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Iranian Society of Medical Oncology and Hematology

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Severe Aplastic Anemia

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Introduction

- The bone marrow failure (BMF) state of aplastic anemia (AA) is marked by **cytopenias and ineffective hematopoiesis** most often due to immune injury to multipotent hematopoietic stem cells

- A significant risk for morbidity and death as a result of its progressive natural history and/or complications related to suboptimal therapy

- Without definitive treatment, **mortality** from severe AA (SAA) approaches **70% at 2 years**
- Establishing an accurate etiology of the AA is challenging but also absolutely critical to appropriate management, especially differentiating between acquired and inherited forms of the disease.

Blood Adv (2021) 5 (12): 2660–2671.

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Epidemiology

- AA is a rare disorder
  - Sex ratio 1:1
  - Half of cases occure in the first three decades of life

- **Acquired AA (idiopathic)**
  - majority (70%) of all newly diagnosed cases
  - 2 per million in Western countries and 4 to 6 per million in Asia
  - 2 incidence peaks: 1 among young adults and a second in the elderly

- **Inherited BMF disorder (IBMFD)**
  - More than 25% of pediatric patients and 5% to 15% of adults age 40 or younger who present with AA have an inherited etiology.

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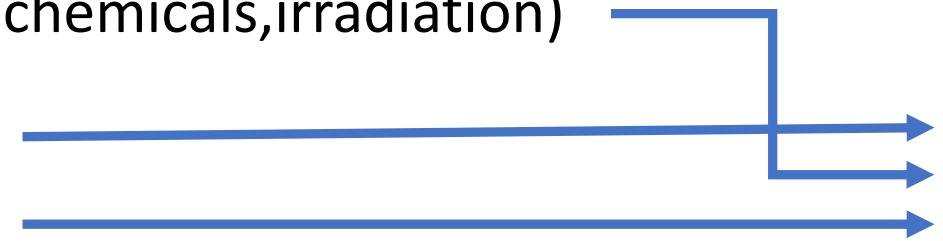
Pathophysiology

❑Loss of hematopoietic stem cells (HSC)is a defining feature of AA

❖ **Pathophysiologic processes:**

✓Autoimmune mechanism(**contributes to most cases of AA)**

- Direct injery to HSC (by drug,chemicals,irradiation)
- Viral infection
- Clonal genetic disorders



Alter the immunologic appearance of HSC and lead to autoimmune destruction

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Few unknown causes of AA

- It is occasionaly associated with certain condition in which the mechanism of HSC loss is poorly understood

  - Anorexia nervosa (gelatinous degeneration and serous fat atrophy)
  - Pregnancy
  - Ortotopic liver transplantation (fulminant hepatic failure)

Uptodate ,Aug 29,2021

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Conventional karyotyping & clonal evolution

- **Diagnosis can be challenging in some patients because AA**
  - Other immune cytopenias, MDS (hypocellular), (PNH), and IBMFD are all considered BMF states

- **Most often AA patients have normal cytogenetics**
- BUT May Coexist or evolve in to another hematologic disorder :**PNH,MDS,AML**

- There are some cytogenetic abnormalities seen in AA that are not considered adverse or indicative of MDS (in the absence of dysplasia)
  - ✓ **del13q, trisomy 8, loss of heterozygosity of short arm of chromosome 6**

- **If <20 metaphases are obtained, perform an <u>MDS FISH panel (5,7,COMPLEX)</u>**

.<u>Monosomy 7, especially in young patients, increases suspicion for an IBMFD and hypo cellular MDS</u>

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Conventional karyotyping &clonal evolution

- **Myeloid malignancy gene sequencing from peripheral blood or bone marrow Strongly consider if any concern for possible hypoplastic MDS**

❑ Purpose:

- Evaluate for mutations in genes recurrently mutated in AA (*PIGA*, *BCOR*, *BCORL1*) and/or MDS (epigenetic mutations, *TP53*).

- Identification of mutations should not necessarily be used as a discriminating tool between AA and hypoplastic MDS, because most MDS-associated mutations are seen in AA, MDS, and aging-related clonal hematopoiesis
- Poor discriminating power for AA or MDS in this context.
- May identify a subset of AA likely to progress to MDS/AML

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Evaluation of a patient with a suspected new diagnosis of AA

- AA is a diagnosis of exclusion
- There is no single test that can be used to consistently diagnose AA from the myriad other causes of BMF
- Diagnosis can be challenging in some patients because AA, other immune cytopenias, myelodysplastic syndrome (MDS; cellular or hypocellular), paroxysmal nocturnal hemoglobinuria (PNH), and IBMFD are all considered BMF states.

AA presentation :

- Fatigue, weakness, pallor, and headaches due to **anemia**
- Petechiae of the skin and mucous membranes, epistaxis, and/or gum bleeding related to severe **thrombocytopenia**
- Fever and infections can also be seen as a result of low white blood cell counts and **neutropenia**
    - AA patients identified earlier in the course of the disease by abnormalities found on routine laboratory testing may not have any physical manifestations of their disease

Standard work-up in the evaluation of a patient with suspected AA being considered for transplantation

Medical and family history assessment[61,64,68,81,*]				
Heme Long-standing cytopenia(s) or macrocytosis? Unexplained cytopenia(s) or macrocytosis, AA, MDS, or AML in 1 or more close relative(s)?	X	Could suggest IBMFD if chronic cytopenias at early age are found in the patient or cytopenias or blood cancers cluster in the family		61,68,80
Developmental Short stature, physical anomalies (especially thumb/radial ray, cardiac, or renal)?	X	FA, STS, DBA, or thrombocytopenia-absent radius		
Immunologic/infectious disease Severe, recurrent, or atypical infections (eg, mycobacterial, viral, fungal)?	X	Could suggest GATA2 or other primary immunodeficiency	If present, consider referral to immunology and immunocompromised infectious disease specialists	
Dermatologic Gray hair prior to 25? Leukoplakia or nail dysplasia? Reticulated skin pigmentation, café au lait macules?	X	Could suggest STS; Cafe au lait macules could suggest FA		
Pulmonary Pulmonary fibrosis and/or early-onset emphysema, pulmonary alveolar proteinosis, fungal or mycobacterial infection?	X	Could suggest STS or GATA2		
Abdominal Pancreatic insufficiency, liver fibrosis, renal anomaly or malplacement?	X	Could suggest SDS, STS, FA, respectively		
Neurologic Ataxia, nystagmus? Cognitive dysfunction?	X	Could suggest SAMD9L, multiple IBMFD, respectively		
Cardiac/lymphatic Cardiac anomaly, lymphedema?	X	Could suggest multiple IBMFD, GATA2, respectively		
Oncologic H&N or anogenital SCC, early-onset GI cancers or multiple cancers in patient or close relatives?	X	Could suggest STS, Li Fraumeni, other hereditary cancer syndromes		

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Laboratory studies on peripheral blood

- **Complete blood count with differential and blood smear review**
  - Assess severity of cytopenias and for alternative etiologies
  - Monocytopenia should prompt consideration of GATA2-deficiency syndrome.
  - many severely neutropenic SAA and VSAA patients are also monocytopenic, so it is not specific to GATA2 deficiency.
- **Reticulocyte count**
  - Assess marrow response to anemia and use in AA severity assessment
- **Percentage of hemoglobin F**
  - Elevated levels can indicate that an IBMFD may be present
- **Vitamin B12, folate, copper, zinc, ferritin**
  - Rule out vitamin or mineral deficiencies as cause or contributor to cytopenias
- **Hepatitis A/B/C, HIV, EBV, parvovirus, X**
  - Rule out infectious disease and CMV serologies contributors to cytopenias and identify comanagement needs during treatment and transplant
- **LDH, haptoglobin**
  - Rule out a hemolysis component to anemia

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Laboratory studies on peripheral blood

- **PNH clone**
  - Assess presence or absence of GPI-anchored protein expression(CD 55,CD59)
  - Clone sizes vary (in monocytes and granulocytes) in acquired SAA
  - but larger clone sizes (.10%) are often associated with response to IST.
- ANA with reflex to anti–double-stranded DNA if positive
  - Assess for systemic lupus erythematosus

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Laboratory studies on peripheral blood

- **Chromosome breakage analysis on peripheral blood**
  - (age < 40 y or those proceeding to BMT)
  - Evaluate for FA; if test is positive and consistent with a diagnosis of FA, patient is at increased risk for transplant-related toxicity, and an FA-specific regimen should be used.
  - If results are normal but clinical suspicion remains high, this test can be performed on cultured skin fibroblasts to rule out a false negative in the peripheral blood.
- **Bone marrow aspirate and biopsy**

  Assess cellularity, iron stores, and reticulin fibrosis and rule out other marrow pathologies.

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Very severe AA

- an absolute neutrophil count <0.2 × 109/L

Sever aplastic anemia

- a decrease in blood counts involving ≥2 hematopoietic lineages
- absolute reticulocyte count <60 × 109/L
- absolute neutrophil count <0.5 × 109/L
- platelet count <20 × 109/L)
- And bone marrow hypocellularity (<25% of the normal cellularity).

moderate AA

- The depression of blood counts not fulfilling the definition of severe disease

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Treatment AA in adults

1- Exclude other causes

   IBMFS –Hypoplastic MDS –Drug-Infection- Detection of PNH (enhance the likelihood of Aq AA)

2- Disease severity

3- Medical fitness

4- Potential candidates for transplantation

5- Fertility and Pregnancy

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Treatment AA in adults/Severe AA /Very Severe AA

Require prompt and judicious treatment decisions

Reduce the risk of life-threatening infection
Limit complications from ongoing transfusion,antibiotics

Consider :

✓medical fitness

✓Ag

✓availability of a suitable transplant donor

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Treatment AA in adults/Severe AA /Very Severe AA

Age < 40 or 50 years

- **Rapidly-available match related donor**
  - Proceeding directly to allo-HSCT rather than IST

- **DON'T have Rapidly-available match related donor**
  - Initiate IST and begin a search for a suitable alternative donor
  - Matched unrelated,mismatch related,haploidentical,umbilical cord source

Suggestion is triple IST

INTENSIVE IST

1. HORSE ATG
2. CYCLOSPORINE
3. ELTROMBOPAG

haematologica
Journal of the Ferrata Storti Foundation

Haematologica. 2018 Feb; 103(2): 212–220. PMCID: PMC5792265
Prepublished online 2017 Nov 23. doi: 10.3324/haematol.2017.176339 PMID: 29170252

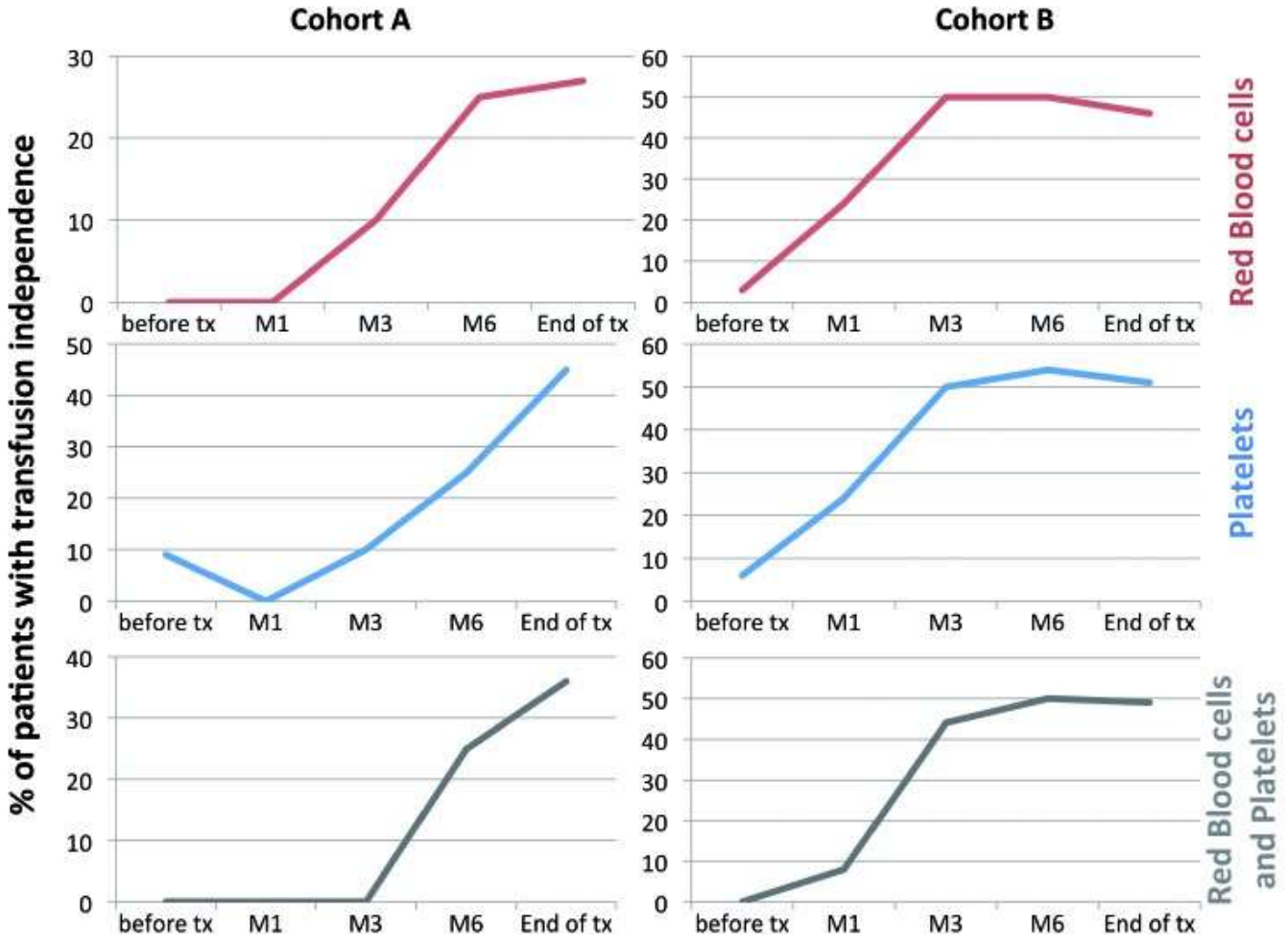
Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia

Etienne Lengline,[1] Bernard Drenou,[2] Pierre Peterlin,[3] Olivier Tournilhac,[4] Julie Abraham,[5] Ana Berceanu,[6]

Eltrombopag study

Eleven ATG-naïve patients (cohort A)

Thirty-five patients refractory or relapsed disease(cohort B)



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AFTER RESULTS OF THIS STUDIES:

Blood. 2014 Mar 20; 123(12): 1818–1825.
Prepublished online 2013 Dec 17. doi: 10.1182/blood-2013-10-534743
PMCID: PMC3962161
PMID: 24345753

Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug

N Engl J Med. Author manuscript; available in PMC 2017 Oct 20.
Published in final edited form as:
N Engl J Med. 2017 Apr 20; 376(16): 1540–1550.
doi: 10.1056/NEJMoa1613878
PMCID: PMC5548296
NIHMSID: NIHMS889813
PMID: 28423296

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

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- “Eltrombopag is registered(2018) **in Europe for second line treatment** of aplastic anaemia, so it is only available to patients who cannot receive bone marrow transplantation and have failed immunosuppressive treatment”

- EBMT Working Party for Severe Aplastic Anemia is running 2 prospective randomized studies:

- compares ATG+CsA with or without EPAG in SAA
- compares CsA with or without EPAG in non-SAA

PRESS RELEASE
August 31, 2020
the results of the phase III RACE trial during EBMTs virtual 46th Annual Meeting

- Preliminary data show that adding Eltrombopag to standard immunosuppressive treatment is safe and increases response rates in patients with Severe Aplastic Anaemia (SAA).

- **The RACE trial data** shows that Eltrombopag increased response rates for **naïve SAA** patients who are not eligible for hematopoietic stem cell transplantation

- The RACE study team is continuing to follow up the trial participants up to two years and furthermore aims to set up a long-term follow-up study to monitor the effectiveness and safety of Eltrombopag up to ten years

The international, investigator-driven, open-label, phase III, randomised trial evaluated 197 patients with SAA

The RACE trial

2 arms and protocols of RACE trial

standard immunosuppression (hATG 40 mg/kg x4d and CsA 5 mg/kg/d)

standard immunosuppression + Eltrombopag at the dose of 150 mg/d from day +14 until 6 months (or 3 months, in case of early complete response)

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Eltrombopag (EPAG)

- Non-peptide thrombopoietin receptor agonist
- Is given at 150 mg orally once daily
- One hour before or two hours after a meal on an empty stomach
- Or with foods that contain **little or no Ca** or dairy products
- >4 hour interval between EPAG and other medications or product containing polyvalent cations(Ca,Mg,Alm,Zc,Selenium,Iron)
- East or Southeast Asian should receive lower doses (75 mg daily)
- Dose should be reduced or held for elevated of transaminases

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Eltrombopag (EPAG)

- Well-tolerated but **adverse effects:**
- Skin reaction
- Elevated hepatic transaminases
- **Most common :**
- Nausea ,fatigue ,cough ,diarrhea ,headache
- Mild to moderate increase in indirect bilirubin
- Effect of long term use of Epag in AA has not been thoroughly evaluated

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