Ritka betegségek a gyulladásos és hemosztázis patomechanizmusok határmesgyéjéről

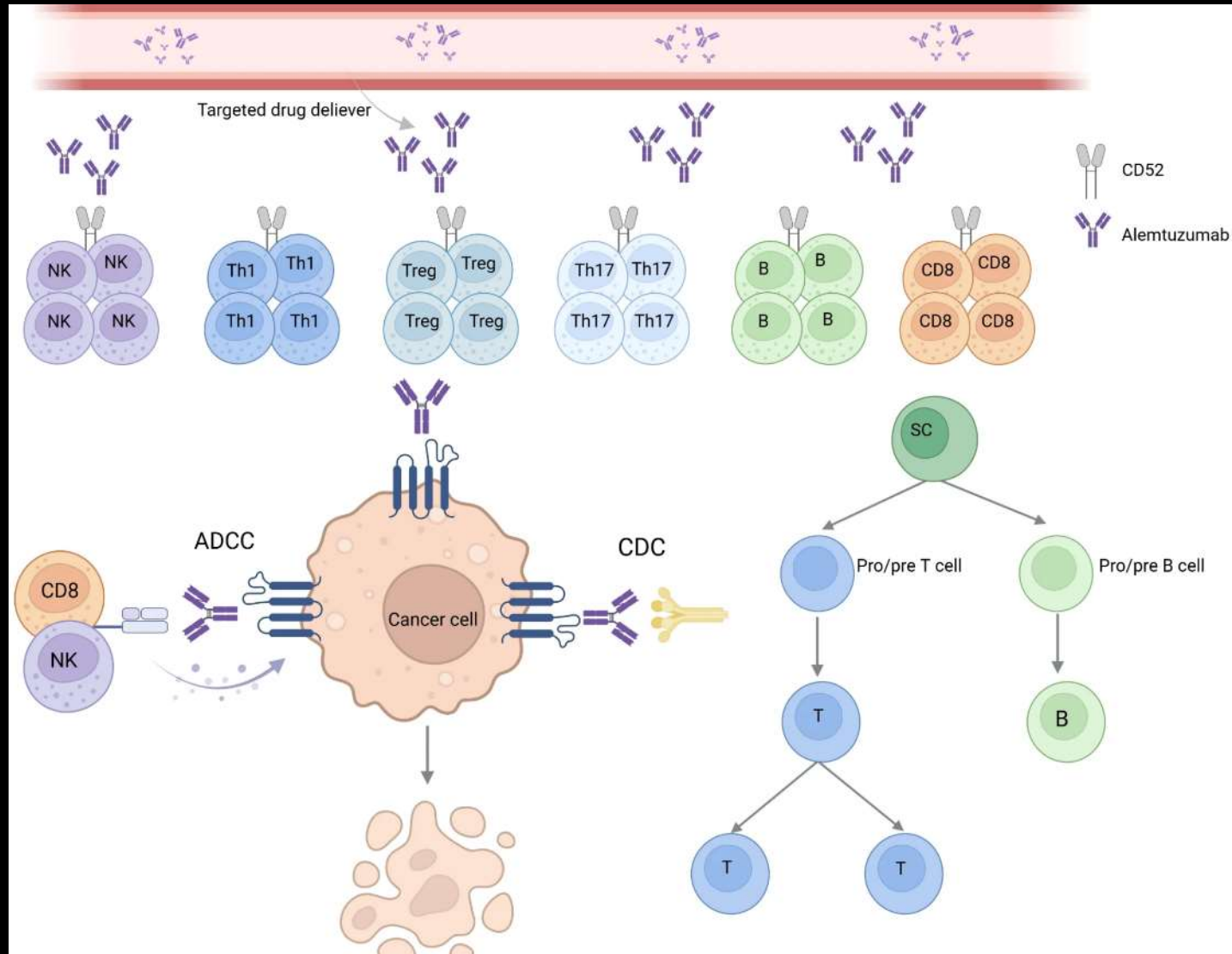
Imre Bodó

Semmelweis University, Budapest, Hungary

48 éves nőbeteg

- Anamnézisben sclerosis multiplex – Dg: 2015
  - 2018-ban alemtuzumab (anti-CD52) kezelést kapott.

Adverse reactions of alemtuzumab		
Infections	Hematologic	Autoimmune



48 éves nőbeteg - FUO

2020.07.15 (HO, KSBO):

- 4 hetes panaszok, hidegrázás, láz (**39,1°C**) nap 3 láz, **Gyenge; felkelni sem képes**. **Hepatosplenomegalia**. Tarkótáji és halántéktáji nyomó, hasogató fejfájás,. Ujjai is fájtak. Neurológiai konzílium első sorban belgyógyászati kérdés: a láz felderítése céljából.
- Laborjaiban emelkedett CRP, (Neg PCT)
  anemia, thrombocytopenia.

48 éves nőbeteg - FUO - folyt

2020.08.04 – 13 (Jahn Ferenc)

- Gastroscopia: NEGATÍV.
- Mk. axilla UH vizsgálata: Hematológiai rendszerbetegség vszínű. Pathológiás nyirokcsomó biopszia javasolt
  Sebészeti Konzílium: Jobb inguinalis nyirokcsomó exscisio.
- Patológiai: Dermatopathias lymphadenitis. Langerhans-sejt szaporulat. *A dermatopathias lymphadenitisnél azonban a paracortex aktivációja lényegesen kifejezettebb*. **Malignus folyamatra utaló elváltozást a mintában nem észleltünk**.

2020.08. 13. – 08.25 (Szt. László Hematológia)

- Crista biopszia: **akut leukémia kizárható**.
- Családi anamnézis: NEGATÍV (3 testvér)

48 éves nőbeteg - FUO - folyt

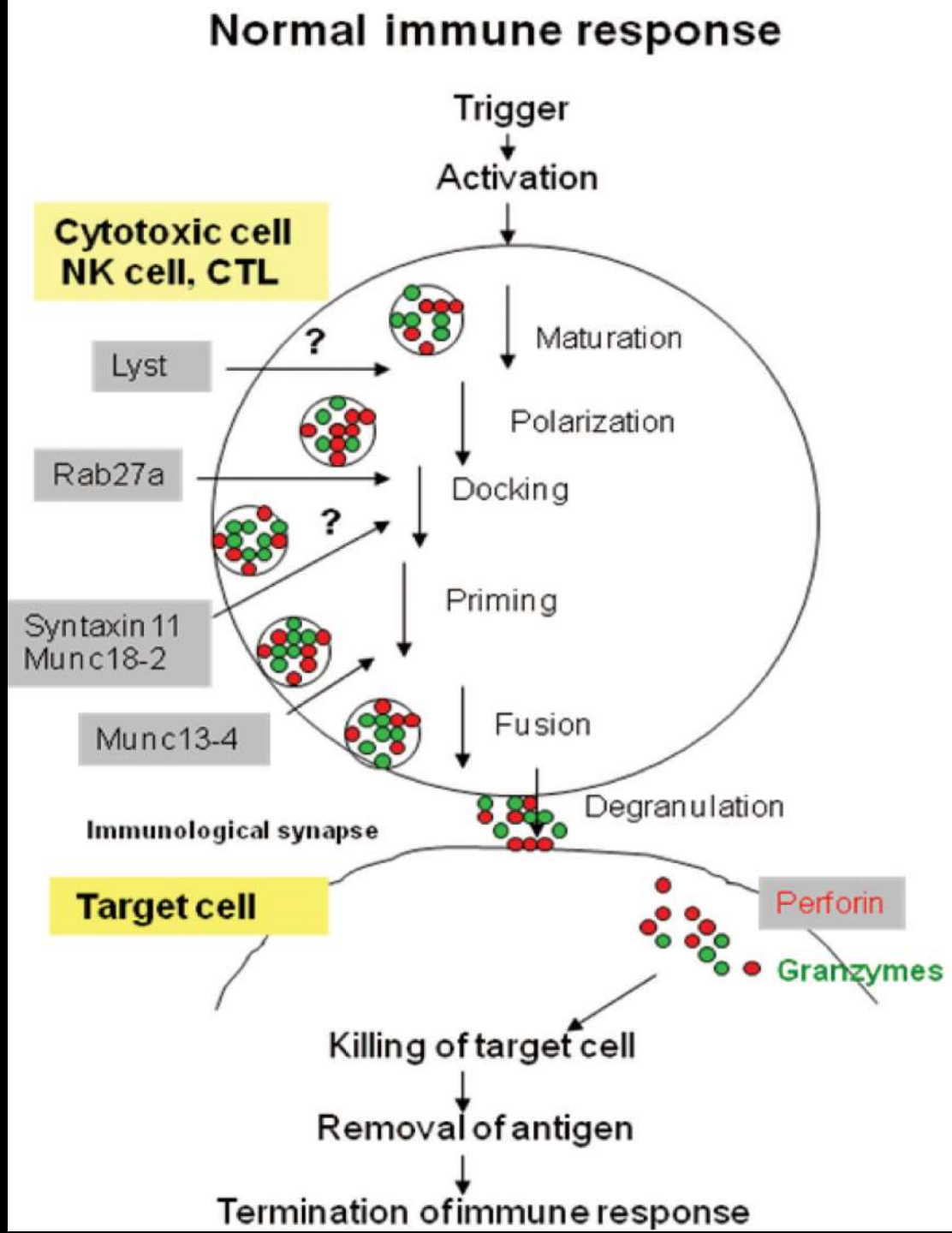
2020.08.25 – 09.03 (BHK)

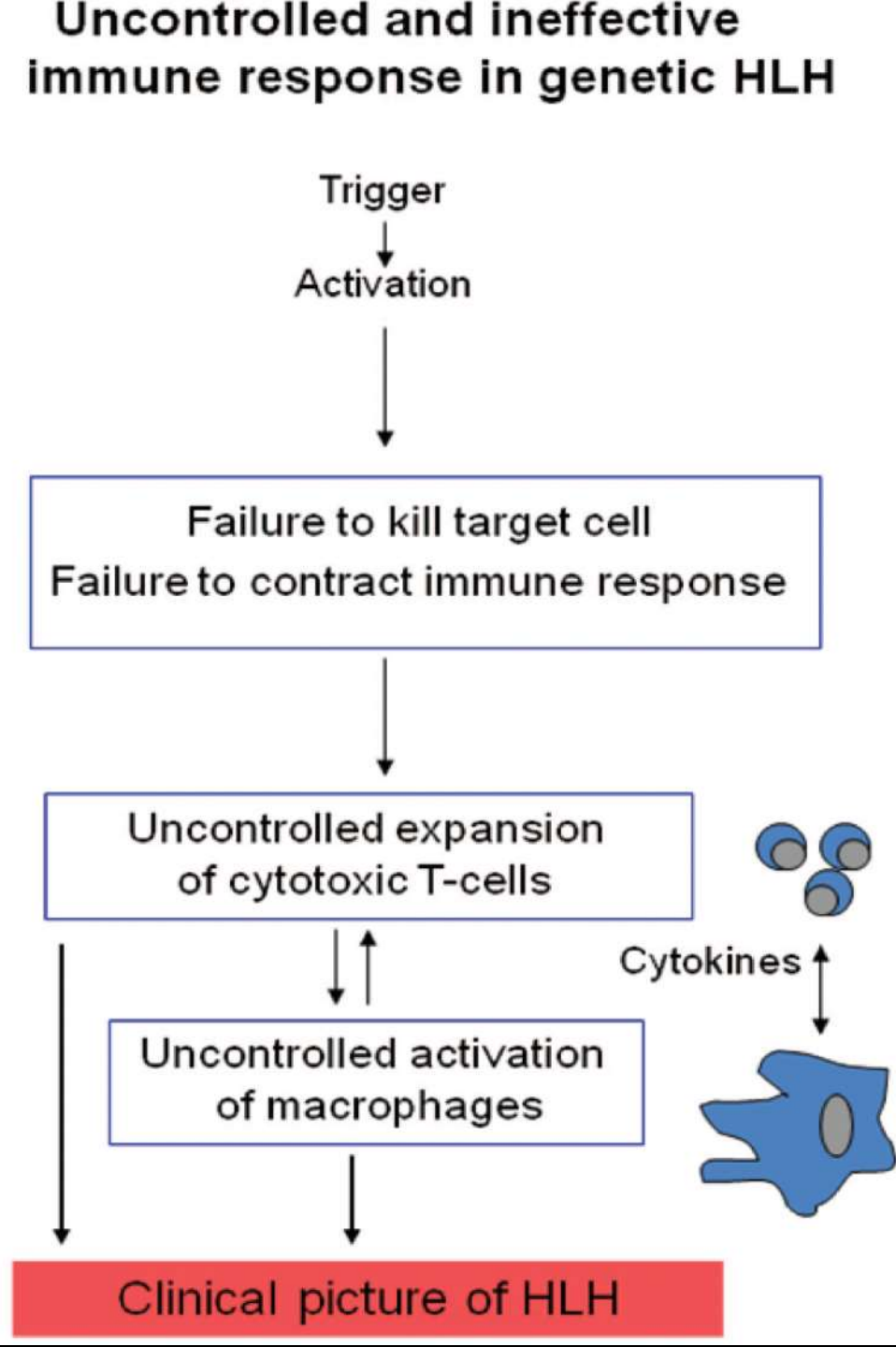
- Kahexiás beteg érkezik, fejét nem tudja fölemelni a párnáról.
- Hepatomegalia 3 hu; Splenomegalia 3 hu.
- Laborok: **Hgb:71** (MCV:65), ANC, ALC, Thr:norm.
  Ferritin: 10 174; LDH:891; D-dimer:>4.3; Fib:2.06; TG:4.6. (Norm<1.7)

HLH-2024 diagnostic criteria — ≥5 of the following

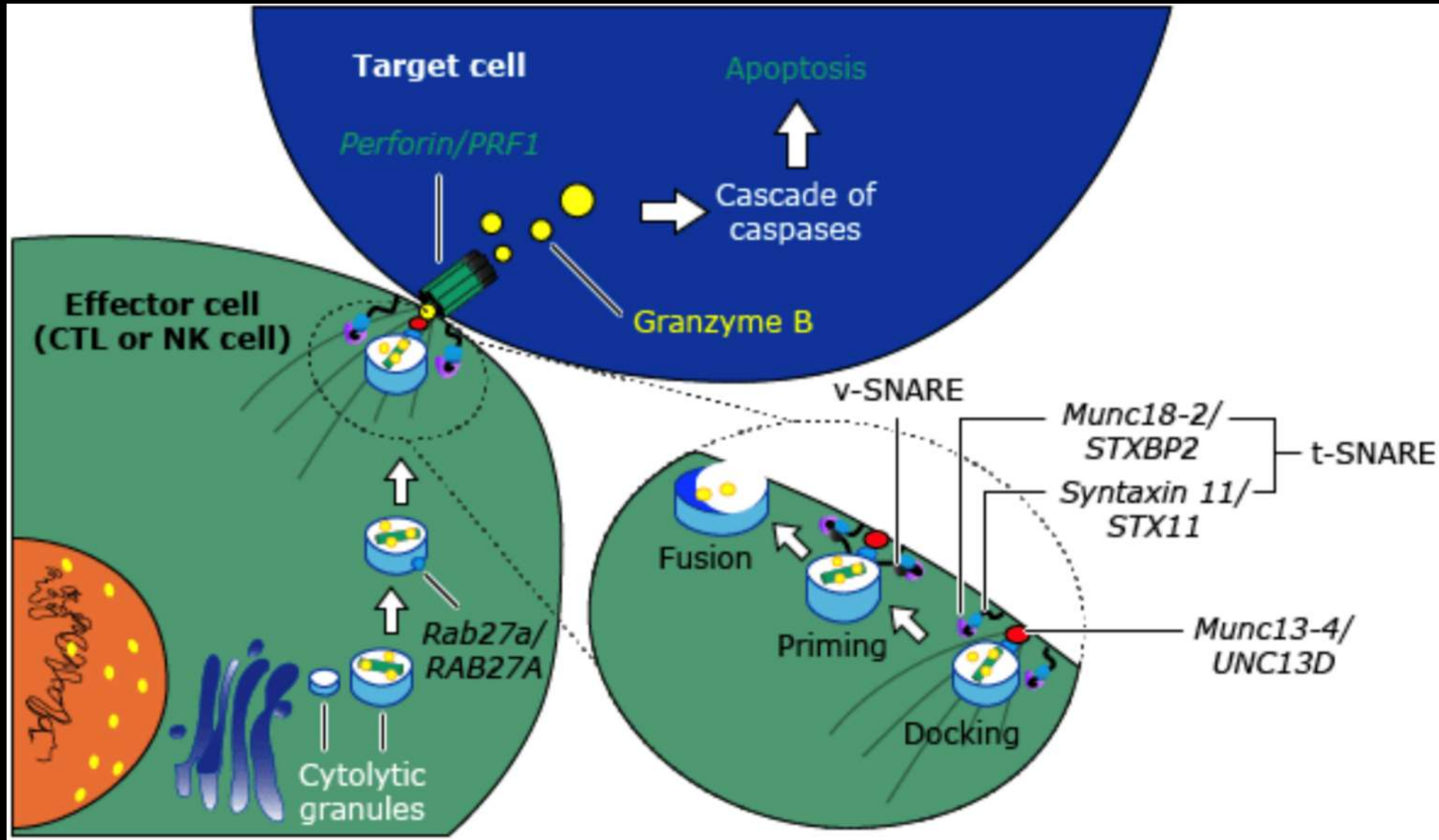
- **Fever** – ≥38.5° C
- **Splenomegaly** – ≥2 cm below the costal margin
- **Cytopenias** – ≥2 of the following
  - Hemoglobin <90 g/L (<100 g/L in neonates)
  - Platelets <100 x 109/L
  - Neutrophils <109/L
- **Hypofibrinogenemia or hypertriglyceridemia** – ≥1 of the following:
  - Fibrinogen ≤1.5 g/L
  - Triglycerides ≥3.0 mmol/L
- **Hyperferritinemia** – ≥500 microg/L
- **Hemophagocytosis** – In bone marrow or other tissues
- **Elevated soluble CD25** (also called soluble interleukin 2 receptor alpha) – ≥2400 U/mL

- HLH

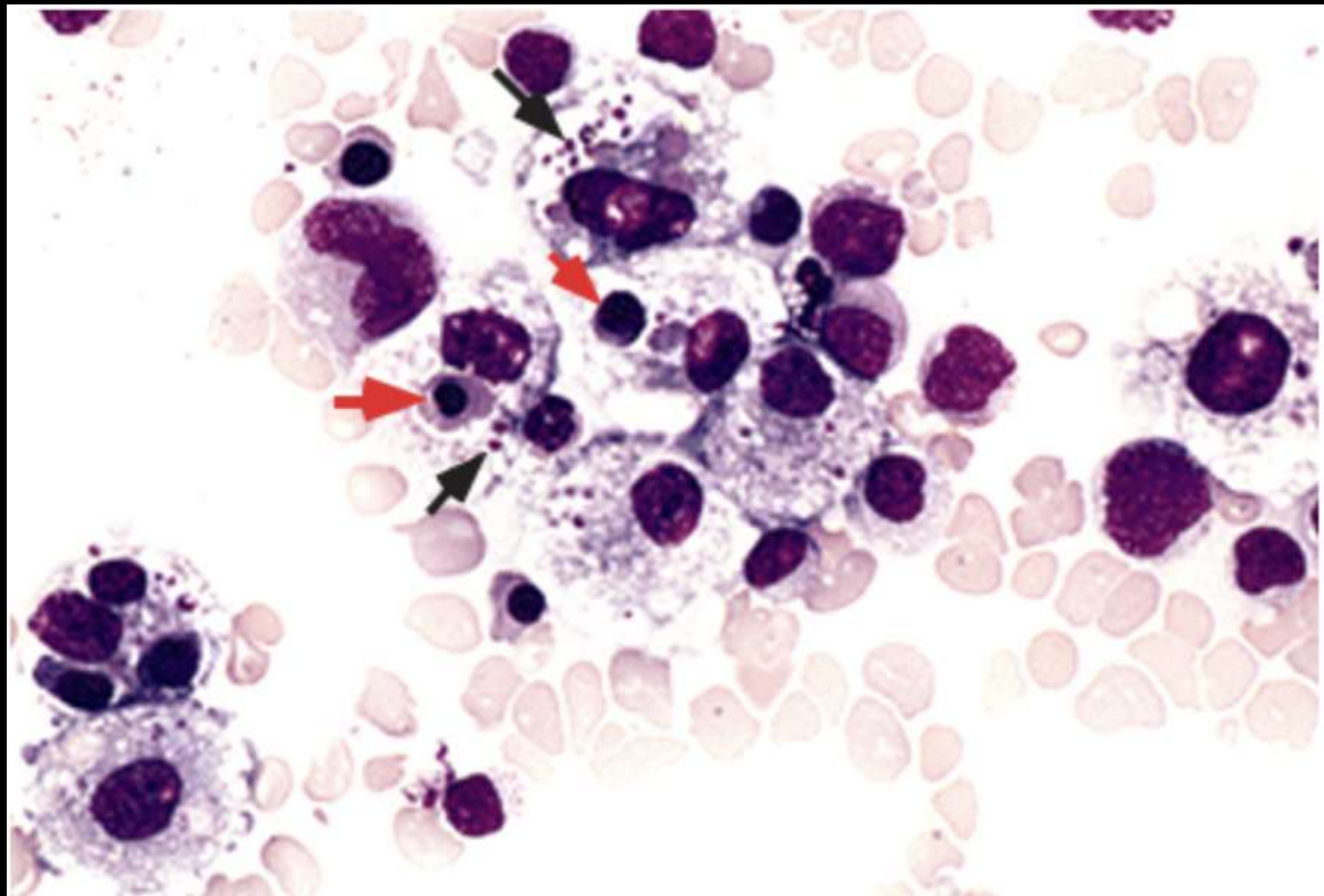

Normal immune response
Trigger
Activation
Cytotoxic cell
NK cell, CTL
Lyst
?
Maturation
Polarization
Rab27a
Docking
?
Priming
Syntaxin 11
Munc18-2
Munc13-4
Fusion
Degranulation
Immunological synapse
Target cell
Perforin
Granzymes
Killing of target cell
Removal of antigen
Termination of immune response


Uncontrolled and ineffective
immune response in genetic HLH
Trigger
Activation
Failure to kill target cell
Failure to contract immune response
Uncontrolled expansion
of cytotoxic T-cells
Cytokines
Uncontrolled activation
of macrophages
Clinical picture of HLH

- HLH


Target cell
Apoptosis
Perforin/PRF1
Cascade of caspases
Granzyme B
Effector cell (CTL or NK cell)
v-SNARE
Munc18-2/ STXBP2
t-SNARE
Syntaxin 11/ STX11
Fusion
Priming
Docking
Munc13-4/ UNC13D
Rab27a/ RAB27A
Cytolytic granules

Hemophagocytosis



HLH triggers

Immune activation

- Infections (mainly viral)
  - EBV, HIV, COVID-19
- Malignancy (mainly lymphomas)
  - B-, T-, NK-NHL, AL, others
- Checkpoint inhibitors
  - Pembrolizumab, nivolumab, ipilimumab
- Immunotherapy
  - CAR-T, bispecific, brentuximab-v etc.
    CRS; alemtuzumab.

Immunodeficiencies

- HIV
- Transplantation & treatment of
- Inherited
  - CGD, etc.
- Rheumatoid disorders
  - Still dz, RA, SLE, etc. -> MAS

HLH treatment

- Stable patient -> treat the trigger

- Unstable patient: **HLH-94 protocol**
  - Dexamethasone 10 mg/m^2 -> taper
  - Etoposide 150 mg /m^2 -> 2x/wk wk 1-2) -> weekly (wk 3-8)

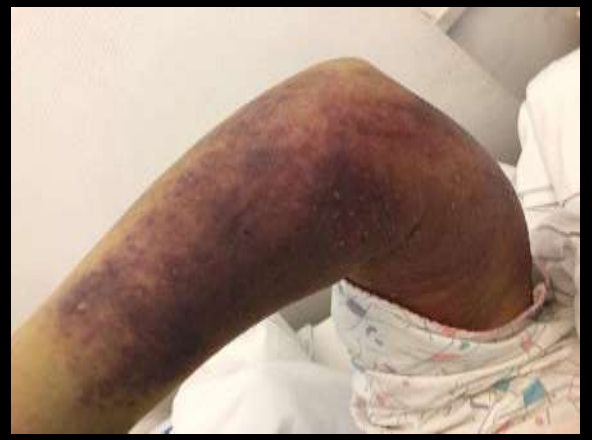
- Fenntartó kezelés: Ruxolitinib.
- Megoldás: Allo-HSCT

86 éves nőbeteg

- Anamnézis: hypertonia, hypaccusis, appendectomia, 2 szülés

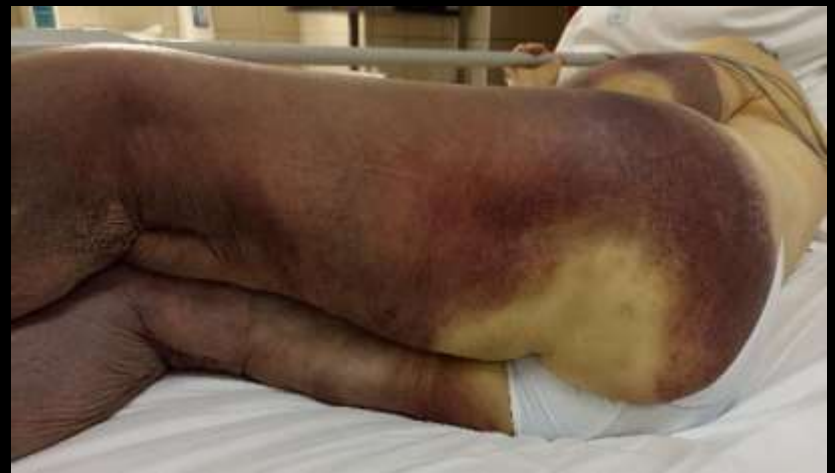
2025. 07.15 (Szt. János Trauma)

- Tornázás után kékesnek látta a karját
  - UH, RTG: NEG.



2025.07.21 (Szt. János Trauma)

- Mindenhol kék
  - Hgb:62; PT: 9.3 s; **aPTI:93 s**



AHA

Incidence 1.48 per million

- Mortality up to 20%

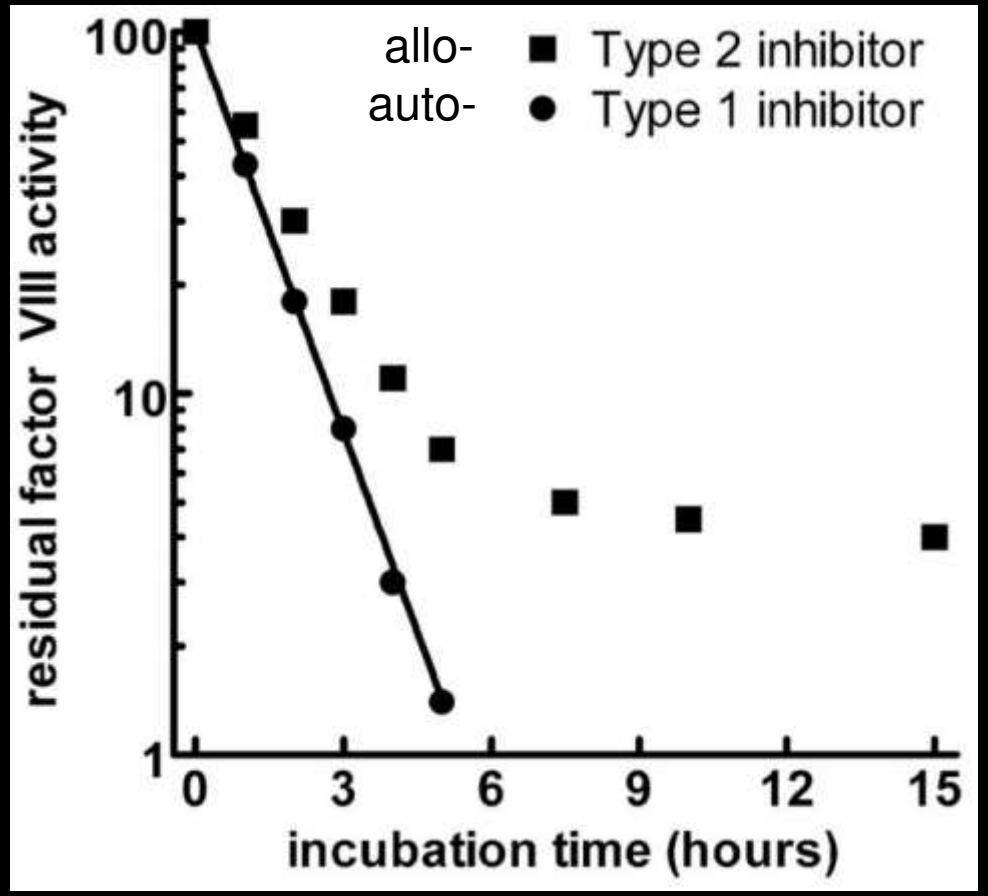
Knoebl P. et al: JTH, 2012; 10:622-

AHA – disease associations, 9 cohorts, 1455 patients

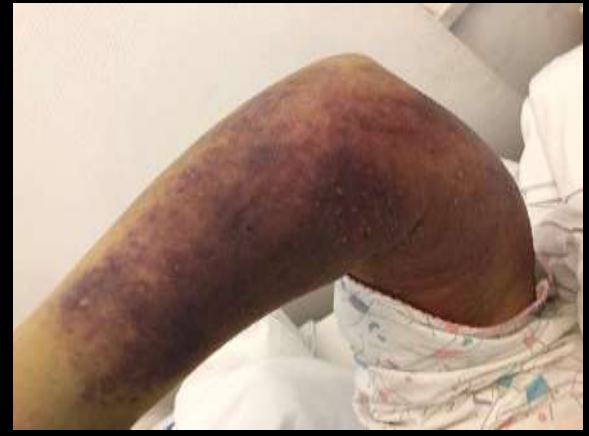
- Idiopathic (54 %)
- Associated with underlying disease
  - Systemic autoimmune disorders (14%)
    - RA, SLE, IBD, Pemphigus/Pemphigoid
  - malignant disorders (12%)
    - Lymphoproliferative
    - Solid organ malignancy
- Other (drugs, infection, etc.)(12%)
- Postpartum (8%)

FVIII inhibitors

- HA - allo-Ab
  - FVIII <1; type 1 kinetics;
  - joint bleeds
- AHA - auto-Ab
  - FVIII can be >1; type 2 kinetics
  - cutaneous and tissue bleeds



Diagnosis -1



- Clinical setup: pt. with a new bleeding
- Isolated APTT prolongation, i.e. normal PT, normal TT
- **Mixing study** (Pt:NP in 1:1 ratio): NO CORRECTION

Time	Patient	1:1	control
0	90	45	32
2 h	94	91	34

Diagnosis-2: confirmation

- Low FVIII – all other factors normal – including VWF
  - FXII, FXI, FIX, VWF – should be all measured
- Inhibitor titration (BU)

- Low titer in AHA ≤ 20 BU

Differential diagnosis

Clinical: Acquired bleeding

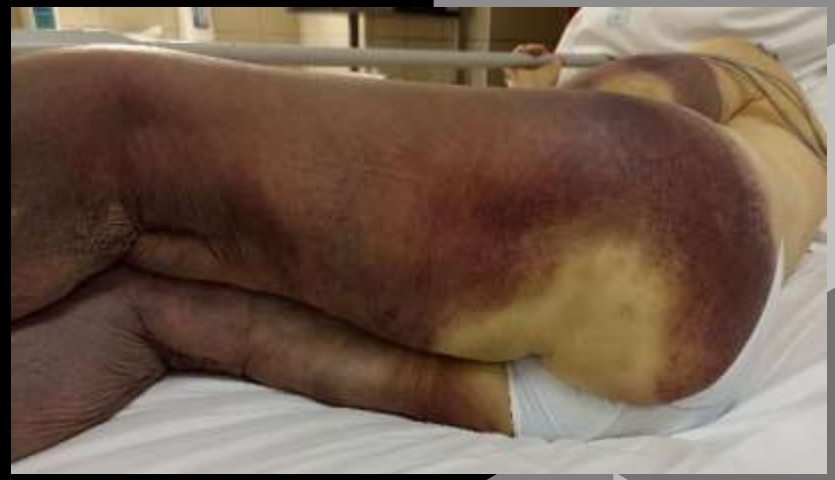
- Systemic (liver, renal etc. disorder)
- AVWS and other coag inhibitors
- Thrombocytopenia
- DIC

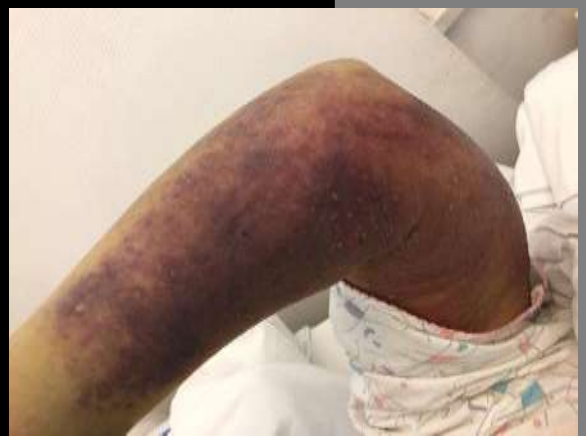
Laboratory: isolated APTT prolongation

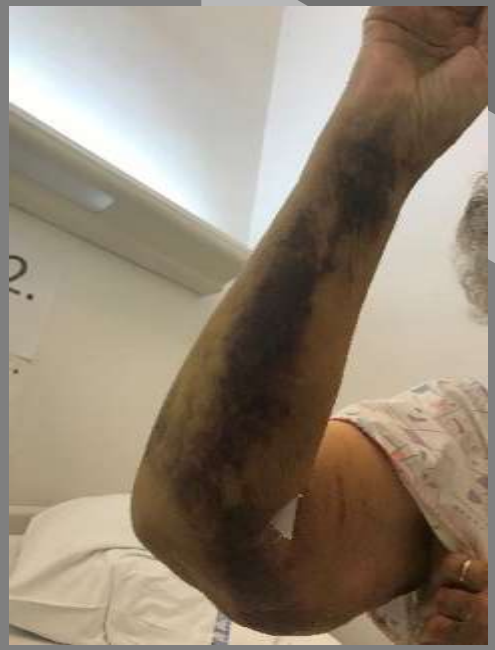
- Lupus anticoagulant
- Specific intrinsic pathway inhibitors

Therapy

- 1. Bleeding control
- 2. Immunosuppression – causative treatment to eliminate the autoantibodies







Bypassing agents

- ***aPCC***: activated prothrombin complex concentrates
  - i.v.; (FVII, FIX, FX, FXI, FII) 50-100 U/kg Q6-12h,
  - max.: 100 U/dose; 200 U/kg/day, (potential thrombogenicity)
- **rFVIIa**, recombinant activated FVII
  - i.v., 90-120 mcg/kg Q2-3h – taper once hemostasis achieved
- **Recombinant porcine FVIII**
  - i.v. 200 U/kg loading; subsequent doses titrated to maintain recomended FVIII levels – Q4-12 h
- **Emicizumab**
  - s.c., 3 mg/kg weekly x4 – followed by maintenance 1.5 mg weekly

AHA

Therapy

- 1. Bleeding control
- 2. Immunosuppression – causative treatment to eliminate the autoantibodies

Guideline recommendations for AHA

Decision Making and Problem Solving

International recommendations on the diagnosis and treatment of patients with acquired hemophilia A

2009

Angela Huth-Kühne,[1] Francesco Baudo,[2] Peter Collins,[3] Jørgen Ingerslev,[4] Craig M. Kessler,[5] Hervé Lévesque,[6] Maria Eva Mingot Castellano,[7] Midori Shima,[8] and Jean St-Louis[9]

[1]SRH Kurpfalzkrankenhaus Heidelberg gGmbH and Hemophilia Center, Heidelberg, Germany; [2]Thrombosis and Hemostasis Unit, Niguarda Hospital, Milan, Italy; [3]Arthur Bloom Haemophilia Centre, University Hospital of Wales School of Medicine, Cardiff University, Cardiff, UK; [4]Center for Hemophilia and Thrombosis, Skejby University Hospital, Department of Clinical Biochemistry, Aarhus, Denmark; [5]Georgetown University Hospital, Lombardi Cancer Center, Division of Hematology/Oncology, Washington, DC, USA; [6]Department of Internal Medicine, Centre Hospitalier Universitaire de Rouen-Boisguillaume, Rouen, France; [7]Regional University Hospital Carlos Haya, Division of Hematology, Málaga, Spain; [8]Department of Pediatrics, Nara Medical University, Nara, Japan, and [9]Hématologie-Oncologie, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada

Haematologica

bjh guideline

The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation

2006

Charles R. M. Hay, S. Brown, P. W. Collins, D. M. Keeling and R. Liesner

University Department of Haematology, Manchester Royal Infirmary, Oxford Road, Manchester, UK

GUIDELINE ARTICLE

International recommendations on the diagnosis and treatment of acquired hemophilia A

Ferrata Storti Foundation

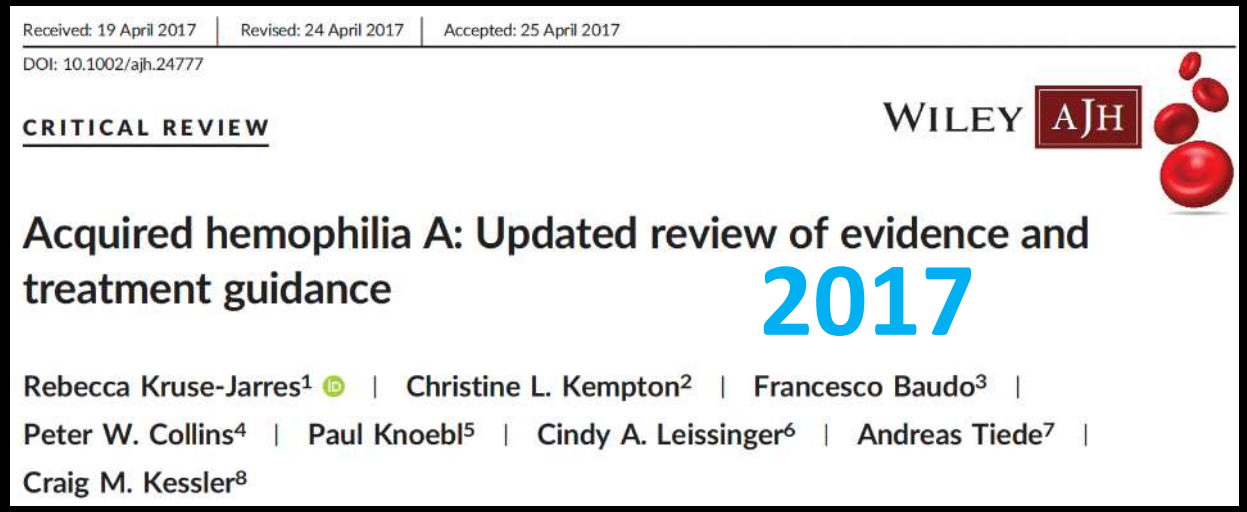
2020

Andreas Tiede,[1] Peter Collins,[2] Paul Knoebl,[3] Jerome Teitel,[4] Craig Kessler,[5] Midori Shima,[6] Giovanni Di Minno,[7] Roseline d'Oiron,[8] Peter Salaj,[9] Victor Jiménez-Yuste,[10] Angela Huth-Kühne[11] and Paul Giangrande[12]

[1]Hannover Medical School, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover, Germany; [2]Arthur Bloom Haemophilia Centre, University Hospital of Wales School of Medicine, Cardiff University, Cardiff, UK; [3]Department of Medicine 1, Division of Hematology and Hemostasis, Medical University of Vienna, Vienna,

Haematologica 2020
Volume 105(7):1791-1801

Haematologica



Received: 19 April 2017 | Revised: 24 April 2017 | Accepted: 25 April 2017

DOI: 10.1002/ajh.24777

CRITICAL REVIEW

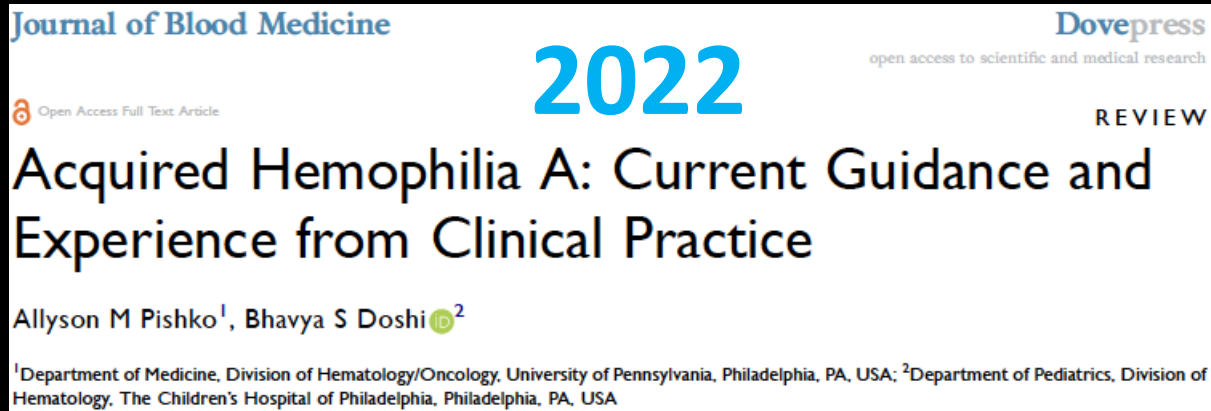
WILEY AJH

Acquired hemophilia A: Updated review of evidence and treatment guidance

2017

Rebecca Kruse-Jarres[1] | Christine L. Kempton[2] | Francesco Baudo[3] | Peter W. Collins[4] | Paul Knoebl[5] | Cindy A. Leissinger[6] | Andreas Tiede[7] | Craig M. Kessler[8]

Am J Hematol



Journal of Blood Medicine

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REVIEW

Acquired Hemophilia A: Current Guidance and Experience from Clinical Practice

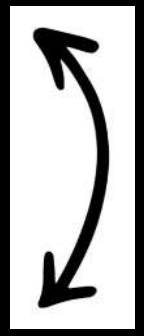
2022

Allyson M Pishko[1], Bhavya S Doshi[2]

[1]Department of Medicine, Division of Hematology/Oncology, University of Pennsylvania, Philadelphia, PA, USA; [2]Department of Pediatrics, Division of Hematology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA

Traditional immunosuppression in historic series and guidelines

- Sequential administration of:
  - Steroids: 1 mg/kg prednisolon or methylpredisolon
    with or without
  - Cyclophosphamide, po. 50-100 mg/day
    4-6 weeks



<u>Second line</u>:

- Rituximab, 375 mg/m^2
- Cyclosporin A, 100-200 mg/day
- Azathioprin, 100 mg/day
- MMF

Traditional immunosuppression is toxic (and has an inadequat efficacy)

	EACH	D	UK	ESP	KWARK	CHIN
n	501	102	172	151	143	187
Mortality %	29	33.3	41.7	23.8	38.2	6.7
Bleeding-mort %	0.4	2.9	7.4	3.3	7.7	0.6
%TRM	4	15.7	6.9	9.9	15.4	1.2
% CR, alive	63	48	45	66	61	74
% alive, no CR	3.5	18.6	4.7	9.9	NA	18.7

Current strategies to avoid toxicity of prolonged steroid exposure

- Delaying immunosuppression
- Bypassing with emicizumab

Clinical Trial > Lancet Haematol. 2023 Nov;10(11):e913-e921.

doi: 10.1016/S2352-3026(23)00280-6. Epub 2023 Oct 16.

Emicizumab prophylaxis in patients with acquired haemophilia A (GTH-AHA-EMI): an open-label, single-arm, multicentre, phase 2 study

Andreas Tiede [1], Christina Hart [2], Paul Knöbl [3], Richard Greil [4], Johannes Oldenburg [5], Ulrich J Sachs [6], Wolfgang Miesbach [7], Christian Pfrepper [8], Karolin Trautmann-Grill [9], Katharina Holstein [10], Jan Pilch [11], Patrick Möhnle [12], Christoph Schindler [13], Carmen Weigt [14], Dorothea Schipp [14], Marcus May [15], Christiane Dobbelstein [15], Fabius J Pelzer [15], Sonja Werwitzke [15], Robert Klamroth [16]

- Creating new immunosuppression regimens that are
  - ➢ less toxic, but
  - ➢ more effective

blood

Regular Article

THROMBOSIS AND HEMOSTASIS

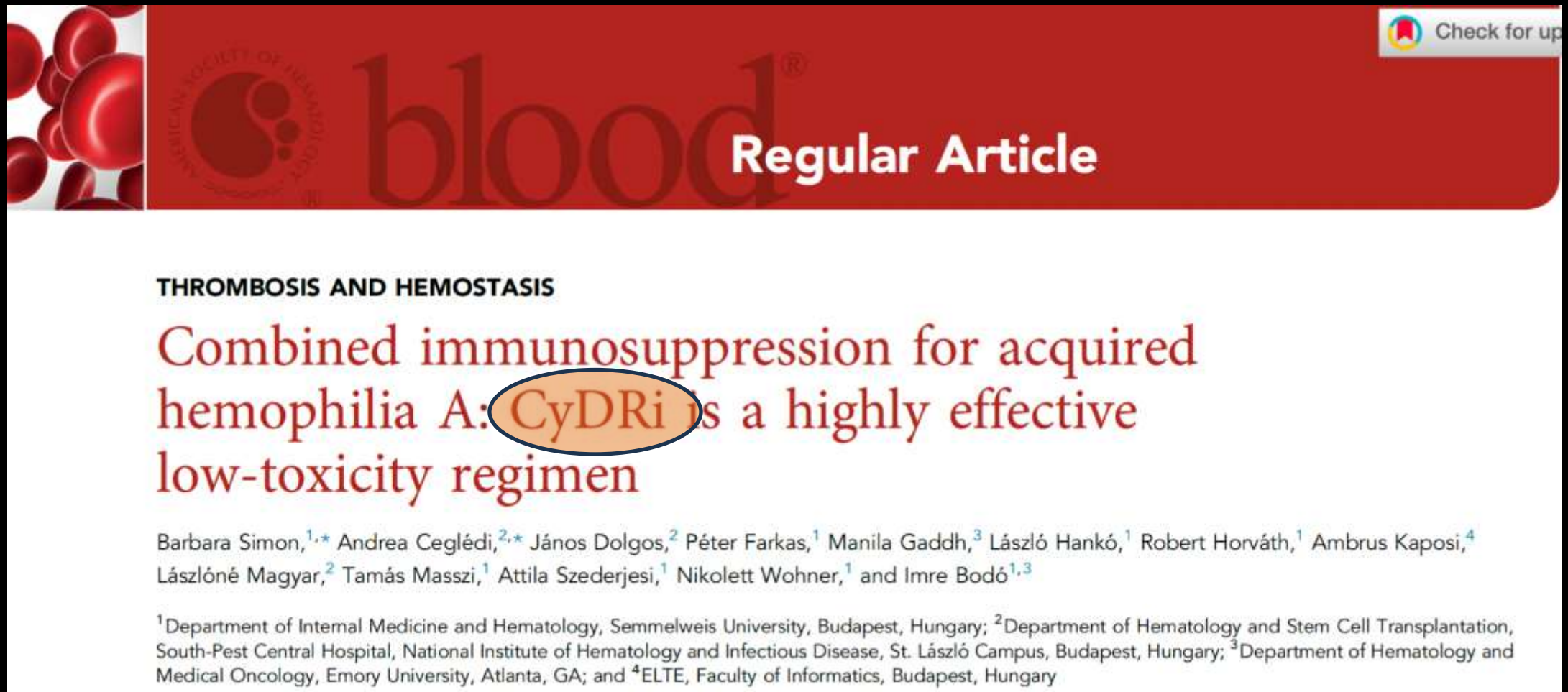
Combined immunosuppression for acquired hemophilia A: CyDRi is a highly effective low-toxicity regimen

Barbara Simon,[1,*] Andrea Ceglédi,[2,*] János Dolgos,[2] Péter Farkas,[1] Manila Gaddh,[3] László Hankó,[1] Robert Horváth,[1] Ambrus Kaposi,[4] Lászlóné Magyar,[5] Tamás Masszi,[1] Attila Szederjesi,[1] Nikolett Wohner,[1] and Imre Bodó[1,3]

[1]Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary; [2]Department of Hematology and Stem Cell Transplantation, South-Pest Central Hospital, National Institute of Hematology and Infectious Disease, St. László Campus, Budapest, Hungary; [3]Department of Hematology and Medical Oncology, Emory University, Atlanta, GA; and [4]ELTE, Faculty of Informatics, Budapest, Hungary

Current strategies to avoid toxicity of prolonged steroid exposure

Creating new immunosuppression regimens that are less toxic, but more effective



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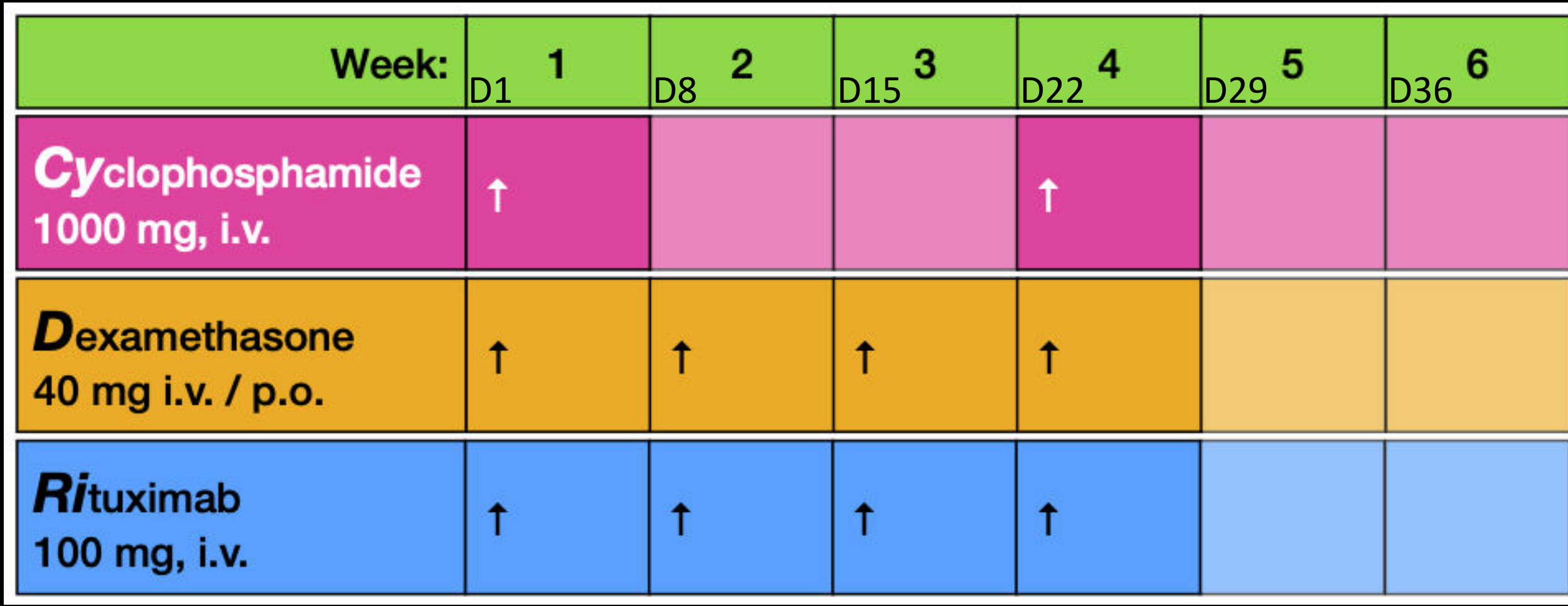
CyDRi

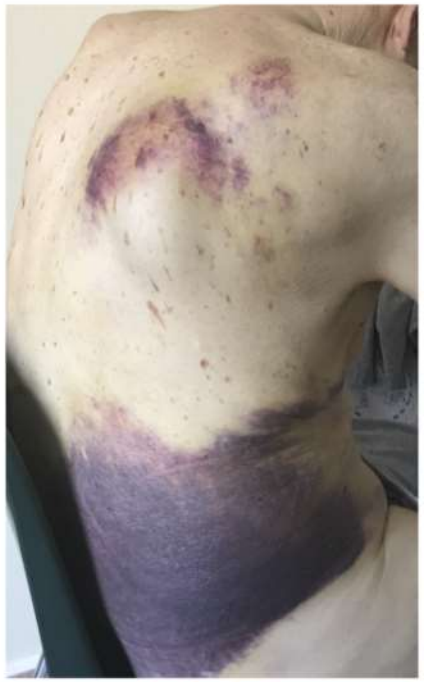

Week:
1
D1
2
D8
3
D15
4
D22
5
D29
6
D36
Cyclophosphamide
1000 mg, i.v.
Dexamethasone
40 mg i.v. / p.o.
Rituximab
100 mg, i.v.

CyDRi novel in that:

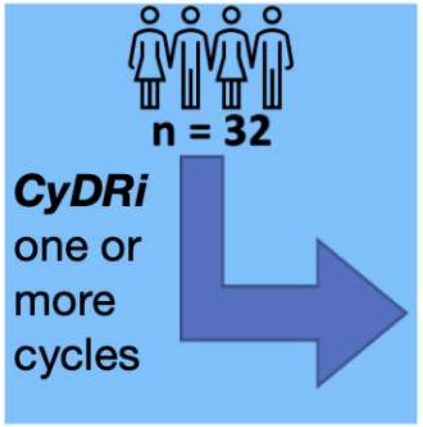
- Three drugs combined upfront
- Pulse administration (i.v., once a week x 4)
- Steroid component: dexamethasone
- Inadequate response or relapse: the very same regimen is repeated

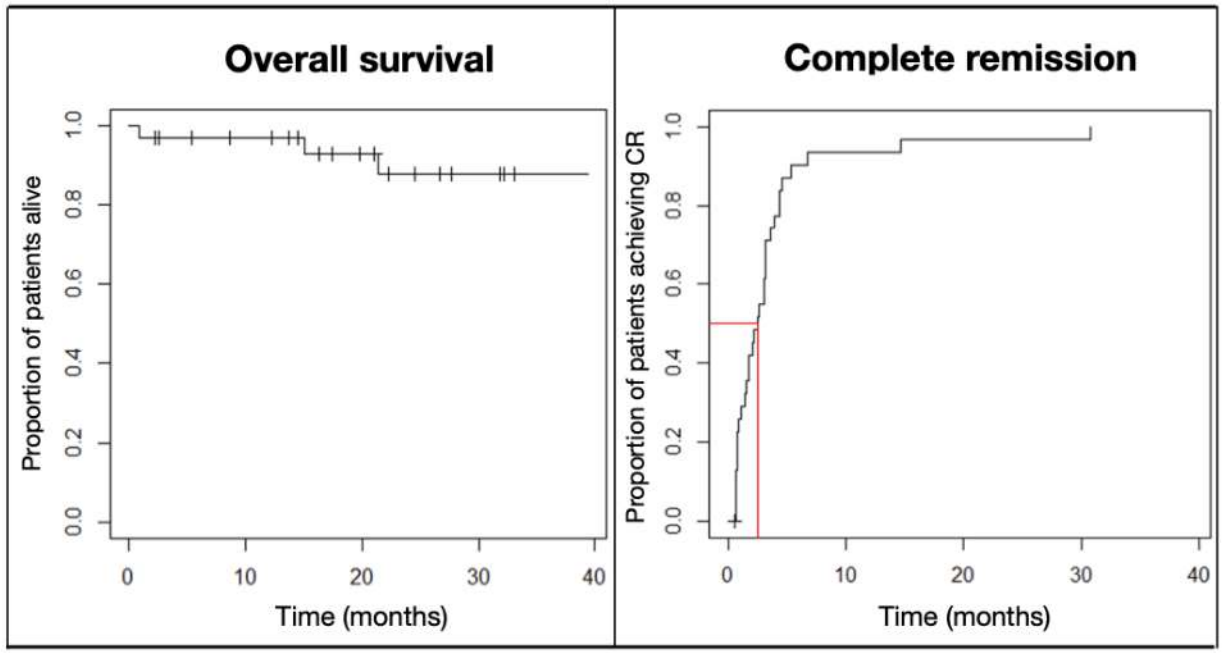
Acquired hemophilia A (**AHA**) is a life-threatening autoimmune bleeding disorder.

CyDRi is a novel, highly effective, low toxicity immuno-suppressive regimen that offers new perspectives in AHA management.



Week:	D1 1	D8 2	D15 3	D22 4	5	6
Cyclophosphamide 1000 mg, i.v.	↑			↑		
Dexamethasone 40 mg i.v. / p.o.	↑	↑	↑	↑		
Rituximab 100 mg, i.v.	↑	↑	↑	↑		





Retrospective analysis

Simon B. et al., Blood 2022,

blood
Regular Article

THROMBOSIS AND HEMOSTASIS

Combined immunosuppression for acquired hemophilia A: CyDRi is a highly effective low-toxicity regimen

Barbara Simon,[1,*] Andrea Ceglédi,[2,*] János Dolgos,[2] Péter Farkas,[1] Manila Gaddh,[3] László Hankó,[1] Robert Horváth,[1] Ambrus Kaposi,[4] Lászlóné Magyar,[2] Tamás Masszi,[1] Attila Szederjesi,[1] Nikolett Wohner,[1] and Imre Bodó[1,3]

[1]Department of Internal Medicine and Hematology, Semmelweis University, Budapest, Hungary; [2]Department of Hematology and Stem Cell Transplantation, South-Pest Central Hospital, National Institute of Hematology and Infectious Disease, St. László Campus, Budapest, Hungary; [3]Department of Hematology and Medical Oncology, Emory University, Atlanta, GA; and [4]ELTE, Faculty of Informatics, Budapest, Hungary

KEY POINTS

Acquired hemophilia A (AHA) is a rare severe autoimmune bleeding disorder with signifi-
cant morbidity and mortality. Although critical for disease control, there is no consensus for

THROMBOSIS AND HEMOSTASIS

Comment on Simon et al, page 1983

Safer steps on a narrow path

Paul Knoebl | Medical University of Vienna

Choosing the best immunosuppression for acquired hemophilia A (AHA) is a narrow path between shortening the time to remission and avoiding deleterious adverse effects. The article in this issue of *Blood* by Simon et al[1] provides some safer steps to accomplish this.

In AHA, autoantibodies block coagulation factor VIII (FVIII), which leads to severe bleeding. This requires very expensive hemostatic therapy with bypassing agents (recombinant FVIIa, activated prothrombin complex), or recombinant porcine FVIII.[2] For immunosuppression (the causal therapy for eradicating the autoantibodies), daily doses of steroids with or without

large European Acquired Haemophilia Registry (EACH2)[3] and the prospective German, Austrian and Swiss Society of Thrombosis and Hemostasis Research (GTH)-AH 01/2010 trial[4] in which half the affected patients were older than age 74 years and were often in frail condition.[5]

Simon et al report on using a different strategy for immunosuppression, which seems to be equally effective in eradicating the autoantibodies but is better tolerated with fewer adverse events. Their strategy is quite similar to some myeloma protocols: pulses of 1000 mg of cyclophosphamide (a moderate dose) on days 1 and 22 and 40 mg of dexamethasone (a high dose) plus 100 mg of rituximab (a low dose) on days 1, 8, 15,

SUMMARY AND COMMENT | ONCOLOGY AND HEMATOLOGY

PRACTICE CHANGING

December 6, 2022

The NEW ENGLAND JOURNAL of MEDICINE

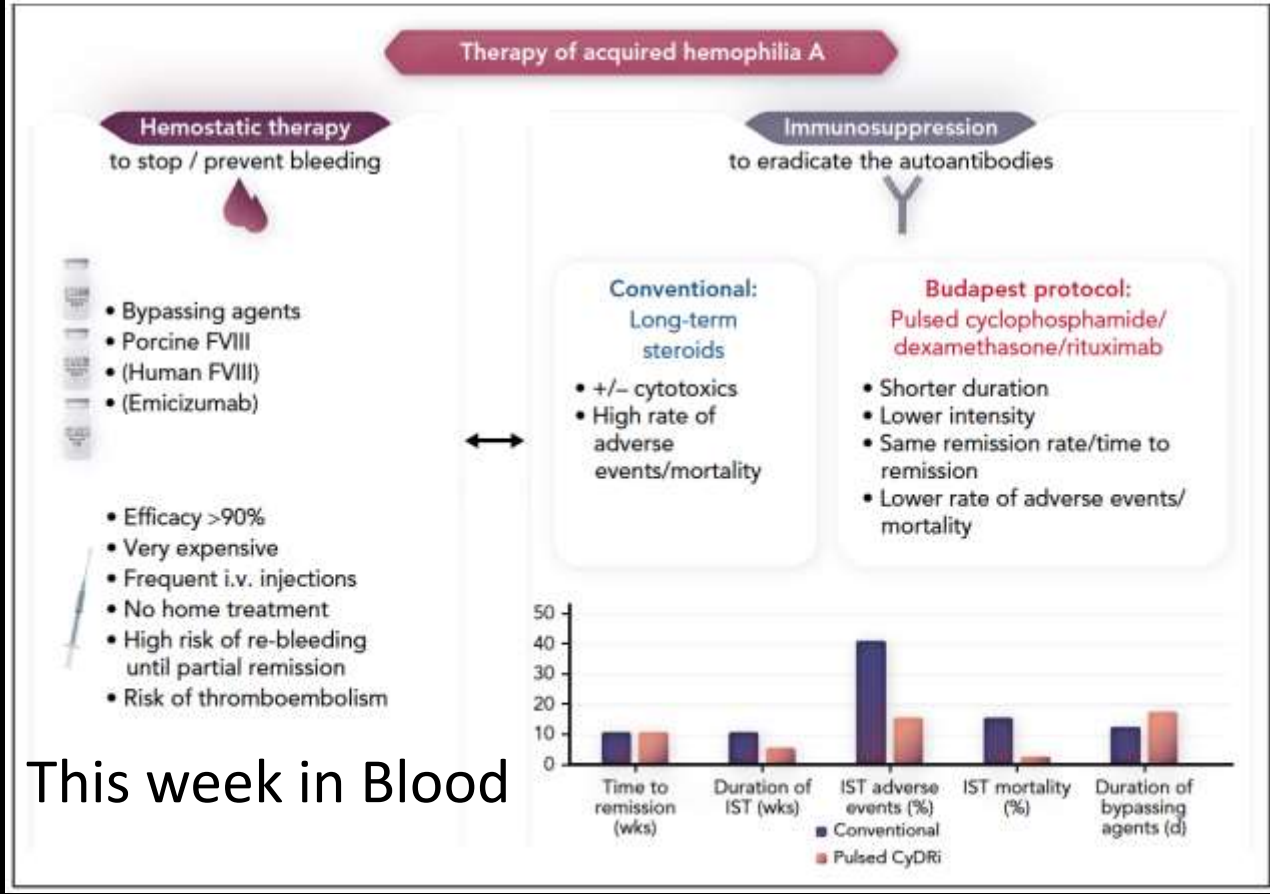
Combined Upfront Immunosuppression for Acquired Hemophilia A

Anjali A Sharathkumar, MBBS, MD, MS, reviewing Simon B et al. Blood 2022 Nov 3

An upfront triple combined immunosuppressive regimen — CyDRi — is highly effective with low toxicity.

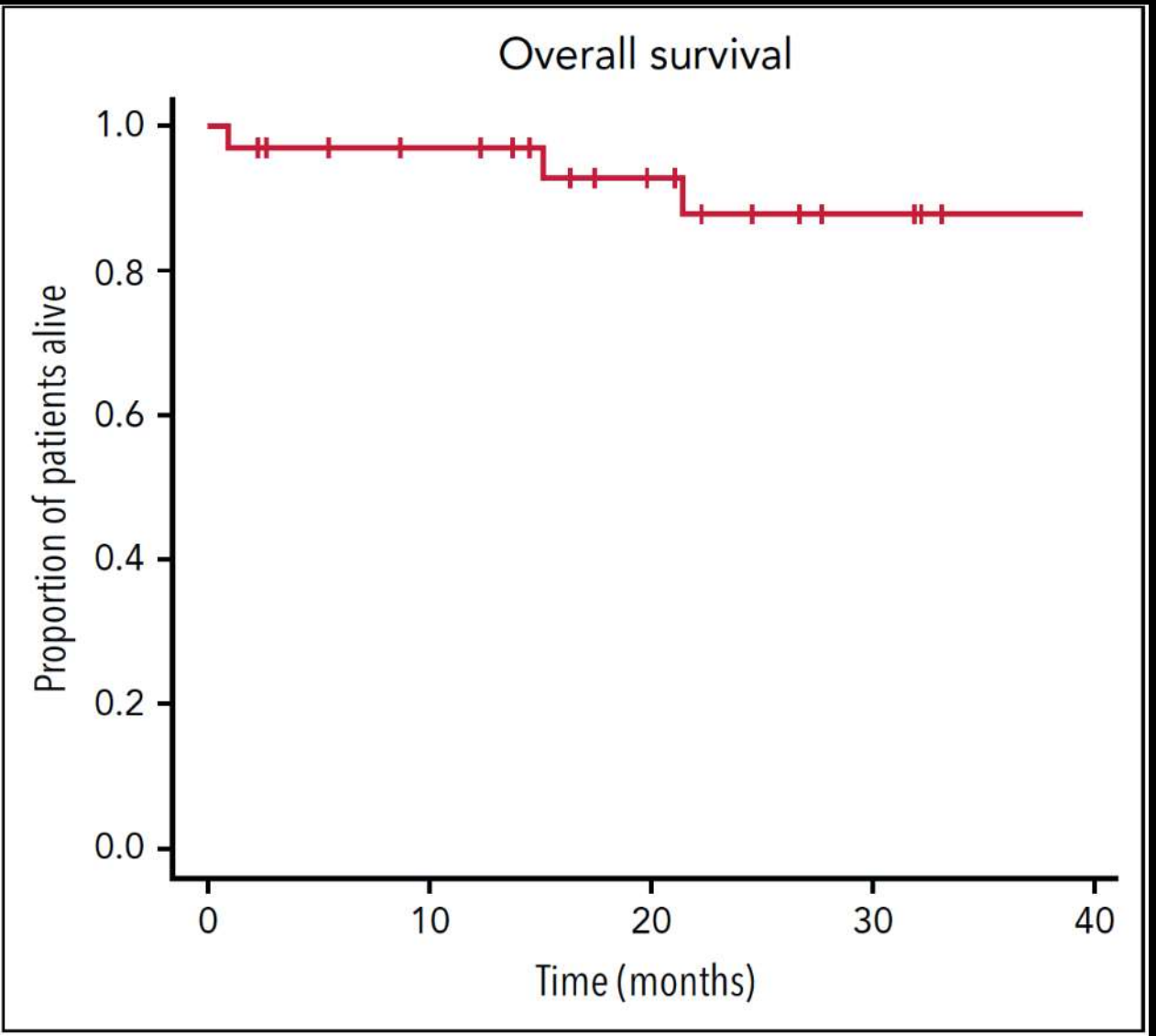
Acquired haemophilia A (AHA) is an extremely rare autoimmune disorder caused by autoantibodies to coagulation factor VIII and characterized by life-threatening bleeding within soft tissues and vital organs. Supportive therapy for bleed control and immunosuppressive therapy remain the backbone of treatment, but there is no consensus about the best immunosuppressive therapy. Most regimens include upfront steroids followed by other immunosuppressive agents (e.g., rituximab, cyclophosphamide, cyclosporine) when steroids fail.

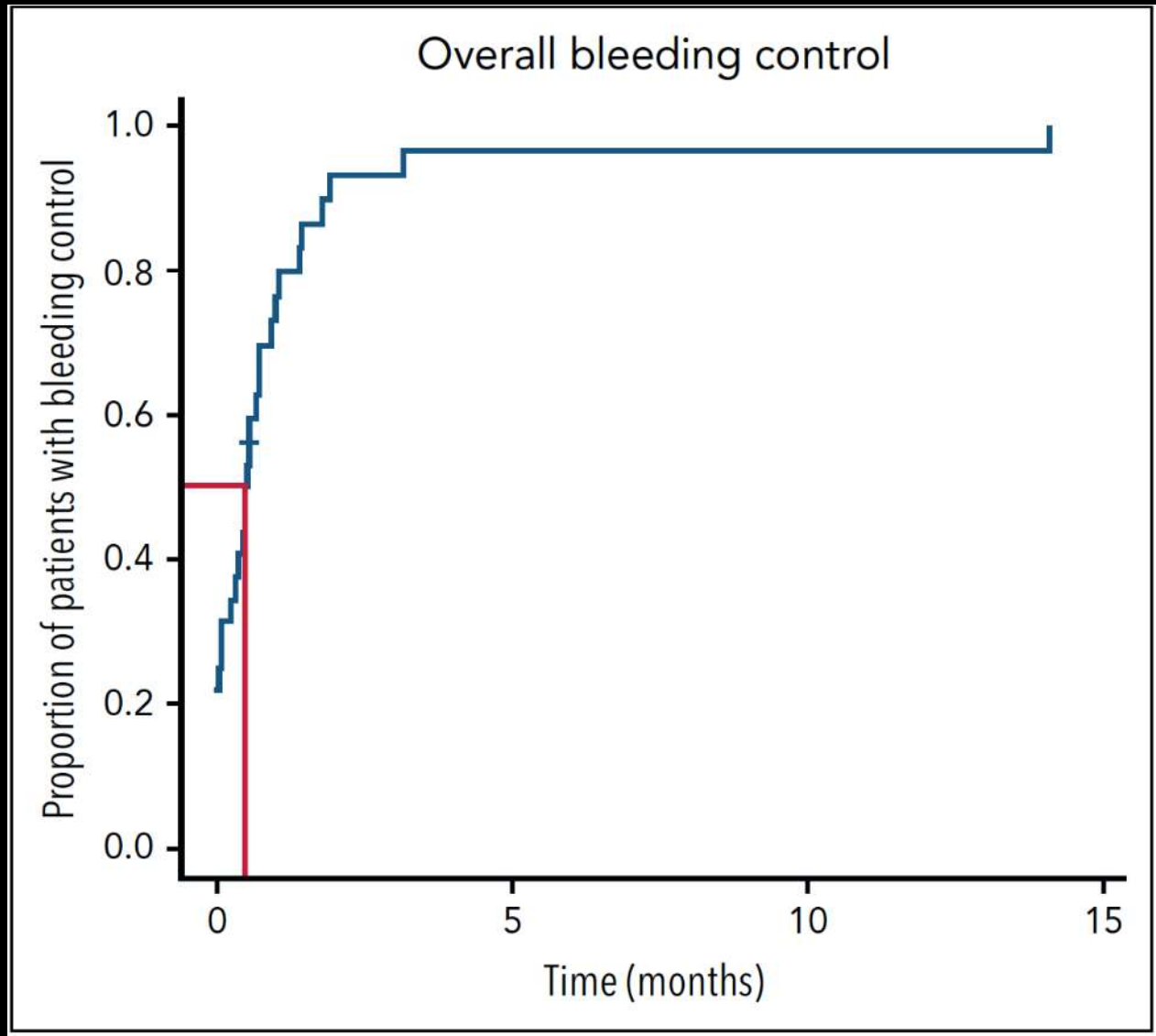
In an attempt to reduce steroid exposure and toxicity, investigators in Hungary instituted an upfront, combined, pulse-dosed immunosuppressive treatment protocol in 2009. Now, they report outcomes for the first 32 patients (median age, 77) treated with the protocol at two institutions from 2009 to 2020. The CyDRi protocol consists of cyclophosphamide (1000 mg on days 1 and 22),

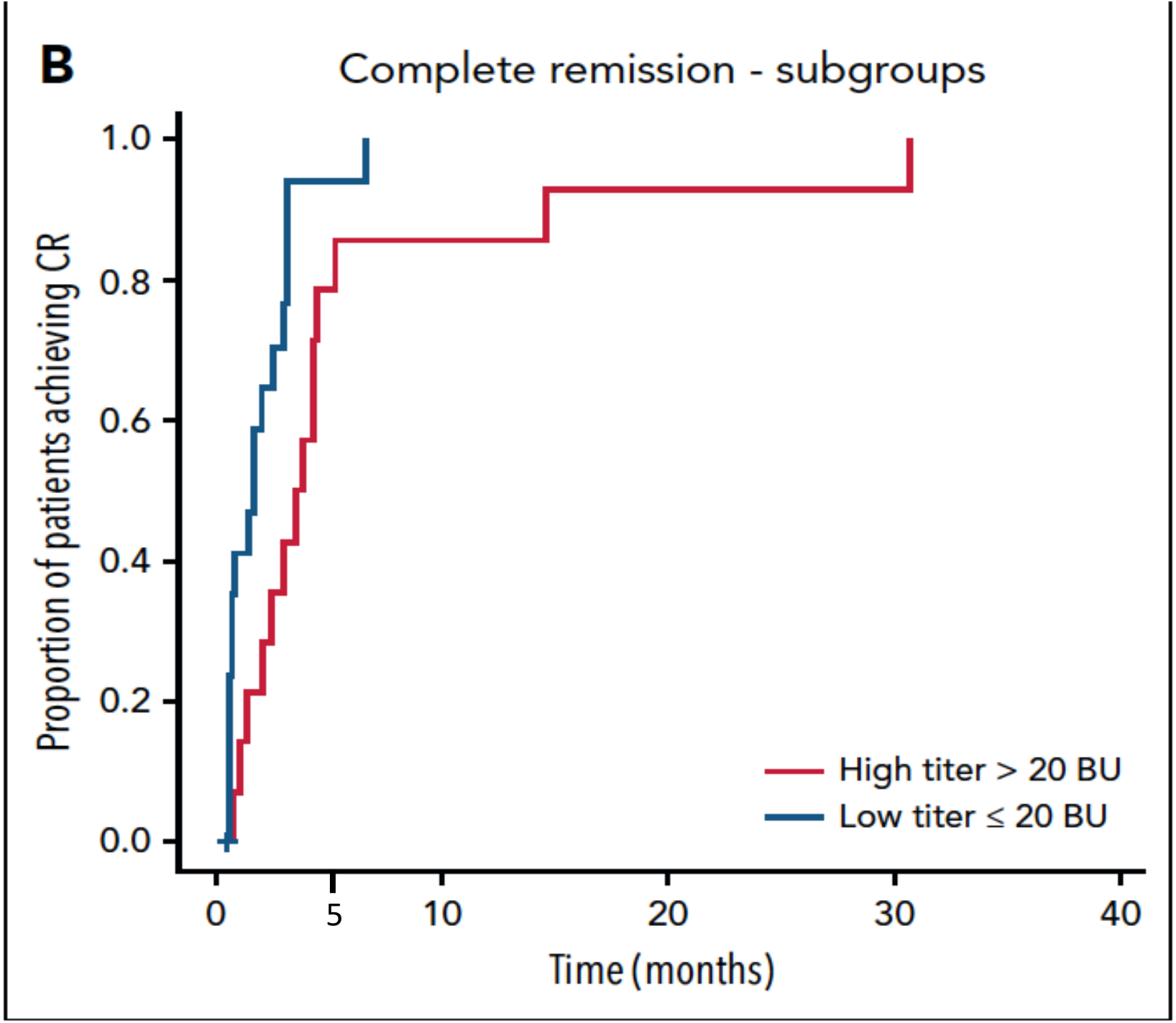


This week in Blood

OS n=32 BC


Overall survival
Proportion of patients alive
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Time (months)


Overall bleeding control
Proportion of patients with bleeding control
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
Time (months)


B
Complete remission - subgroups
Proportion of patients achieving CR
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
20
30
40
Time (months)
High titer > 20 BU
Low titer ≤ 20 BU

CR

How do you compare data from different cohorts?

- Compare the patient populations
- Find comparable outcomes

Comparison with previous cohorts

	HU	EACH	D	UK	ESP	CHIN
n	32	501	102	172	151	187
Age, y, median	77	74	74	78	74	52
>80	28	19	N/A	N/A	29	6
>85	13	8	N/A	23	N/A	2
%	56	51	43	57	44	55
FVIII	1	2	1.4	3	1.7	1.7
BU, median	17	12.8	19	13	13	13
%BU >20	43.8	N/A	39.2	N/A	N/A	N/A
%BU >100	31.3	12.4	13.7	9.3	10.3	9.6
%BU >1000	3.1	0	1	0	2.8	0.5

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Comparison with previous cohorts

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n	32	501	102	172	151	187
%CR, alive	90.6	63	48	45	66	74
%alive, no CR	0	3.5	18.6	4.7	9.9	18.7
% relapse	6.5	18.1	24.2	20	7.1	8.4
Mortality	9.4	29	33.3	41.7	23.8	6.7
Bleeding-mort	0	0.4	2.9	7.4	3.3	0.6
%TRM	3.1	4	15.7	6.9	9.9	1.2
Mort-underly	3.1	4.2	2.9	N/A	10.6	1.2
AE	15.6	31	66	51	N/A	7.1


Thank you!

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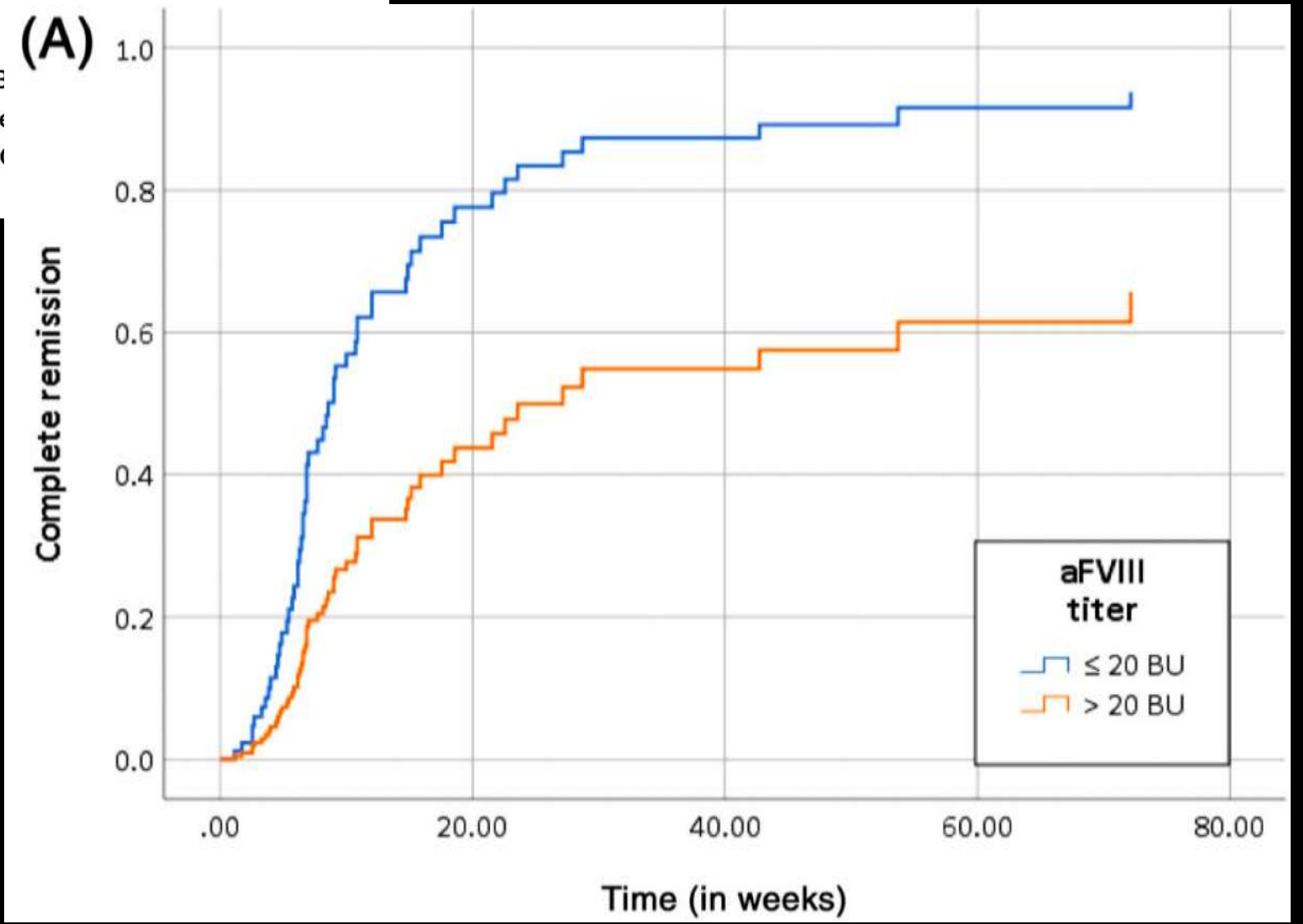
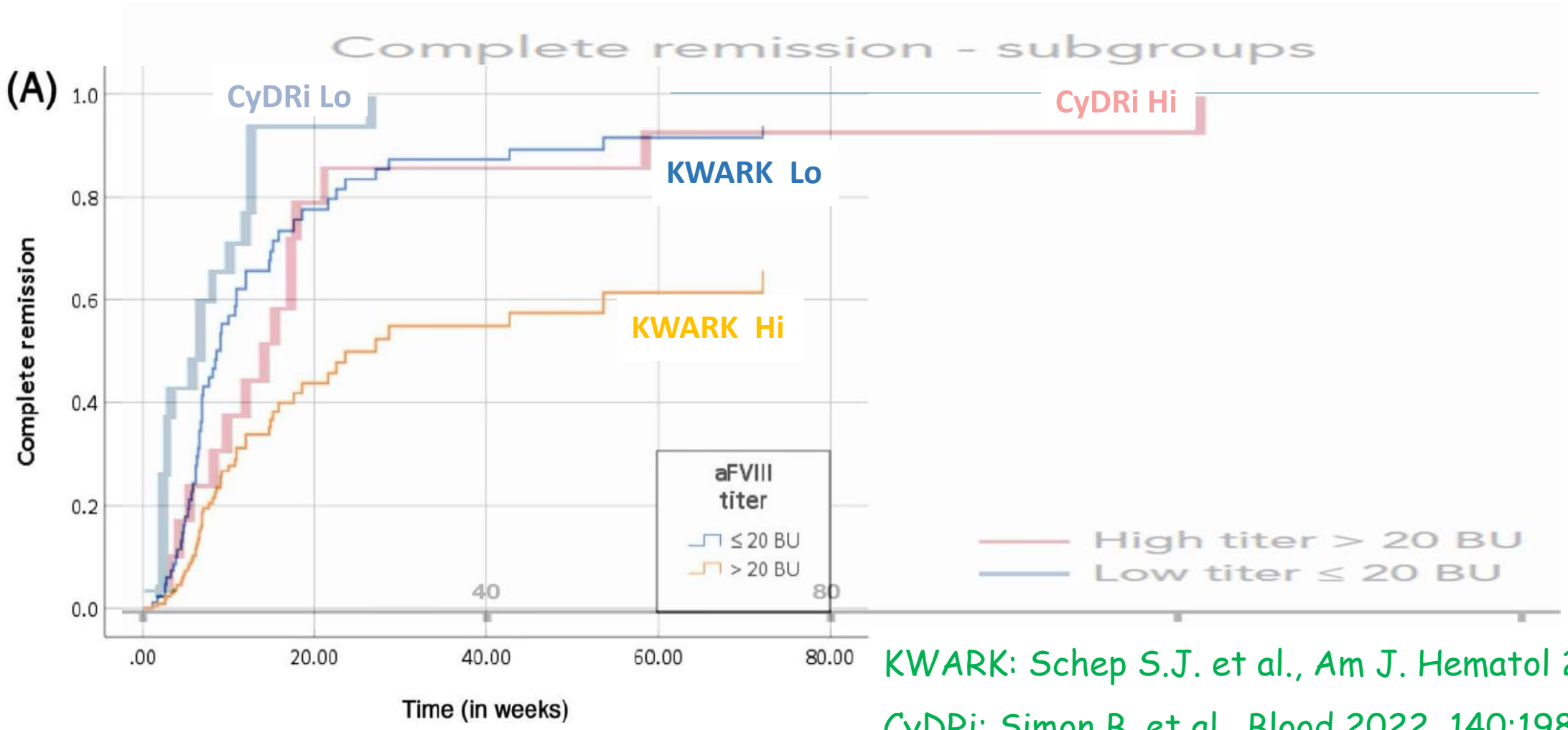
RESEARCH ARTICLE

AJH WILEY

Treatment of acquired hemophilia A, a balancing act: results from a 27-year Dutch cohort study

Sarah J. Schep[1] | Wobke E. M. van Dijk[1] | Erik A. M. E
Michiel Coppens[4] | Jeroen Eikenboom[5] | Frank W. G. Le
Lize F. D. van Vulpen[1] | Kathelijn F. Fischer[1] | Roger E. (
Society of Haemophilia Treaters, The Netherlands





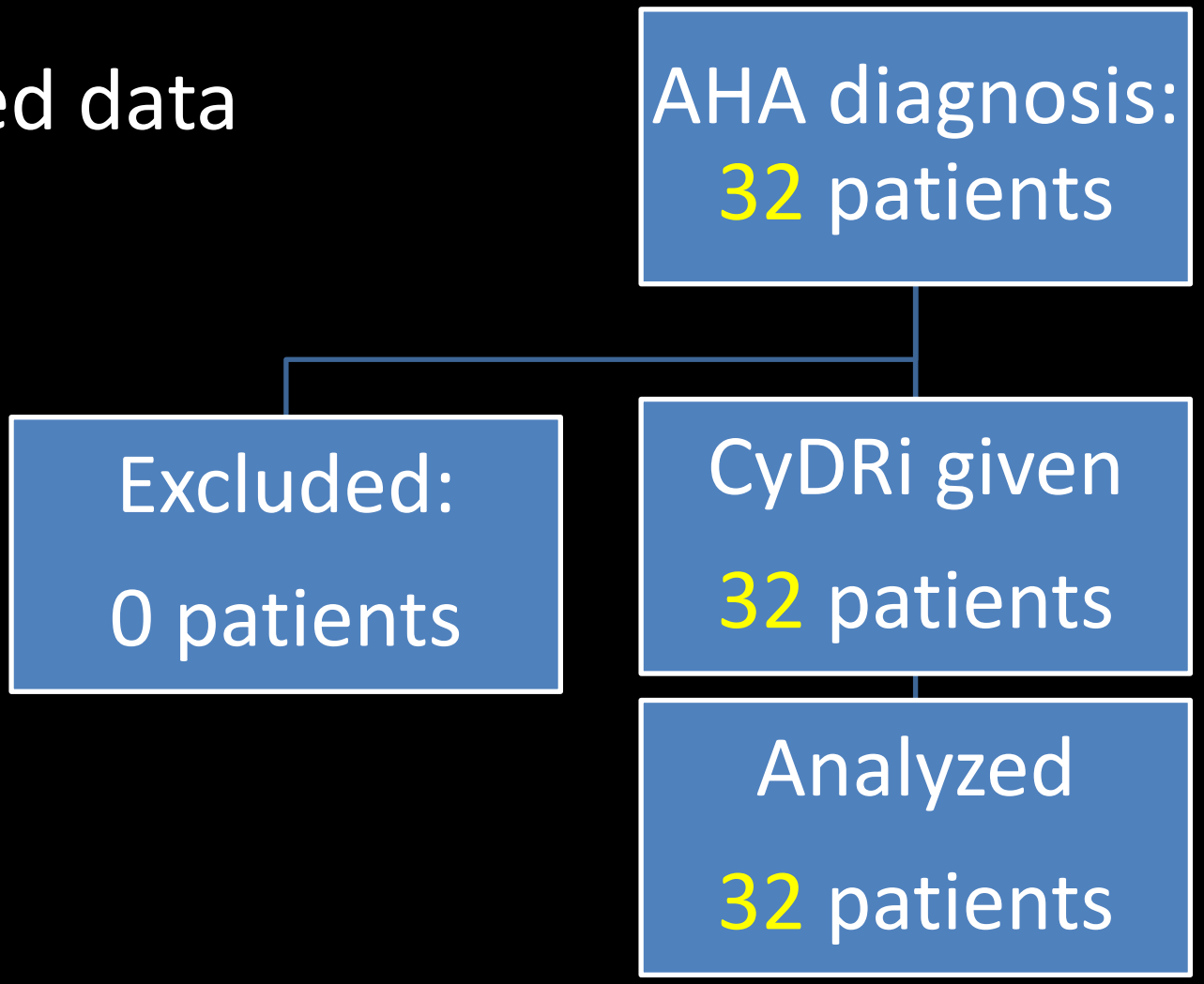
KWARK: Schep S.J. et al., Am J. Hematol 2021, 96:51

CyDRi: Simon B. et al., Blood 2022, 140:1983

Comparison of Kaplan-Meier Curves showing time to complete remission in patients treated for AHA in TWO SEPARATE reptrospective studies. Both studies analysed **low-titer** (<20 BU) and **high-titer** (>20 BU) inhibitor patients separately. The two Kaplan-Meier curves were overlayed from the published figures.

Is a retrospective study to be trusted?

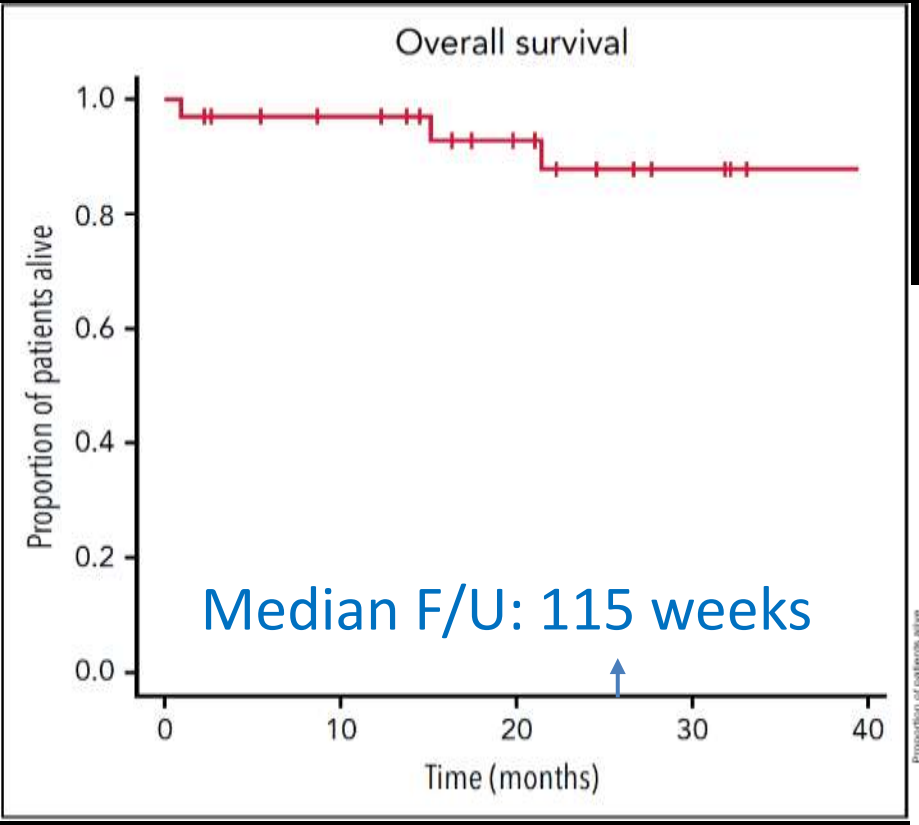
- In fact: prospectively collected data
  – analyzed retrospectively
- Consecutive patients
  – none missing, no exclusion



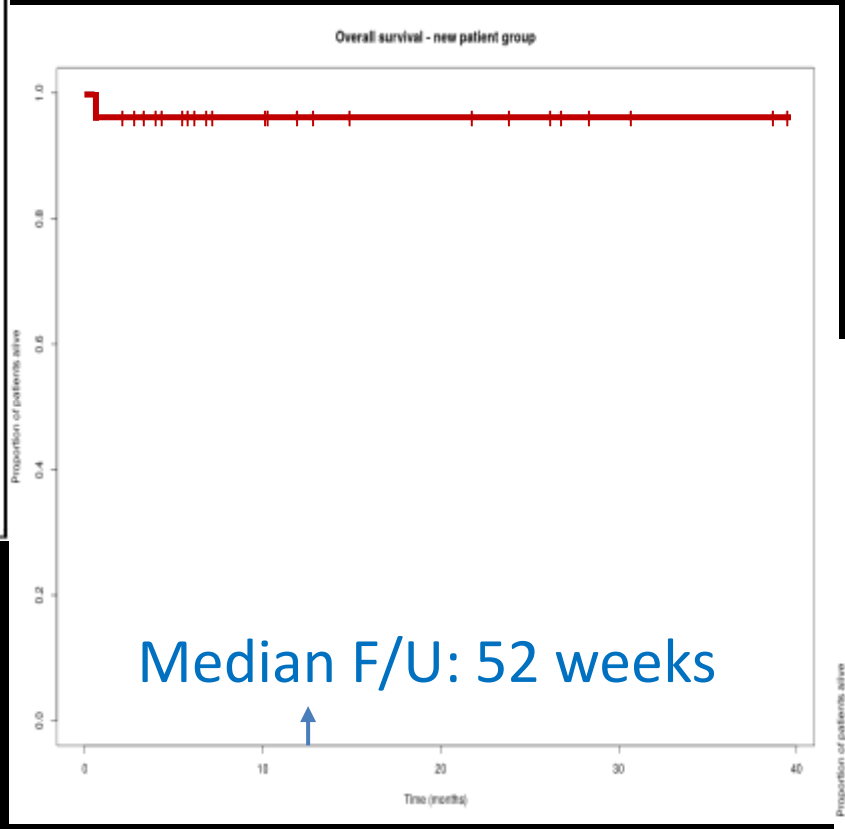
Are these outcomes reproducible?

- Additional 27 patients
- 7 centers in Hungary and Poland
- AHA patients treated with the CyDRi protocol

OS

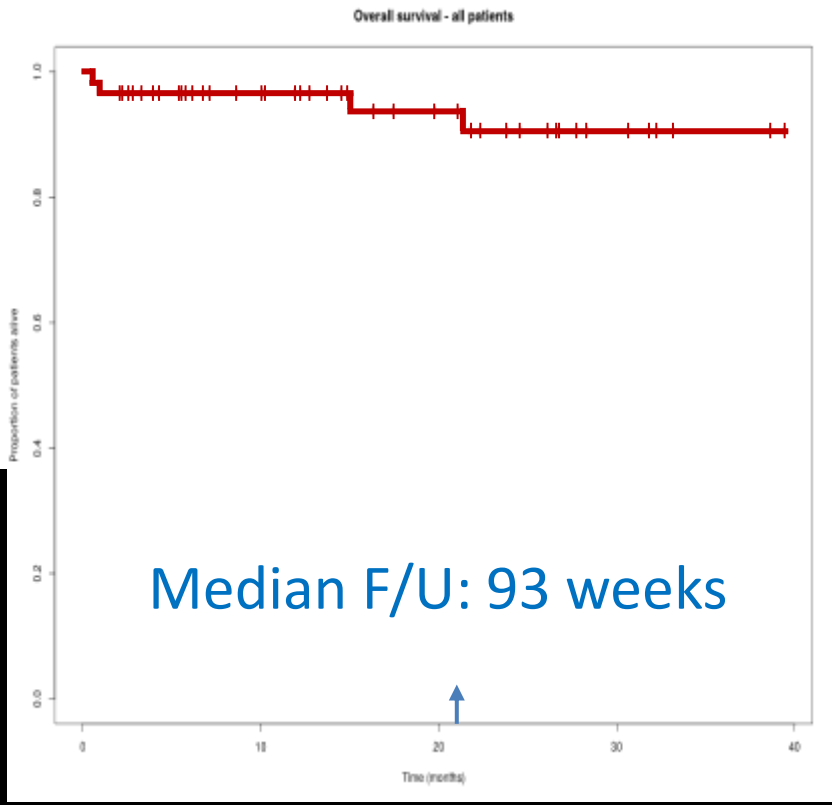


Original cohort n=32

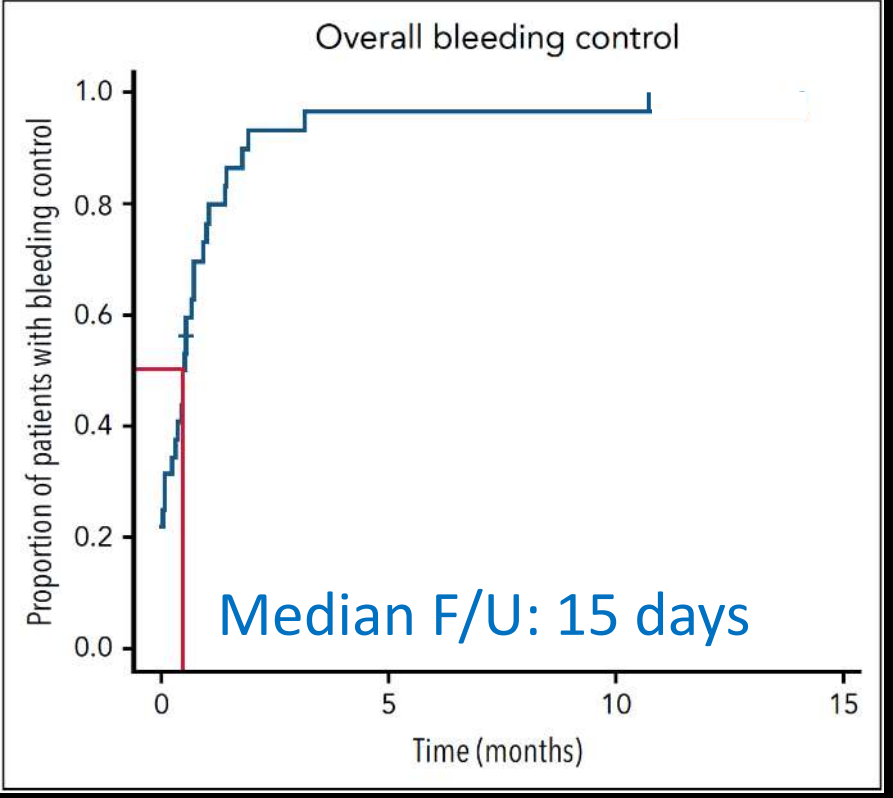


Follow-up cohort n=27

Combined n=59



BC



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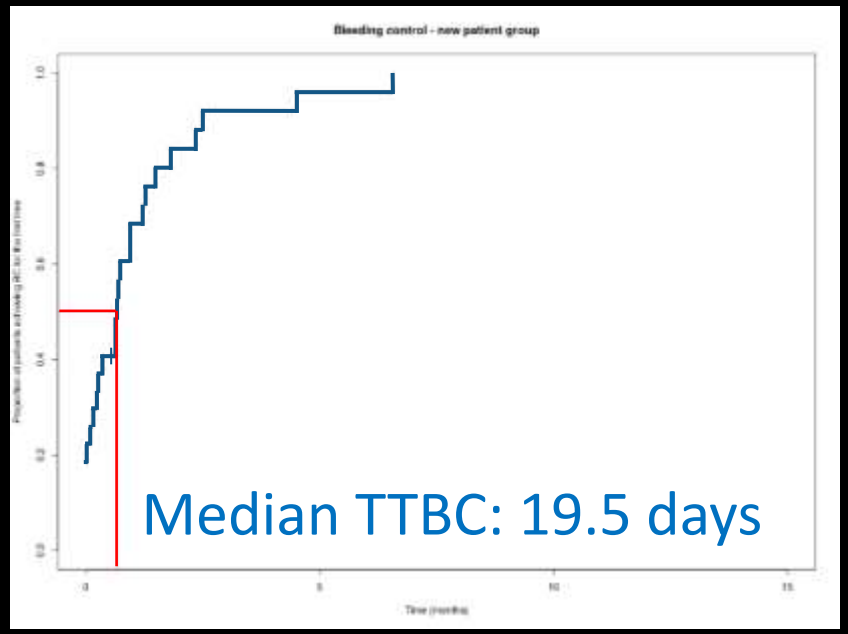
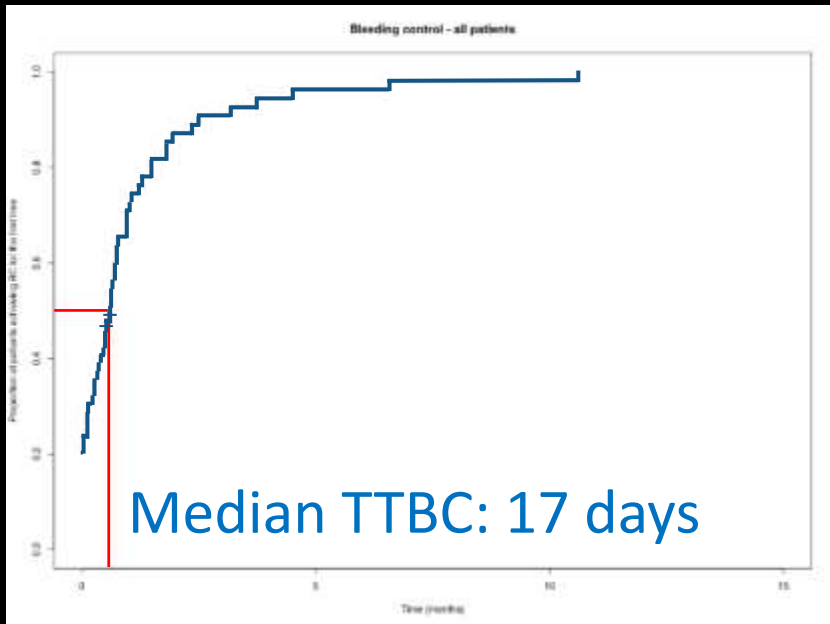


Follow-up cohort n=27

Combined n=59



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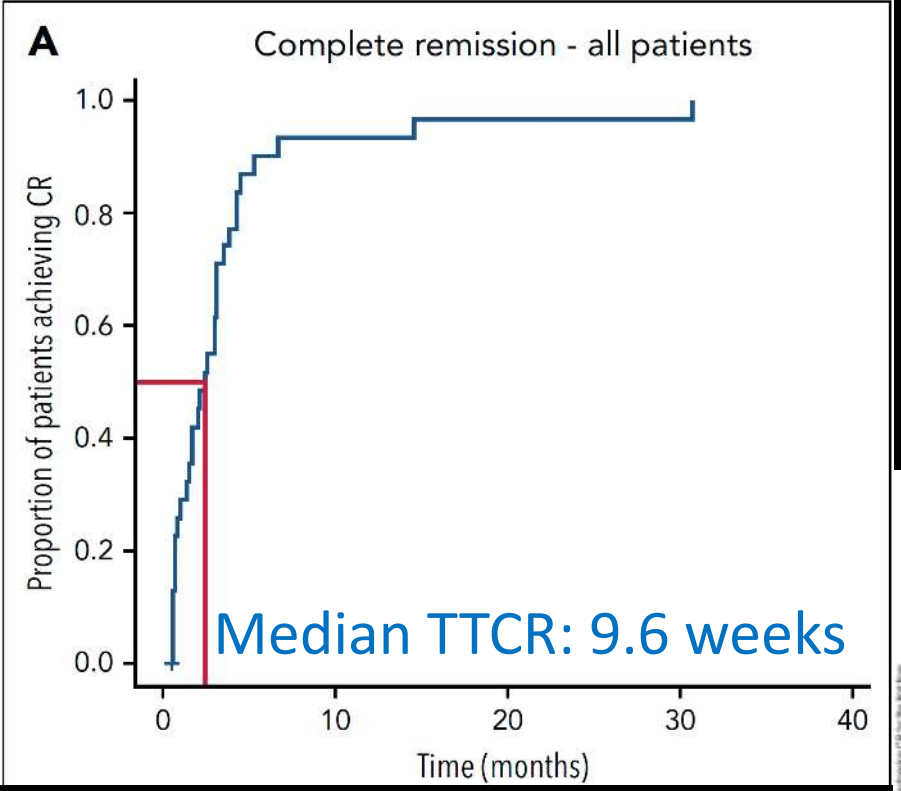

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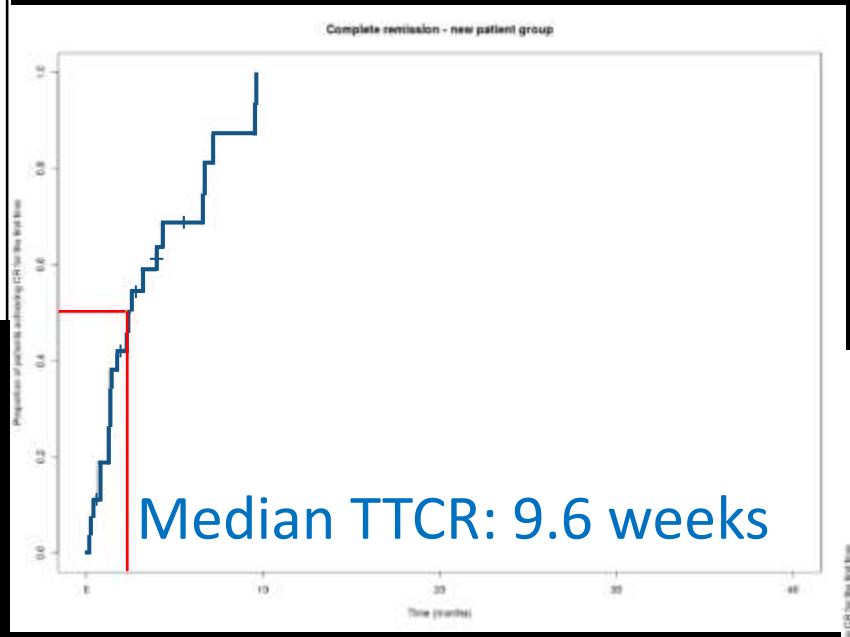

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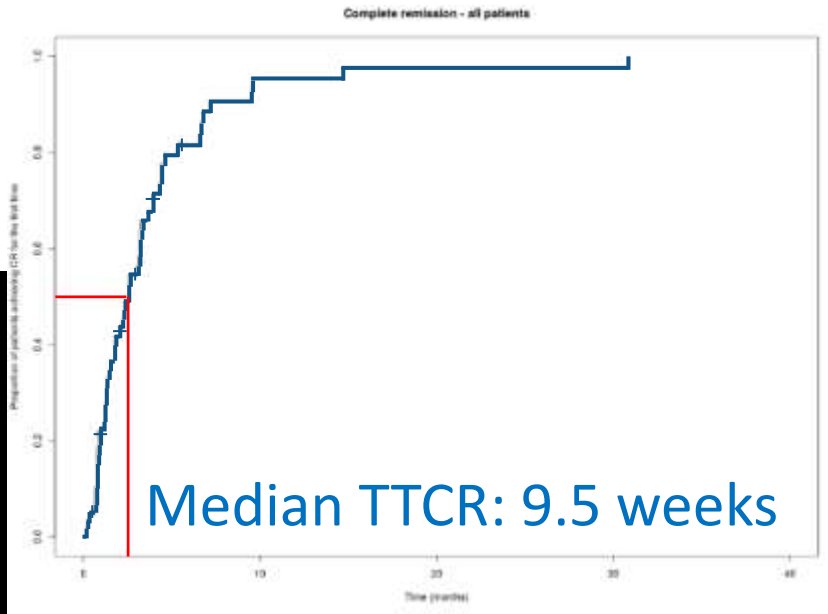

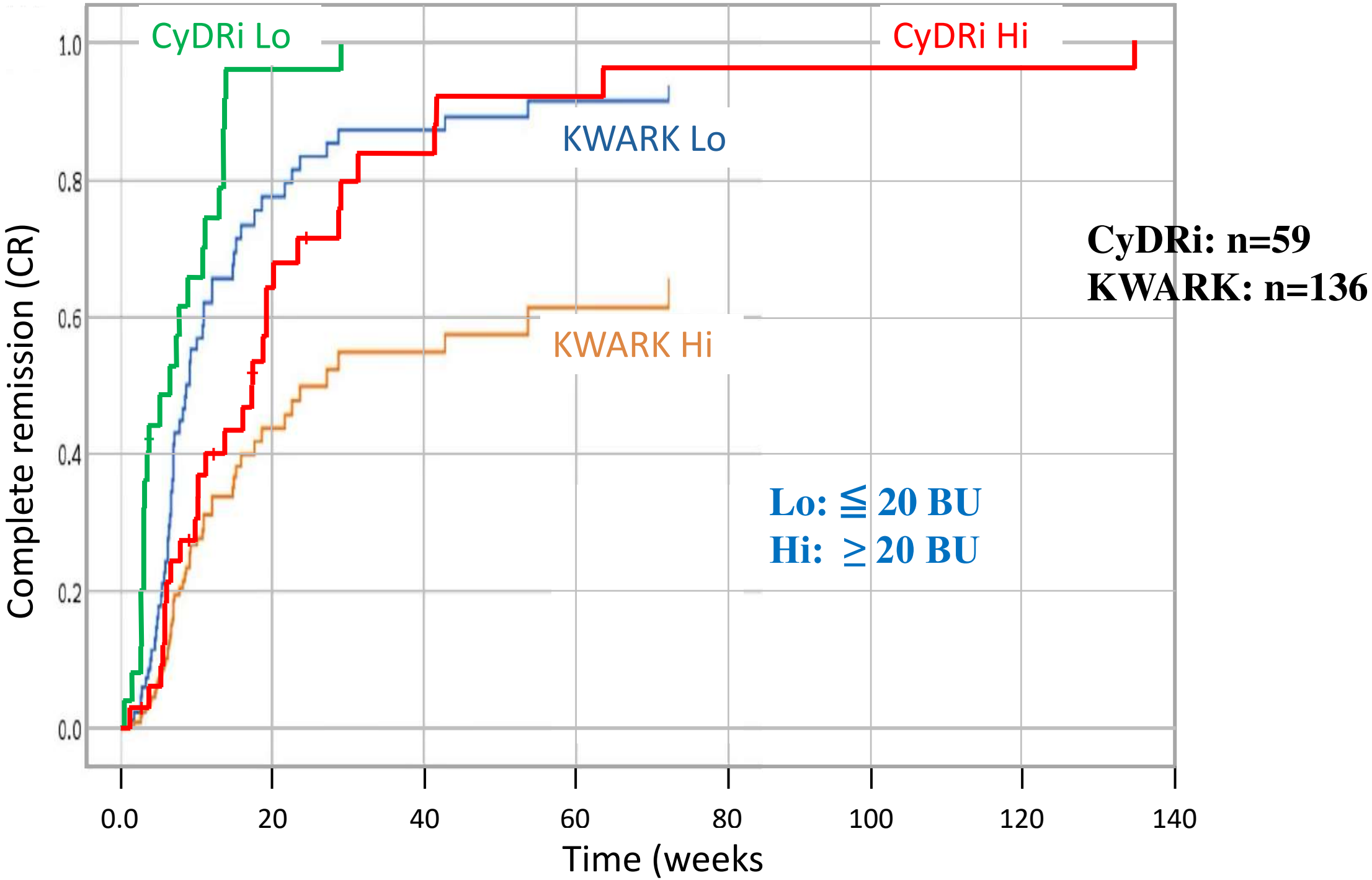
CyDRi Lo
CyDRi Hi
KWARK Lo
KWARK Hi
Complete remission (CR)
1.0
0.8
0.6
0.4
0.2
0.0
0.0
20
40
60
80
100
120
140
Time (weeks
CyDRi: n=59
KWARK: n=136
Lo: ≦ 20 BU
Hi: ≧ 20 BU

Comparison of three approaches

Study (n)	Traditional IST[1] GTH-AH 01/2010 (102)	CyDRi[2] (59)	Delayed immunosuppression GTH-AHA-EMI[3] (47)
OS (F/U, median, wks)	64/102 = 66.7% (37)	54/59 = 91.5% (93)	43/47 = 91.5% (24)
OS at week 24:	≈ 79/102 = **77.5**%	57/59 = **96.6**%	**91.5**%
Alive, in CR at F/U	49/102 = 48%	50/59 = 84.7%	14/47 = 29.8%
Alive, in CR at week 24:	≈ 44/102 ≈ **43**%	49/59 = **83.1**%	**29.8**%
Alive but no CR at F/U	19/102 = **18.6**%	4 (**6.8**)	**61.7**%
Bleeding rate*, by wk 12	0.13	0.031	0.04
Bleeding mortality:	3/102 = **2.9**%	**0**	2/47 = **4.3**%

*Average # events/week

[1] *Tiede A et al, Blood 2015, 125:1091*
[2] *Simon B et al, Blood 2022, 140:1983*
[3] *Tiede A et al, Lancet Haematology 2023, 10:e913*

Summary and future

- AHA – rare, life-threatening disease; a “medical emergency”
- CyDRi seems a very effective, low-toxicity causative treatment
- Delaying causative treatment is not necessary
- This needs to be confirmed in a **prospective trial**

AHILLES – a prospective, single-arm confirmatory trial

AHA **I**mmunosuppression with **L**ow-Dose, Pu**l**s**e**-Admini**s**tered CyDRi

Acknowledgement

Contributors:

- Andrea Ceglédi
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- Péter Ilonczai
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- Tamás Masszi
- Agata Ogłoza
- Márk Plander
- Ágota Schlammadinger


Thank you!

Relapse after CyDRi

Patient No.	Line	FVIII at diagnosis (IU/dL)	BU at diagnosis	CyDRi (no. of cycles)	TTBC (d)	Days on bypass	TTCR (d)	CR duration (d)
LA#7	1	5	8.5	1	45	45	92	357
LA#7	2	11	NA	1	0	0	22	1385
LA#7	3	10	0.9	1	0	0	99	1372
LA#13	1	1	140	2	8	3	67	160
LA#13	2	19	0	1	0	0	28	161