Aplastic Anemia

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National Institutes of Health

AA MDS

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National Heart, Lung, and Blood Institute

Introduction

- Aplastic Anemia
  - Immune mediated
  - What is it and what causes it?
- Diagnosis
- Treatment
  - Immunosuppression
  - Transplant
- Pure Red Cell Aplasia
  - What is it and what causes it?
- Ongoing research

A historical disease

Charite Hosp Ann 1888

Ueber einen Fall von Anämie mit Bemerkungen über regenerative Veränderungen des Knochenmarks.

Von

Professor Dr. **P. Ehrlich,**

Assistent der II. medicinischen Klinik.

diesem negativen Verhalten, dass in diesem Falle die Regeneration der rothen Blutscheiben nicht in sufficienter Weise vor sich ginge und glaubte hierauf, sowie auf das Fehlen der eosinophilen Zellen gestützt, solches auf ein mangelhaftes Functioniren des Knochenmarkes beziehen zu müssen.

Arch Intern Med 1917

DIMINISHED BLOOD PLATELETS AND MARROW INSUFFICIENCY

A CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS OF PURPURA HEMORRHAGICA, APLASTIC ANEMIA, AND ALLIED CONDITIONS *

GEORGE R. MINOT, M.D.

BOSTON

Bost Med Surg J 1927

Case Records
of the
Massachusetts General Hospital

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICO-PATHOLOGICAL EXERCISES

EDITED BY R. C. CABOT, M.D.

F. M. PAINTER, A.B., ASSISTANT EDITOR

CASE 13321

BLEEDING FROM THE GUMS

MEDICAL DEPARTMENT

Soc Med Hop 1904

L'ANÉMIE PERNICIEUSE D'APRÈS LES CONCEPTIONS ACTUELLES,

par M. H. VAQUEZ

Agrégé, médecin de l'hôpital Saint-Antoine,

et CH. AUBERTIN,

Interne des hôpitaux.

Ici, la forme aplastique apparaît dans toute sa pureté.

Harrison Martland Alice Hamilton

Arch Pathol 1931

General Review

BENZENE (BENZOL) POISONING

ALICE HAMILTON, M.D.

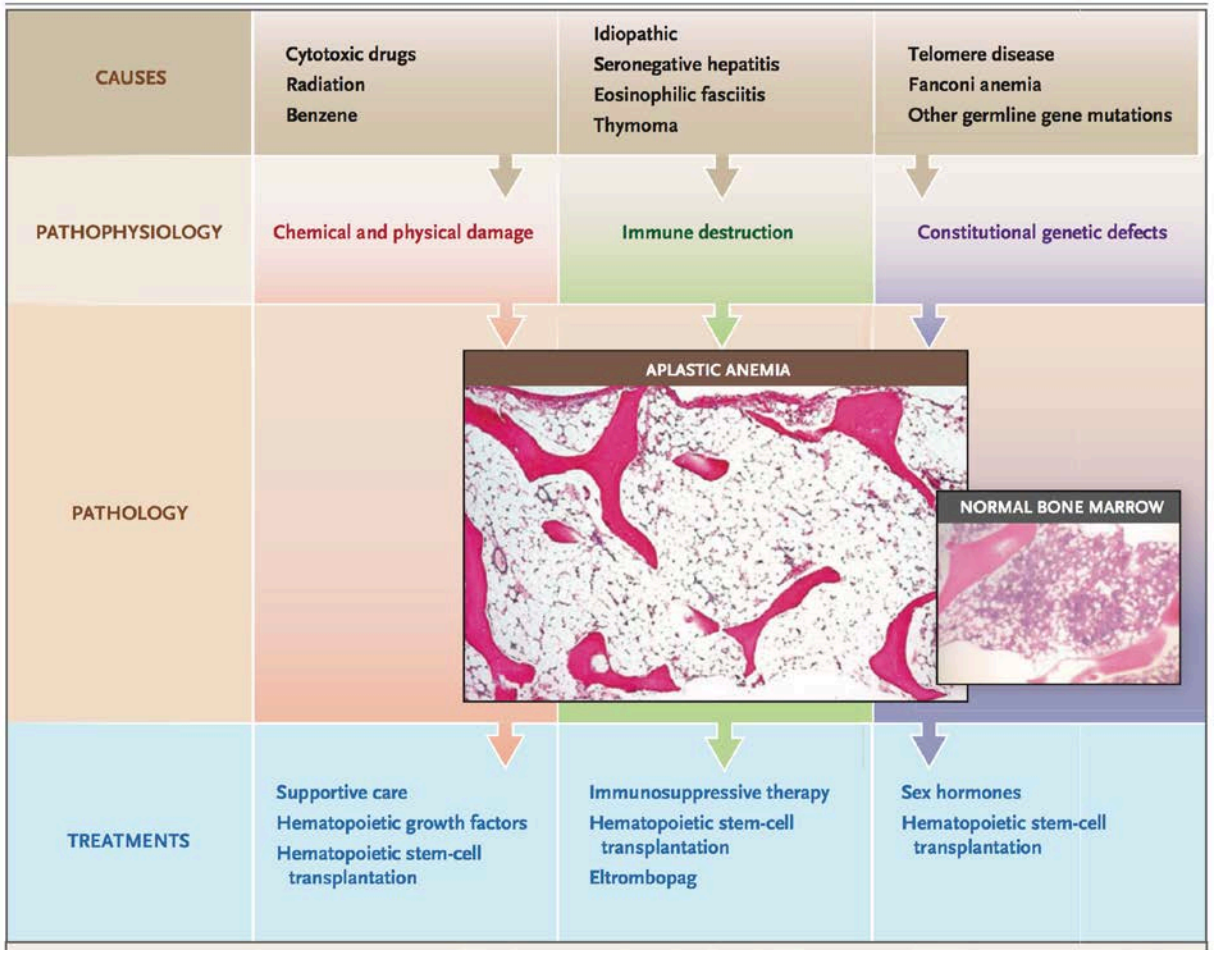
BOSTON

Aplastic Anemia

- Rare blood disorder
  - 2-3 per million / year
- Low blood counts and empty bone marrow
- Peak age distributions
  - 10-25 years old and >60 years old

Causes of Aplastic Anemia

- **Immune system destroying bone marrow cells**
  - “idiopathic”
  - 70%
- Inherited abnormal genes
  - Telomere diseases
  - Fanconi anemia
- Bone marrow toxins
  - Rare



Young, N. S. (2018). "Aplastic Anemia." N Engl J Med **379**(17): 1643-1656.

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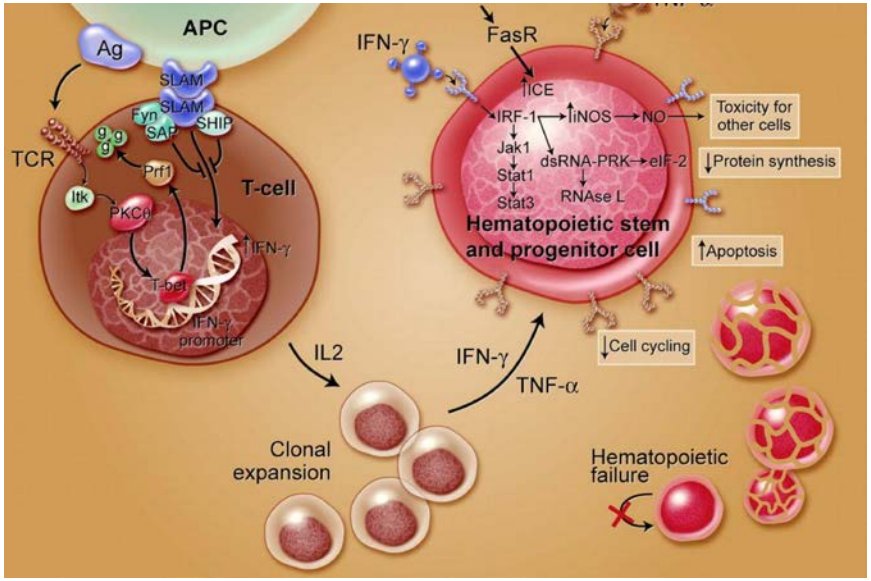
Mechanism of Aplastic Anemia

- Immune system attacks the bone marrow
  - Active lymphocytes (T cells)
  - Increase in inflammation
  - Cells die



Young, N.S. et al. Blood.2006

Aplastic Anemia

Young, N. S. (2018). "Aplastic Anemia." N Engl J Med **379**(17): 1643-1656.

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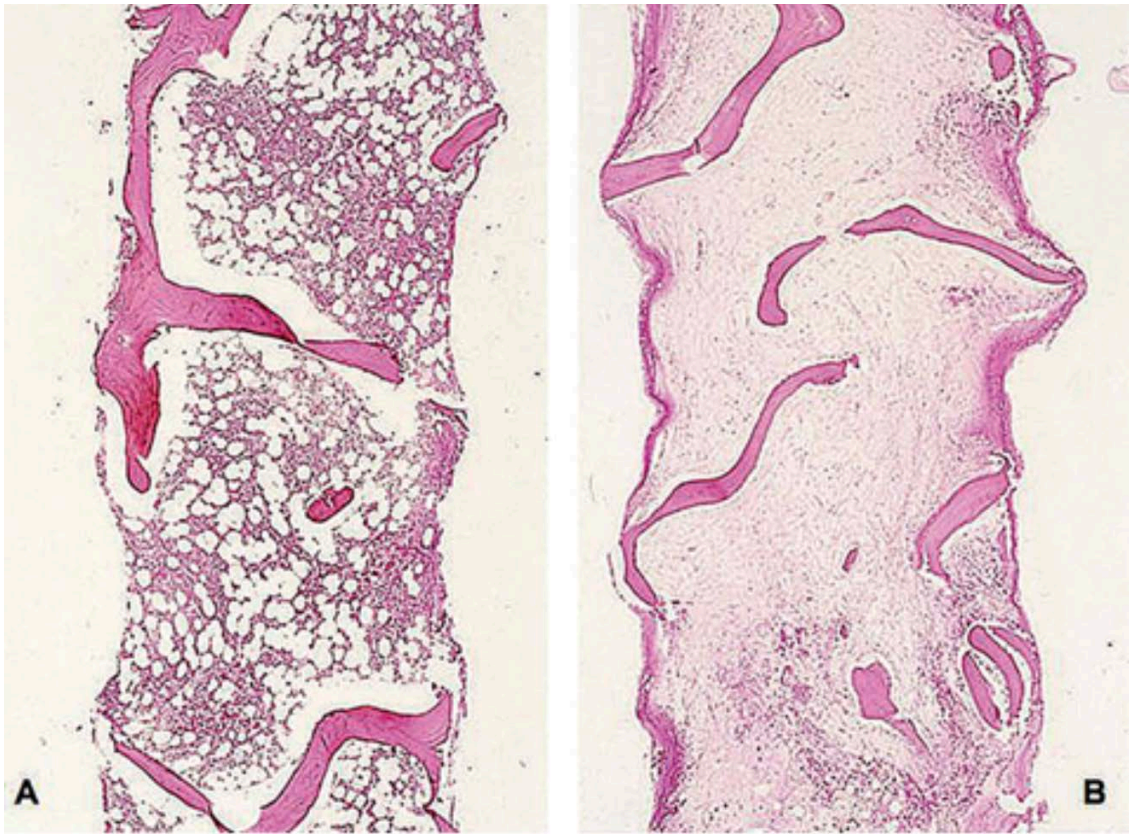
Marrow is “empty”



Courtesy of Dr. Stanley Schreier, American Society of Hematology Image Bank

How does it affect the patient?

- Neutropenia (low white cells)
  - Risk of infection
    - If less than 500 – risk of infection
    - If less than 200 – high risk of infection

- Thrombocytopenia (low platelets)
  - Risk of bleeding
    - Risk of bleeding with trauma / procedures if <50
    - Some risk bleeding <20
    - Higher risk bleeding <10
      - Platelet transfusion

- Anemia (low red cells or hemoglobin)
  - Red cells carry oxygen in the blood
    - Symptoms include:
    - Tiredness
    - Shortness of breath
  - If hemoglobin <7 or symptoms
    - blood transfusion

Clonal evolution

- Development of a new **cytogenetic abnormality**

Or

- Development of **MDS/leukemia**

Case Study

- 16 year old
- Felt generally unwell for 1 month
  - Short of breath
  - Very tired
- Parents brought him to visit his GP who performed a blood check

Case Study

Hemoglobin	4.8
Neutrophils	0.1
Platelets	11

Differential Diagnoses

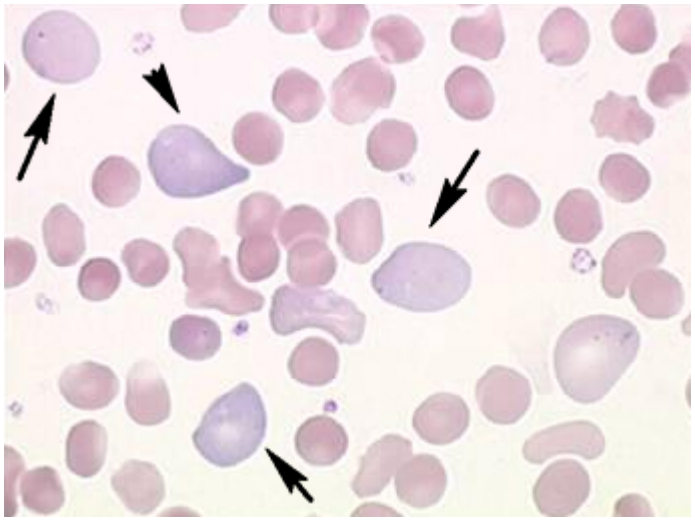
- Severe vitamin deficiency
  - B12 / folic acid
- Blood cancers / leukemia
- Infections
- Medications
- Bone marrow failure syndromes

Case Study

- No recent infections
- No medications or toxic exposures
- Non smoker / non drinker / toxin exposure
- No family history of blood disorders

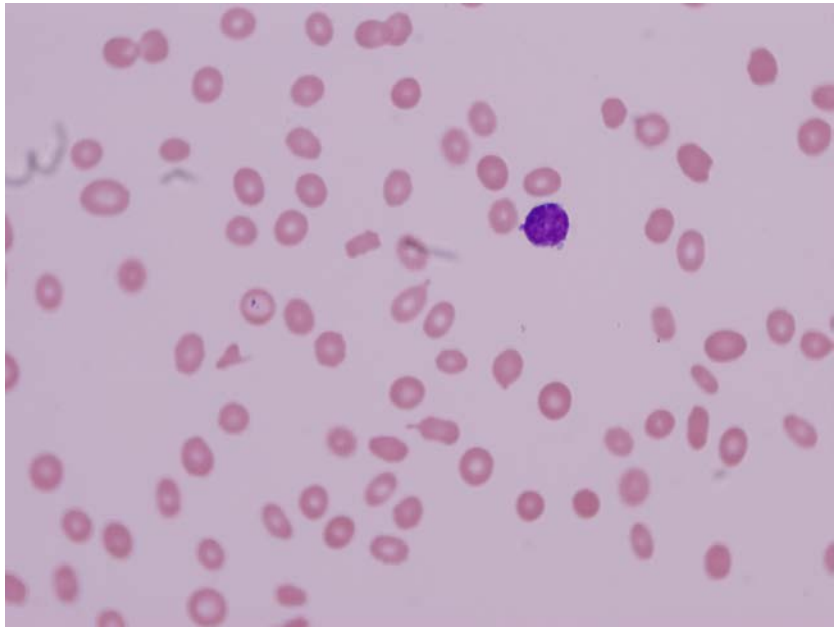
Case Study

- Kidney tests
  - Normal
- Liver tests
  - Normal
- Viral tests
  - Negative for HIV/Hepatitis
- Vitamin tests
  - Normal B12 and folic acid
- Reticulocytes
  - 13 (normal is 30-90)

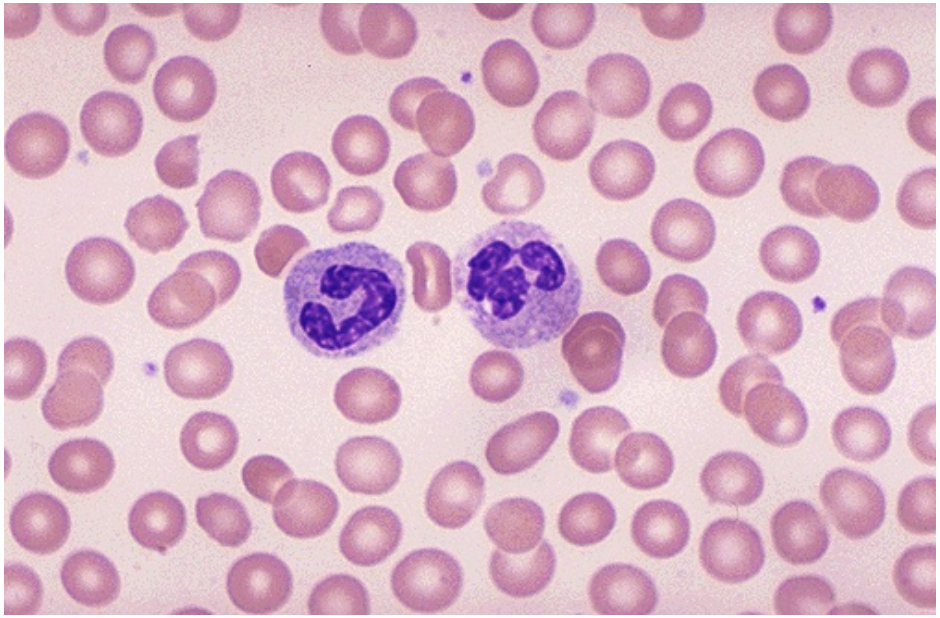


Case Study

Patient's blood

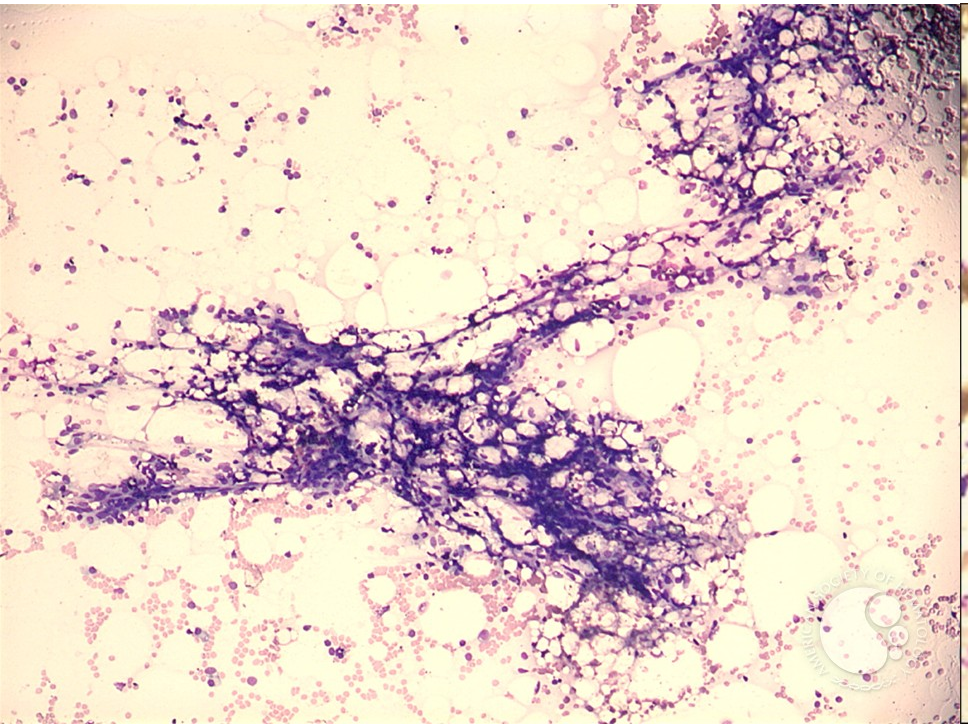


Normal blood

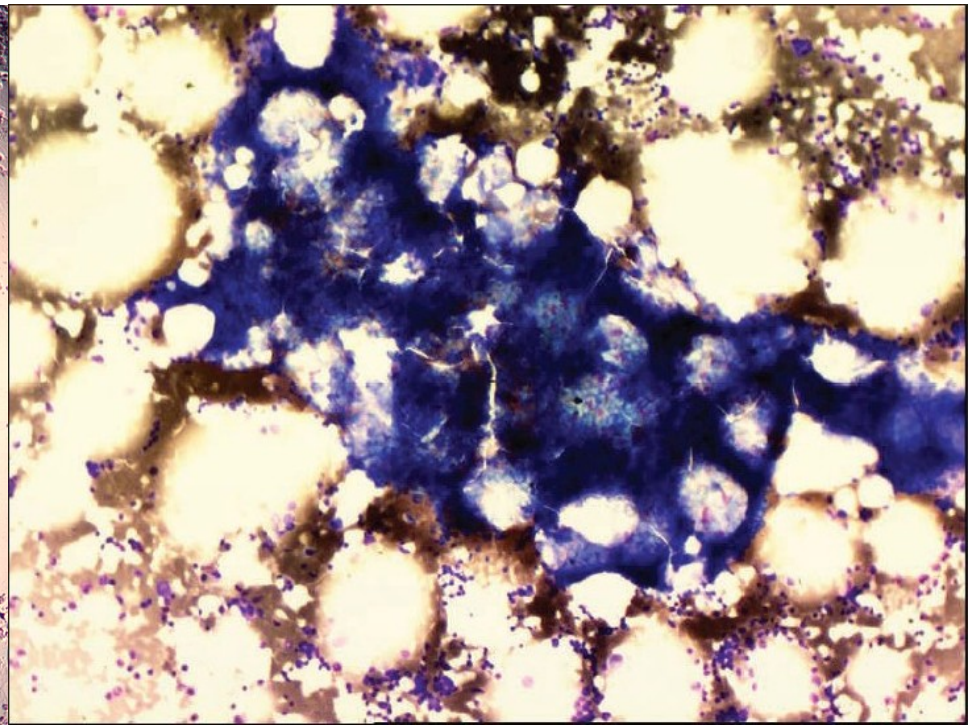


Bone Marrow

Patient's marrow

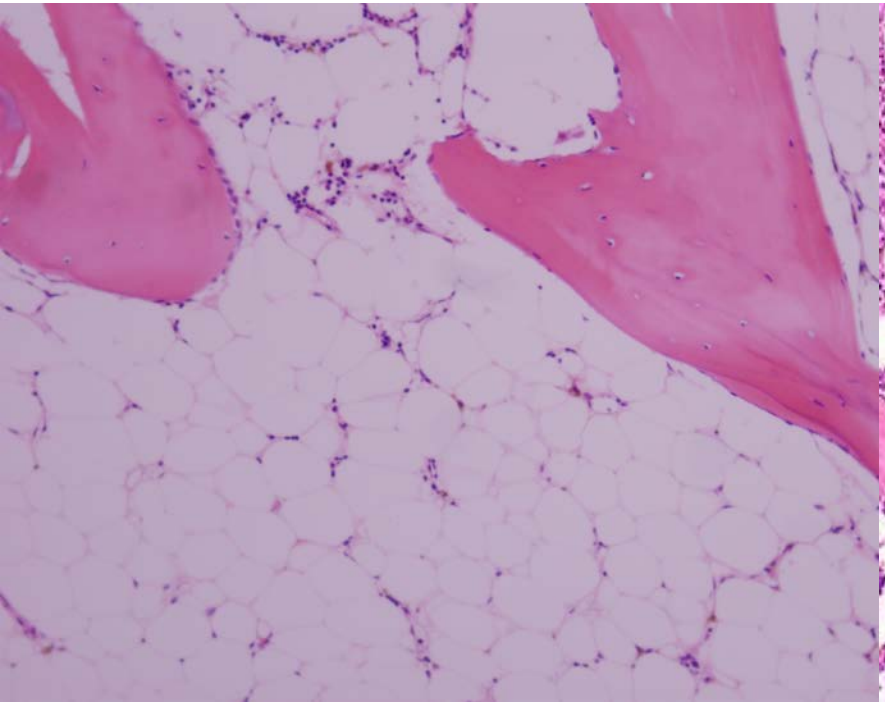


Normal marrow

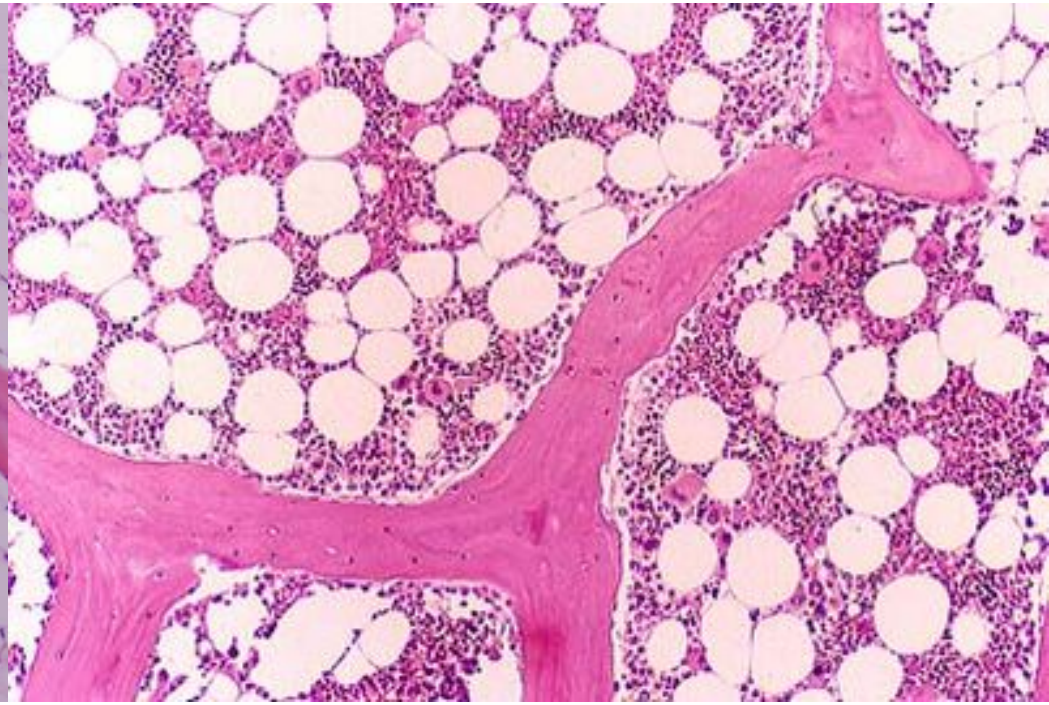


Bone Marrow

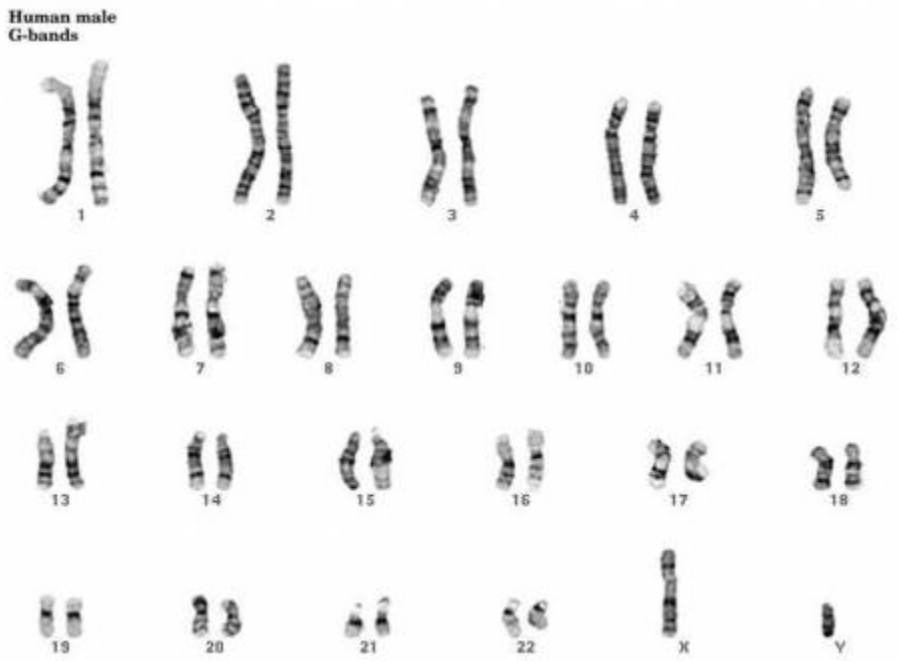
Patient’s marrow



Normal marrow



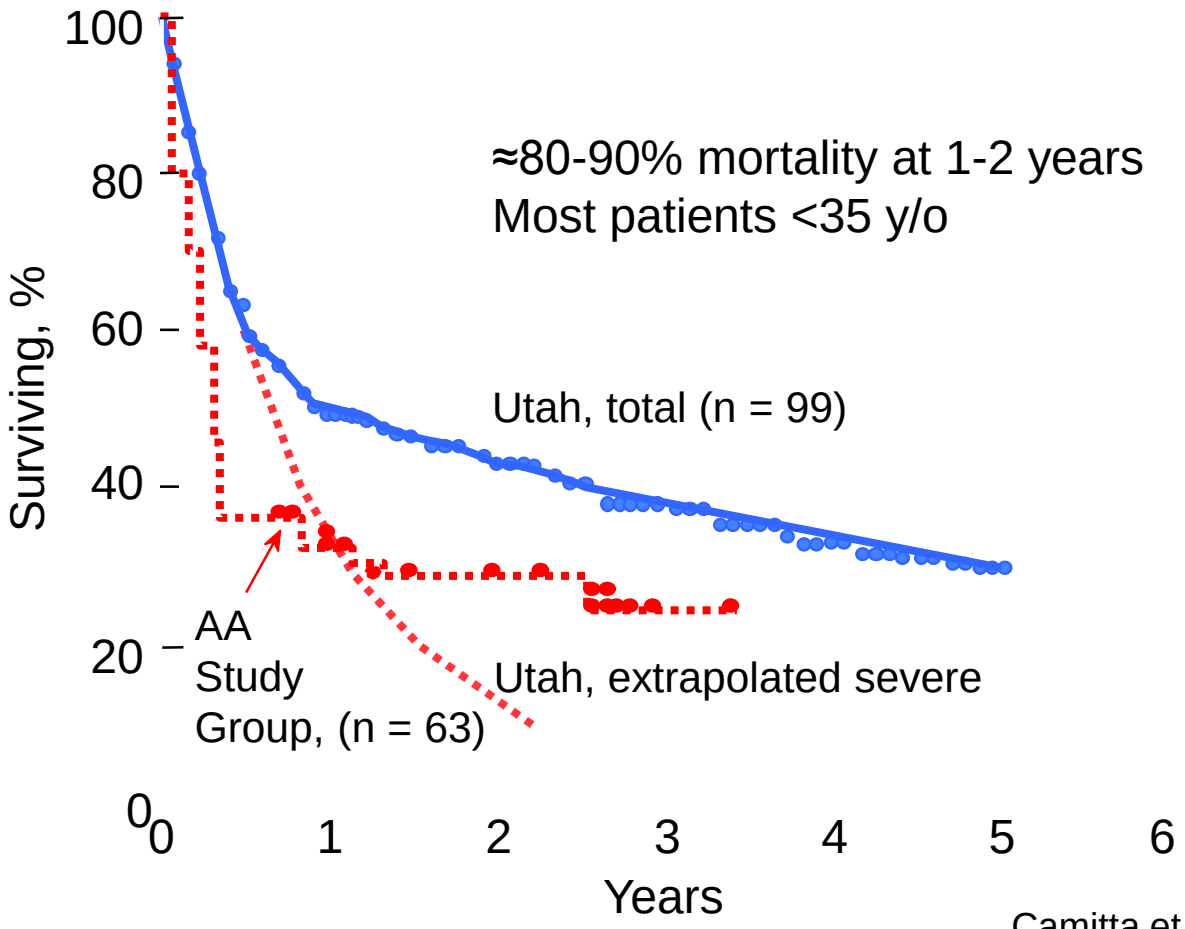
Cytogenetics



Diagnosis?

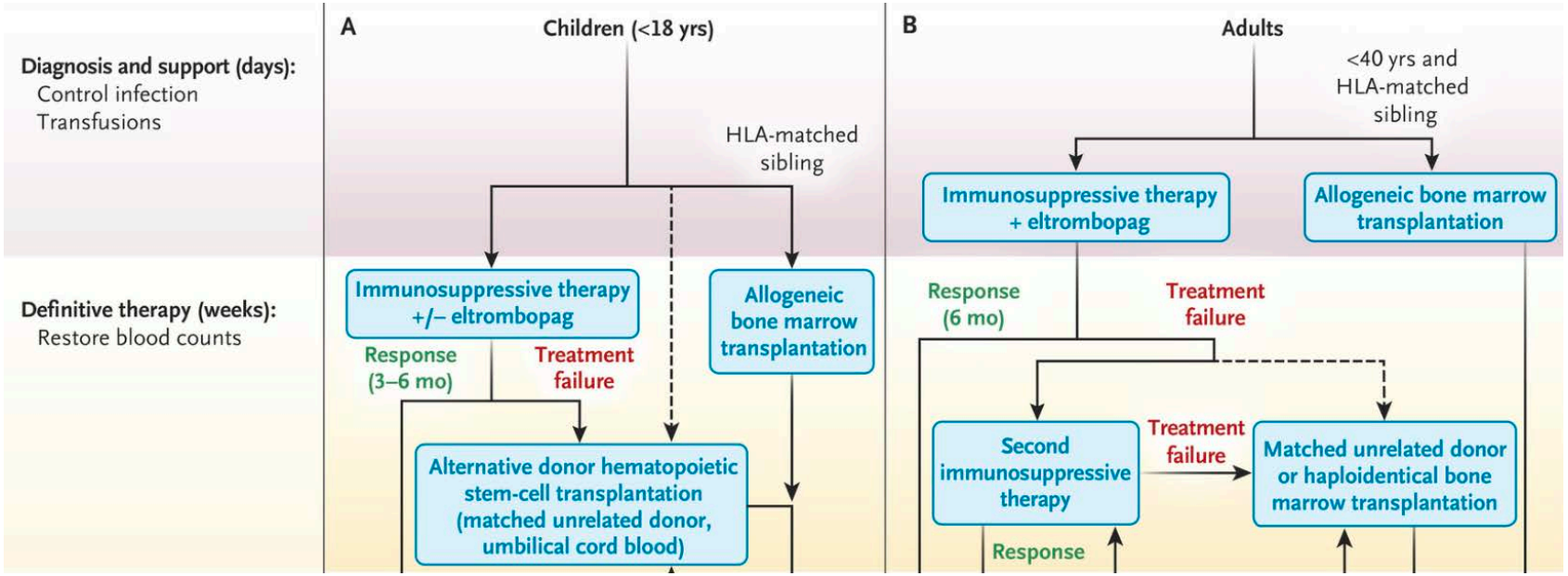
Severe Aplastic Anemia

Natural History of SAA



Camitta et al, Blood 1979; 53:504
Williams et al, Sem Hematol 1973; 10:195

Treatment approach to SAA



Young NS. N Engl J Med.2018

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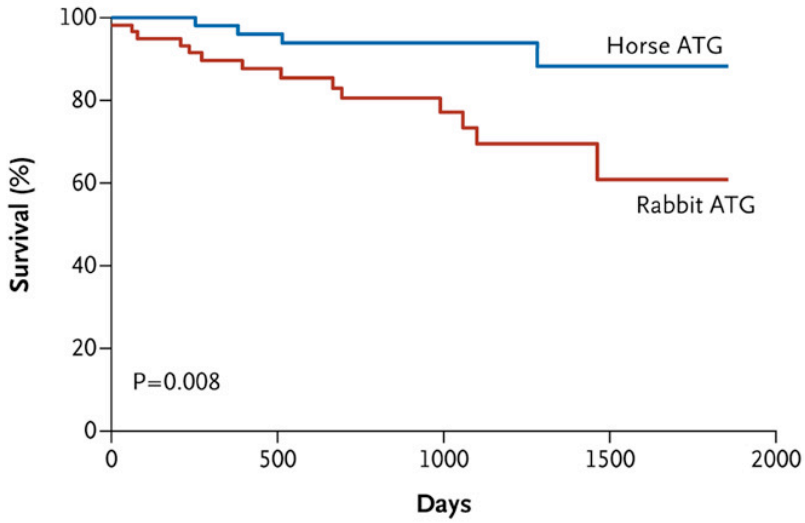
ATG – Horse versus Rabbit



No. at Risk				
Horse ATG	60	44	27	12
Rabbit ATG	60	41	22	6

Scheinberg P, Young NS. N Engl J Med.2012

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Addition of Eltrombopag

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., et al.

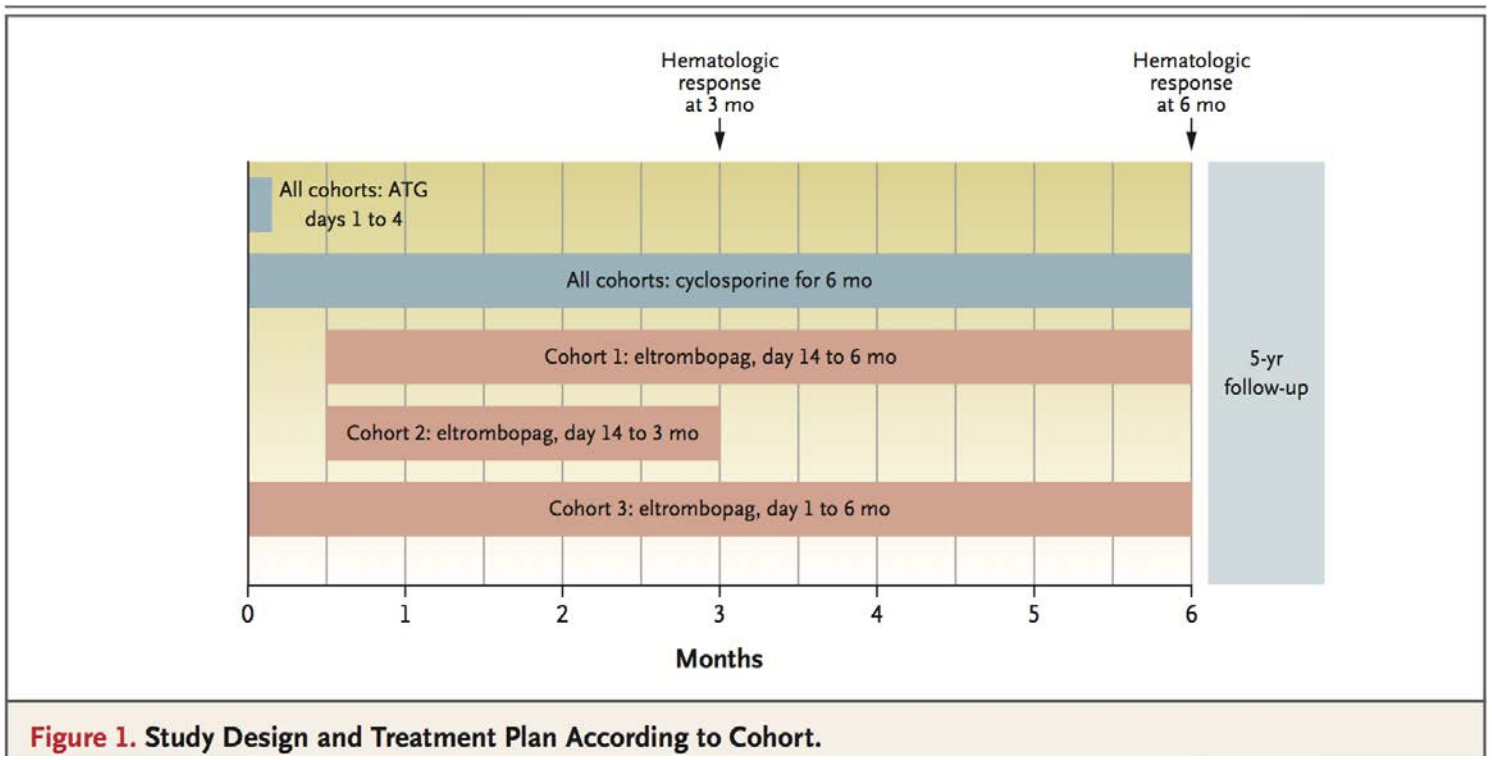


Figure 1. Study Design and Treatment Plan According to Cohort.

Townsley D, et al. N Engl J Med. 2016

Response rates

Table 2. Hematologic Response in Patients Treated with Immunosuppression and Eltrombopag.*

Cohort and Response	Rate at 3 Mo	Rate at 6 Mo	P Value
Cohort 1			
No. of patients	30	30	
Response — no. (% [95% CI])			
Overall response	23 (77 [61–93])	24 (80 [65–95])	
Partial response	18 (60 [41–79])	14 (47 [28–66])	
Complete response	5 (17 [3–31])	10 (33 [15–31])	0.01
Cohort 2			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	24 (77 [62–93])	27 (87 [75–100])	
Partial response	16 (52 [33–70])	19 (61 [43–79])	
Complete response	8 (26 [9–42])	8 (26 [9–42])	0.06
Cohort 3			
No. of patients	31	31	
Response — no. (% [95% CI])			
Overall response	27 (87 [75–100])	29 (94 [84–103])	
Partial response	12 (39 [21–57])	11 (35 [18–53])	
Complete response	15 (48 [30–67])	18 (58 [40–76])	<0.001
All cohorts			
No. of patients	92	92	
Response — no. (% [95% CI])			
Overall response	74 (80 [72–89])	80 (87 [80–94])	<0.001†
Partial response	46 (50 [40–60])	44 (48 [37–58])	
Complete response	28 (30 [21–40])	36 (39 [29–49])	<0.001

Medication side effects

Cyclosporine

Tremor
Kidney damage
High blood pressure
Hairiness
Gum swelling

Horse ATG

Must be given in hospital
Fever, chills, rigors
Fluid retention
Serum sickness (typically within 7-14 days of administration
- Rash, joint pain, fever

Eltrombopag

Liver dysfunction
- Reversible

Rash
Yellow eyes

Case study

- Patient did not have a matched sibling donor
- Commenced on hATG and Cyclosporine
  - 4 days hATG
  - 6 mos CSA
- Complete count recovery

Case Study

- 3 months later….
- Relapsed
- Options?

Reintroduction of CSA +/- EPAG

- Recovery of blood counts in the approximately half of patients with reintroduction of CSA

- This is increased with the reintroduction of EPAG along with CSA

Rabbit ATG or Alemtuzumab

Alemtuzumab versus rATG/CSA for people who failed hATG/CSA (refractory)

Scheinberg et. al. Activity of alemtuzumab monotherapy in treatment-naïve, relapsed, and refractory severe acquired aplastic anemia. Blood 2012.

Table 2. Hematopoietic Stem-Cell Transplantation for Severe Aplastic Anemia.*

Study	Transplant Source and Recipient Status	No. of Patients	Age	Conditioning and Prophylaxis	Overall Survival	Acute and Chronic GVHD†	Graft Failure
			yr		%	%	%
IBMTR prospective RCT, 1994–2001[64]‡	MFD — 50% of recipients had no previous treatment	70	Median, 23	Conditioning: Cy, ATG Prophylaxis: CsA, MTX	80 at 5 yr	Acute: 11 Chronic: 32	16
King's College retrospective study, 1999–2009[65]§	MFD — most recipients had no previous treatment; MUD — most recipients had refractory disease	100	Median, 18	Conditioning: Alemtuzumab+Cy Prophylaxis: CsA for MSD, FLU+Cy for MUD, FLU+Cy+TBI for mismatched MUD	90 at 5 yr	Acute: 29 Chronic: 3	9
EGBMT registry, children, 2000–2009[61]	MFD — no previous treatment	396	Range, 0–12	Conditioning: mainly Cy, some Cy+FLU Prophylaxis: CsA±ATG±MTX	87 at 3 yr	Acute: 8 Chronic: 6	2
EGBMT registry, adolescents, 2000–2009[63]	MFD — no previous treatment	394	Median, 15	Conditioning: mainly Cy, some Cy+FLU±ATG Prophylaxis: mostly MTX+CsA, some CsA+MMF	86 at 3 yr	Acute: 12 Chronic: 8	8
EGBMT registry, 2005–2009[66]	MFD — previous recipient treatments not described	940	50% >20	—	83 at 5 yr	Acute: 13 Chronic: 6	9
EGBMT registry, 2005–2009[66]	MUD — previous recipient treatments not described	508	53% >20	—	76 at 5 yr	Acute: 26 Chronic: 11	9
French national prospective study, 2011–2015[67]	UCB — refractory SAA	26	Median, 16	Conditioning: FLU+Cy+ATG+TBI Prophylaxis: CsA	85 at 2 yr	Acute: 46 Chronic: 36	12
JSHCT registry, 2001–2012[68]	UCB — refractory adult SAA	69	Median, 49	Conditioning: mainly FLU+melphalan+low-dose TBI Prophylaxis: MTX or MMF± glucocorticoids±CIN	69 at 3 yr	Acute: 32 Chronic: 21	29
Eurocord and EBMT retrospective registry, 1988–2014[69]	Sibling UCB with or without bone marrow — mainly for refractory disease	20	Median, 5.6	Conditioning: variable but mainly Cy+FLU Prophylaxis: variable but mainly CsA+glucocorticoids	81 at 7 yr	Acute: 6 Chronic: 8	10

* ATG denotes antithymocyte globulin, CIN calcineurin inhibitor, CsA cyclosporine, Cy cyclophosphamide, EBMT European Society for Bone Marrow Transplantation, EGBMT European Group for Bone Marrow Transplant, FLU fludarabine, GVHD graft-versus-host disease, IBMTR International Bone Marrow Transplant Registry, JSHCT Japan Society for Hematopoietic Cell Transplantation, MFD matched family donor, MSD matched sibling donor, MTX methotrexate, MUD matched unrelated donor, RCT randomized, controlled trial, TBI total-body irradiation, and UCB umbilical cord blood.

† Data for acute GVHD are for grades II, III, and IV disease. Data for chronic GVHD are usually for grades II, III, and IV (for extensive disease) and occasionally for all chronic GVHD.

‡ This RCT compared Cy alone with Cy plus ATG. There were no significant differences between the conditioning regimens with respect to outcomes. For simplicity, only data for the group that received CTX plus ATG are shown, since this is the more common conditioning regimen.

§ Only data from alemtuzumab-treated patients are shown; MSD and MUD are combined, as they were in the original report.

Case Study

- Did not respond to the reintroduction of CSA
- Transplant work up initiated
  - No fully matched sibling donor
  - Poor unrelated donor options
- Failed rATG/CSA
- EPAG commenced

Eltrombopag for refractory SAA

- Initially approved for this indication
- Approximately 50% response rate
- In most patients, eltrombopag could be stopped because of good response
- When patients who stopped eltrombopag relapsed they were salvaged by restarting it

Eltrombopag for refractory SAA

Winkler et al. Eltrombopag for refractory severe aplastic anemia: dosing, duration, long term outcomes and clonal evolution. Blood 2019.

Pure Red Cell Aplasia

- Anemia due to decreased bone marrow production of red cells

- Multiple causes:
  - Congenital
  - **Primary Immune**
  - Secondary
    - Parvovirus B19
    - Thymomas
    - Lymphomas

Presentation

- Anemia
- Low reticulocytes
- Bone marrow shows no or very few red cell precursors

Treatment of PRCA

- Steroids +/- cyclosporine
  - Front line treatment
  - 2/3 respond
- Azathioprine
- Tacrolimus
- Cyclophosphamide

Ongoing Research at NIH

- **Eltrombopag With Standard Immunosuppression for Severe Aplastic Anemia** (clinicaltrials.gov: NCT01623167)

- Ongoing trial looking at hATG/CSA/EPAG

- Eltrombopag approved for front-line treatment of SAA based on this trial

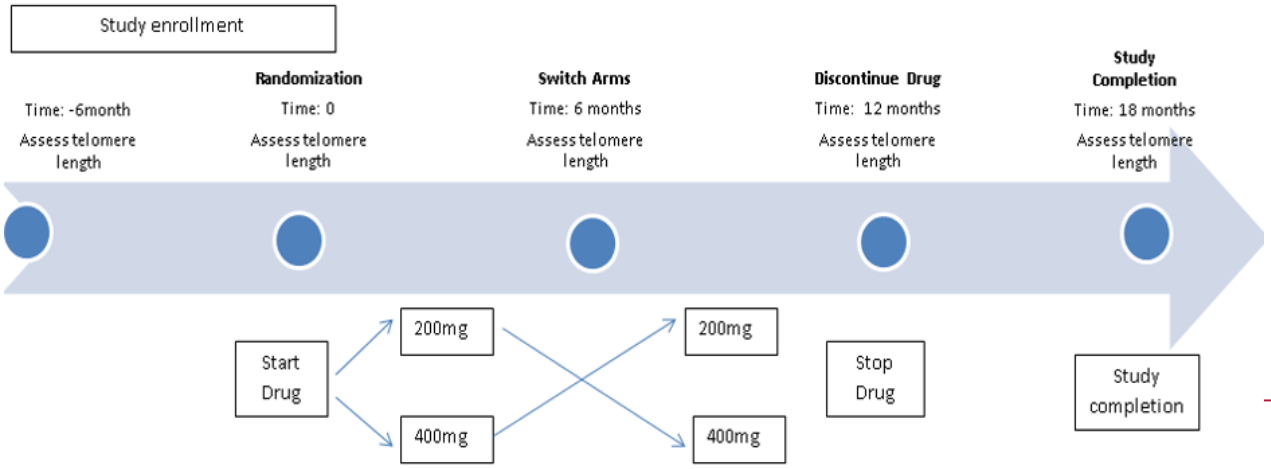
Ongoing Research at NIH

- **Sirolimus (Rapamune) for Relapse Prevention in People With Severe Aplastic Anemia Responsive to Immunosuppressive Therapy** (clinicaltrials.gov: NCT02979873)

- Aim is to prevent relapse of AA after stopping cyclosporine

Low Dose Danazol for the Treatment of Telomere Related Diseases (NCT03312400)

- Study Goals
  - Create a dose comparison study to identify a lowest effective dose of danazol
  - Define the clinical benefit of danazol in treating pulmonary fibrosis, hepatic fibrosis, and cytopenias associated with telomere disease



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Upcoming Research at NIH

- Early initiation of treatment for SAA
  - Start CSA + Eltrombopag quickly as an outpatient while waiting for ATG

- Immunosuppressive therapy for MDS and moderate aplastic anemia

Upcoming Research at NIH

- Natural History Protocol for Patients with Clonal Cytopenia of Uncertain Significance (**CCUS**)
  - Low blood counts + a genetic mutation but no evidence of MDS
  - Patients will be followed yearly and receive lots of testing to investigate CCUS

Other Active Research

- **Eltrombopag Combined With Cyclosporine as First Line Therapy in Patients With Severe Acquired Aplastic Anemia (SOAR)**
  - (clinicaltrials.gov: NCT02998645)

- **Eltrombopag + hATG + CsA vs. hATG + CsA in Severe AA**
  - (clinicaltrials.gov: NCT02099747)

Questions?

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