Is the allogeneic stem cell transplantation still an option for PNH therapy?

Camilla Frieri, MD, PhD

AORN San Giuseppe Moscati, Avellino

Firenze, 3-4 Ottobre 2024

Conflicts of interest

Advisory board : Sobi, Novartis.
Speakers bureau: Alexion, Novartis.

Ask to AI:

Is there a role for transplant in PNH?

“It can potentially cure the disease by replacing the patient’s bone marrow with that of a healthy donor, which can restore normal blood cell production and eliminate the PNH clone”

Ask to AI:

Is the allogeneic stem cell transplantation still an option for PNH therapy?

Yes, allogeneic stem cell transplantation (HSCT) is still an option for the treatment of PNH, though its use has become more selective due to the effectiveness of newer therapies, such as complement inhibitors.

Ask to AI:

Is there a role for transplant in PNH in the era of complement inhibitors?

“In the context of complement inhibitors like eculizumab and ravulizumab, the role of transplantation in paroxysmal nocturnal hemoglobinuria (PNH) has evolved…(…).. it remains a viable option for select patients, particularly those with severe or refractory disease.”

Ask to AI:

Is there a role for transplant in PNH in the era of proximal complement inhibitors?

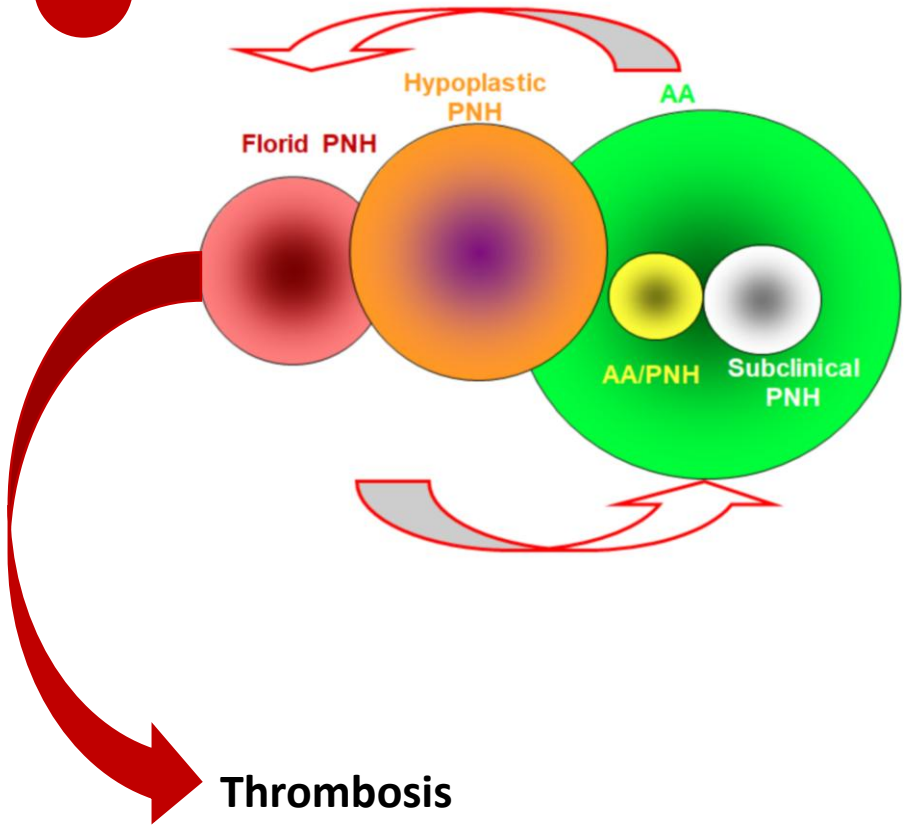
“In the context of proximal complement inhibitors the role of transplantation in PNH remains nuanced….(..)The choice should be made in collaboration with a specialized medical team.”

ChatGPT can make mistakes. Consider verifying important information.

Expert opinions

Is the allogeneic stem cell transplantation still an option for PNH therapy?

Disease's characteristics:



Patient's characteristics:

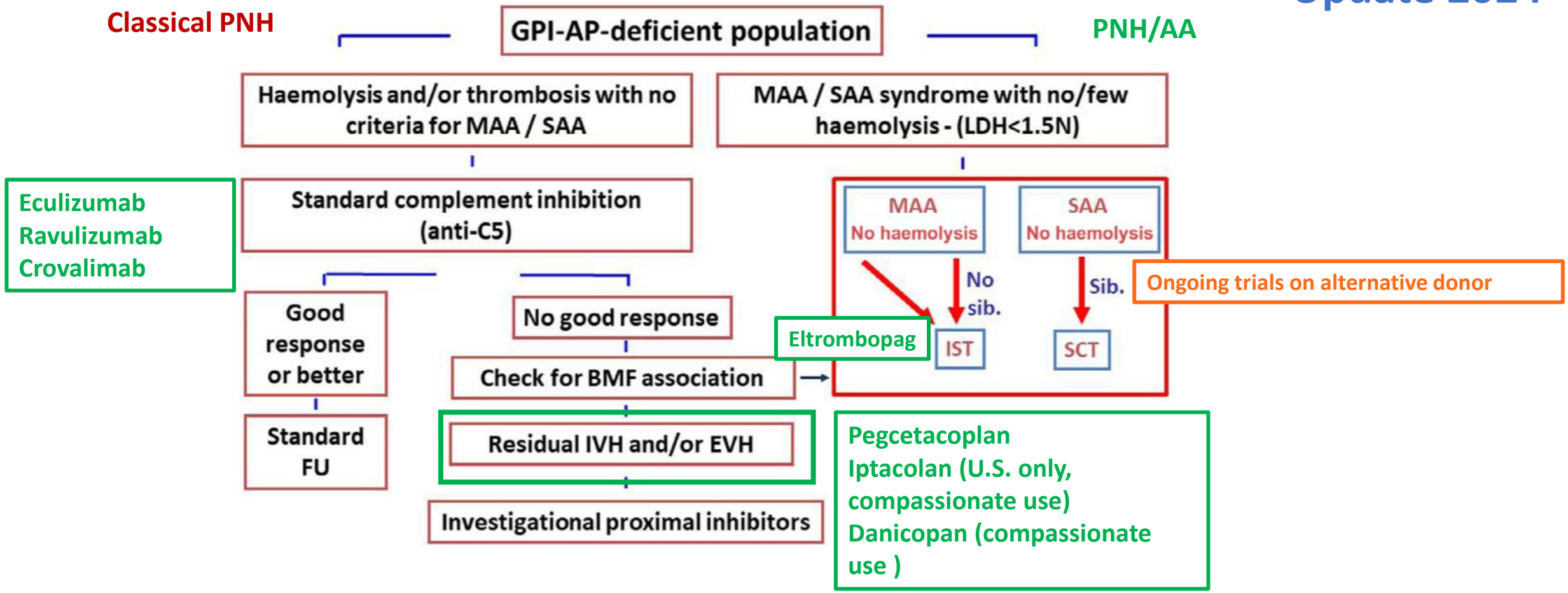
- ✓ Age
- ✓ Comorbidities
- ✓ Organ function
- ✓ Infections

Donor's availability

What therapies do I have available?
(where I am)
(what economic means I have)

Tentative treatment algorithm in PNH by Risitano and Peffault de Latour, BJH 2022

"Update 2024"



History of HSCT in PNH never treated with CI

British Journal of Haematology, 1973, **24**, 743.

Paroxysmal Nocturnal Haemoglobinuria and Refractory Marrow Failure Treated by Marrow Transplantation

RAINER STORB, ROBERT S. EVANS, E. DONNALL THOMAS, C. DEAN BUCKNER, REGINALD A. CLIFT, ALEXANDER FEFER, PAUL NEIMAN AND STEPHEN E. WRIGHT

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(*Received 29 August 1972; accepted for publication 2 October 1972*)

SUMMARY. A patient with pancytopenia and paroxysmal nocturnal haemoglobinuria (PNH) following exposure to insecticide spray developed complete marrow failure after inhalation of vapours containing benzol. There was no sign of spontaneous recovery after more than 6 mth of conventional and supportive therapy. The patient was treated with the immunosuppressive agent cyclophosphamide, 50 mg/kg on each of four days, followed in 36 hr by transplantation of marrow from a sibling compatible at the major human histocompatibility locus (HL-A). Intermittent methotrexate therapy was given for 102 days after grafting to prevent graft-versus-host disease. The patient showed prompt haemopoietic engraftment indicated by restoration of marrow cellularity and a rise in peripheral blood cell counts beginning on day 11 after the graft. The patient is alive and well with normal haemopoietic function and continued absence of PNH more than 1 yr and 4 mth after transplantation.

Hematopoietic Cell Transplantation for Paroxysmal Nocturnal Hemoglobinuria in the Age of Eculizumab

Jason P. Cooper[1,2], Rafic J. Farah[1,3,†], Philip A. Stevenson[1], Ted A. Gooley[1,4], Rainer Storb[1,3], Bart L. Scott[1,3,*]

BJH, 2019

"At the time of this report, he was alive, in good health, and disease-free for almost 47 years .."

History of HSCT in PNH never treated with CI

1973, R. Storb: 1st pt transplanted for PNH/AAS	1984, Antin: 4 pts transplanted for PNH/AAS(PNH clone range 7-50%)	1999, Saso: 57 pts transplanted (32% AAS, other ?)	2000, Raiola: 7 pts transplanted (PNH clone range 0.4-17%) 4pt PNH/AAS 3hPNH	2009, Santarone: 26 pts transplanted (4 pts AAS/PNH, 46% tPNH)	2012, RPDL: 211 pts transplanted (62% AAS/PNH, 70%, RHC, tPNH 25%, MDS/LAM 7%)
Alive after 47yrs	All alive after 5 yrs	2-y prob of survival 56%	All alive (mean follow-up range 6-103 mo)	10 yrs probability of DFS 57%	5-y OS probability 68%

Main considerations:

- ✓ Only retrospective data;
- ✓ Heterogeneous transplant indications (hPNH, AAS/PNH, tPNH, clonal evolution);
- ✓ Heterogeneous conditioning regimens;
- ✓ Heterogeneous type of donor;
- ✓ Heterogeneous source of stem cells;
- ✓ Heterogeneous GVHD prophylaxis.

History of HSCT in PNH treated with CI (eculizumab)

Table 2
Eculizumab Treatment Combined with HSCT in Patients with PNH

Article	No. of Cases	Sex, F/M, n	Age, yr, median (range)	Indication for HSCT	Disease Duration, mo, median (range)	Donor Source	Conditioning Regimen	Pre-HSCT Eculizumab Dose	Post-HSCT Eculizumab Dose	aGVHD/ cGVHD, n	Follow-Up, mo, median (range)	Deaths, n	Cause of Mortality	Relapse Rate, %
Cooper et al. (2018) [11],* **USA**	7	5/2	27.8 (14.9~54.9)	Clonal evolution to MDS, 3; progressed to BMF, 3; hemolytic attacks during eculizumab, 1	2.9 (1~30.3)	MRD, 1 MUD, 5 UCB, 1	MAC, 5 RIC, 2	Three patients 900~1200 mg every 2 wk until HSCT, 1 patient 600 mg on day -9, and 1 patient 600 mg every 7 d for 2 mo	One patient 600 mg on days -9, -1, +5, +12, and +19; one patient 900 mg on days -1, +12, +26, and +40*	5/4	27.6 (2.4~82.8)	0	NA	NA
DeZern et al. (2018) [7] **USA**	8	4/4	24.5 (17-47)	Progressed to BMF	NA	MRD, 5 MUD, 3	NMA	600 mg every 7 ± 2 d for 4 doses, then 900 mg every 7 ± 2 d, then maintenance dose of 900 mg every 14 ± 2 d	None	0	37 (2~83)	0	NA	NA
Vallet et al. (2018) [18] **France**	21	NA	NA	Clonal evolution to MDS; recurrent thrombosis; AA/PNH; transfusion- dependent classical PNH	NA	MRD, 10 MUD, 8 Syng, 2 Haplo, 1	NMA, l8 MAC, 2 NCR, 1	600 mg weekly for 4 wk, then 900 mg (maintenance dose) every 14 d	Three patients 900~1200 mg every 2 wk until HSCT; 1 patient 600 mg on day -9 and 1 patient 600 mg every 7 d for 2 mo	7/0	45 (1~120)	6	Infection, 3 GVHD, 2 MDS transformation, 1	1 (4.8)
Mei et al. (2019) [30] **USA**	8	2/6	42 (25~63)	Progressed to BMF	NA	MRD, 4 MUD, 4	RIC	600 mg every 7 ± 2 d for 4 doses, then 900 mg for 7 ± 2 d, then 900 mg every 14 ± 2 d (maintenance dose)	Eight patients accepted 1~3 doses of eculizumab within 30 d post-HSCT	4/5	36 (1~86)	3	Infection, 2 Evolution to MDS, 1	0

AML indicates acute myelogenous leukemia.
* Cooper et al reported 55 cases, among them 7 patients were treated with eculizumab pre- or peri-HSCT.

Yali Du, Bing Han, Transplantation and cellular therapy, 2020

Main considerations:

- ✓ Only retrospective data. Small series, in a few geographical areas;
- ✓ Indications to transplant: AAS or clonal evolution;
- ✓ Heterogeneous conditioning regimens;
- ✓ Heterogeneous type of donor;
- ✓ Heterogeneous source of stem cells;
- ✓ Heterogeneous GVHD prophylaxis;
- ✓ Different ways of using Ecu.

Clinical Case

November, 2020

Male, 40 y:

Severe anemia (Hb 6 g/dL), thrombocytopenia, (Plt 18 x 10^9/L), WBC <1 x 10^9/L e Ret 25 x 10^9/L

Bone marrow biopsy revealed hypocellularity, without evidence of dysplasia, pathological cells and fibrosis.

Karyotype was normal

Flow cytometry of peripheral blood showed the presence of 10% of GPI-deficient cells

Diagnosis of severe aplastic anemia with associated PNH clone

Guidelines for the diagnosis and management of adult aplastic anaemia: A British Society for Haematology Guideline
Kulasekararaj A, 2024, BJH

HLA-id sibling donor not available

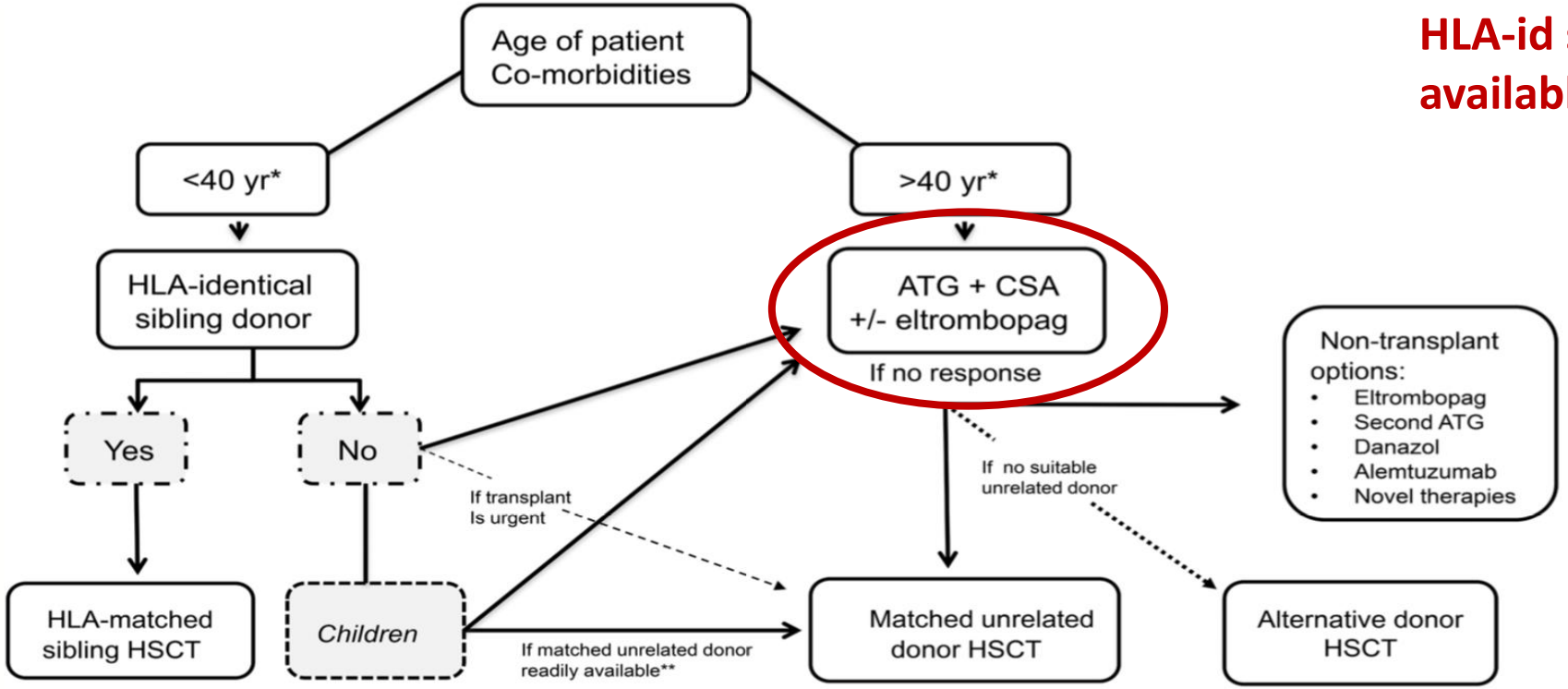
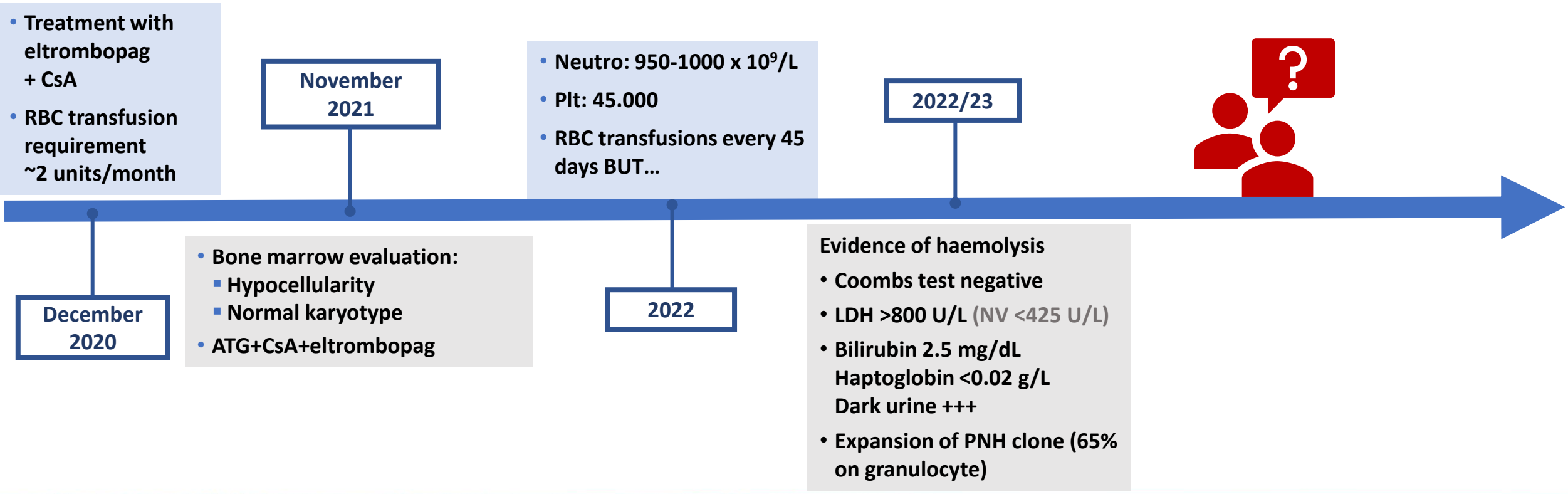


FIGURE 1 Treatment of acquired severe aplastic anaemia. *For patients aged between 40 and 50 years, an individual patient assessment based on comorbidities, performance status, expertise of transplant centre and rapid availability of sibling donor can be made to help decide whether to treat with first line IST or MSD HSCT. **Within 8 weeks. IST, immunosuppressive therapy; MSD, matched sibling donor.

Clinical Case

Male, 40 y

HLA sibling donor not available



1. Do you consider transplantation a viable option (at this point in history) and why?

2. If available, do you consider CI a viable option (at this point in history) and why?

What would you do?

1. Start complement inhibitor ?

2. Search a donor ?

3. Start complement inhibitor and search a donor ?

Clinical Case

Male, 40 y

December 2020

- Treatment with eltrombopag + CsA
- RBC transfusion requirement ~2 units/month

November 2021

- Bone marrow evaluation:
  - Hypocellularity
  - Normal karyotype
- ATG+CsA+eltrombopag

2022

- Neutro: 1000 x 10^9/L
- Plt: 45.000
- RBC transfusions every 45 days BUT…

2022/23

Evidence of haemolysis

- Coombs test negative
- LDH >800 U/L (NV <425 U/L)
- Bilirubin 2.5 mg/dL
  Haptoglobin <0.02 g/L
  Dark urine +++
- Expansion of PNH clone

March 2023

- Patient starts ravulizumab

July 2023

Normalisation of hemolysis parameters, Hb 10,5, Neutro 1000, PLT 45.000

1. **Do you consider transplantation a viable option (at this point in history) and why?**

2. **Do you consider transplantation a viable option (at this point in history), if a MUD is available ?**

3. **Do you consider transplantation a viable option (at this point in history), if only a MMUD 9/10 or haplo is available ?**

Clinical Case

Male, 40 y

HLA identical sibling donor not available

December 2020

- Treatment with eltrombopag + CsA
- RBC transfusion requirement ~2 units/month

November 2021

- Bone marrow evaluation:
  - Hypocellularity
  - Normal karyotype
- ATG+CsA+eltrombopag

2022

- Neutro: 950-1000 x 10^9/L
- Plt: 45.000
- RBC transfusions every 45 days BUT…

2022/23

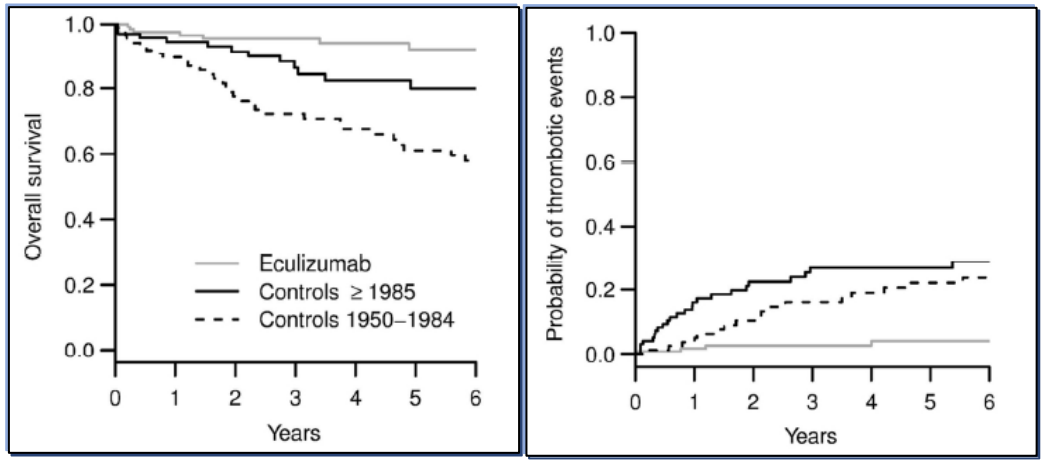
Evidence of haemolysis

- Coombs test negative
- LDH >800 U/L (NV <425 U/L)
- Bilirubin 2.5 mg/dL
  Haptoglobin <0.02 g/L
  Dark urine +++
- Expansion of PNH clone
- PORTAL VENOUS THOMBOSIS

1. Do you consider transplantation a viable option (at this point in history) and why?

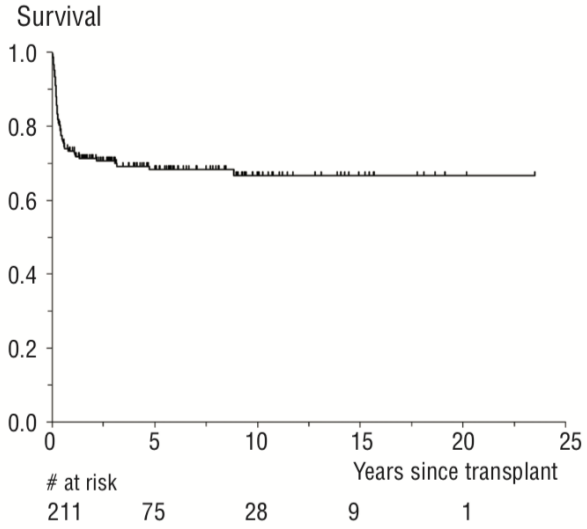
2. If available, do you consider CI a viable option (at this point in history) and why?

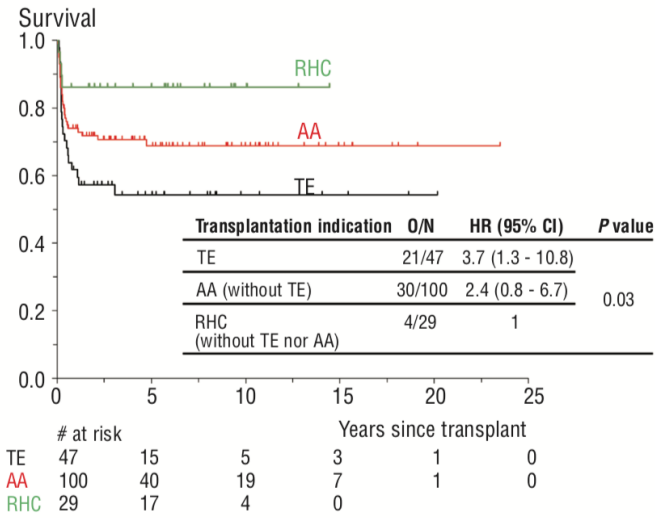
Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study
(Loschi et al, AJH 2016)



Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria

Régis Peffault de Latour,[1] Hubert Schrezenmeier,[2] Andrea Bacigalupo,[3] Didier Blaise,[4] Carmino A. de Souza,[5] Stephane Vigouroux,[6] Roelf Willemze,[7] Louis Terriou,[8] Andre Tichelli,[9] Mohamad Mohty,[10] Sophie de Guibert,[11] Judith C. Marsh,[12] Jakob Passweg,[13] Jean Yves Mary,[14]* and Gerard Socié[1,15]*

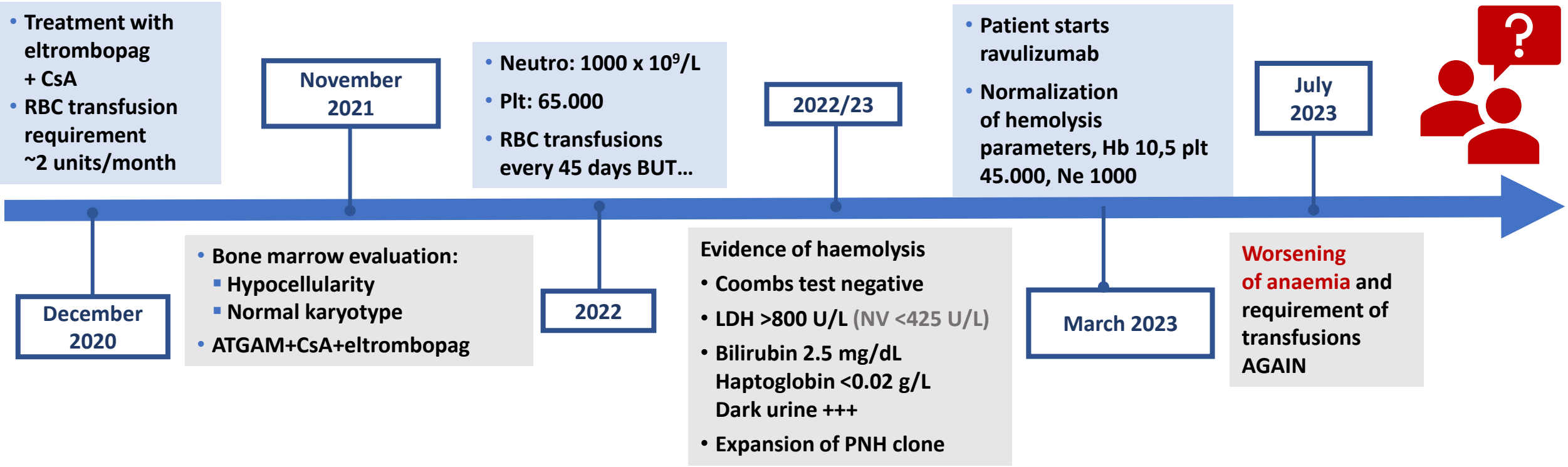




Transplantation indication	O/N	HR (95% CI)	*P* value
TE	21/47	3.7 (1.3 - 10.8)	
AA (without TE)	30/100	2.4 (0.8 - 6.7)	0.03
RHC (without TE nor AA)	4/29	1	

Clinical Case

HLA sibling donor not available

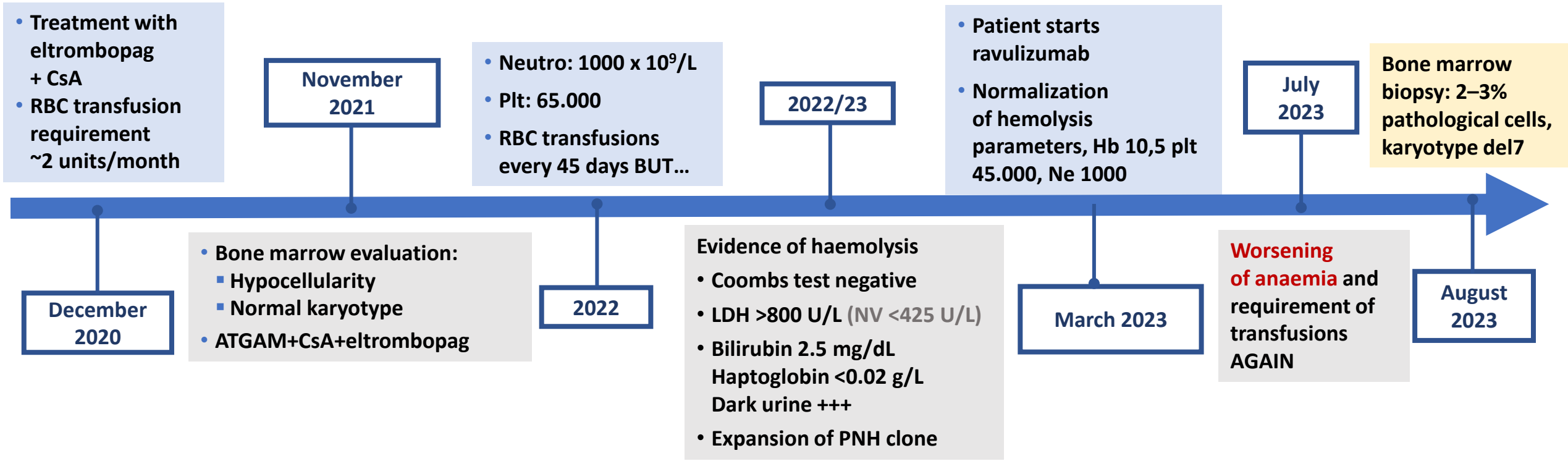


What are the possible diagnoses ?

What is the best therapeutic approach?

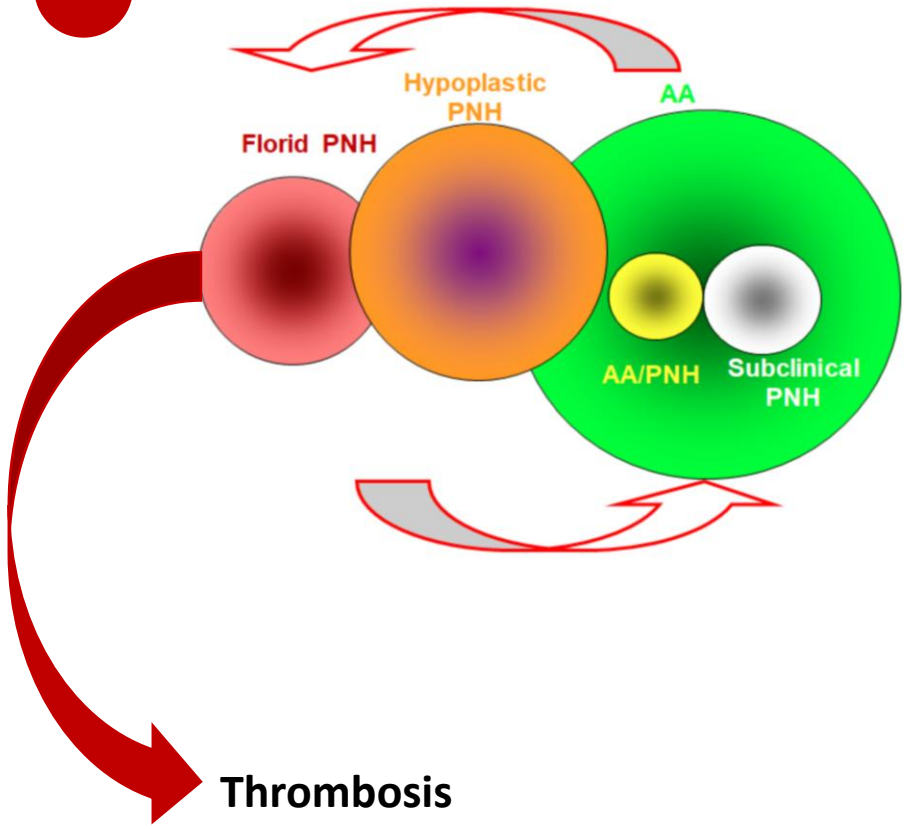
Clinical Case

HLA sibling donor not available



Is the allogeneic stem cell transplantation still an option for PNH therapy?

Disease's characteristics:



Patient's characteristics:

- ✓ Age
- ✓ Comorbidities
- ✓ Organ function
- ✓ Infections

Donor's availability

What therapies do I have available?
(where I am)
(what economic means I have)

Discussion and conclusions

Transplant in PNH? Only retrospective data!

In the "ideal" world (where CI are available and not expensive): Which element is most important in the decision "transplant" VS "no transplant"?

1. **Clinical manifestations of disease and complications?**
2. **Patient's characteristics..?**
3. **Donor's availability …?**

- **WHO?**

✓ **PNH/AAS**
✓ **Clonal evolution in MDS/AML**
✓ **Transfusion-dependent classical PNH?**
✓ **Recurrent thrombotic events ?**

In the "real" world …

- **COST AND AVAILABILITY OF COMPLEMENT INHIBITORS**

✓ **Lifelong therapy …?**

Looking to the future…

Retrospective Study request proposal for the Severe Aplastic Anemia Working Party

Title of the retrospective study: Outcome of transplant in PNH patients in the era of complement inhibitors

Background: Peffault de Latour et al. Haematologica. 2012;97(11):1666-1673.

The analysis will be initially stratified by indication to transplant (haemolytic , thrombotic, PNH in the context of BMF)

Primary objective: To describe the outcome of PNH patients receiving an allogeneic transplant in the period 2011-2020, especially looking **OS**.

Secondary objectives: DFS, EFS, GRFS, graft failure, aGVHD, cGVHD.

Study Population: Based on feasibility study, about 248 potentially evaluable.

See you in San Diego!

Session Name: 508. Bone Marrow Failure: Acquired: Emerging Data in the Treatment of Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria
Session Date: Saturday, December 7, 2024

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