GIORNATE EMATOLOGICHE VICENTINE

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Palazzo Bonin Longare - Vicenza

I nuovi inibitori del complemento: cosa cambia nella terapia dell'EPN

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COIs disclosure

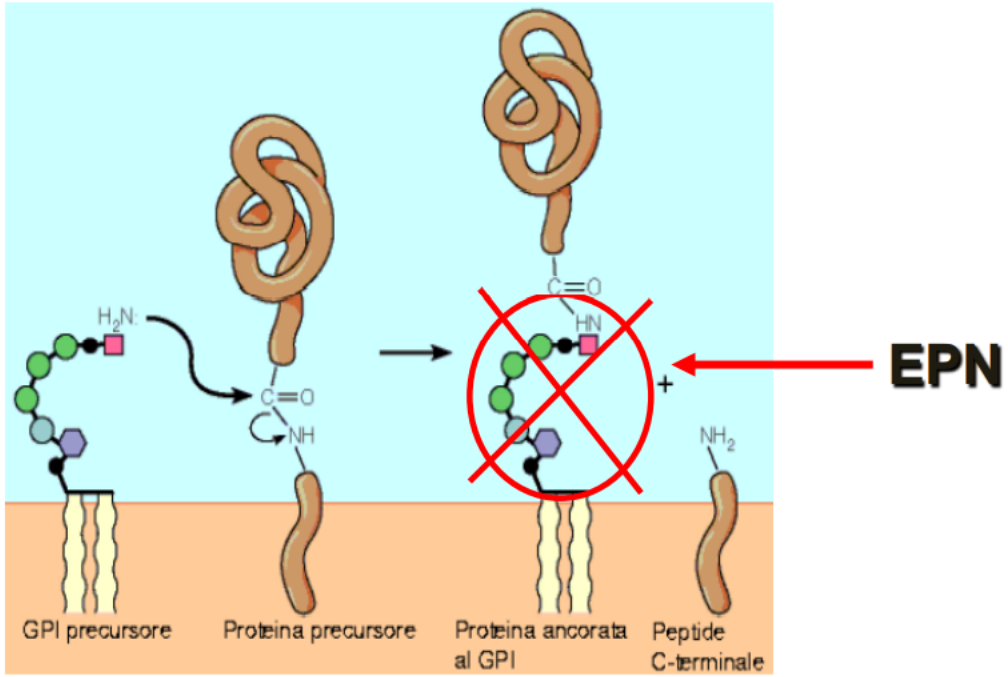
	No, nothing to disclose
X	Yes, as specified below:

Company Name	Specification
Alexion	Consultancy and Speakers’ bureau
Annexon	Consultancy
Sanofi	Consultancy and Speakers’ bureau
Janssen	Consultancy and Speakers’ bureau
Agios and Zenas	Research funds

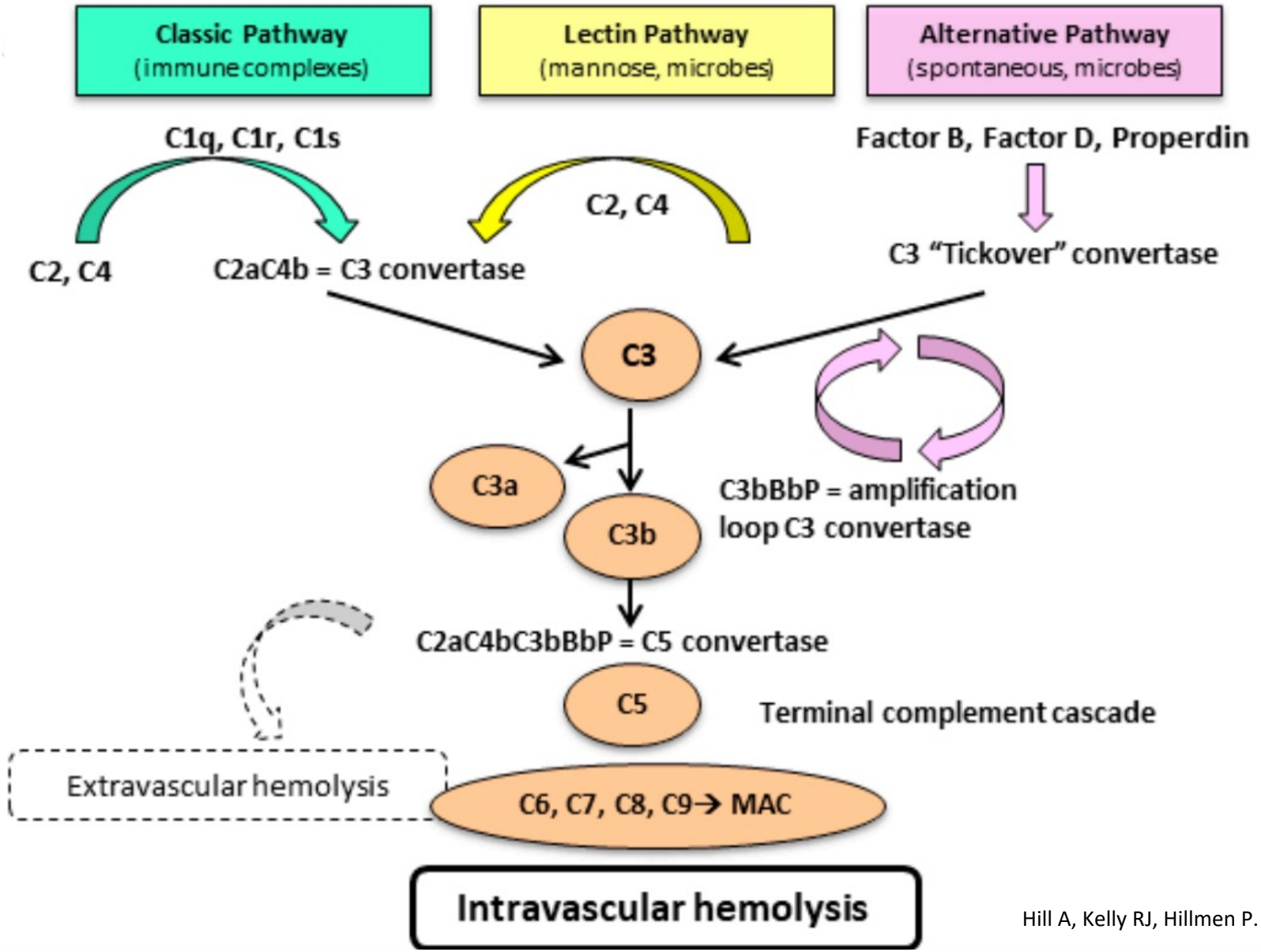
Physiopathology

- Paroxysmal nocturnal hemoglobinuria (PNH) is a clonal disease characterized by the acquisition of the somatic mutation of PIGA gene.
- PIGA encodes a glycoprotein that anchors several molecules on cell surface.
- GPI-anchored molecules include the complement inhibitors CD55 and CD59 that will be therefore deficient on mutated (PNH-)cells.
- PNH+ erythrocytes are sensitive to complement mediated lysis thus resulting in anemia of various severity, vasospasms, and thrombosis.

Glicosil-Fosfatidil-Inositolo (GPI)



How does hemolysis occur?



Hill A, Kelly RJ, Hillmen P. Blood. 2013 Jun 20;121(25):4985-96

Fattizzo B et al, JCM 2021

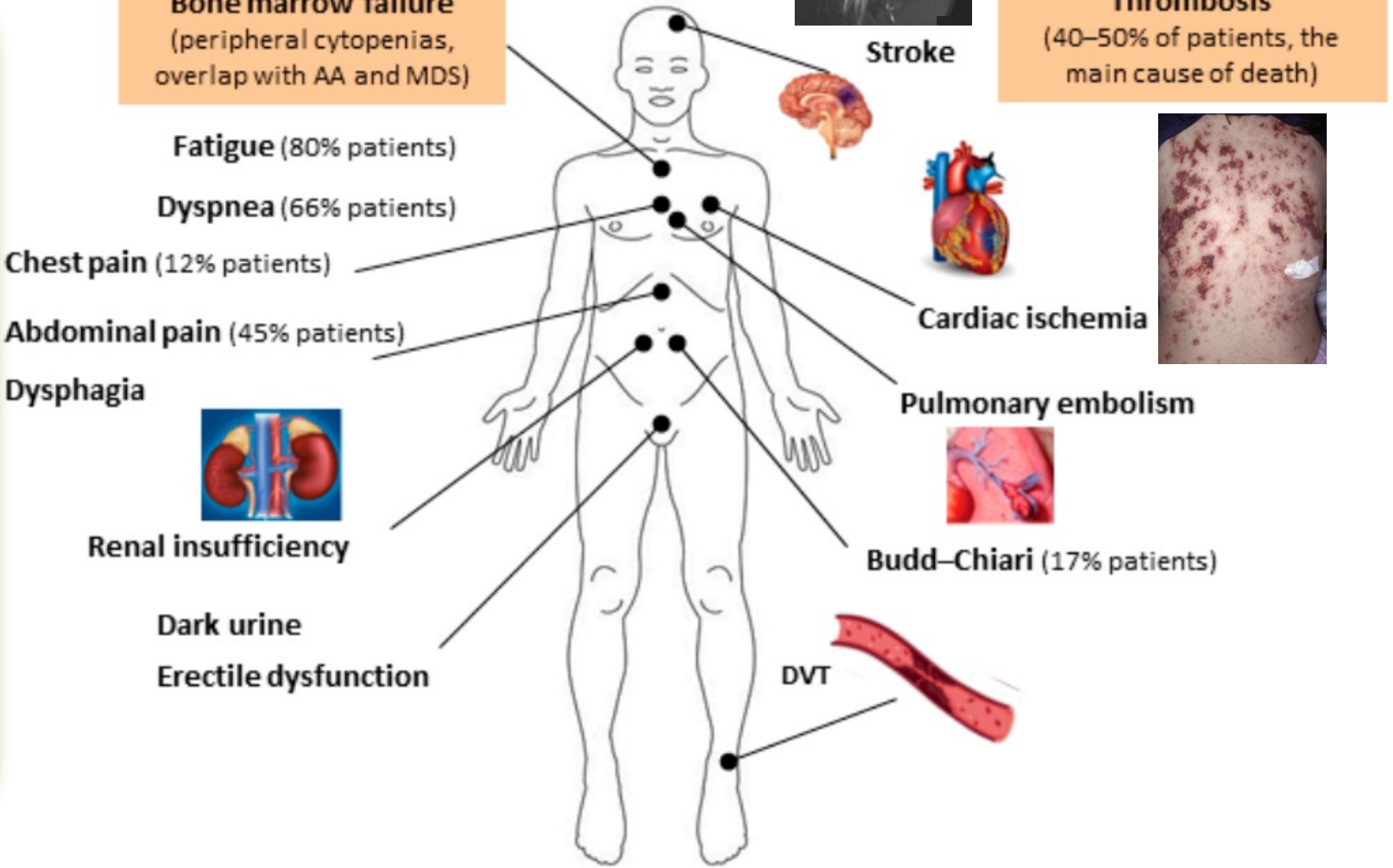
Clinical consequences

ANEMIA
Asthenia,fatigue, palor, jaundice, malaise

CHRONIC HEMOLYSIS
microthrombi and vasospasms:
Dark urine and abdominal pain, dysphagia, erectile dysfunction, pulmonary hypertension

BMF
Infections, bleeding

THROMBOSIS



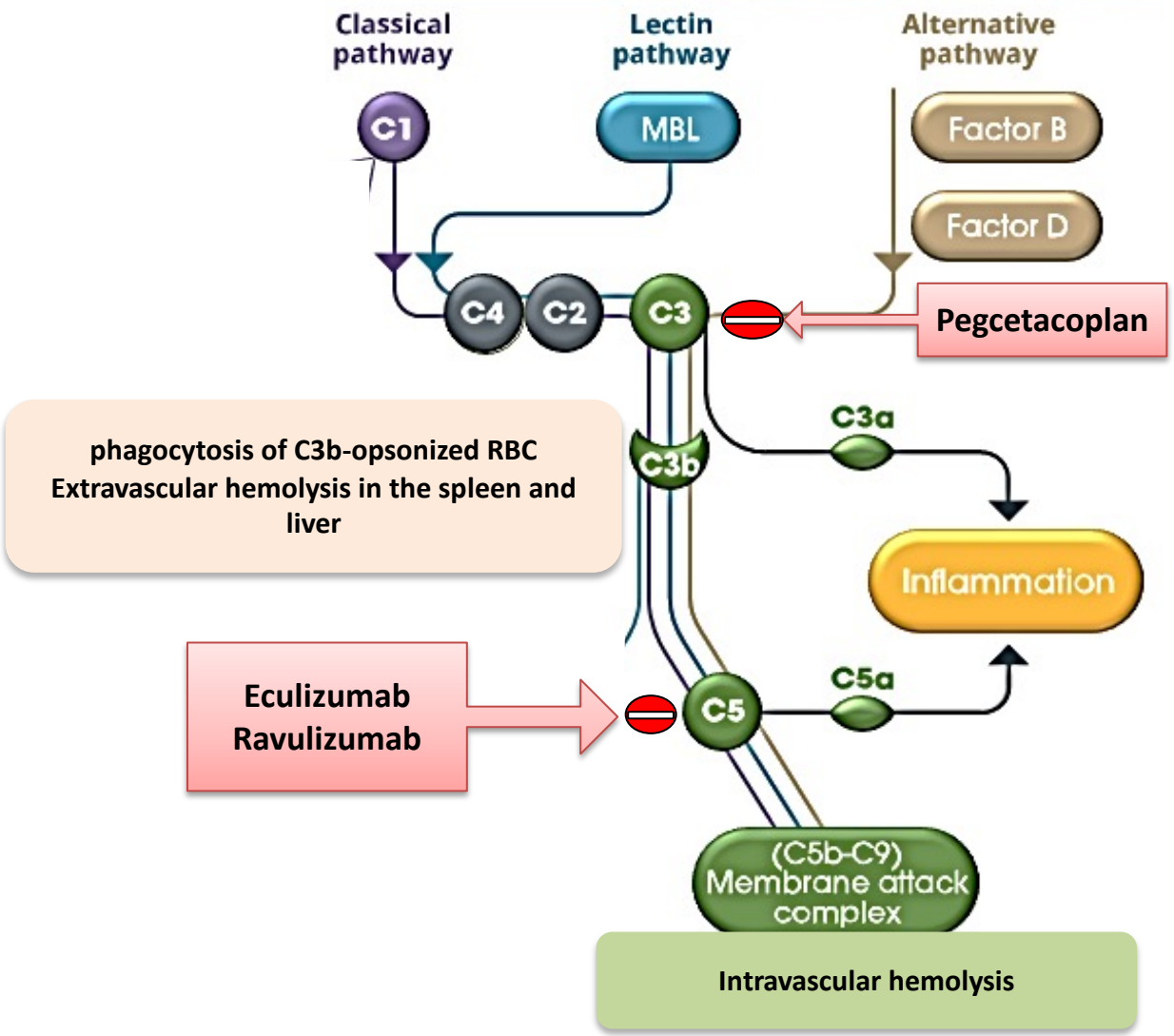
Fattizzo B et al, JCM 2021

Current PNH therapy in Europe

- **Terminal complement inhibition (C5)** with **eculizumab and ravulizumab**.
- Patients need to receive infusions every 2 weeks or every 8 weeks
- High medicalization, vaccines required
- Not all patients respond due to various causes including
  - ❖inadequate bone marrow compensation,
  - ❖ **residual C5 activation →BTH,**
  - ❖C5 polymorphisms,
  - ❖**persistent extravascolar hemolysis due to C3 deposition**.

- **Proximal complement inhibition (C3)** with **pegcetacoplan** for suboptimal responders ***(residual anemia after >3 months on C5i)***
- Several novel inhibitors are under investigation in clinical trials in the last 5-7 years.

Available drugs in Europe



When shall we start anti-C therapy?

- **PNH clone >10%**
- **Anemia → what degree? Transfusion dependence?**
- **Hemolysis → LDH elevation >1.5 xULN?**
- **PNH related symptoms → like B symptoms they are very difficult to discriminate from causes other than PNH**
- **Thrombosis → superficial vein thrombosis or provoked (i.e. catheter related, etc.) thrombosis would be enough?**
- **Pregnancy → any clone size? At what time?**

Clinical vignette– F 41 years

2006 → 2010 → 2022

Diagnosis of classic PNH

Tx+ Iron + vitamins LMWH

Renal thrombosis

Accepted ECU > Hb 8.8 g/dL

- The patient went from transfusion dependence before ECU
- To moderate anemia under ECU and frequent BTH (PK? PD?)

Doctor, I feel better but I'm always at the day care facility!

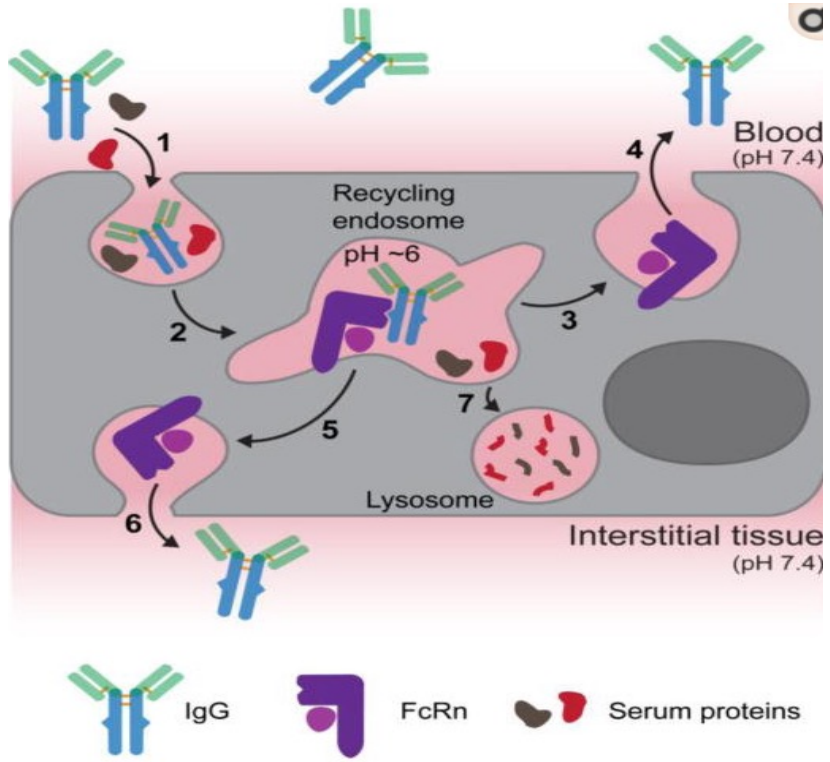
I keep seeing dark urine before every eculizumab dosing!

Doctor, will I keep on with this IV drug every 14 days?

Ravulizumab

Modification of eculizumab for increased half-life

- Histidine substitution at two positions within the first and second heavy chain complementarity-determining regions of eculizumab generates a novel mAb
- This extends its PK and PD in the presence of human C5 in a mouse model
- Additional modifications were made to the Fc region from eculizumab to further increase the half-life by increasing its affinity for FcRn



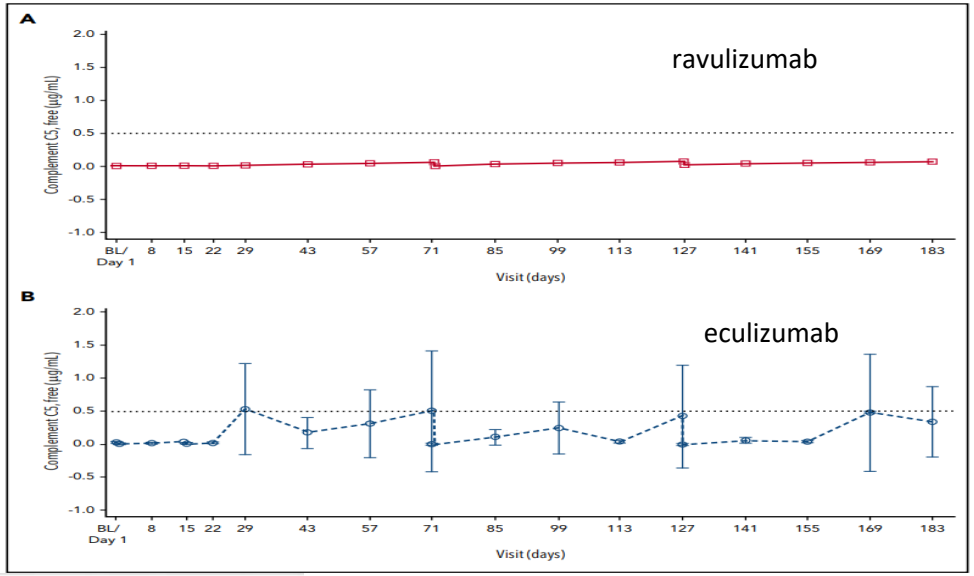
- The neonatal Fc Receptor (Fc-Rn) was firstly described about 50 years ago, and is responsible for the salvage of IgG from catabolism
- FcRn is structurally homologous to the MHC Class I heterodimeric receptor family, and is expressed by several cells including macrophages, monocytes, B cells, and dendritic cells·
- Ab recycling by FcRn engineering protect Ab from degradation
- Conversely, blocking Fc-Rn may increase IgG clearance (including pathogenic autoantibodies), resulting in reduced IgG

Ravulizumab has a half-life ～4x longer than eculizumab
Administration every 8 weeks!

Ravulizumab vs eculizumab

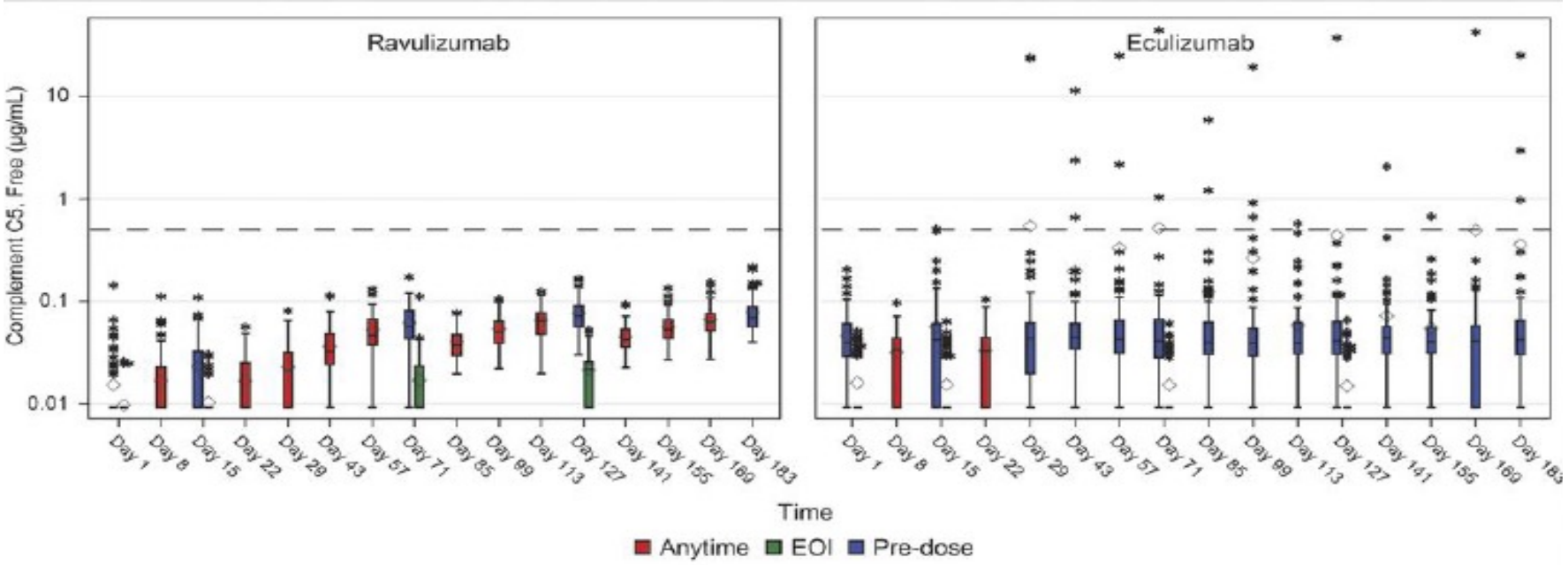
Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor–experienced adult patients with PNH: the 302 study

Austin G. Kulasekararaj,[1] Anita Hill,[2] Scott T. Rottinghaus,[3] Saskia Langemeijer,[4] Richard Wells,[5] F. Ataulfo Gonzalez-Fernandez,[6] Anna Gaya,[7] Jong Wook Lee,[8] Emilio Ojeda Gutierrez,[9] Caroline I. Piatek,[10] Jeff Szer,[11] Antonio Risitano,[12] Shinji Nakao,[13] Eric Bachman,[3] Lori Shafner,[3] Andrew I. Damokosh,[3] Stephan Ortiz,[3] Alexander Röth,[14] and Regis Peffault de Latour[15-17]



Mean serum free C5 concentrations were suppressed to <0.5 µg/mL by the end of the first infusion and at all subsequent visits for all patients receiving ravulizumab

This threshold was not consistently met in the eculizumab group



Safety

The most frequently reported AE was headache (26.8% and 17.3% in ravulizumab and eculizumab)

SAEs obseved in 4 ravulizumab and 8 eculizumab

No cases of meningococcal infections observed.

No treatment-emergent antidrug antibodies in patients treated with ravulizumab

Crovalimab: C5 inhibitor active on C5 polymorphisms and very convenient

CLINICAL TRIALS AND OBSERVATIONS

The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria

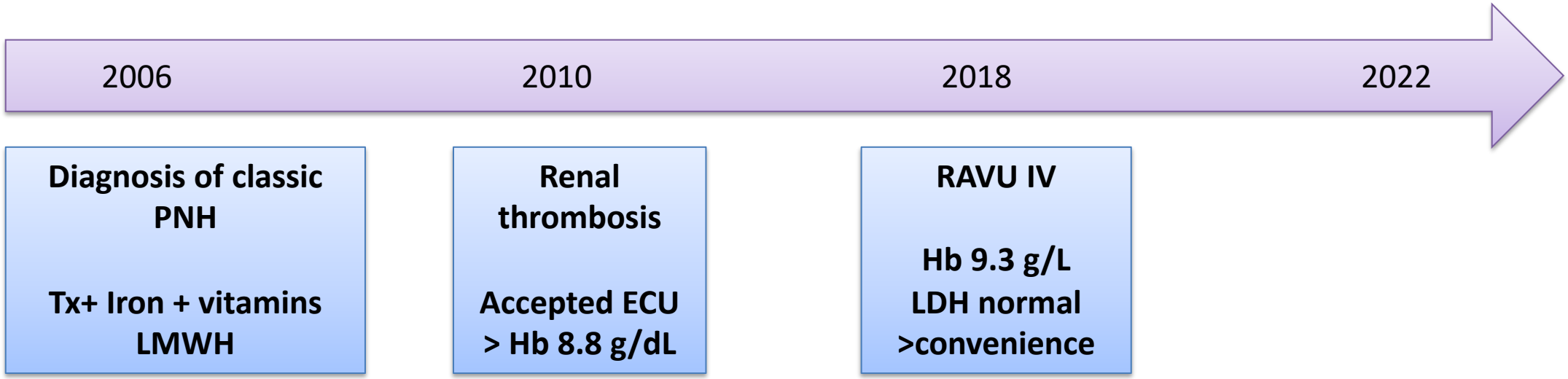
Alexander Röth,[1] Jun-ichi Nishimura,[2] Zsolt Nagy,[3] Julia Gaàl-Weisinger,[3] Jens Panse,[4] Sung-Soo Yoon,[5] Miklos Egyed,[6] Satoshi Ichikawa,[7]

→ **Crovalimab is unique: its properties allow for subcutaneous (SC) injections once every 4 weeks**
→ **can be self-administered**
→ **binds to C5 mutational variants.**
→ **Efficacy and safety confirmed in the Phase I/II COMPOSER trial (NCT03157635; Röth et al, Blood. 2020) conducted in patients with PNH, with or without prior anti–C5 treatment.**
→ **During the OLE LDH maintained at ≤1.5× ULN, transfusion avoidance 83%-92% of patients and haemoglobin stabilisation was reached in 79%-88% of patients across each 24-week interval.**
→ **Five BTH events occurred with none leading to withdrawal**

→ The Phase 3 single-arm COMMODORE 3 study → complement inhibitor-naive patients
→ **78% achieved hemolysis control → 1 BTH**

Roth et al, Blood 2020
Roth et al, Eur J Hematol 2023
Liu et al, AJH 2023

Clinical vignette – F 41 years



- The patient went from transfusion dependence before ECU
- To moderate anemia under ECU and frequent BTH (PK? PD?)
- To moderate anemia with no BTH under RAVU IV

Shall we consider proximal inhibitor?

frontiers in Immunology

REVIEW
published: 14 June 2019
doi: 10.3389/fimmu.2019.01157

Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT

OPEN ACCESS

Edited by:
John D. Lambris,
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How can we assess response to therapy?

At what time? 6 months versus 3 months

No anemia
No tx

TABLE 1 | Tentative classification of hematological response to anti-complement agents in PNH.

Response category	Red blood cell transfusions	Hemoglobin level	LDH level*‡	ARC*
Complete response	None	≥12 g/dL	≤1.5x ULN	***and*** ≤150,000/μL§
Major response	None	≥12 g/dL	>1.5x ULN	***or*** >150,000/μL§
Good response	None	≥10 and <12 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
Partial response	None or occasional (≤2 every 6 months)	≥8 and <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
Minor response#	None or occasional (≤2 every 6 months) Regular (3–6 every 6 months) Reduction by ≥50%^	<8 g/dL <10 g/dL <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°
No response#	Regular (>6 every 6 months)	<10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure°

*LDH, lactate dehydrogenase; ULN, upper limit of the normal; ARC: absolute reticulocyte count. *Response categories are mostly based on red blood cell transfusion and hemoglobin level, but LDH and ARC serve as ancillary indicators to discriminate between complete and major response, as well as within suboptimal response categories. ‡A. and B. indicate subcategories without or with residual significant intravascular hemolysis, respectively. §To rule out increased erythropoietic response to compensate ongoing hemolysis; the value of 150,000/μL is a tentative index based on 1.5x ULN (which in most laboratories is set at 100,000/μL). °To assess the relative contribution of the degree of bone marrow failure to any response less than complete: a value of ARC below 60,000/μl could be a tentative index to establish such a contribution; bone marrow investigation may be appropriate. ^For patients with previous transfusion history (with a pre-treatment follow up of at least 6 months). #For patients who do not accept red blood cell transfusions, minor response can be defined based on hemoglobin level ≥6 and <8 g/dL, and no response based on hemoglobin <6 g/dL. All hemoglobin, LDH and ARC values should be assessed based on the median value over a period of 6 months.*

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At what time? 6 months versus 3 months

Mild anemia
No Tx

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→ Anemia ≥moderate → Transfusions from little to regular

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Several causes of “suboptimal response” to be considered

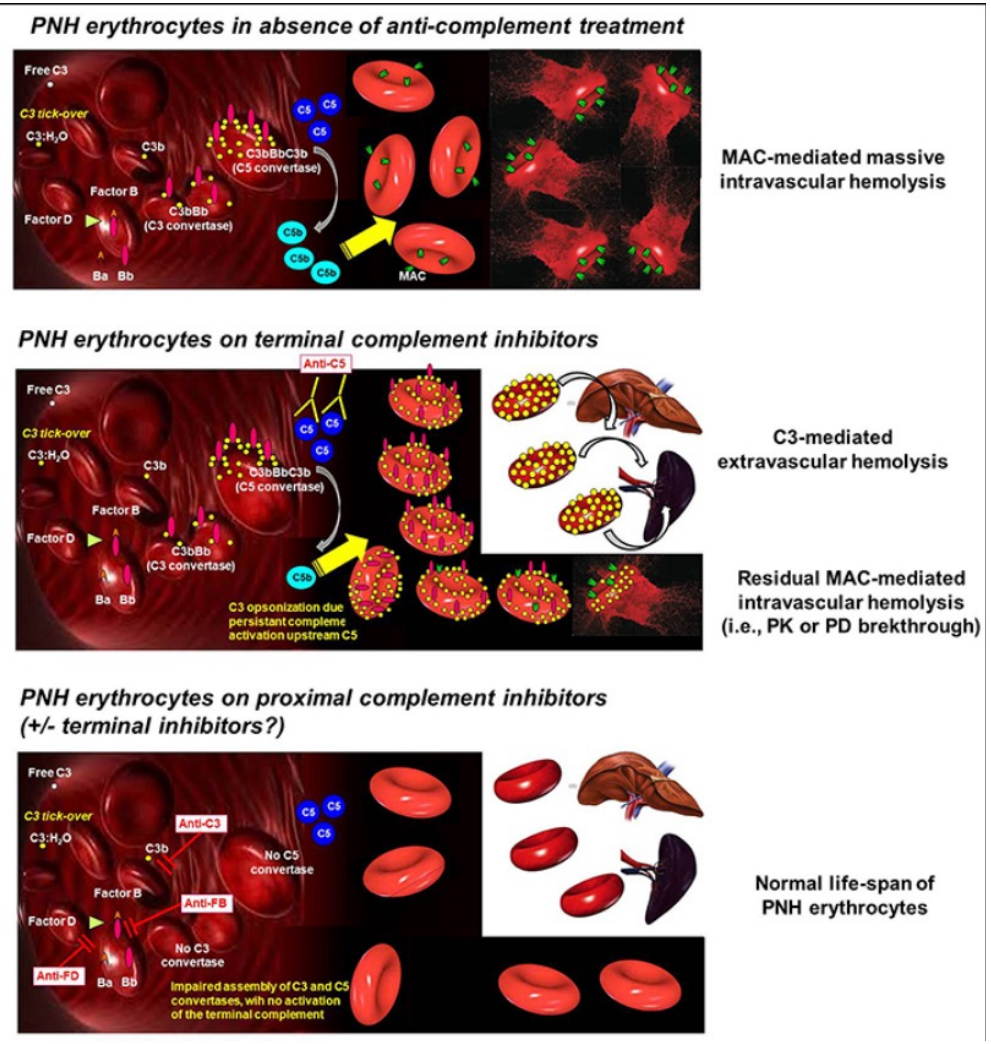
Doctor, why my Hb is still low?

One of the main unmet needs of PNH: «suboptimal responders»

Reasons	Remedies
• Persistent intravascular hemolysis	Higher dose of Eculizumab or change to Ravulizumab or another complement inhibitor
• Significant extravascular hemolysis	ESAs or C3i or C5i +C3i combination
• CR1 polymorphism	Unresolved issue
• Underlying bone marrow failure	IST or HSCT together with C5 inhibitor
• Hypersplenism	Selective plenic embolization/irradiation
• Relative EPO deficiency	ESAs supplementation
• C5 polymorphism	Second generation C5i
• Hematinic deficiency	Replace vitamin (Folate and B12)
• Iron overload	Effective chelation
• Unknown mechanism	Open issue

Fattizzo B and Kulasekararaj AG, Biodrugs 2020

Iatrogenic Extravascular hemolysis → Proximal complement inhibitors

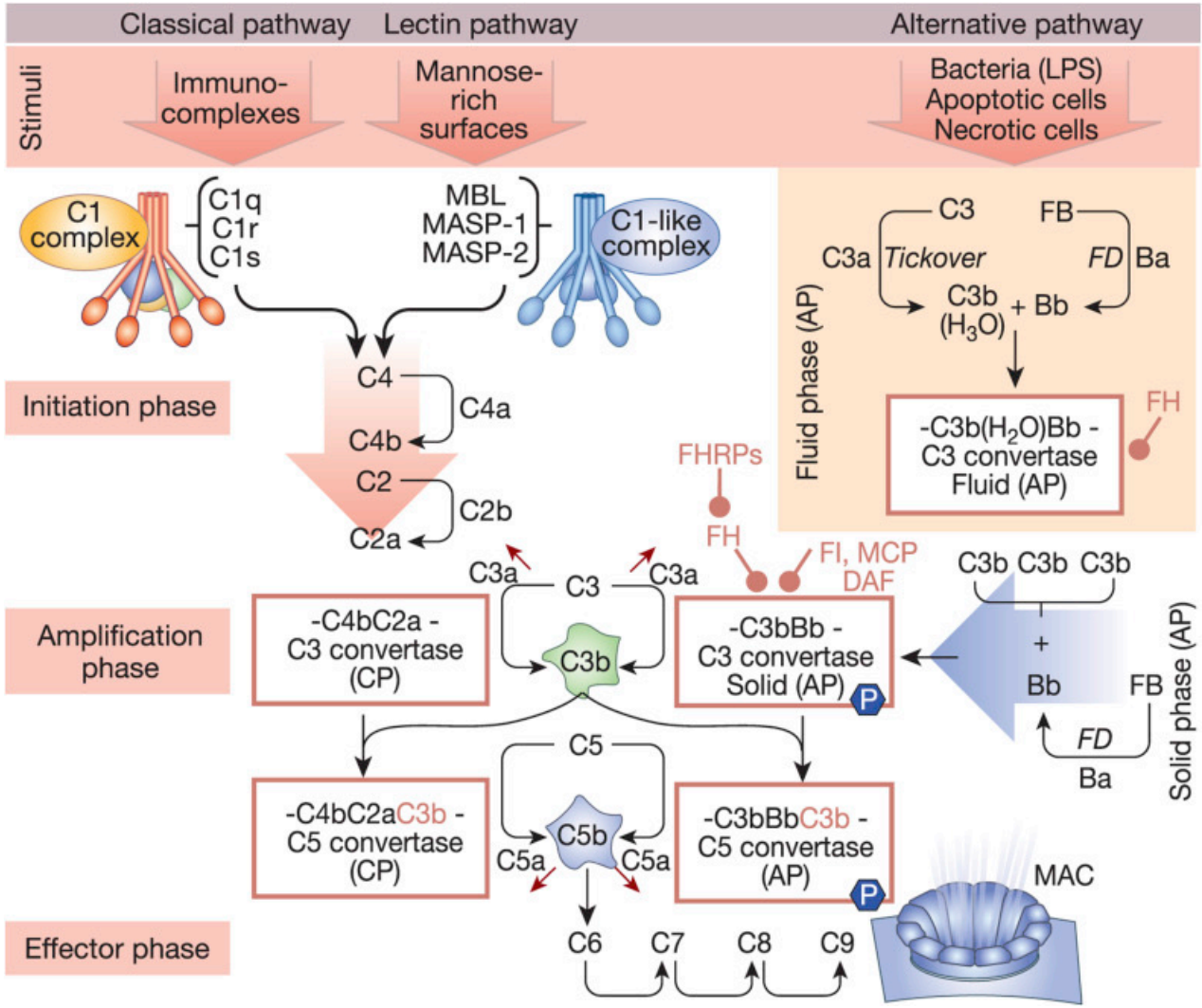


Anti-C5 agents:
- mAbs: eculizumab, ravulizumab, SKY59, LFG316, ABP959, REGN3918
- RA101495
- Coversin
- ALNCC5

Anti-C3 agents:
- AMY-101
- APL-2

Anti-FD agents:
- ACH4471

Anti-FB agents:
- LNP023



Risitano et al, Front Immunol 2019

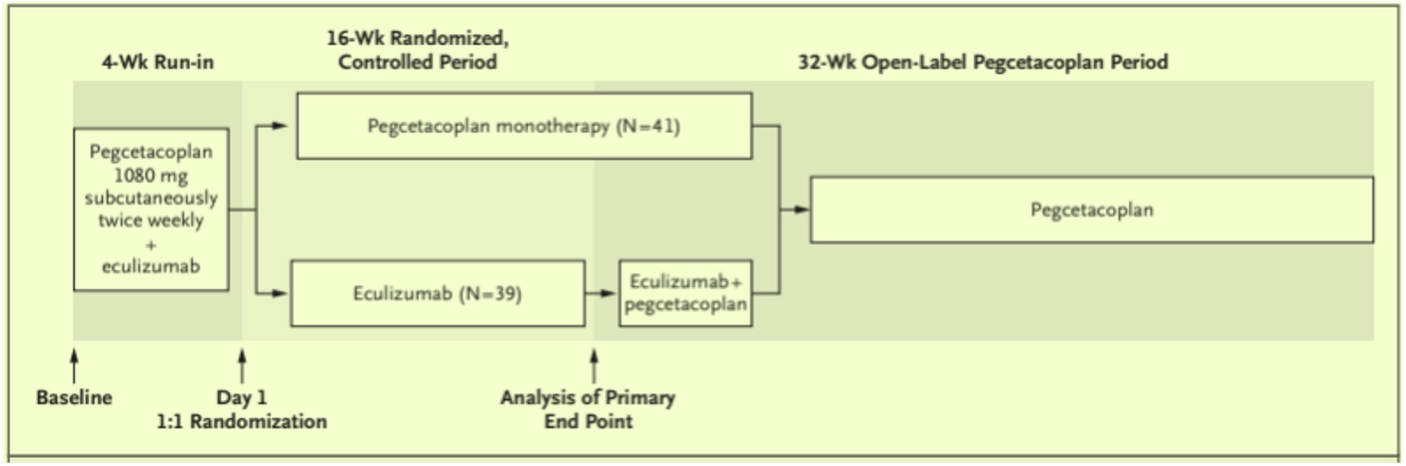
Pegcetacoplan (anti-C3)

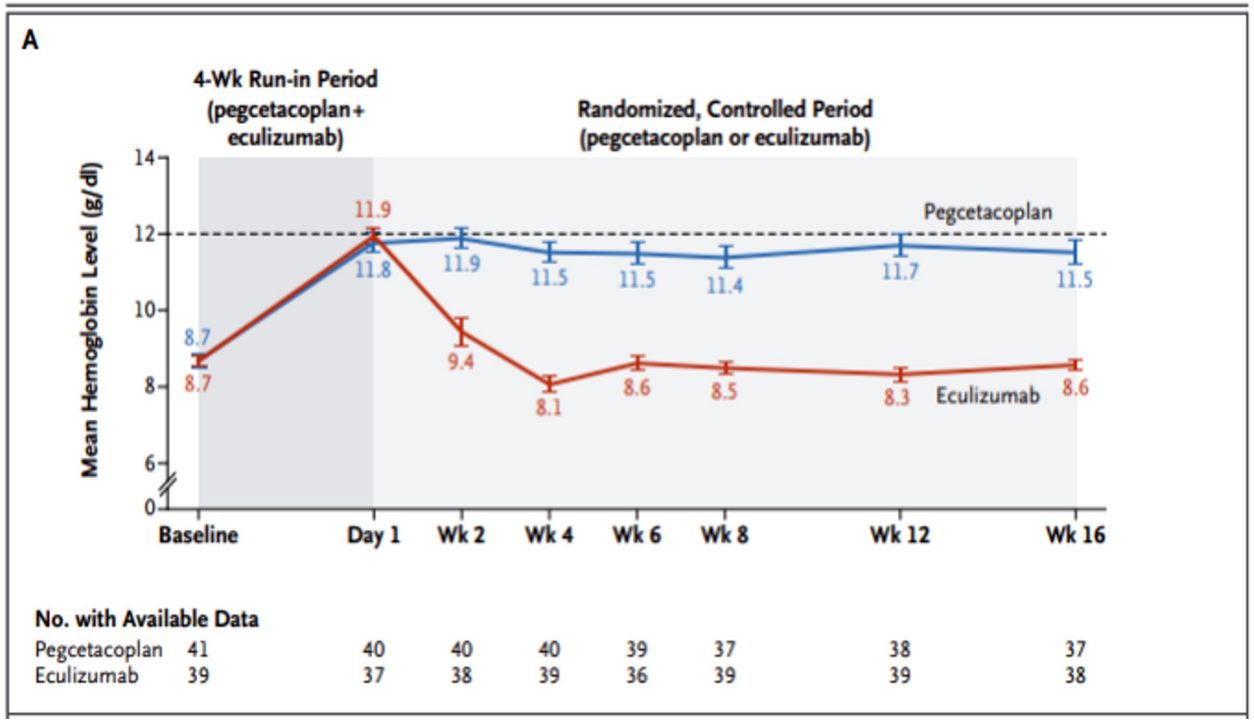
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE 2021

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

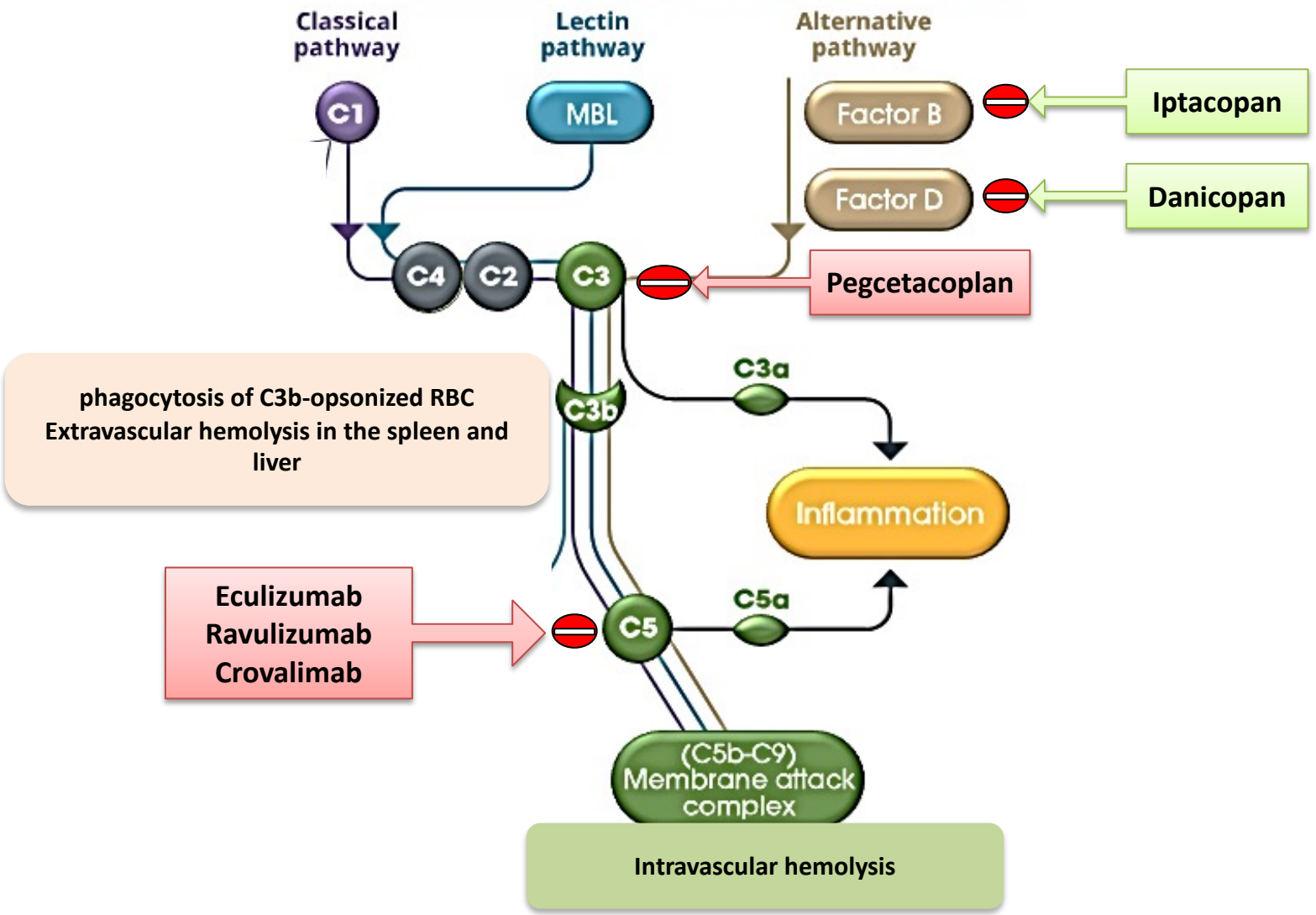
Peter Hillmen, M.B., Ch.B., Ph.D., Jeff Szer, M.B., B.S., Ilene Weitz, M.D., Alexander Röth, M.D., Britta Höchsmann, M.D., Jens Panse, M.D., Kensuke Usuki, M.D., Ph.D., Morag Griffin, B.M.Sc., M.B., Ch.B., Jean-Jacques Kiladjian, M.D., Ph.D., Carlos de Castro, M.D., Hisakazu Nishimori, M.D., Ph.D., Lisa Tan, R.N., Mohamed Hamdani, M.S., Pascal Deschatelets, Ph.D., Cedric Francois, M.D., Ph.D., Federico Grossi, M.D., Ph.D., Temitayo Ajayi, M.D., Antonio Risitano, M.D., Ph.D., and Régis Peffault de la Tour, M.D., Ph.D.



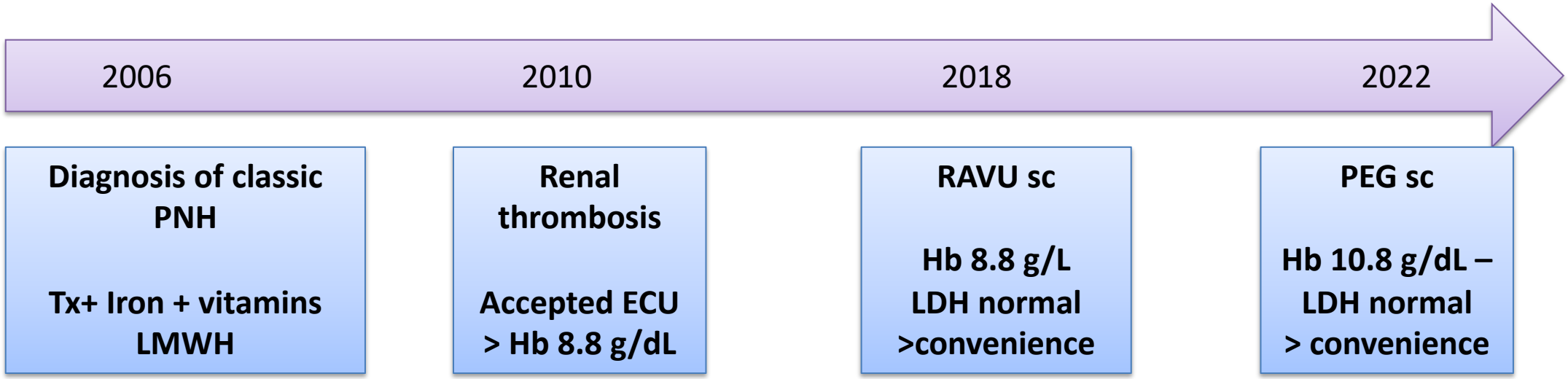


- **Pegcetacoplan, a pegylated peptide targeting proximal complement protein C3, was superior to eculizumab in:**
- **Change in Hb level** from baseline to week 16, with an adjusted mean difference of **3.84 g per deciliter (P<0.001);** 35 patients
- **85% receiving pegcetacoplan no longer required transfusions** vs **15% in eculizumab**.
- **breakthrough hemolysis (BTH) was observed in 10% (pegcetacoplan) vs 23% (eculizumab)**
- **FACIT –Fatigue scores improved from baseline in the pegcetacoplan group.**
- **The most common adverse events** in the pegcetacoplan and eculizumab groups were injection site reactions (37% vs. 3%), diarrhea (22% vs. 3%), headache (7% vs. 23%), and fatigue (5% vs. 15%).
- **There were no cases of meningitis in either group.**

The panorama of complement inhibitors increased to involve the alternative pathway inhibitors



Clinical vignette – F 41 years



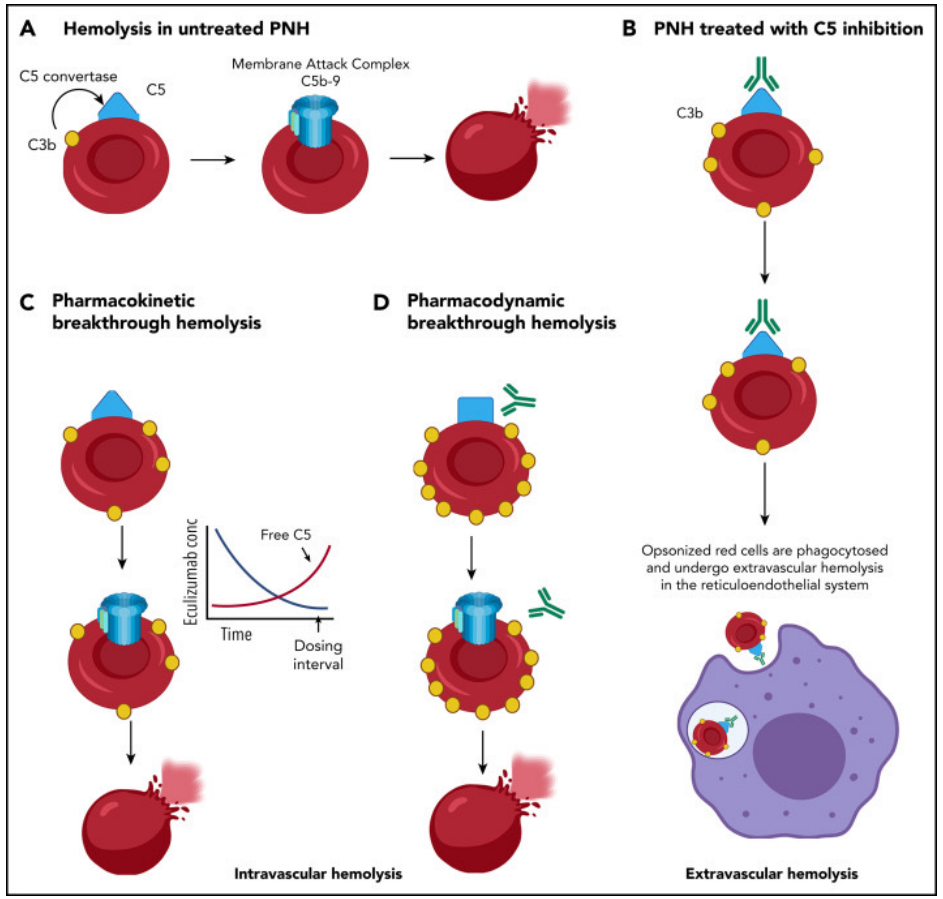
- The patient went from transfusion dependence before ECU
- To moderate anemia under ECU and frequent BTH (PK? PD?)
- To moderate anemia and no BTH under RAVU IV
- To mild anemia and markedly improved QoL since switching to PEG but …

Doctor, I fee generally better, but why dark urine are round the corner again?

Precipitating conditions & breakthrough hemolysis

Any complement amplifying condition (**infections, traumas, surgery, pregnancy, vaccines**, etc.) may result in increased hemolytic rate with:

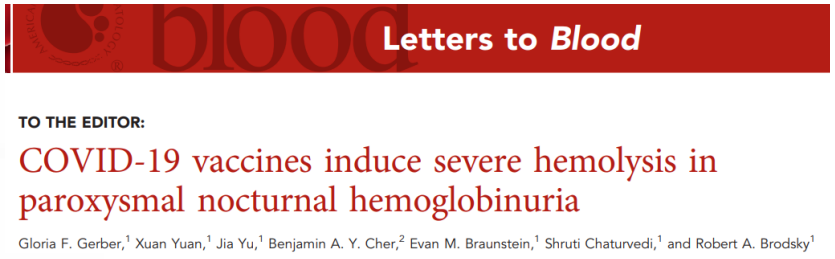
- Worseninf of dark urine and PNH symptoms
- Worsening of anemia and possible transfusion need
- Increased free Hb release and risk of thrombosis
- **If the patient is on Ci hemolytic flares are called BTH**

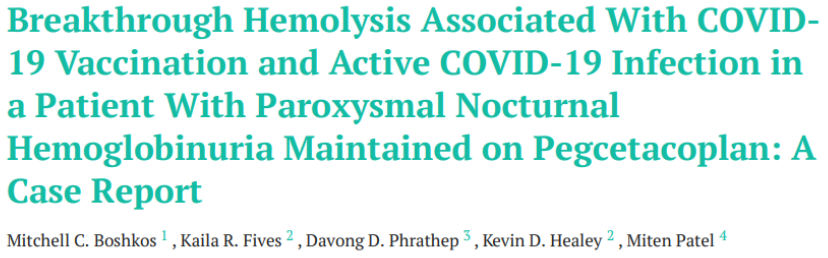


	Timing	Frequency	Concomitant conditions	Free C5	Eculizumab plasma level	Mechanism	Intervention
Pharmacokinetic breakthrough	>7–10 days from previous dosing	Recurrent	Usually none*	Always >0.5–1 µg/mL	Inadequate	Residual free C5 available for steady-state (normal) C5 convertase activity	Decrease interval of dosing (10-12 days) or increase dose of eculizumab (1,200 mg)
Pharmacodynamic breakthrough	Any time	Sporadic	Infectious events (both bacterial and viral, such as common seasonal viruses) or any event leading to inflammation (i.e., surgery, possible comorbidities)	Usually ≤0.5–1 µg/mL (but it may occur with any free C5 plasma level)	Adequate	Massive complement activation leading to excess C5 convertase activity, which might displace C5 from eculizumab	None (treat the underlying cause triggering complement activation)

Doctor, no more dark urine and jaundice with novel drugs?

RAVU reduced PK BTH
but PD BTH may still occur even with novel drugs





→**PEGCETACOPLAN** → 10% (vs 23% ECU) in the phase 3 trial
→**IPTACOPAN** → No «clinical» BTH in the phase 1/2 studies
→**DANICOPAN** → 17% patients had BTH in the phase 2 study

With proximal inhibitors

> % PNH-RBCs are spared
If blockade is incomplete activation is exponential → possible severe BTH

How to manage? Combination therapy?

Boshkos et al, Cureus, 2023
Hillmen et al, NEJM 2021
Risitano et al, Lancet Hem 2022
Jang et al, Blood Adv 2022
Kulasekararaj et al, Blood 2022
Notaro & Luzzatto NEJM 2022

Infections may occur even with novel drugs and despite vaccination

Doctor, shall I still fear infections?

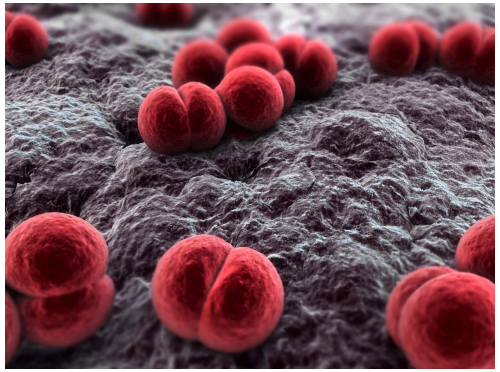
Abstract: EP596, EHA 2021

RISK OF SERIOUS INFECTIONS IN PATIENTS WITH OR WITHOUT PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: A REAL-WORLD MATCHED COHORT ANALYSIS

Bhumika J Patel, Richard Ofori-Asenso, Aijing Shang, Andy Surinach, Ari Alexandrou, Nadiesh Balachandran, Pablo Katz, Sasha Sreckovic, Jaroslaw Maciejewski

→1083 pts with PNH (200 [18.5%] with AA; 322 [29.7%] who received anti-C5 agents during follow-up) and 3249 control pts.

→ **20.9% of pts with PNH and 4.7% of control pts experienced ≥1 SI**; incidence of 12.7 (95% CI: 11.5, 14.0) and 1.7 (95% CI: 1.5, 2.0) per 100 person-years for pts with PNH and control pts, respectively, **irrespective of AA concomitance.**



- **Vaccinate**
- **Educate**
- **Alert clinical community**

Several novel drugs for a better control of IVH and EVH and patients' convenience

Since >5 years several clinical trials

Ravulizumab, iv every 8 weeks, targeting C5, approved FDA/EMA

Pegcetacoplan, sc twice weekly, targeting C3, approved FDA/EMA

Crovalimab, sc every 4 weeks, targeting C5

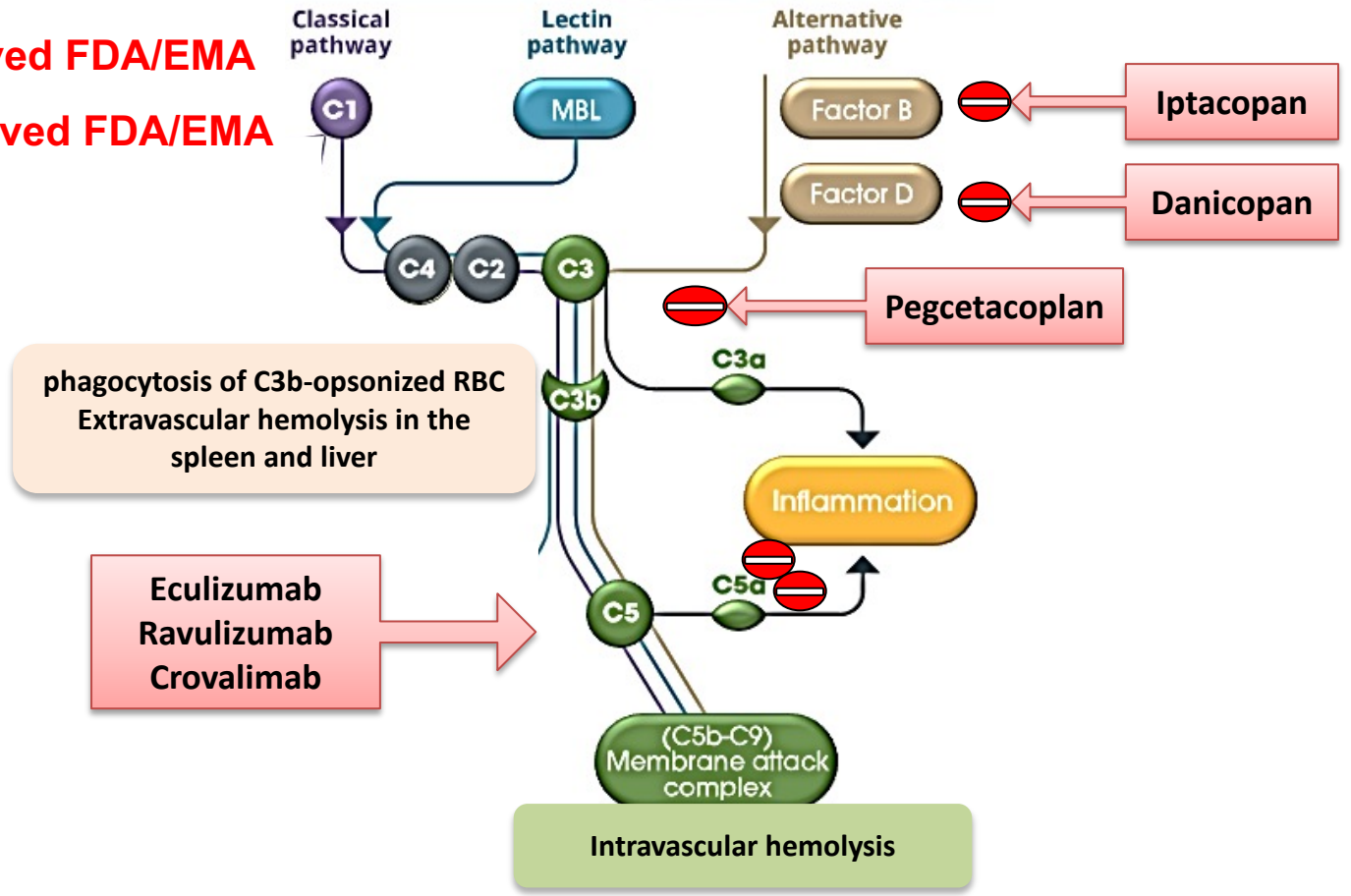
Danicopan, oral thrice daily, targeting factor D

Iptacopan, oral twice daily, targeting factor B

And more coming….

Vemircopan, oral monotherapy, targeting factor D

BCX9930, oral twice daily, targeting factor D



Emerging Treatments for PNH

Doctor, which is the best drug for me?

Griffin M, et al. *Ther Adv Rare Dis*. 2020;1:1-12.