Treatment of Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria

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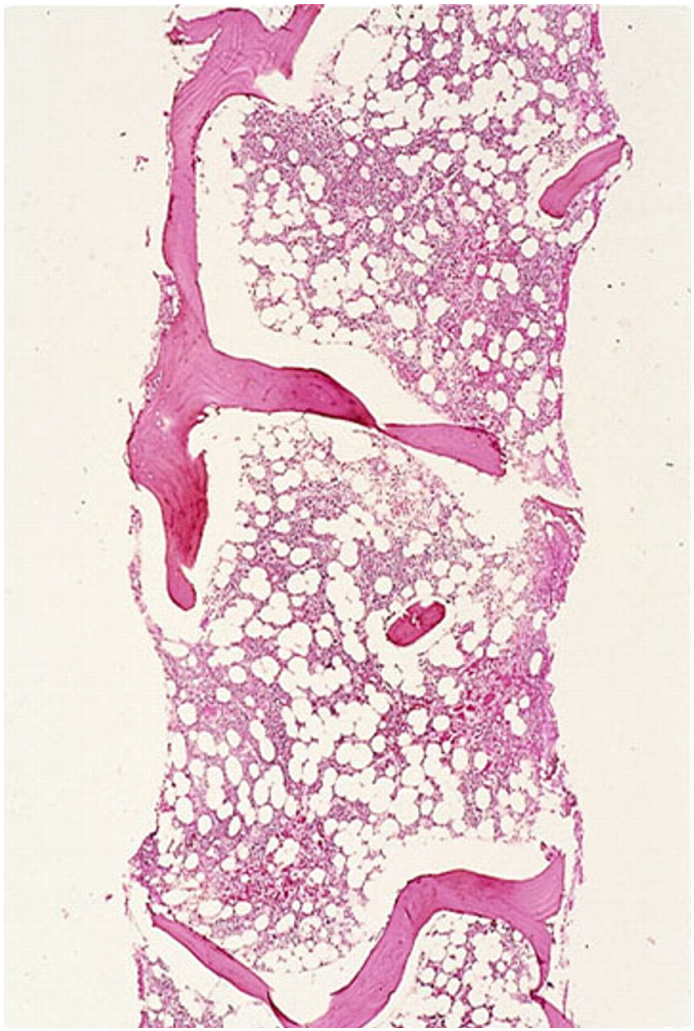
Disclosures

Disclosures

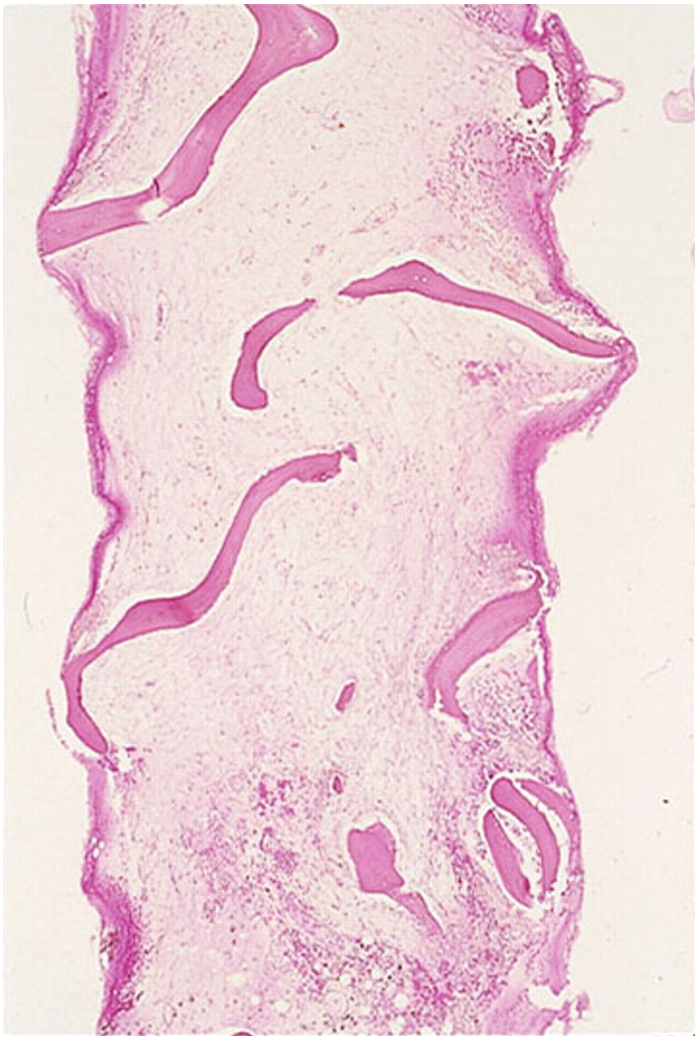
Consultant for	Celgene, Novartis, Pfizer,
Speaker Bureau	
Grant/Research support	Celgene, Roche, Novartis
Stockholder	
Honoraria	Celgene, Pfizer, Merck, Novartis
Employee	

Objectives

- To understand the role of the immune system in
  - Aplastic Anemia
  - Paroxysmal nocturnal hemoglobinuria
- To understand the tools in the treatment of these disease
- To understand how these tools are used and affect these diseases

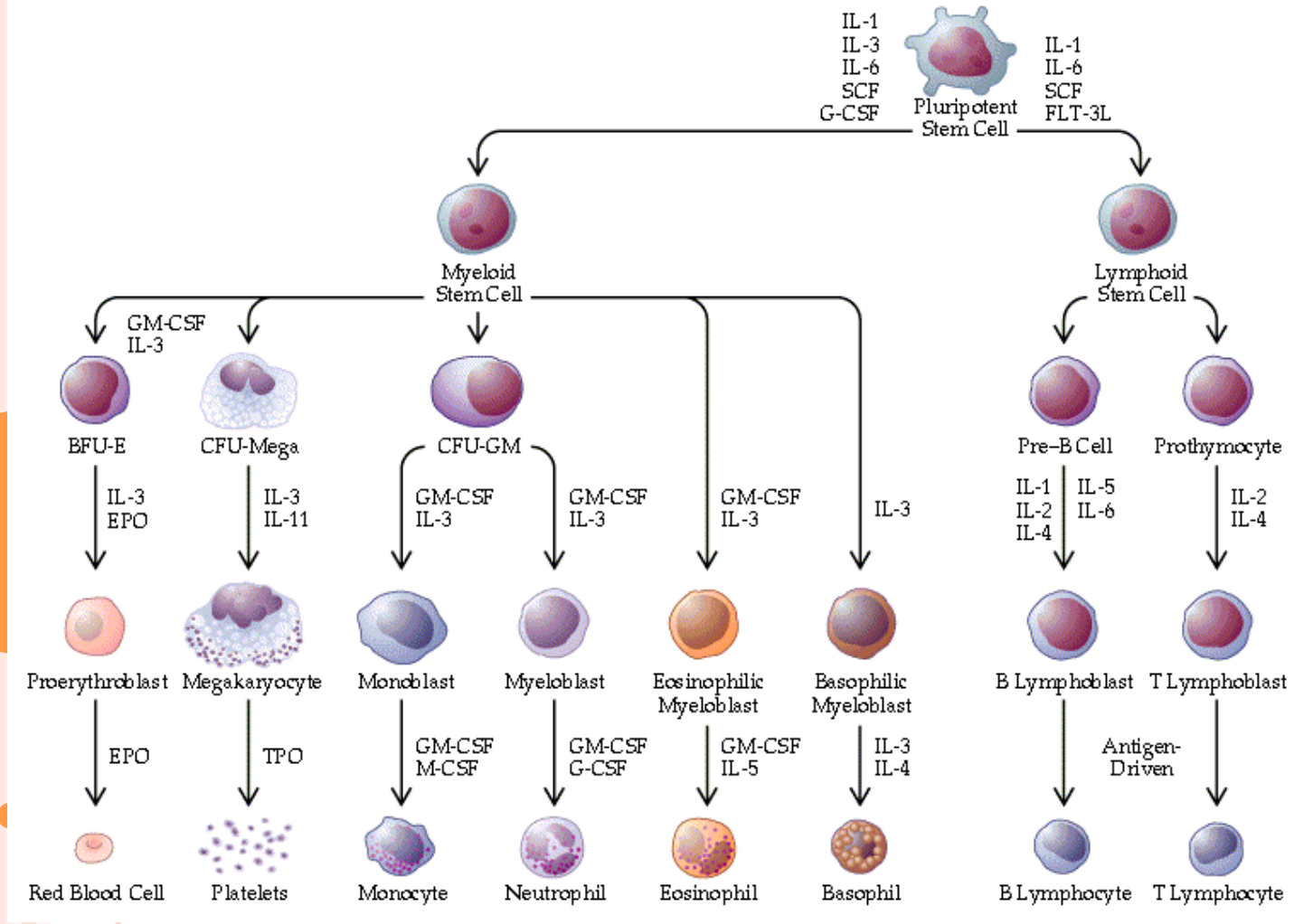


Normal Bone Marrow



Aplastic Bone Marrow

ASH Image Bank

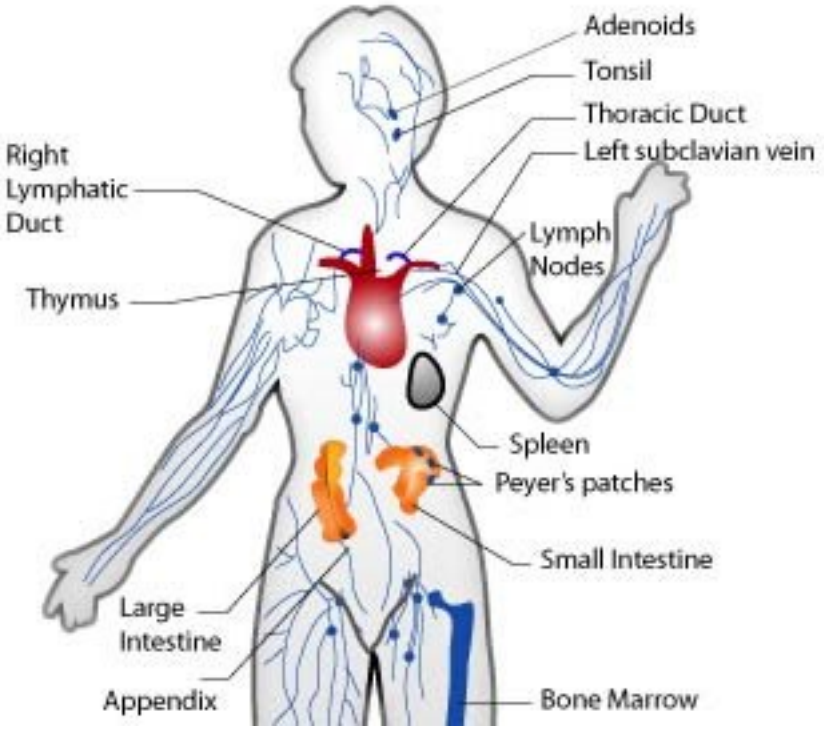

IL-1
IL-3
IL-6
SCF
G-CSF
Pluripotent Stem Cell
IL-1
IL-6
SCF
FLT-3L
Myeloid Stem Cell
Lymphoid Stem Cell
GM-CSF
IL-3
BFU-E
CFU-Mega
CFU-GM
Pre–B Cell
Prothymocyte
IL-3
EPO
IL-3
IL-11
GM-CSF
IL-3
GM-CSF
IL-3
GM-CSF
IL-3
IL-3
IL-1
IL-2
IL-4
IL-5
IL-6
IL-2
IL-4
Proerythroblast
Megakaryocyte
Monoblast
Myeloblast
Eosinophilic Myeloblast
Basophilic Myeloblast
B Lymphoblast
T Lymphoblast
EPO
TPO
GM-CSF
M-CSF
GM-CSF
G-CSF
GM-CSF
IL-5
IL-3
IL-4
Antigen-Driven
Red Blood Cell
Platelets
Monocyte
Neutrophil
Eosinophil
Basophil
B Lymphocyte
T Lymphocyte

Review background aplastic anemia

- Inherited
  - Fanconi's anemia
  - Dyskeratosis Congenita
  - Diamond-Blackfan Anemia
  - Schwachman-Diamond Syndrome
  - Congenital neutropenia

- Acquired
  - Infections
  - Toxins/chemicals
  - Medication
  - Immune

Basics of the immune system



- All cells made in the bone marrow
- T-cells get "educated" in the thymus
- In aplastic anemia T-cells appear to be directed against early blood cells
  - Initiating event is not clear.

http://www.the-immune-system.org/images/immune-system.jpg

Acquired aplastic anemia

- After ruling out other etiologies
  - Usually immune
  - 2/1 000 000
  - Then decide on severity
    - Mild, severe, very severe

Grading of AA

- Mild
  - Hypocellular marrow
- Severe
  - Bone-marrow cellularity < 25% and
    - neutrophil count < 0·5x 109/L
    - platelet count < 20x109/L
    - and absolute reticulocyte count 60x109/L.
- Very severe
  - neutrophil count <0·2x109/L

Mild AA

- Monitor for symptoms
- May not need any therapy
- Transfuse
- Look for any exacerbating factors
  - Vitamins
  - Bleeding
  - Infections

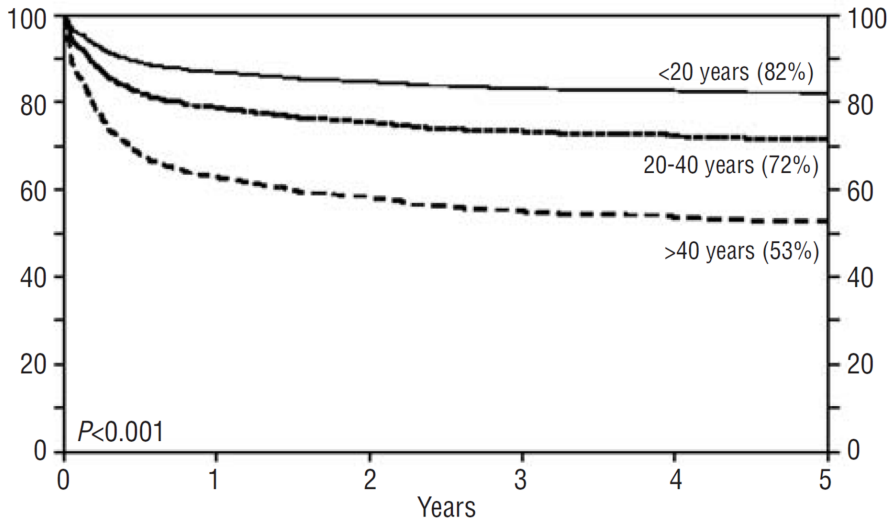
- Specific therapy
  - Immune- suppression

Severe and very severe AA

- Always requires therapy
- Exacerbating factors
- Associated disorders
  - i.e. PNH, MDS,
- Specific therapy
  - Stem cell transplant
  - Immune suppression

Stem cell transplant for AA

- Replace the blood and immune cells with a donor's
- Curative in large proportion from matched donor
- Limited to age <40
- Complicated by graft vs host disease 20-40%



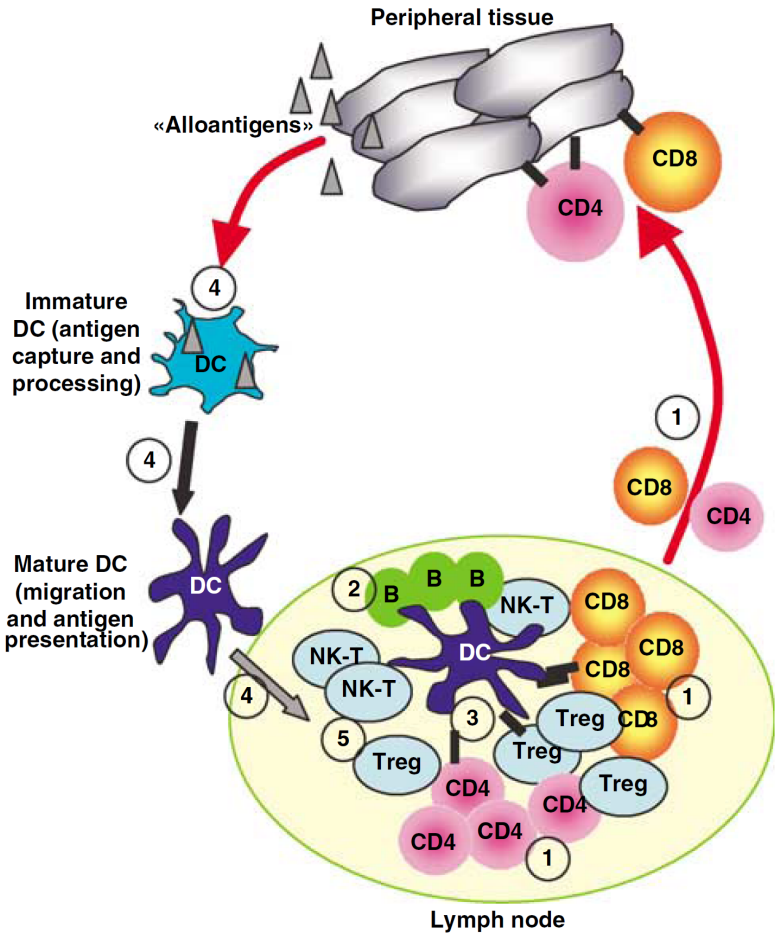
Gupta V. *Haematologica 2010;95(12);2*

Immune-suppression: Antithymocyte globulin (ATG)

- Anti-immune system product
- Created in either horse of rabbits.
- Pieces of thymus from donors undergoing cardiac surgery
- Injected into rabbits
- Serum is collected and prepared for use
- Many targets identified
- Mostly T-cells

Mohty M Leukemia (2007) 21;1387

How ATG impairs the immune system



1. T-cell depletion
2. B-cell depletion
3. Interfere with interaction between immune cells
4. Interfere with function of immune cells
5. Induction of certain immune cells

Mohty M. Leukemia (2007) 21;1387

Immune-suppression: Antithymocyte globulin (ATG)

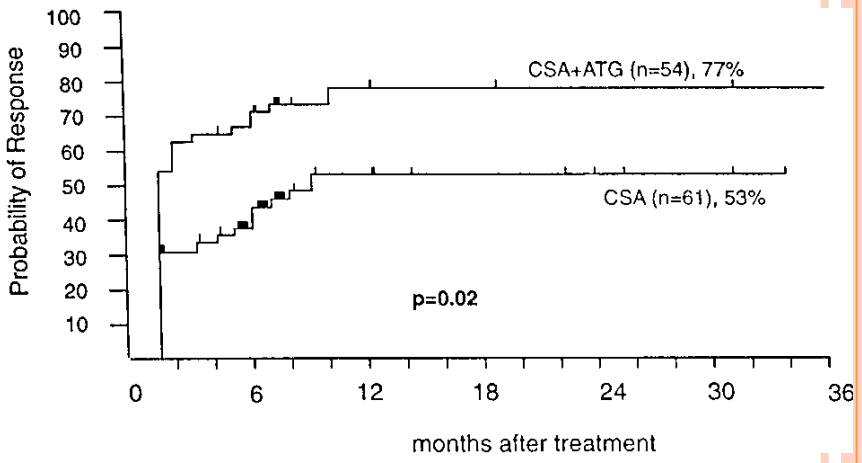
Side effects

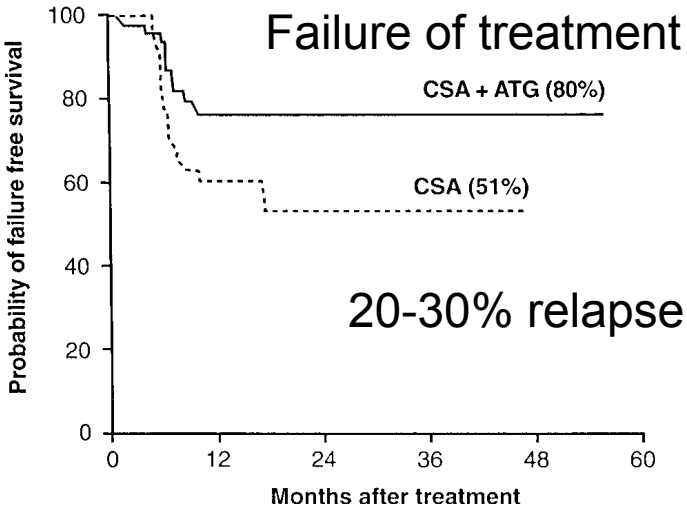
- Infusion-related
  - Fevers, rigors, rash, low blood pressure
- Serum sickness
  - 1-2 weeks after infusion
  - Fever, rash, sore joints and muscles, …
- Decrease in blood counts temporarily

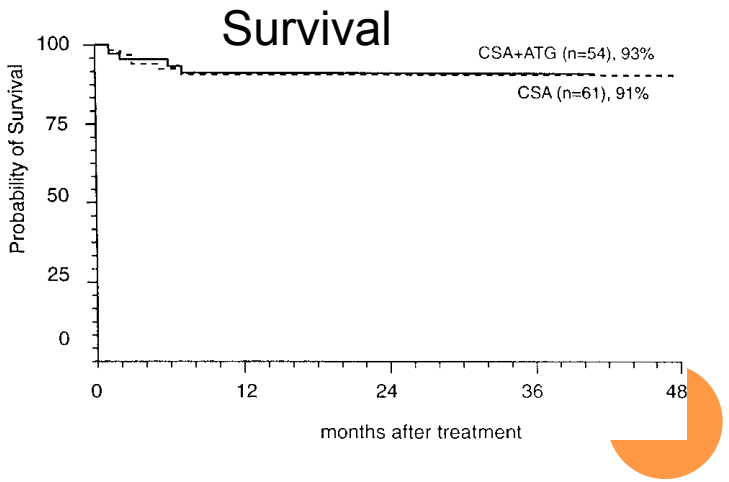
Immune-suppression: Cyclosporin

- Blocks signals in T-lymphocytes
- Dampening or interfering with their immune response.

Probability of Response to therapy







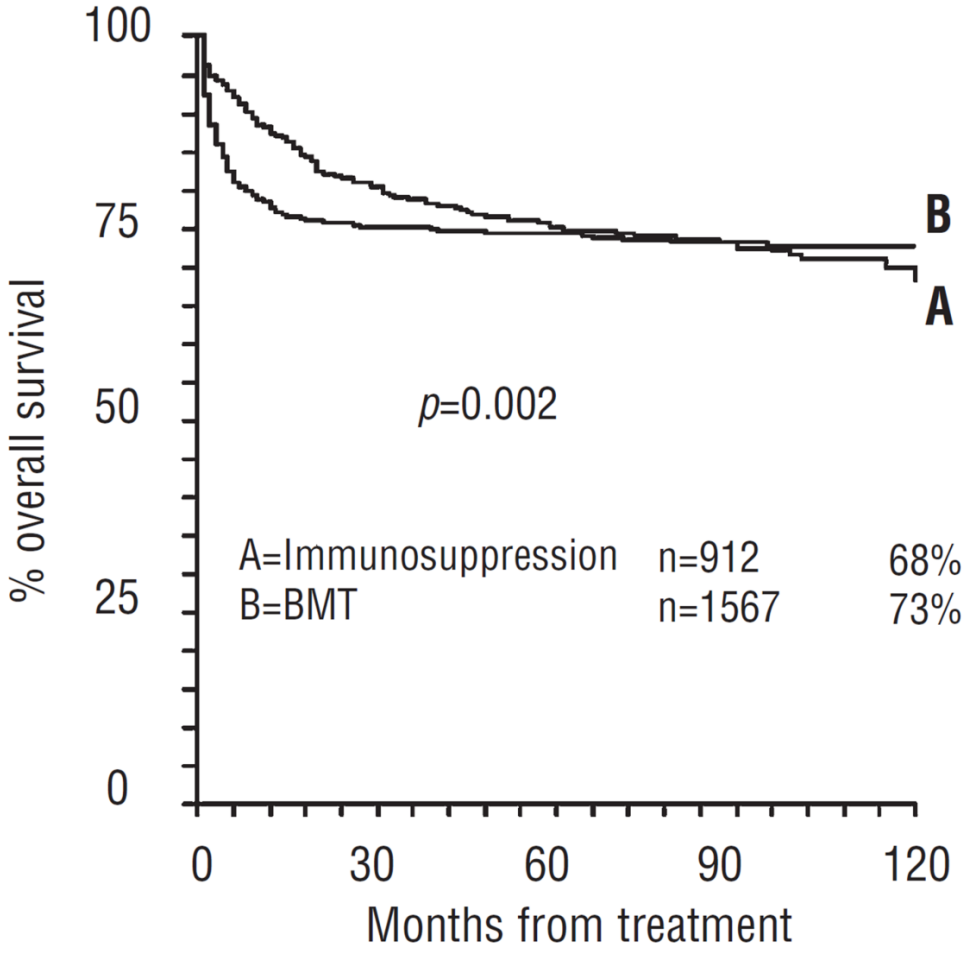
Marsh J Blood (1999) 93(7);2191

Immune-suppression: **Cyclosporin**

Side effects

- High blood pressure
- Kidney failure
- Hair growth
- Muscle aches
- …

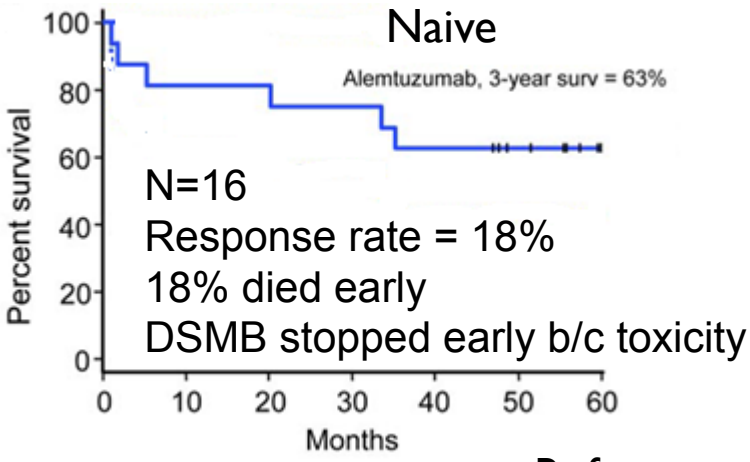
BMT vs. IST



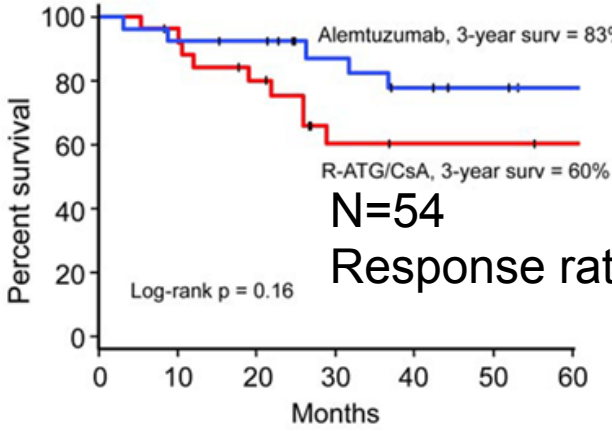
Median age
= 23 (1 – 94)
= 19 (1 – 67)

Locasciulli A. Haematologica 2007 92:11

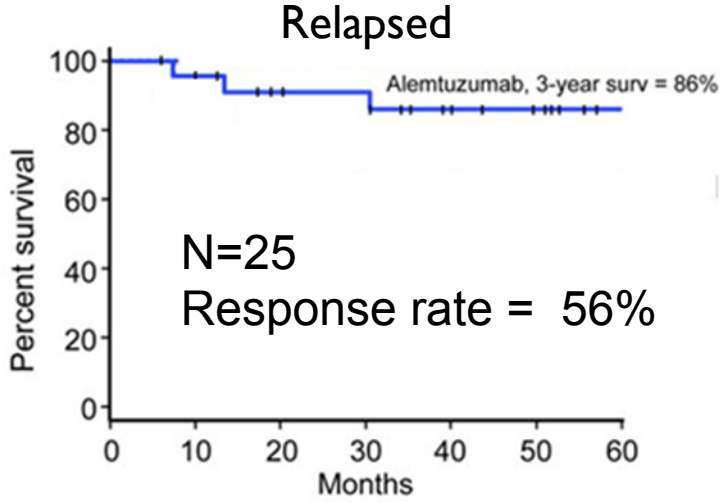
Other forms of immune suppression: Alemtuzumab



N=16
Response rate = 18%
18% died early
DSMB stopped early b/c toxicity



N=54
Response rate = 37 and 33%



N=25
Response rate = 56%

Alemtuzumab

- antibody
- Blocks lymphocytes
- 90 patients
- Median age = 40
- 10 day treatment

Scheinberg P. Blood (2012) 119(2);345

Paroxysmal Nocturnal Hemoglobinuria

- Frequency: 1-2/million
- Median age: 40
- Median survival 10-15 years

PNH - SOME HISTORY

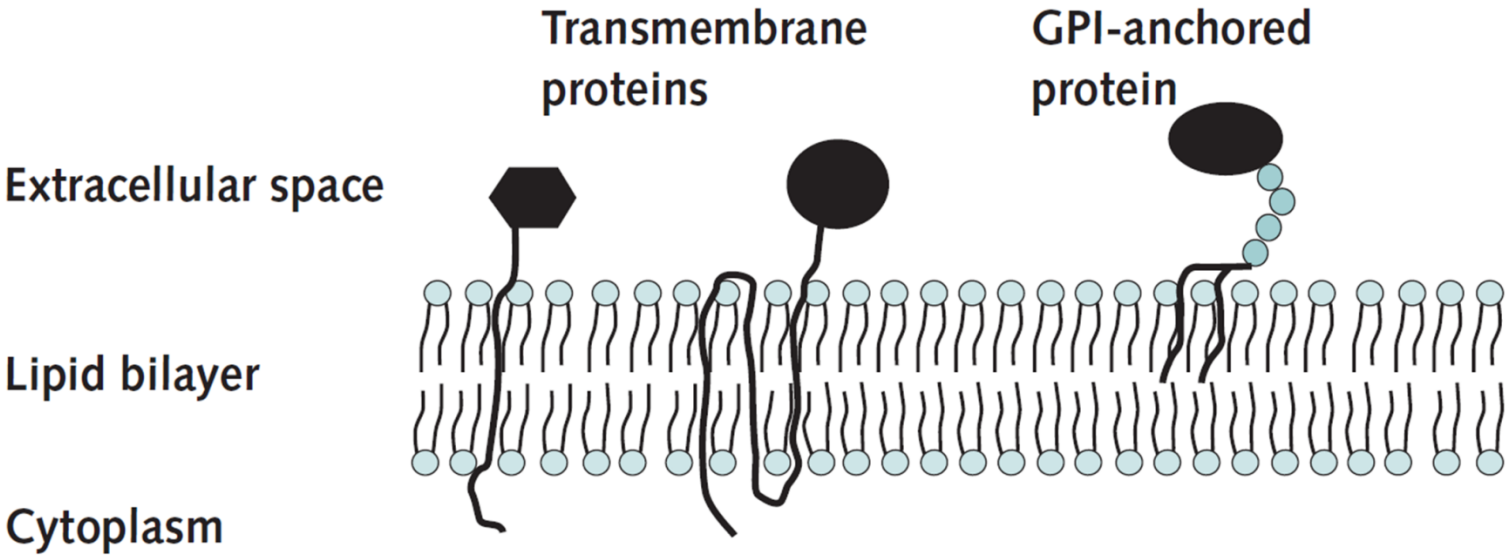
- 1882 – first description by Dr. Paul Strubing
  - 29-year-old with fatigue, abdominal pain, and severe episodes of dark urine at night (nocturnal paroxysms of hemoglobinuria)
- 1925 term paroxysmal nocturnal hemoglobinuria introduced
- 1938 – Ham's test developed
  - Dr. Thomas Hale Ham and Co. discovered that the red cells were more fragile in an acidic environment
- 1954 alternate pathway of complement activation described

PNH - SOME HISTORY

- 1967 – Dr. William Dameshek
  - proposed that PNH, aplastic anemia, and acute leukemia were related
  - bone marrow injury might be initiating event
- 1980s GPI anchors were missing
  - 2 GPI proteins CD55 and CD59 regulators of the complement system
- 2004 Dr. Hillmen and Co. published
  - Eculizumab demonstrated effective

PNH - Etiology

Red cells have many proteins on its surface
Many are linked through GPI anchor

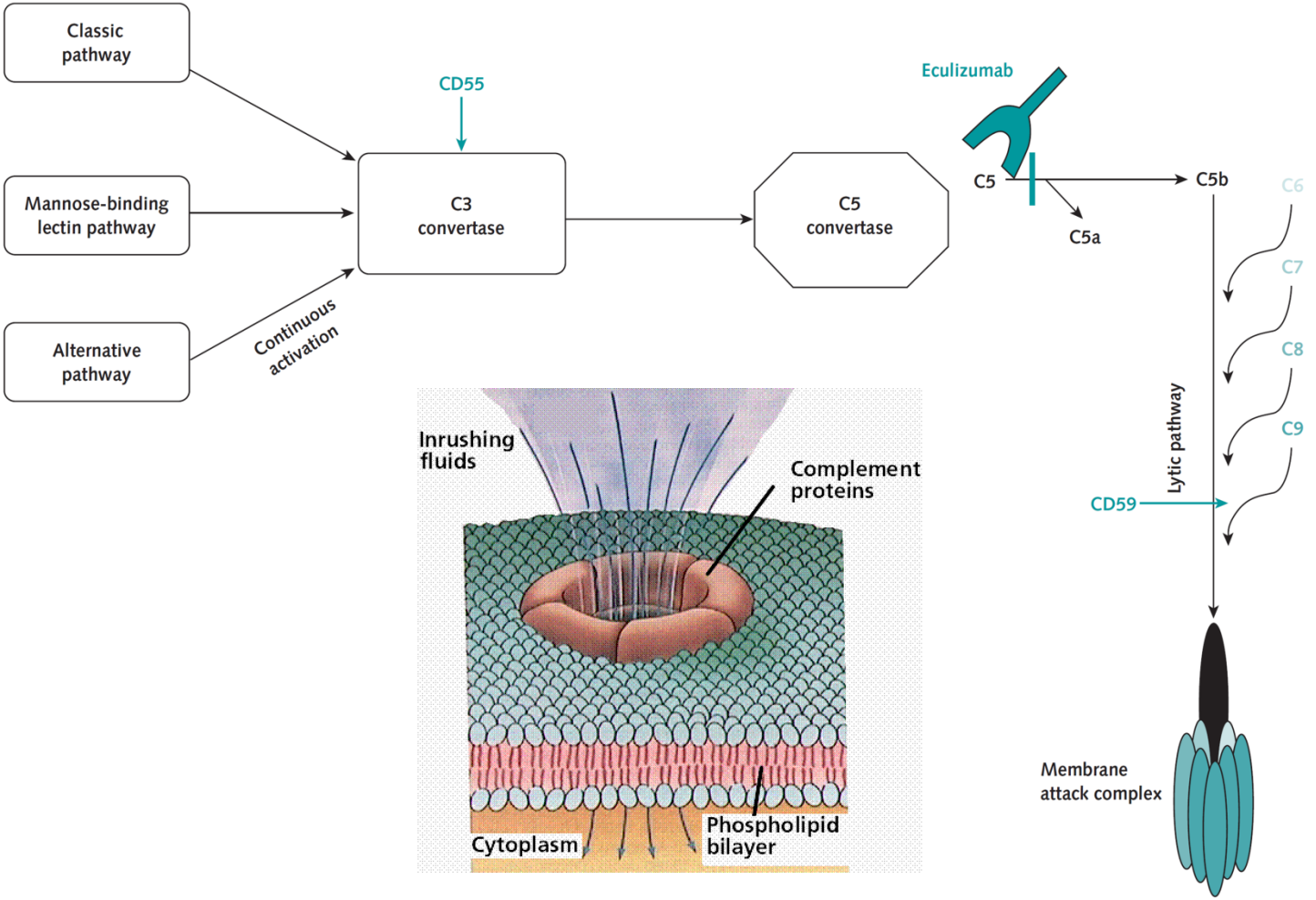


Brodsky RA. (2008) Ann Intern Med 148;587

PNH - Etiology

- Mutated PIGA gene
- PIGA essential for synthesis of a membrane anchor of many proteins (GPI-anchor).

PNH- ETIOLOGY



- CD 55 and CD59 central proteins affected.
- Results in uncontrolled complement activation

Consequences of PNH

- Hemolysis
  - Breakdown of red cells
- Muscle spasms
  - Abdominal pain, esophageal pain, erectile dysfunction
  - Nitric oxide depletion
- Thrombosis
  - Blood clotting
  - Unusual locations
  - Leading cause of death
- Bone marrow failure
  - No or dysfunctional precursors in the bone marrow (AA or MDS)
  - Low blood counts leading to transfusion dependence

Classification

Category	Rate of intravascular hemolysis[b]	Bone marrow	Flow cytometry analysis	Benefit from eculizumab
Classic	Florid (markedly abnormal LDH often with episodic macroscopic hemoglobinuria)	Hypocellular with areas of erythroid hyperplasia and normal or near-normal morphology[c]	Large (50–100%) population of GPI-AP-deficient PMNs[e]	Yes
PNH in the setting of another bone marrow failure syndrome[d]	Mild (often with minimal abnormalities of biochemical markers of hemolysis)	Evidence of a concomitant bone marrow failure syndrome[d]	Moderate (25–50%) population of GPI-AP-deficient PMNs[e]	Typically no, but some patients in this subcategory have clinically significant hemolysis and may benefit
Subclinical	No clinical or biochemical evidence of intravascular hemolysis	Evidence of a concomitant bone marrow failure syndrome[d]	Small (<25%)[f] population of GPI-AP-deficient PMNs[e]	No

Parker C. Blood (2005) 106;3699

Treatment approach

- Symptomatic treatment
- Specific treatment

Symptomatic treatment

- low blood counts
  - Transfusions
  - Folic acid
- thrombosis
  - Anticoagulation
- hemolysis
  - Steroids
  - Androgens
  - Eculizumab

Specific therapies

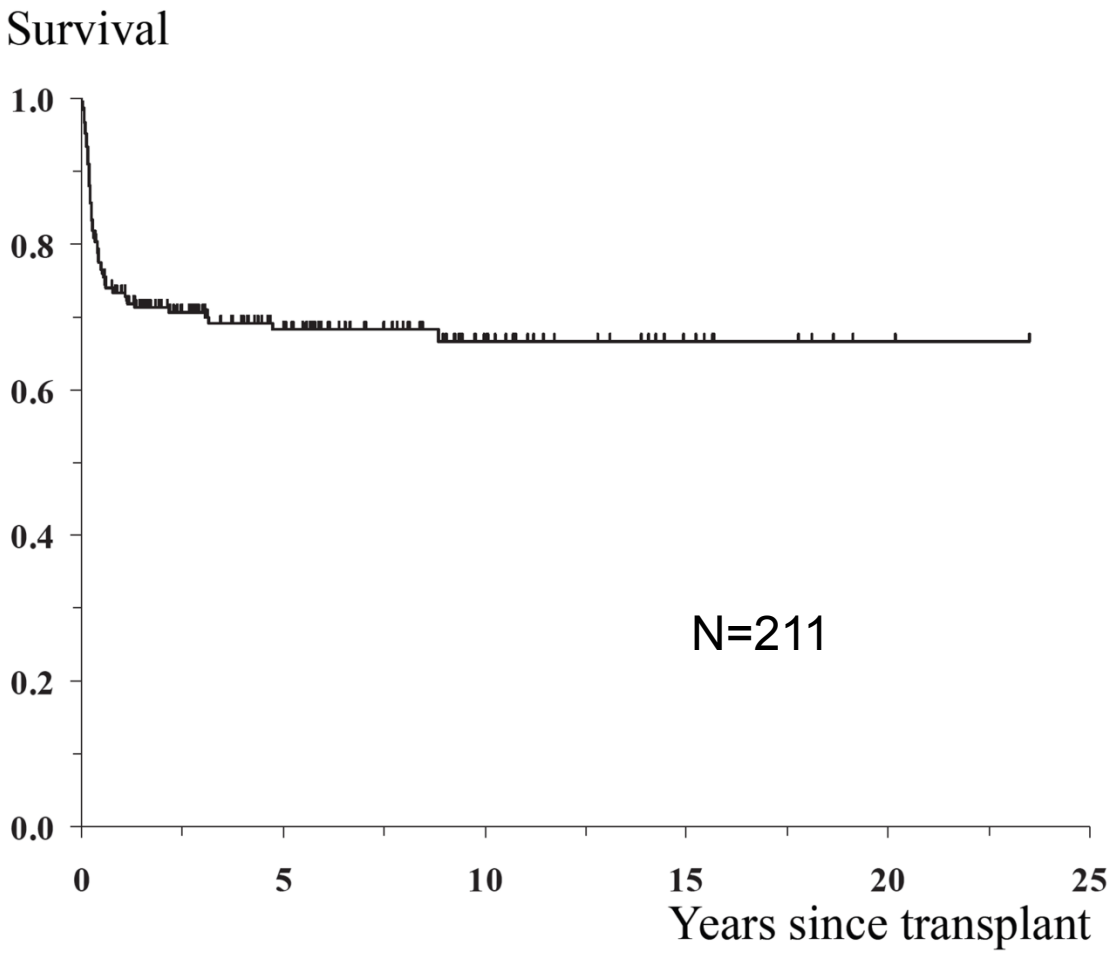
- Hemolysis
  - Eculizumab
- Bone marrow failure
  - Immune suppression
  - Stem cell transplant

Marrow Failure
Immune therapy

- Similar approach to AA

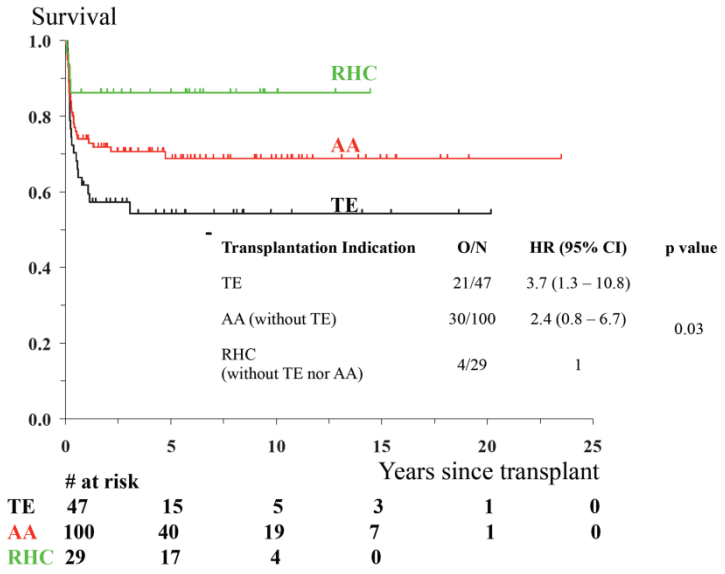
- Higher responders to immune therapy than those without PNH clone

Bone marrow transplant



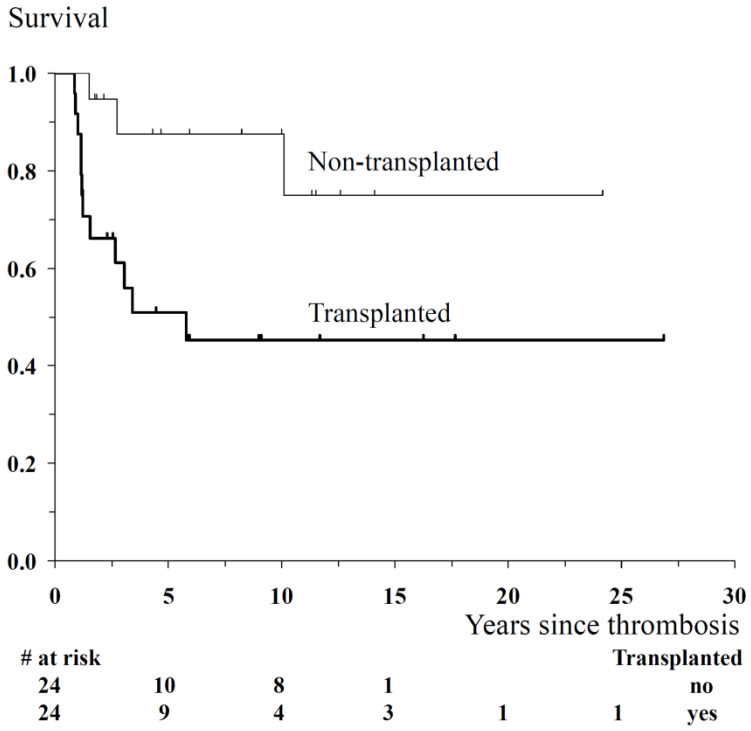
Peffault de Latour R. Haematologica (2012) Epub

OS for different indications

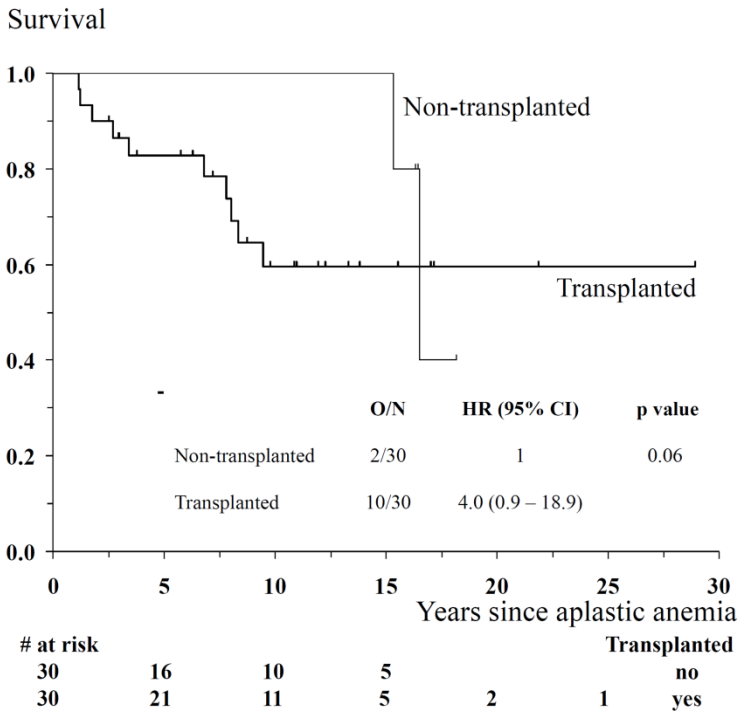


Transplantation Indication	O/N	HR (95% CI)	p value
TE	21/47	3.7 (1.3 – 10.8)	
AA (without TE)	30/100	2.4 (0.8 – 6.7)	0.03
RHC (without TE nor AA)	4/29	1	

OS after thrombosis



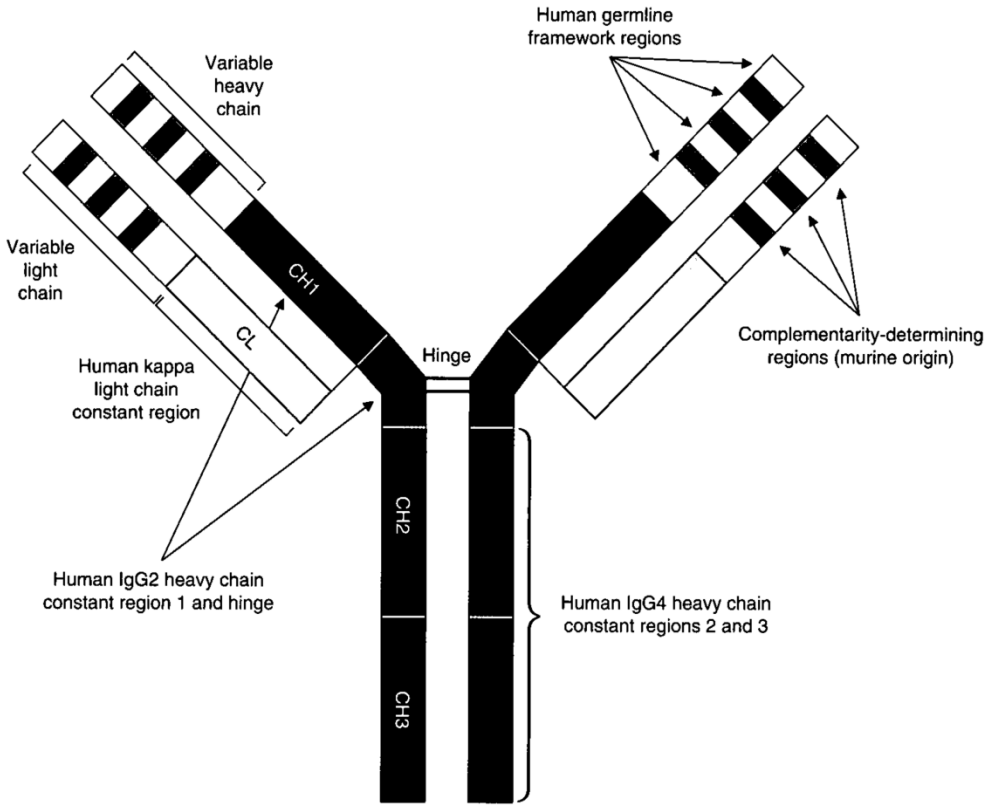
OS for aplastic anemia

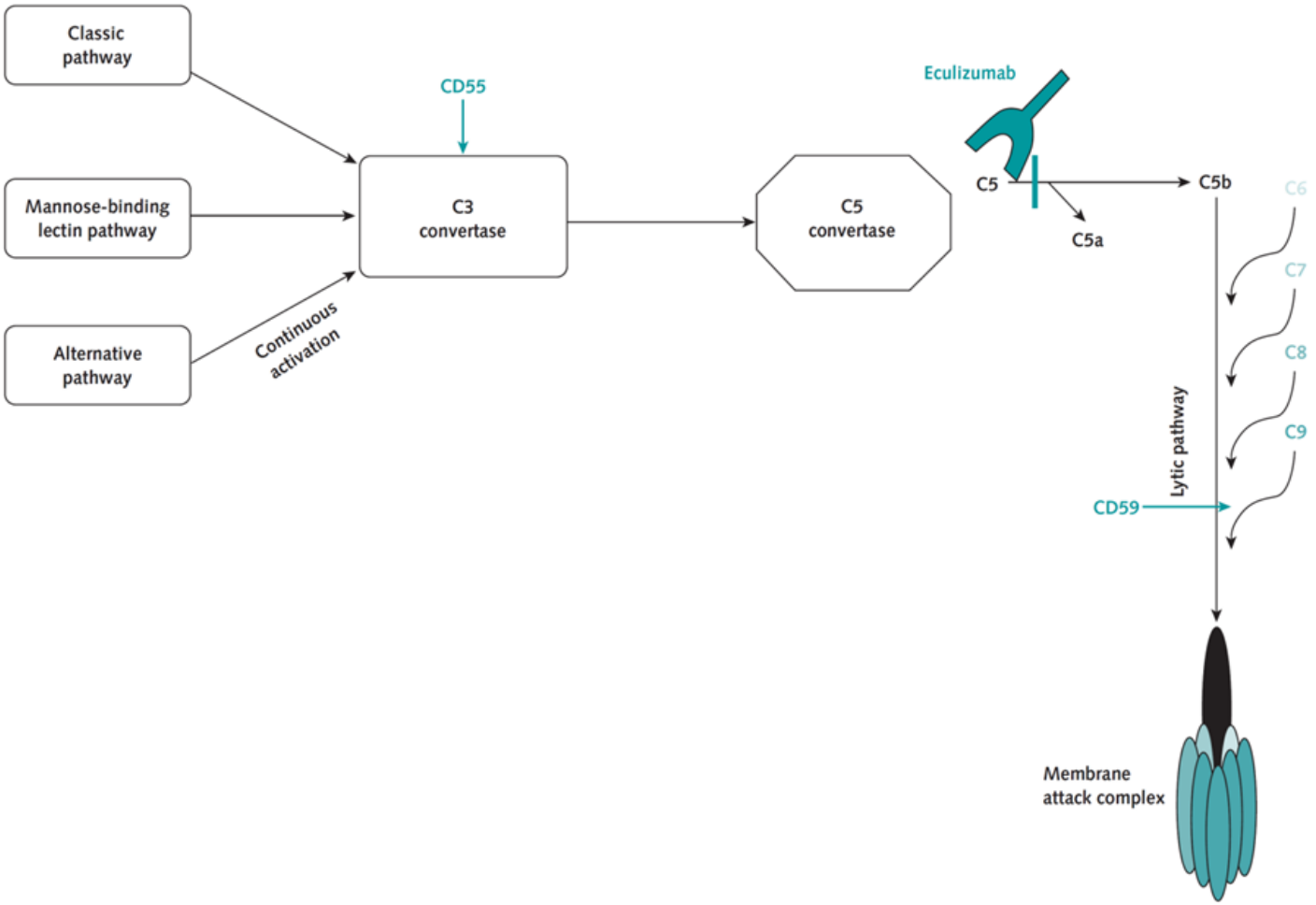


Eculizumab

- Antibody targeted to C5
- Reduces rate of hemolysis and transfusions

- Cautions
  - Headaches
  - Neisseria infections
  - Effective for hemolysis (classic PNH)
  - Expensive
  - Therapy is lifelong



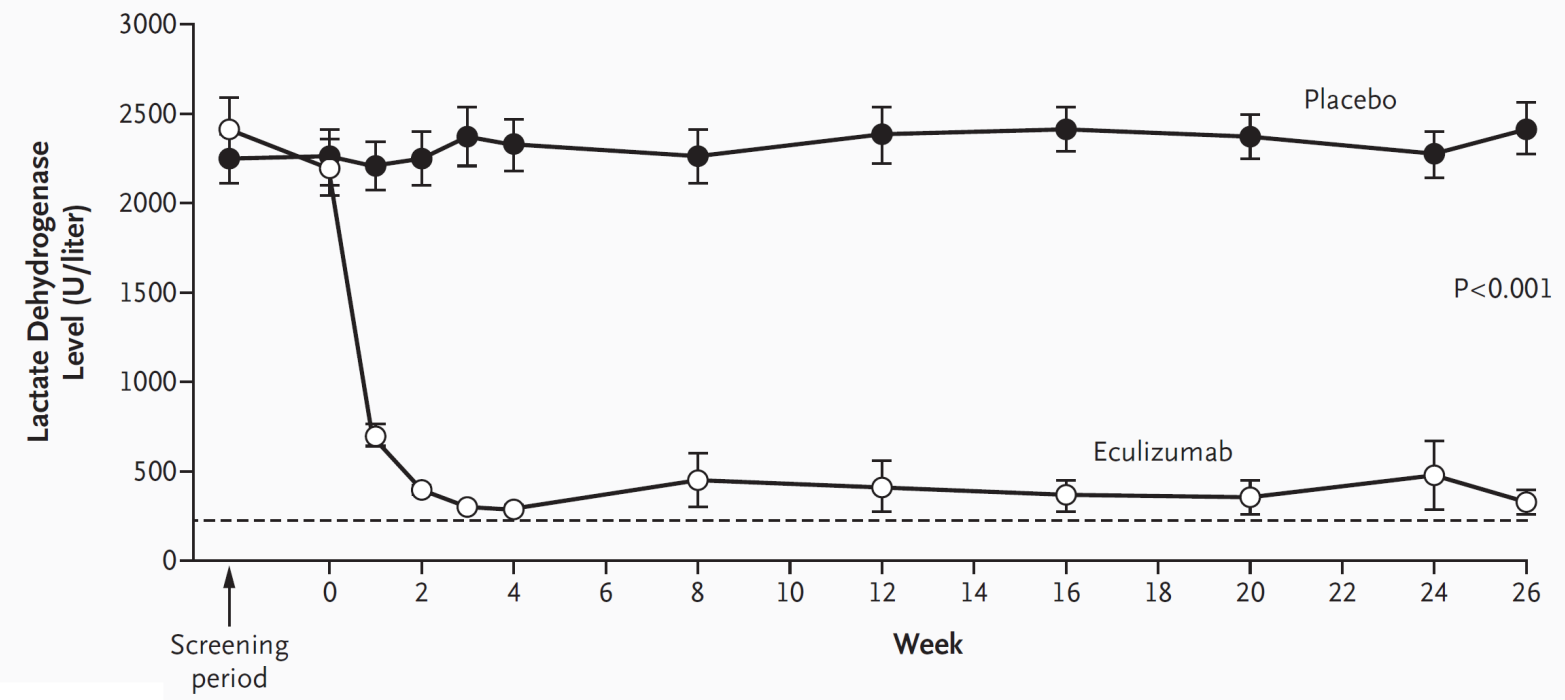

Classic pathway
Mannose-binding lectin pathway
Alternative pathway
Continuous activation
CD55
C3 convertase
C5 convertase
Eculizumab
C5
C5a
C5b
C6
C7
C8
C9
Lytic pathway
CD59
Membrane attack complex

Eculizumab

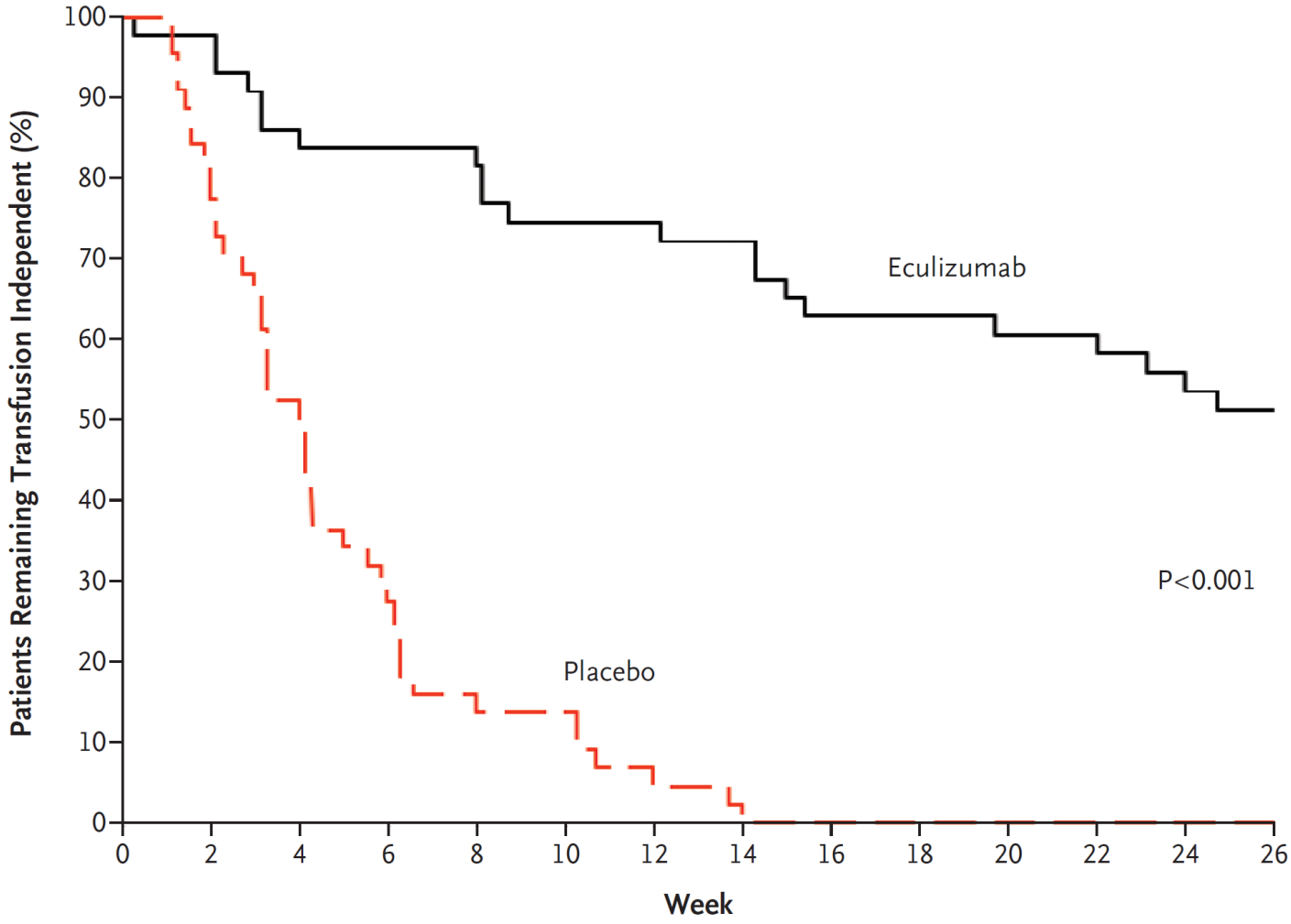
- Based on work over a decade prior
- 2006 TRIUMPH study
  - Randomized study
  - Reduced hemolysis
  - Reduced transfusion requirements
  - Improved fatigue
- 2008 SHEPHERD study
  - Evaluated long-term safety and efficacy
  - Not randomized
  - Less stringent entry criteria

Hillmen P. (2006) NEJM 355;12
Brodsky RA. (2008) Blood 11;1840

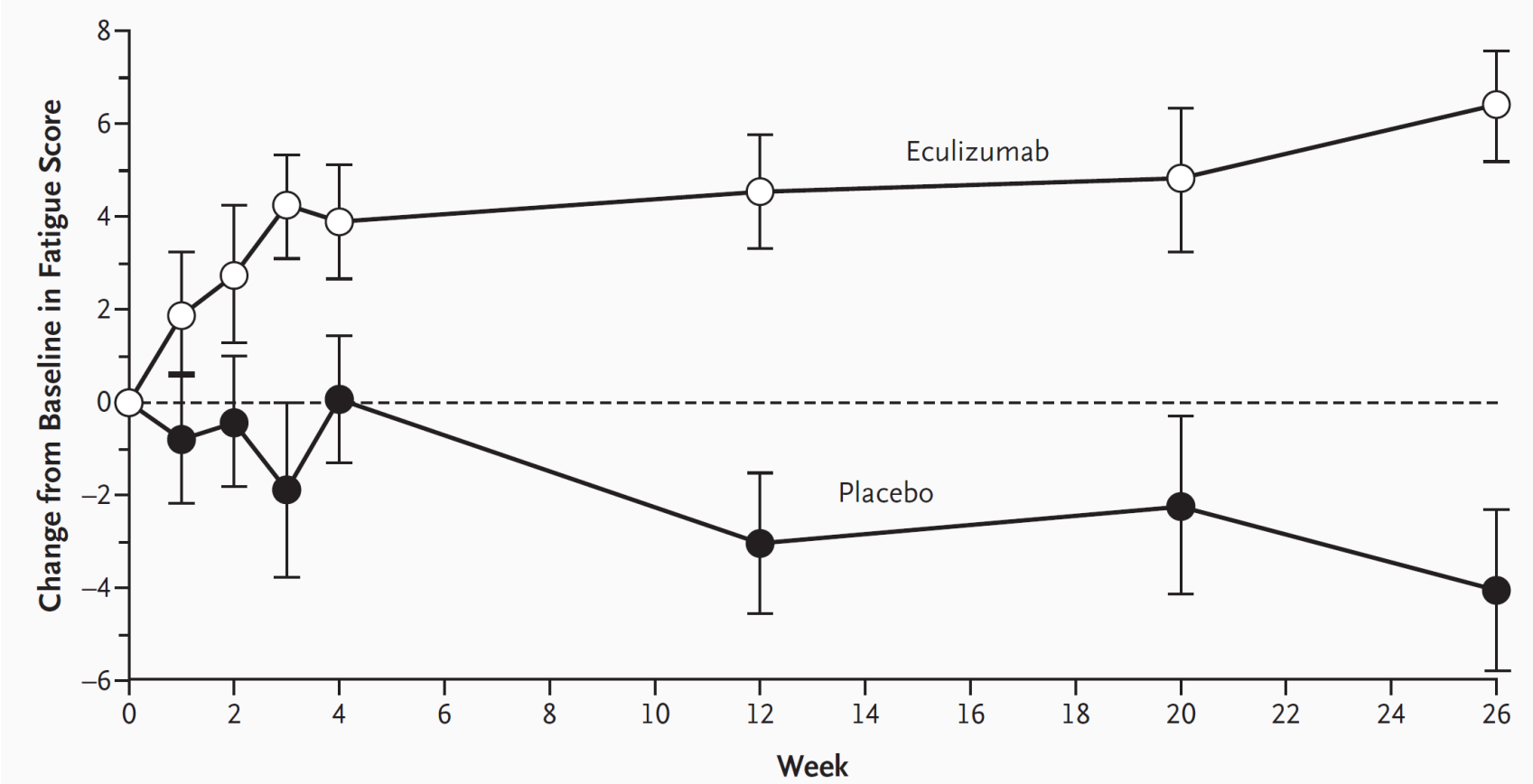
TRIUMPH – results - LD



TRIUMPH – results – time to need for first transfusion.



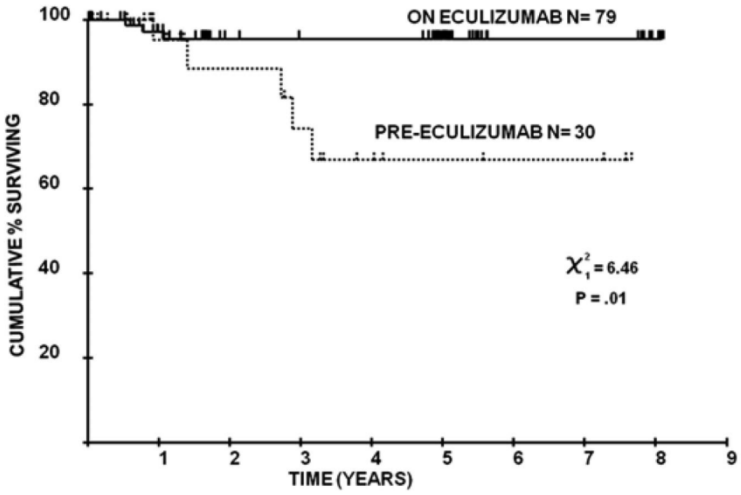
TRIUMPH – results - FATIGUE

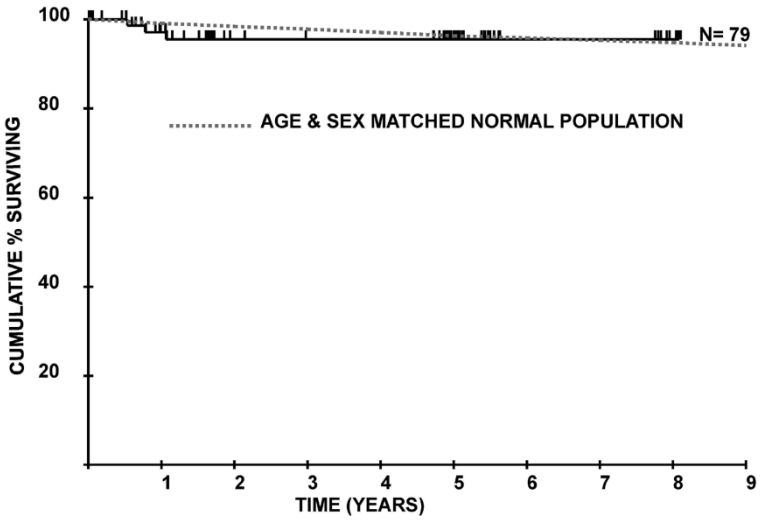


THROMBOSIS

- One of the major problems in PNH
  - 40% incidence
- Rate reduced significantly on eculizumab
- 5.6 compared to 0.8 events/100 patient years

Long-term survival





Kelly RJ Blood (2011) 117;6786

Conclusions

- AA and PNH
  - Treated based on understanding the immunological basis of the disease
  - Attack different aspects of the immune system
  - Treatment are improving with time
  - More effective treatment are competing with stem cell transplants


THANK
YOU

Treatment based on classification

- Subclinical PNH
  - MDS or AA
  - PNH clone <1%
  - No specific PNH treatment
  - Appear to respond better to immunosuppressive therapy.

Treatment based on classification

- PNH in the setting of another BM failure syndrome
  - Again no specific PNH therapy
  - Treatment directed at underlying marrow failure syndrome (i.e. AA or MDS)
    - Allogeneic stem cell transplant
    - Immunosuppressive therapy.

Treatment based on classification

- Classic PNH
  - Large clone (>50%)
    - Hemolysis, elevated LD, hemoglobinuria
    - Lethargy, malaise
    - Treated with eculizumab
    - +/- anticoagulation
    - Treatment of any other causes for cytopenias (i.e. vitamins, bleeding, infections, other medications…)
    - +/- danazol
    - +/- steroids
    - +/- splenectomy

To do

- Understand alemtuzumab study
- History of AA treatment
- NEJM editorial
- Organize