forms of aplastic anemia, including immune-mediated aplastic anemia or acquired (idiopathic) aplastic anemia (AA), are not drug induced, and marrow function can be improved with immunosuppressive therapy (IST). Understanding the cause of hematopoietic cell diminution, in addition to bone marrow morphology, necessitates further analyses by pathologists.[1] Figure 1 shows the bone marrow of a healthy individual (A) and an individual with AA(B).[1]

Figure 1: (A) Bone marrow of a healthy individual; (B) Bone marrow with aplastic anemia.[1]



Severity criteria in SAA

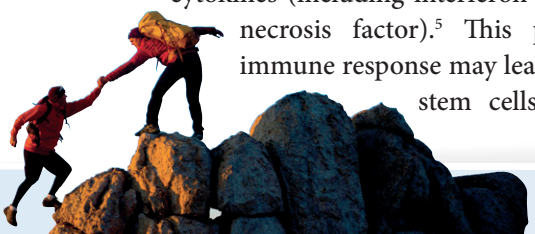
In the 1970s, SAA was associated with a mortality rate of 80%–90%[2] within 2 years of diagnosis. However, in the recent years, fatality rates have considerably improved with advancements in treatment options, such as IST or hematopoietic stem cell transplantation (HSCT), the use of preventive antifungals, and supportive care.[3,4]

The modified Camitta criteria are used to assess the severity of AA, with SAA being defined as follows:[3]

- Marrow cellularity <25% (or 25%–50% with <30% residual hematopoietic cells), plus at least 2 of:
  1. Neutrophils $<0.5 \times 10^9$/L
  2. Platelet count $<20 \times 10^9$/L
  3. Reticulocyte count $<20 \times 10^9$/L
- Very severe AA (VSAA) is described as SAA where the absolute neutrophil count (ANC) $<0.2 \times 10^9$/L.

Pathophysiology of aplastic anemia (AA)

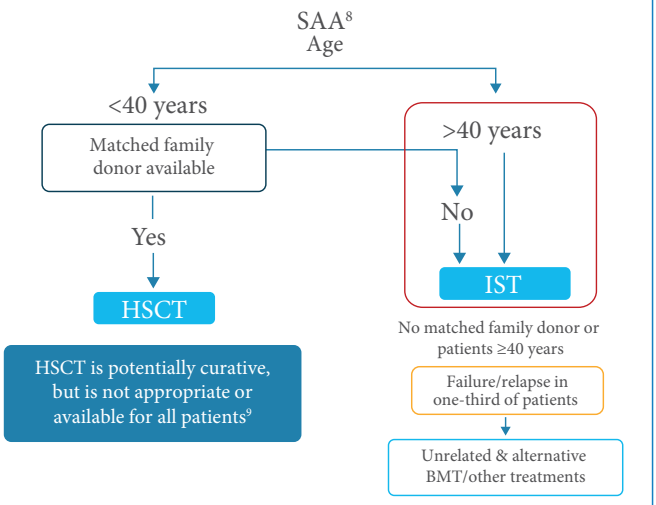
In acquired AA, hematopoietic stem cells (HSCs) and progenitor cells are destroyed, and marrow suppression is led by cytotoxic T-cells (including CD8 cytotoxic T-cells) and cytokines (including interferon-γ and TNF/tumor necrosis factor).[5] This pathophysiological immune response may lead to diminution of stem cells, marrow failure, and pancytopenia, which may result in death without early treatment in SAA.[6] Aplastic anemia is characterized by pancytopenia, a deficiency in all three blood cell types: red blood cells, white blood cells and platelets, which may manifest as hypocellular bone marrow.[5,7]



Clinical manifestations of AA

Aplastic anemia can manifest abruptly over days or more slowly over weeks to months with a biphasic age-specific incidence.[7] Some typical signs and symptoms of AA include anemia, skin or mucosal hemorrhage (petechiae), and retinal hemorrhage.[8] In patients with SAA, the following diagnostic criteria are met: less than 25% of bone marrow cellularity, or 25%–50% of bone marrow cellularity with <30% residual HSCs and, at least, two of the following peripheral blood criteria neutrophil count $<0.5 \times 10^9$/L, platelet count $<20 \times 10^9$/L, and reticulocyte count $<20 \times 10^9$/L.[3]

Figure 2: Treatment of SAA.[8,9]



HSCT: Hematopoietic stem cell transplantation, IST: Immunosuppresive therapy, BMT: Bone marrow transplantation.

Treatment options for SAA

In patients <40 years of age and with a human leukocyte antigen (HLA)-matched sibling, donor bone marrow transplantation (BMT) is the preferred treatment option. In patients >40 years of age and without an HLA-matched sibling donor, non-transplant approaches like IST should be considered.[8,9] The treatment options are detailed in Figure 2.

The outcomes of an intent-to–treat analysis, conducted in the 1970s under the registry of European Group for Blood and Marrow Transplantation (EBMT), revealed the failure-free survival (FFS) in patients receiving first-line BMT from an HLA identical sibling as compared to first-line IST. Bone marrow transplantation (BMT) thus became the preferred choice in younger patients with HLA identical sibling.[10]

Use of anti-thymocyte globulin (ATG) as an immunosuppressive agent:

Immunosuppressive therapy (ATG + CSA) has been shown to be effective in 60%–70% of patients;[11] the typical patient

profile comprises patients with low platelet, Hb, and neutrophil counts, who have undergone IST treatment for 10–11 weeks.[1] With antithymocyte globulin (ATG) alone, the response rates are 40%–50%; with ATG and cyclosporine (CSA), the response rate improves to 60%–70%, and response is usually observed in two-thirds of AA patients. Antithymocyte globulin plus CSA is a standard regimen for treating SAA; the addition of CSA improves the response rates by 15%–20%.[1]

Use of eltrombopag in SAA

Synthetic thrombopoietin receptor agonists (TPO-RAs) were first approved by the US Food and Drug Administration (FDA) in 2008, for the treatment of chronic immune thrombocytopenia (ITP). Eltrombopag was approved by the European Medicines Agency (EMA) as second-line treatment of SAA in 2012 and by the FDA as first-line combination treatment with IST for SAA, in 2018, respectively.[12]

Treatment options in refractory SAA:[2,11,13–17]

Treatment options for non-responders to IST include CSA monotherapy, androgens (more suitable for patients with telomeropathy or telomerase gene mutation), rabbit ATG+CSA, horseATG+CSA, or matched/unrelated donor HSCT. Bone marrow transplantation is usually considered in younger patients; in patients ≥40 years of age, the mortality rates are 30%–40% within one or two years of BMT.

With ATG (rATG+hATG) plus CSA and monoclonal antibodies (e.g., alemtuzumab), hematologic response is observed at 6 months in 30%–40% of patients.

Role of TPO in hematopoiesis:

To understand the functionality of TPO-RAs such as eltrombopag, the role of TPO needs to be understood. Cytokines, such as thrombopoietin, are essential for normal thrombopoiesis.[18] Thrombopoietin receptors are expressed on HSCs and early progenitor cells.[19] In patients with rare disorders such as amegakaryocytic thrombocytopenia, TPO deficiency may lead to pancytopenia and marrow failure.[20]

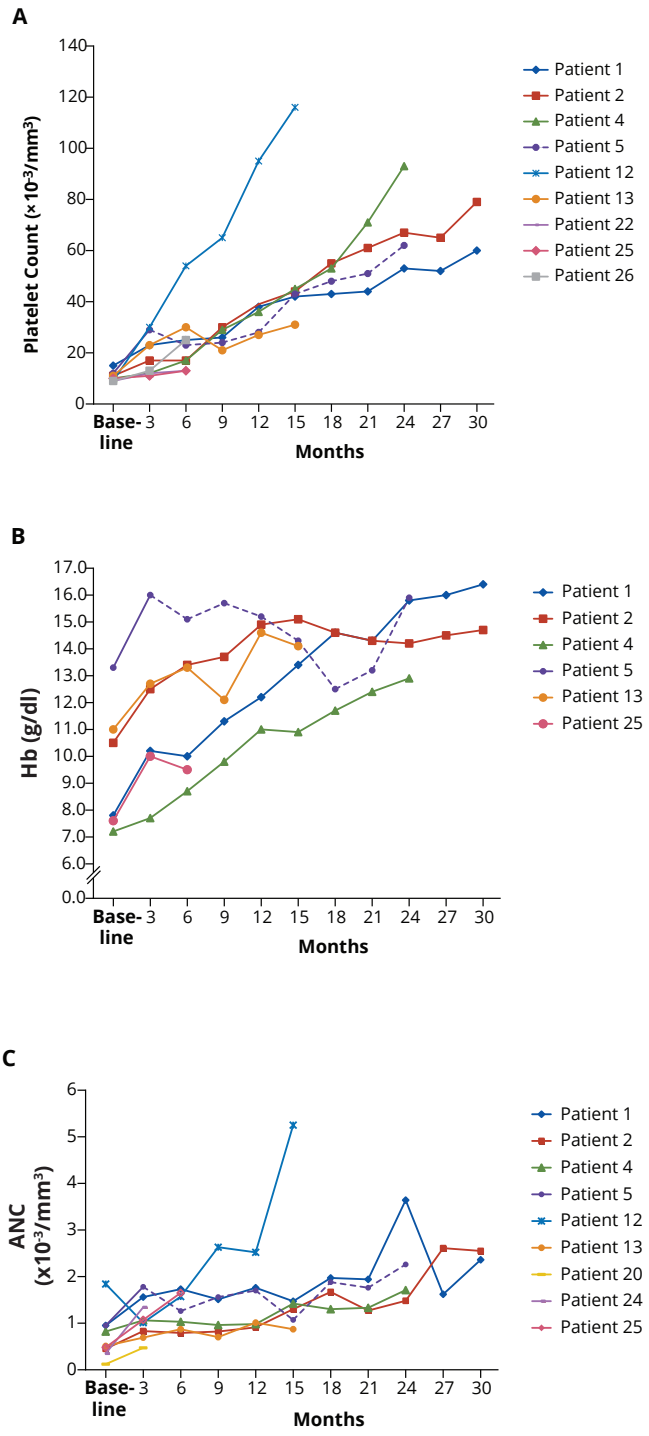
Serum TPO levels are markedly elevated in patients with AA:

In patients with SAA, the serum TPO levels are distinctly elevated, and the therapeutic challenge lies in overcoming the endogenous thrombopoietin levels.[21,22] Clinical trials with eltrombopag in refractory SAA had successfully restored multilineage hematopoiesis and demonstrated a response rate of up to 40% in patients on single-agent oral therapy. Eltrombopag therapy significantly increased blood counts and/or decreased transfusion requirements in 40% of patients with refractory SAA (Figure 3). It has other advantages as well: It is transfusion independent and is a well-tolerated treatment option.[23,24]

Eltrombopag as first-line treatment option for SAA

A recent study, Townsley DM, *et al. N Engl J Med.* 2017;376(16):1540–1550, investigated the clinical efficacy of combining eltrombopag with standard IST, that is, hATG and CSA in treatment-naive SAA patients.[25] In this study, three eltrombopag dosing schemes were implemented in consecutively enrolling cohorts. Eltrombopag was administered at a dose of 150 mg daily in patients ≥12 years of age.

Figure 3: (A) Increase in median platelet increase to 39×10⁹/L (at censure)[1,24]; (B) Increase in median Hb to 3.8 g/dL (range 1.5–8.2 g/dL)[1,24]; (C) Increase in median ANC to 590×10⁹/L (460–990×10⁹/L).[1,24]

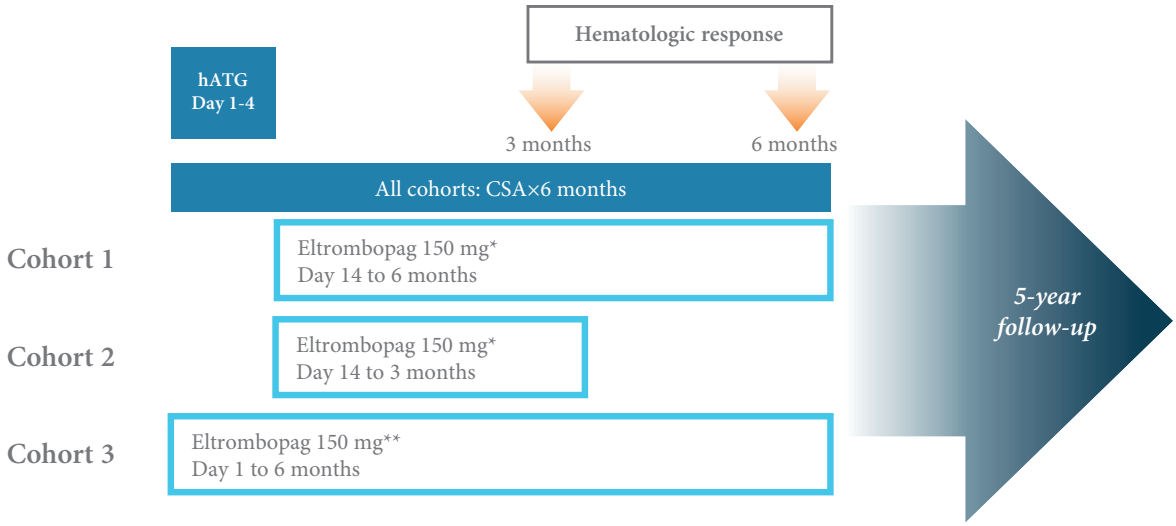


ANC: Absolute neutrophil count, Hb: Hemoglobin.

Study design:

All patients received hATG and CSA, (Figure 4).

Figure 4: Study design: Dosing and treatment plan according to cohort.[25]



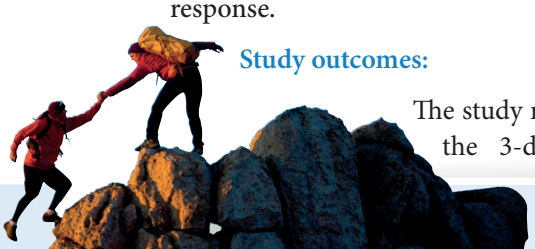
* Dose in Japan is 75 mg; ** Day 1 not approved in Japan; CSA: Cyclosporin.

In cohort 1, eltrombopag was initiated after hATG and continued until the end of 6 months. In cohort 2, eltrombopag was discontinued at 3 months to limit its exposure. Owing to the infrequent hepatotoxic effects and comparatively lower rate of complete response in cohort 2, eltrombopag along with hATG was initiated on day 1 in cohort 3 and further continued until end of 6 months. All subjects in cohort 1 and the first 14 subjects in cohort 2 stopped cyclosporine at 6 months. After protocol amendment, starting from subject number 46 in cohort 2 and all subjects in cohort 3, subjects continued cyclosporine at 2 mg/kg/day fixed dose for an additional 18 months.

Endpoints:

The primary efficacy endpoint was complete response (CR) at 6 months: ANC ≥1 × 10^9/L, hemoglobin (Hb) ≥10g/dL, and platelet count ≥100 × 10^9/L. Complete response was most frequent in cohort 3 (occurring in 58% of the patients), in which eltrombopag was administered from day 1 and then continued for 6 months.

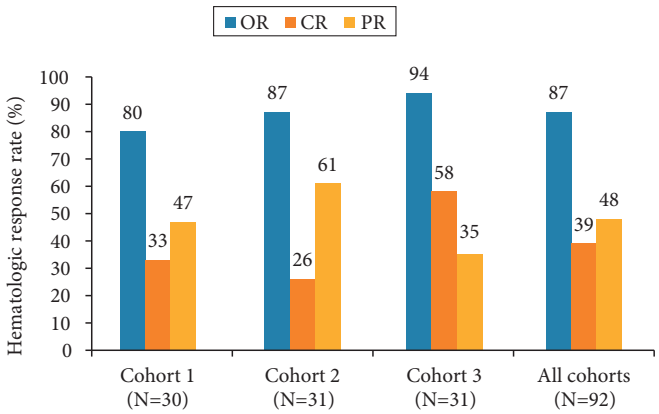
Hematologic overall response rate was observed in 94% of patients in cohort 3; hematologic response rates for cohort 1, 2 3, and all cohorts are detailed in Figure 5. The rate of CR was lowest in cohort 2 (occurring in 26% of the patients) having the shortest exposure to eltrombopag. In this study, partial response was defined as blood counts that no longer met the criteria for SAA but also did not meet the criteria for complete response. The overall response rate corresponded to the proportion of patients who had a partial or complete response.



Study outcomes:

The study results showed that the 3-drug combination, comprising hATG, CSA, and eltrombopag, improved quality of response and overall response rate (ORR). The addition of eltrombopag to standard IST improved the response rate (up to 87%) as compared to historical IST hematologic response (66%).[25]

Figure 5: Hematologic response at 6 months.[25]



OR: Overall response; CR: Complete response; PR: Partial response.

Key Highlights

- HSCT, when appropriate, remains the choice of treatment for SAA.
- Eltrombopag combined with standard immunosuppressive therapy (IST) has been shown to be an effective first-line treatment option for SAA.
- Compared to historical cohorts, eltrombopag + IST delivered improved CR and ORR in treatment-naive SAA patients.

Session 2: SAA case sharing

Speaker: Dr. Ng Chin Hin
Senior Consultant Haematologist,
Centre for Clinical Haematology

A recent case study of a patient with SAA with no previous medical illness was discussed.

Case study: **A 39-year–old male with SAA from Indonesia was presented to the clinic.**

Patient history: No history of jaundice or other medical ailment; spontaneous petechiae with progressive fatigue and exertional dyspnea was observed in late 2019.

Presenting symptoms: Hb: 6.9 g/dL; platelet count: 8 × 10^9/L; ANC: 0.24 × 10^9/L; absolute reticulocyte count: 13,000/microliter; trephine biopsy: <10% cellularity island of normoblasts observed; *DNMT3A* mutation: 0.19%. Other blood tests: Positive ANA test with titer of 1:320 (speckled; in Indonesia); repeat test showed positive in Singapore; serum B-12 level was normal.

Diagnosis: SAA was confirmed with repeat bone marrow aspirate (BMA).

Treatment plan: Allogenic stem cell transplant was considered, given the patient's young age. However, this could not be carried out owing to the prevailing COVID-19 pandemic situation. The patient was offered triple therapy; the dosing schedule followed was: hATG (horse) of 40mg/kg/day was given for 4 days; PO CSA of 200 mg bd (twice a day); and PO eltrombopag of 75 mg od (once daily).

Treatment outcomes: Steady improvements in platelet, Hb, and ANC counts were observed after 4 months of triple therapy; Hb>10 g/dL; ANC >1.0× 10^9/L. The platelet count improved to >100 × 10^9/L, despite gradual decrease of eltrombopag dosing.

Key Highlights

- In patient with SAA, CR was attained within 4 months of triple therapy, that is, eltrombopag in combination with hATG and CSA.
- Platelet count improved to 150 ×10^9/L and improved further despite gradual decrease of eltrombopag dosing.

Conclusions:

- Eltrombopag in addition to standard IST is an effective first-line treatment option for SAA patients with improved complete response rate and overall response rate compared to historical cohorts.
- Triple therapy—eltrombopag in combination with ATG and CSA—can significantly improve FBC in patients with SAA.

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