Aplastic Anemia: Understanding Your Diagnosis and Treatment Options

AAMDS Foundation

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June 24, 2017

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Case

15 year old previously healthy white adolescent female referred to Hematology Clinic for evaluation of thrombocytopenia

History:

CBC obtained at primary care physician's office
9/2016: WBC 7.7; Hb 11; platelet count 33
12/2016: WBC 3.7; Hb 10.6; platelet count 25

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Case

Past Medical History: Born FT by uncomplicated C-section for breech position. No hospitalizations or recurrent infections. Normal development. Immunizations up to date.

Medications: Lisdexamfetamine, Nu-Iron

Family History: No known bleeding disorders, anemia, thrombocytopenia, childhood cancers.

Social History: No full siblings. *Jehovah's witness*.

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Case

Exam: Ht 171 cm (92%), Wt 51.1 kg (45%),

Normal except for one small bruise on anterior left leg

No dysmorphic features, congenital lesions, radial ray or nail abnormalities

Labs:

4.3 > 9.6 < 18, MCV 112, ANC 1800, ARC 56k

HbF 9.4% (elevated)

B12 704 pg/mL, Folate > 22.3 ng/mL (normal)

Peripheral blood smear consistent with pancytopenia

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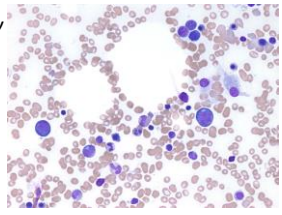
Bone marrow aspirate/biopsy



Hypocellular marrow 5-30%, normal cytogenetics

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Further testing:

CMV, EBV, Hepatitis A/B/C, Parvovirus, HHV6 negative

Normal chromosome breakage studies

Normal telomere lengths

PNH screen with 10% neutrophil clones and 8% monocyte clones

Shwachmann-Diamond gene sequencing negative

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Case

Diagnosis: **Acquired Idiopathic SAA**

Treatment:

Horse anti-thymocyte globulin (ATG) x 4 days
Methylprednisolone/Prednisone x 10 days
Cyclosporine A twice a day
Eltrombopag (50 mg/day beginning day 4)

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Aplastic Anemia: Definitions

- Severe Aplastic Anemia (SAA)

ANC*	Platelets	ARC*	BM cellularity
< 500/uL	< 20,000/uL	< 40,000/uL	< 25% for age

2 out of 3 blood count criteria

*ANC = absolute neutrophil count
ARC = absolute reticulocyte count

- Very Severe Aplastic Anemia (vSAA): ANC <200/uL

Camitta et al., Blood, 1976;48:63-70.
Williams et al., PBC, 2014;61(5):869-874.

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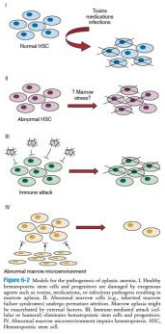
Possible Mechanisms



1. Direct progenitor cell death due to marrow toxins
2. Underlying HSC abnormality
   - Post Immunosuppression, low stem cell #s persist and macrocytosis may not return to normal
   - Late clonal abnormalities
3. Immunologic destruction of hematopoietic stem cells
   - Clinical response to immunosuppressive therapies
4. Abnormal stromal microenvironment inhibiting hematopoiesis

Nathan & Oski, 2015.

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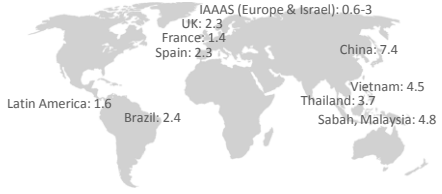
Epidemiology



- Incidence ~ 2 per million per year
- Peaks at ages 15-25 years and > 60 years

Cartwright et al., Leuk Res, 1988;12:459.
Mary et al., Blood, 1990;75:1646.
Issaragrisil et al., Blood, 1991;77(10):2166-2168.
Kaufman et al., Oxford University Press, 1991.
Maluf et al., AJH,2002;71:268-274.
Maluf et al., Haematologica, 2009;94(9):1220.
Montane et al., Haematologica, 2008;93(4):518.
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Young & Kaufmann, Haematologica, 2008;93(4):489-492.

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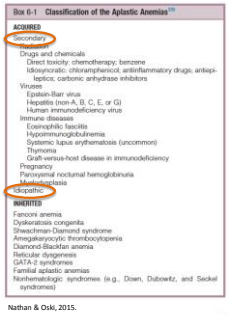
Etiologies


Box 6-1 Classification of the Aplastic Anemias[10]

ACQUIRED
Secondary
Drugs and chemicals
Direct toxicity: chemotherapy; benzene
Idiosyncratic: chloramphenicol; antiinflammatory drugs; antiepileptics; carbonic anhydrase inhibitors
Viruses
Epstein-Barr virus
Hepatitis (non-A, B, C, E, or G)
Human immunodeficiency virus
Immune diseases
Eosinophilic fasciitis
Hypoimmunoglobulinemia
Systemic lupus erythematosis (uncommon)
Thymoma
Graft-versus-host disease in immunodeficiency
Pregnancy
Paroxysmal nocturnal hemoglobinuria
Myelodysplasia
Idiopathic
INHERITED
Fanconi anemia
Dyskeratosis congenita
Shwachman-Diamond syndrome
Amegakaryocytic thrombocytopenia
Diamond-Blackfan anemia
Reticular dysgenesis
GATA-2 syndromes
Familial aplastic anemias
Nonhematologic syndromes (e.g., Down, Dubowitz, and Seckel syndromes)

Nathan & Oski, 2015.

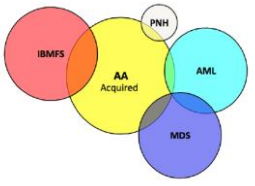


Fig. 1. Overlapping syndromes. The differential diagnosis for apparently acquired aplastic anemia includes paroxysmal nocturnal hemoglobinuria (PNH), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and inherited bone marrow failure syndromes (IBMFS).

Shimamura, Blood Reviews, 2010;24:101-122.

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Diagnosis

- Careful and thorough H&P

History

Bleeding, fatigue, serious infections
Steatorrhea, diarrhea
FH blood disorders, malignancies, hepatitis, congenital anomalies, etc.
Developmental history
Meds, environment exposures, infections

Physical Exam

Petechiae, bruises, pallor, oral sores
Lymphadenopathy, hepatosplenomegaly
Growth curves, short stature
Congenital anomalies esp. radial ray abnormalities
Hyper/hypopigmented areas, dystrophic nails

Basic labs: CBC with diff, retic, PBS +/- HbF

Diagnostic Workup

Test	% Centers
Bone Marrow Asp/Bx	100%
Cytogenetics	100%
HLA typing of siblings	94%
Chromosome breakage analysis-MMC[1]/DEB[2]	89%
PNH[3] Screen by Flow	89%
EBV[4], CMV[5]	83%
Hepatitis screen	78%
SBDS[6] gene sequencing	71%
Telomere length	67%
FISH (chr 5, 7, 8)	61%
BM Flow for T, B, CD34	67%
Immunological work-up	55%
Vit B12, Folate	50%
DC[7] Genetic Testing	43%
HSV[8], VSV[9], HHV6[10]	33%
Ferritin	28%
Pancreas U/S	22%
Kidney U/S	16%
Skeletal survey/Hand film	0%

Williams et al., PBC, 2014;61(5):869-874.

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Treatment Algorithm

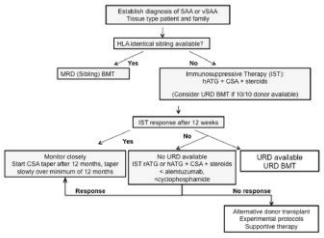

Figure 5.
Treatment algorithm for AA and sAA. MRD, matched related donor; hATG, horse antithymocyte globulin; rATG, rabbit antithymocyte globulin, CSA cyclosporine, URD unrelated donor; BMT bone marrow transplant; IST, immune suppressive therapy.

Hartung et al., Pediatr Clin North Am, 2013;60(6):1311-1336.

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Supportive Care

- Antimicrobials as needed
- Prompt evaluations for neutropenia and fever
- +/- G-CSF & GM-CSF
- Restrictive transfusion thresholds
- Iron chelation as needed

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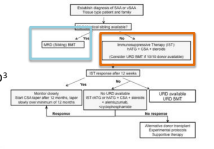
Matched Related Donor Transplants

- Conditioning
  - Cy-ATG — Engraftment rate 96%[1], OS 91%[2]
  - Cy alone — No difference in OS, graft failure, or GVHD[3]
- Graft Source
  - Prefer BM > PBSC or UCB
    Improved OS for BM (85%) vs PBSC (73%) grafts[4]
- Graft Failure & GVHD — 5% / 10-30%
  - MTX-CSA — Standard of care for GVHD prophylaxis
  - MMF-CSA — Potentially similar GVHD incidence with quicker engraftment[5]
  - CSA vs. Tacrolimus — Potentially equivalent efficacy[6], Continue ≥ 6 months post HCT with slow taper to prevent GVHD, late graft failure, AA relapse



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Hartung et al., Pediatr Clin North Am, 2013;60(6):1311-1336.

[1]Kahl et al., Br J Haematol, 2005;130:747-751.
[2]Locasciulli et al., Haematological, 2007;92:11-18.
[3]Champlin et al., Blood, 2007;109:4582-4585.
[4]Schrezenmeier et al., Blood, 2007;110:1397-1400.
[5]Ostronoff et al., Clin Transplant, 2009;23:33-38.
[6]Yagasaki et al., Biol BMT, 2009;15:1603-1608.
Marsh et al., Br J Haematol, 2009;

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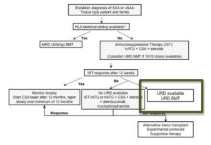
Matched Unrelated Donor Transplants

- 10/10 high-resolution HLA MUD
- Conditioning
  - Cy-ATG + Low-dose TBI (2 Gy)
    OS 85%, aGVHD 70%, cGVHD 52%[1]
  - Low-dose Cy-rATG + Flu
    OS 84% ≤ 14 yrs, 61% ≥ 15 yrs
    Graft failure 5% ≤ 14 yrs, 32% ≥ 15 yrs[2]
  - Cy + Flu-Alemtuzumab
    OS 95%, aGVHD 2.3%, cGVHD 6.8%[3]
- Graft Source
  - Prefer BM > PBSC or UCB



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Mismatched unrelated donor -Retrospective data with reasonable outcomes

OS (2 yr) 78% for 8/8, 60% for 7/8[4]

[1]Deeg et al., Blood, 2006;108:1485-1491.
[2]Bacigalupo et al., BMT, 2005;36:947-950.
[3]Samarasinghe et al., Br J Haematol, 2012;157(3):339-46.
[4]Eapen and Horowitz, Hematology, 2010;43-46.

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Immunosuppressive Treatment

ATG + CSA — 6 months — 10 yrs — 10 yrs — 10 yrs

Table V. Paediatric studies of immune suppressive therapy (IST) with horse ATG and ciclosporin.

Study	Number of patients	Treatment (IST)	Study period	Follow up (years)	Overall response	Overall survival	Relapse rate	Clonal evolution
Fuhrer *et al* (2005)	146	ATG, CSA, GCSF	1993–2001	4·1 (median)	CR 69% VSAA, CR 44% SAA	93% VSAA, 81% SAA	13% VSAA, 14% SAA	NR
Kamio *et al* (2011)	441	ATG, CSA, ±Dan ±GCSF	1992–2007	10	59·9%	82% VSAA, 82% SAA, 98% NSAA	11·9%	NR
Saracco *et al* (2008)	42	ATG, CSA± GCSF	1991–1999	10	71%	83%	16%	15%
Scheinberg *et al* (2008)	77	ATG, CSA, ±MMF, ±sirolimus	1989–2006	10	77%	80%	33%	8·5%

ATG, Anti-Thymocyte Globulin; CSA, ciclosporin; Dan, Danazol; GCSF, granulocyte colony-stimulating factor; MMF, mycophenolate mofetil; SAA, severe aplastic anaemia; VSAA, very severe aplastic anaemia; NSAA, non severe aplastic anaemia; NR, not reported; CR, Complete remission rate.

[1]Samarasinghe et al., Br J Haematol, 2012;157:26-40.

- Response to IST typically starts at ~ 1-3 months[1]
- ATG + CSA > OR (but not OS) compared to ATG[2]
- Horse ATG > Rabbit ATG for OR and OS[3]
- Slow CSA wean[4]

Predictors of response to IST
vSAA > SAA
Younger age
Higher Retic and ALC
Quicker treatment

Fuehrer et al., Blood, 2005;106:2102-2104.
Yoshida et al., Haematologica, 2011;97:771-774.

[2]Frickhofen et al., Blood, 2003;102:1236-1242.
Guinan, Hematology, 2005;104-109.
Kurre et al., PBC, 2005;45:770-780.
Marsh et al., Br J Haematol, 2003;123:782-801.
[3]Scheinberg et al., NEJM, 2011;365:430-438.
[4]Saracco et al., Br J Haematol, 2008;140:197-205.

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Thrombopoietin (TPO)

- Most potent regulator of megakaryopoiesis and thrombopoiesis
- Binds to receptor (MPL) on hematopoietic stem cells and megakaryocyte colony-forming units (CFU-MK)
- Stimulates megakaryocytic maturation, increases megakaryocyte size and ploidy
- rh-TPO in cancer patients on chemotherapy increases platelet count, but also causes antibodies that cross-react with endogenous TPO

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Eltrombopag

- Binds to transmembrane domain of MPL
- Rapidly absorbed after oral administration
- Should not be taken within 4 hour of food rich in cations such as Ca^{++}
- Metabolized in liver, $T_{½}$ = 21-32 hours
- Clearance 33-52% lower in Asians; therefore starting dose approximately ½ in Asians (in some trials)

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2012 VOL. 367 NO. 1

Eltrombopag and Improved Hematopoiesis in Refractory Aplastic Anemia

Matthew J. Olnes, M.D., Ph.D., Phillip Scheinberg, M.D., Katherine R. Calvo, M.D., Ronan Desmond, M.D., Yong Tang, M.D., Ph.D., Bogdan Dumitriu, M.D., Ankur R. Parikh, M.D., Susan Soto, B.S.N., Angelique Biancotto, Ph.D., Xingmin Feng, M.D., Ph.D., Jay Lozier, M.D., Ph.D., Colin O. Wu, Ph.D., Neal S. Young, M.D., and Cynthia E. Dunbar, M.D.

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Eltrombopag and refractory aplastic anemia

- Phase 2 study in adults with aplastic anemia refractory to immunosuppression (IS)
- N=25; median age= 44 years (18-77)
- Eltrombopag dose: 50 → 150 mg/d x 12 weeks
- 11/25 (44%) had response in at least one lineage at 12 weeks
- 9 no longer needed platelet transfusion; 3 no longer needed PRBC transfusion; 9 had increase in ANC
- Conclusion: eltrombopag was associated with multilineage response in some patients with refractory SAA
- Follow-up study; 40% response rate

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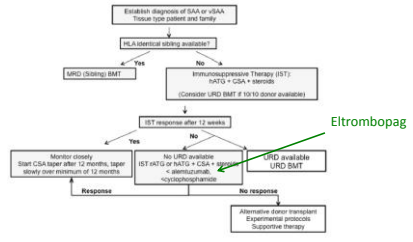
Treatment Algorithm



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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eltrombopag Added to Standard Immunosuppression for Aplastic Anemia

Danielle M. Townsley, M.D., Phillip Scheinberg, M.D., Thomas Winkler, M.D., Ronan Desmond, M.D., Bogdan Dumitriu, M.D., Olga Rios, R.N., Barbara Weinstein, B.S.N., Janet Valdez, P.A., Jennifer Lotter, P.A., Xingmin Feng, Ph.D., Marie Desierto, B.S., Harshraj Leuva, M.B., B.S., Margaret Bevans, Ph.D., Colin Wu, Ph.D., Andre Larochelle, M.D., Ph.D., Katherine R. Calvo, M.D., Cynthia E. Dunbar, M.D., and Neal S. Young, M.D.

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Eltrombopag and standard immunosuppression for aplastic anemia

- Phase 1-2 study of immunosuppression + eltrombopag in previously untreated patients with severe aplastic anemia (SAA)
- Patients (N = 92) consecutively enrolled in 3 cohorts; median age = 32 years (3-82)
- Primary outcome = CR at 6 months
- Secondary outcomes = OR, survival, relapse, clonal evolution

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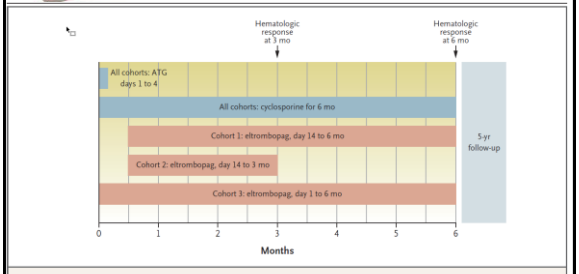
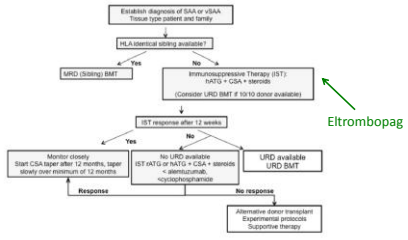


Figure 1. Study Design and Treatment Plan According to Cohort.

Results

- CR at 6 mo. = 32%, 26%, 58% in cohorts 1, 2, and 3
- OR at 6 mo. = 80%, 87%, 94%
- In historical controls, CR = 10% and OR = 66%
- Survival = 97% at median follow-up of 2 years
- Relapse and clonal evolution similar to historical experience
- Toxicity: severe rash leading to discontinuation of eltrombopag in 2 patients
- Conclusion: Addition of eltrombopag to immunosuppression is associated with markedly higher rate of hematologic response in patients with SAA

Treatment Algorithm



Eltrombopag

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NAPAAC
NORTH AMERICAN PEDIATRIC APLASTIC ANEMIA CONSORTIUM

The North American Pediatric Aplastic Anemia Consortium (NAPAAC) is a collaborative research effort that seeks to develop better therapies for children with **aplastic anemia** by combining the expertise and resources of the **leading pediatric hematologists** in North America.

www.NAPAAC.org

NAPAAC/Novartis: Study Objectives

- 1^0: Characterize the pharmacokinetics of eltrombopag at steady state in refractory, relapsed or previously untreated patients with SAA
- Key 2^0: Safety and tolerability; efficacy (overall response rate)
- Other 2^0:
  - Platelet and RBC transfusion independence
  - Hematologic counts, BM cellularity
  - Clonal evolution to PNH
  - Acceptability and palatability

Summary

- Eltrombopag is a promising new agent for improving the response to upfront immunosuppressive treatment in SAA
- Eltrombopag is of benefit for some patients that have refractory or relapsed SAA
- However, the improving results from alternative hematopoietic stem cell transplants must also be considered in treatment decisions

Questions?

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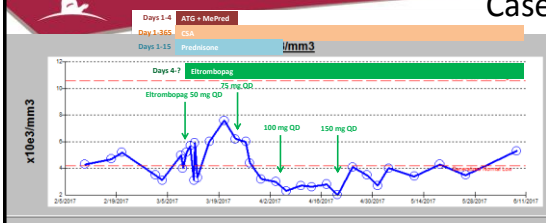
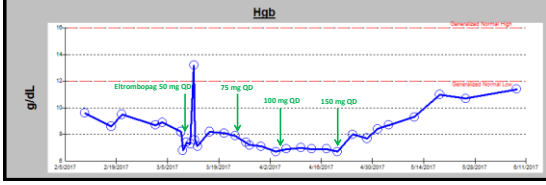
Case





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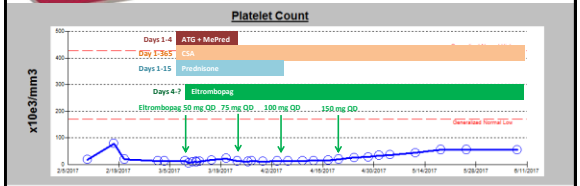

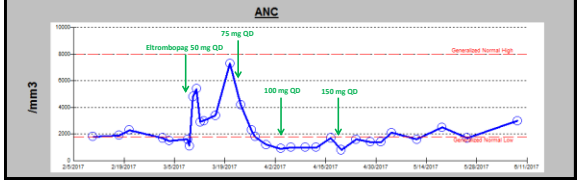

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