Aggiornamenti terapeutici nelle Anemie Emolitiche Autoimmuni (AEA)

Dott.ssa Roberta Sala

UOC Ematologia Ospedale "Fabrizio Spaziani" Frosinone
UOS Emopatie ad Alta Complessità

La sottoscritta Dott.ssa Roberta Sala, in qualità di Relatore
dichiara che

negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

- Shire (sponsorizzazione a convegno; grant relatore corso)
- Sanofi-Genzyme (sponsorizzazione a convegno)
- Jazz Pharmaceutical (sponsorizzazione a convegno)

Indicazione a Terapia nelle AEA

Anemia moderata-grave e/o sintomatica

- **Possibilità di remissione spontanea, soprattutto nelle AEA da Ab freddi e secondarie ad infezioni, meno frequente nelle forme da Ab caldi**

- **In caso di anemia lieve (Hb> 10 g/dl) e parzialmente compensata può essere appropriato monitorizzare il paziente senza trattamento Watch and Wait**

Razionale della Terapia nelle AEA

- Riduzione produzione anticorpale
- Riduzione effetti autoanticorpi
- Rimozione sito di distruzione eritrocitaria

Nelle AEA secondarie inoltre

- Trattamento della patologia primitiva
- Sospensione di eventuali farmaci scatenanti

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Blood Reviews xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

Review

Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting

Ulrich Jäger[a,1], Wilma Barcellini[b], Catherine M. Broome[c], Morie A. Gertz[d], Anita Hill[e], Quentin A. Hill[e], Bernd Jilma[f], David J. Kuter[g], Marc Michel[h], Marco Montillo[i], Alexander Röth[j], Sacha S. Zeerleder[k,l,m], Sigbjørn Berentsen[n,o,*]

- **Inquadramento diagnostico delle AEA**

- **Raccomandazioni terapeutiche:**
  - **AEA primitive e secondarie (calde, fredde, miste)**
  - **Linea di trattamento**
  - **Terapia di supporto**
  - **Terapia delle emergenze**

AEAI da Ab caldi – Terapia di I linea

. Corticosteroidi: 1 mg/Kg/die per 2-3 settimane da scalare poi molto lentamente (3-6 mesi)

80% di risposte

. Corticosteroidi + Rituximab

Criteri di valutazione della risposta

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Response definitions	*Complete response (CR)*: Normalization of hemoglobin, no evidence of hemolysis (normal bilirubin, LDH, haptoglobin and reticulocytes), absence of transfusions. For CAD, additional CR criteria include disappearance of acrocyanosis, absence of clonal B cells, and absence of clonal IgM. *Response (R)*: Increase in hemoglobin by > 2 g/dL or normalization of hemoglobin without biochemical resolution of hemolysis; and absence of transfusion for the last 7 days. *No response*: Failure to achieve a response.
Response duration	Measured from achievement of complete response (CR) or response (R) to loss of CR or R.
Remission	Measured from achievement of CR off all AIHA directed treatment, to loss of CR.
Steroid resistance and dependence	*Steroid resistance*: Failure to obtain hematologic response within 3 weeks on at least 1mg/kg predniso(lo)ne. *Steroid dependence*: Need to continue on predniso(lo)ne at a dose of > 10mg/day to maintain a response.
Refractory disease	Failure to respond to at least 3 lines of therapy; in wAIHA including splenectomy and/or at least one immunosuppressant.

AEAI da Ab caldi – Terapia di II linea

- **Rituximab** **375 mg/mq a settimana per 4 settimane** **80% di risposte**
  (generalmente associato a corticosteroidi)

- **Agenti citotossici**
  - » **Ciclofosfamide 50-100 mg/die oppure 1-2 mg/Kg** **60% di risposte**
- **Agenti imunosoppressivi**
  - » **Azatioprina 2-2,5 mg/Kg** **60% di risposte**
  - » **Ciclosporina 2,5 mg/Kg due volte al dì** **50% di risposte**
  - » **Micofenolato 500-1000 mg x 2** **80% di risposte**

- **Splenectomia** **rischio infettivo e trombotico** **80% di risposte**

AEAI da Ab caldi – Terapia di III linea

- **Splenectomia**
- **Agenti immunosoppressivi**
- **Ciclofosfamide**
- **Basse dosi di prednisolone ≤ 10 mg/die**
- **Danazolo 200 mg tre volte al dì**
- **Rituximab ritrattamento se ad almeno un anno di distanza dal trattamento precedente**
- **Bortezomib 1,3 mg/mq 1,4,8,11 primo ciclo poi settimanale per tre cicli**

AEA da Ab caldi – Terapia di salvataggio per condizioni di emergenza

- Corticosteroidi in bolo (ad es. 500 mg ev)
- Immunoglobuline umane aspecifiche: 400 mg/Kg/die per 5 giorni consecutivi
- Emotrasfusioni
- Plasma-exchange con albumina
- R-EPO
- Splenectomia o embolizzazione parziale splenica
- Indicazione a tromboprofilassi

Terapia della AEA da Ab caldi secondaria

Leucemia Linfatica Cronica

trattamento in funzione dello stadio di malattia

Negli stadi non avanzati trattamento della AEAI:

- **Corticosteroidi**
- **Rituximab (II linea)**

Negli stadi avanzati e/o nei casi refrattari trattamento della LLC:

- **Ibrutinib nei pazienti con delezione del cr 17p o mutazione TP53 o multirefrattari**
- **R-Bendamustina, R-CVP, R-CD**
- **Evitare Fludarabina in monoterapia**

Terapia della AEA da Ab caldi secondaria

LES

trattamento in funzione delle manifestazioni cliniche della patologia

I linea: Corticosteroidi

II linea o successive:

- Rituximab
- Micofenolato
- Azatioprina
- Steroidi + Idrossiclorochina

Evitare splenectomia

Immunodeficienza comune variabile

I linea: Corticosteroidi (dosaggio minimo efficace)

II linea o successive:

- immunosoppressori
- Rituximab
- splenectomia (in casi selezionati)

terapia sostitutiva con Immunoglobuline

AEAI Ab caldi – algoritmo terapeutico

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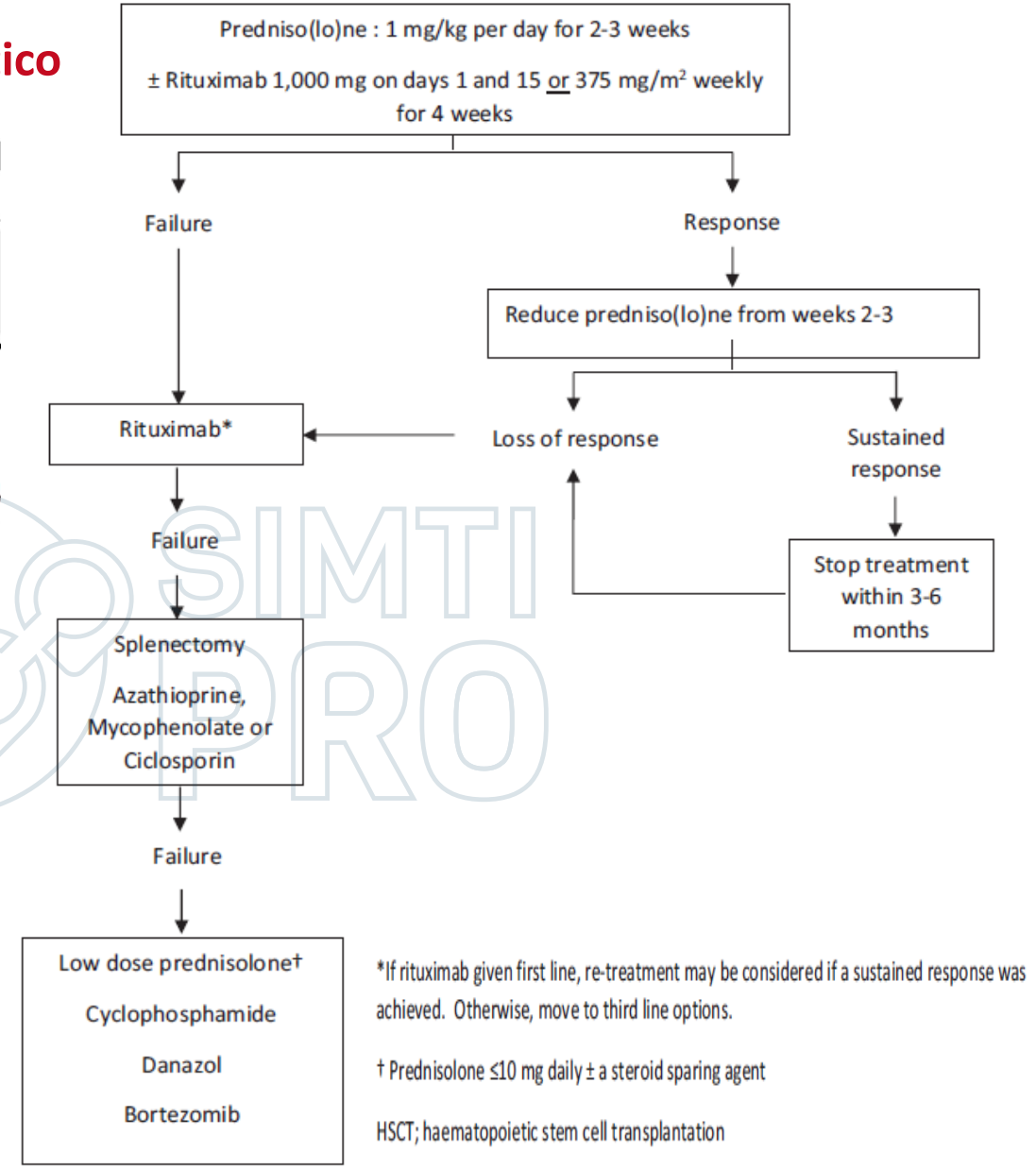


AEA da Ab freddi

TCD positivo per C3d ≥ 1:64

- **CAD (Cold agglutinine disease)**

  clone B linfocitario senza segni e sintomi di malattia linfoproliferativa, autoimmune o infettiva

- **CAS (Cold agglutinine syndrome)**

  associato a manifesta patologia linfoproliferativa, autoimmune o infettiva

Terapia della AEA da Ab freddi – CAD

I linea

- **Rituximab 375 mg/mq/settimana per 4 sttimane** **50% di risposte**
- **Rituximab + Bendamustina (90 mg/mq gg 1-2 ogni 28 gg per 4 cicli)**
  70% di risposte
- **Splenectomia non efficace**

II linea

- **Rituximab + Bendamustina se non utilizzato in I linea o ritrattamento dopo almeno due anni dal precedente**
- **Ritrattamento con Rituximab dopo almeno un anno dal precedente**
- **Rituximab + Fludarabina nei pazienti fit**
- **Bortezomib**

III linea (Possibilmente Trials clinici)

- **Ibrutinib, Acalabrutinib, Venetoclax (off label)**
- **Inibitori del complemento: Eculizumab (C5), Sutimlimab (C1), Pegcetacoplan (C3)**

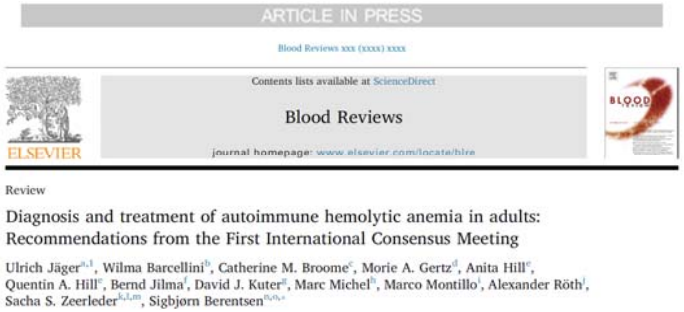
Terapia delle AEA da Ab freddi - CAS

- **Trattamento della patologia primitiva (S. linfoproliferativa)**
- **Infezioni (Micoplasma, EBV):**
  - **Autolimitantesi in 4-6 settimane**
  - **Terapia di supporto**
  - **Steroidi nei casi severi a scarsa efficacia**

Terapia della AEA da Ab freddi – Emergenza

- Emotrasfusione con sangue riscaldato
- Alte dosi di steroidi + Rituximab
- Immunoglobuline umane aspecifiche
- Plasma exchange con albumina
- Ultrafiltrazione con colonne immunoassorbimento
- Eculizumab (off label)

Malattia da agglutinine fredde – algoritmo terapeutico



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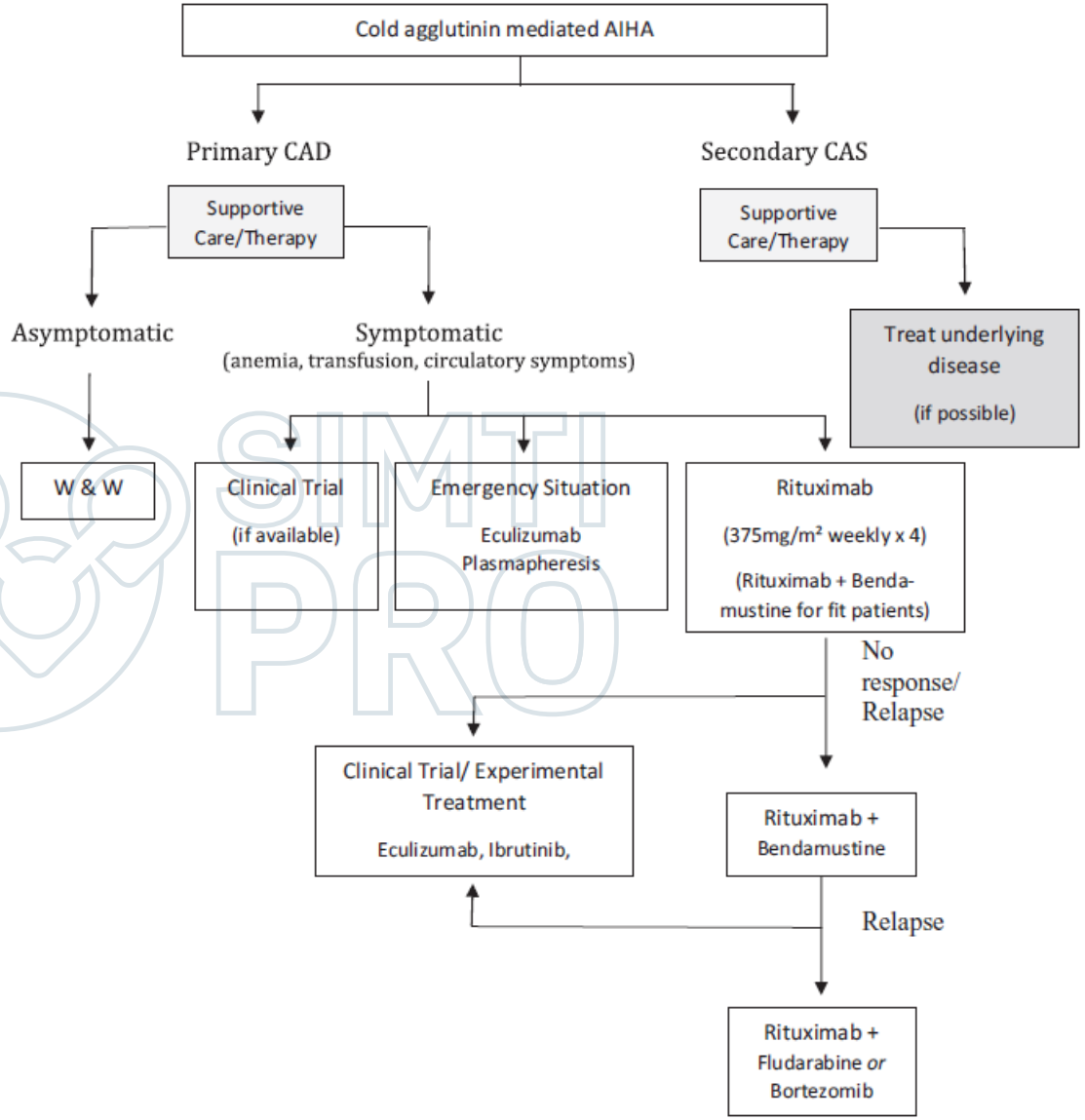

Terapia della AEA da Ab caldi e freddi - miste

- Terapia aggressiva con alte dosi di corticosteroidi e Rituximab possibilmente da arruolare in studi clinici
- Splenectomia inefficace

Terapia di supporto

- Emotrasfusioni
- Immunoglobuline umane aspecifiche 400 mg/Kg/die per 5 giorni
- Terapia vitaminica con folati, vitamina B12 e/o ferro
- Prevenzione osteoporosi e fratture ossee in corso di terapia steroidea
- Profilassi Pneumocistis Jirovecii
- Tromboprofilassi

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
2018, VOL. 14, NO. 10, 857–872
https://doi.org/10.1080/1744666X.2018.1521722

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REVIEW

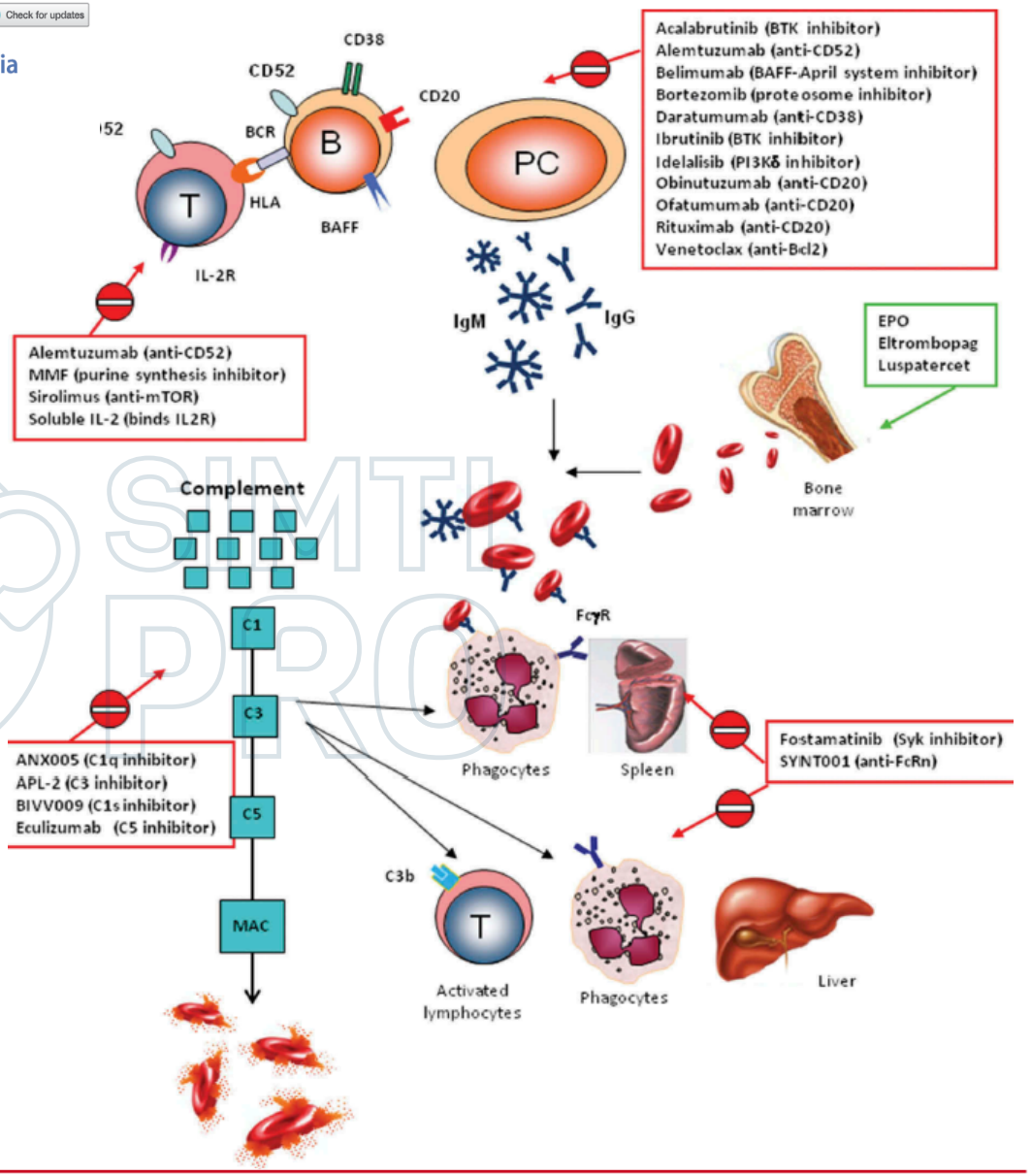
Check for updates

Current and emerging treatment options for autoimmune hemolytic anemia

Wilma Barcellini, Bruno Fattizzo and Anna Zaninoni

UOC Ematologia, Fondazione IRCCS Ca' Grande Ospedale Maggiore Policlinico, Milano, Italy

TARGET THERAPY



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REVIEW

Current and emerging treatment options for autoimmune hemolytic anemia

Wilma Barcellini, Bruno Fattizzo and Anna Zaninoni

UOC Ematologia, Fondazione IRCCS Ca' Grande Ospedale Maggiore Policlinico, Milano, Italy

B-cell receptor inhibitors					
Ibrutinib	BTKi	Oral	Case reports	Secondary AIHA	Manda S, Br J Haematol 2015 [32] Cavazzini F, Leuk Lymphoma 2016 [33] Galinier A, Case Rep Oncol 2017 [34]
Acalabrutinib	BTKi	Oral	Murin model	Preclinical	Rogers KA, Blood 2016 [80]
Venetoclax	Bcl2	Oral	Case reports	Secondary AIHA	Lacerda MP, Ann Hematol 2017 [35]
Idelalisib	δPI3Ki	Oral	No studies	–	–
Proteasome inhibitor					
Bortezomib	Proteasome inhibitor	IV	Case reports	CAD/Secondary AIHA	Carson KR, Blood 2010 [40] Danchaivijitr P, Am J Hematol 2011 [41] Metha B, Blood Cancer 2014 Khandelwal P, Biol Blood Marr Trans 2014 Hosoba S, Transfusion 2015 [42]
Bortezomib	Proteasome inhibitor	IV	Phase 2	CAD	Rossi G, Blood 2018 [43]

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	Mechanism	Route of administration	Study phase	Setting	References
B-cell-directed monoclonal antibodies					
Rituximab	Anti-CD20	IV	Indicated	wAIHA/CAD	Barcellini W, Blood 2012 [16] Birgens H, Br J Haematol 2013 [17] Barcellini W, Eur J Haemat 2013 Michel M, Am J Hematol 2017 [19]
Rituximab	Anti-CD20	SC	Phase 3	wAIHA/CAD	–
R-fludarabine	Anti-CD20 + purine analog	IV	Phase 2	CAD	Berentsen S, Blood 2010 [15]
R-CTX-Dex	Anti-D20 + alkylator	IV	Phase 2	wAIHA	Bocian H, Blood 2016
R-bendamustine	Anti-CD20 + alkylator	IV	Phase 2	CAD	Berentsen S, Blood 2017 [18]
Ofatumumab	Anti-CD20	IV	Case report	Secondary AIHA	Nader K, Clin Lymph Myel Leuk 2013
Alemtuzumab	Anti-CD52	SC	Case reports	Secondary AIHA	Osterborg A, J Curr Hemat Mal Rep 2009 [82] Lauro A, Case Rep Transplant 2014
Daratumumab	Anti-CD38	IV	Case reports	Secondary AIHA	Vanessa P, Blood 2016

Therapeutic Advances in Hematology *Review*

Novel insights into the treatment of complement-mediated hemolytic anemias

Ther Adv Hematol
2019, Vol. 10: 1–20
DOI: 10.1177/2040620719873321

Sigbjørn Berentsen, Anita Hill, Quentin A. Hill, Tor Henrik Anderson Tvedt and Marc Michel

***Abstract*:** Complement-mediated hemolytic anemias can either be caused by deficiencies in regulatory complement components or by autoimmune pathogenesis that triggers inappropriate complement activation. In paroxysmal nocturnal hemoglobinuria (PNH) hemolysis is entirely complement-driven. Hemolysis is also thought to be complement-dependent in cold agglutinin disease (CAD) and in paroxysmal cold hemoglobinuria (PCH), whereas warm antibody autoimmune hemolytic anemia (wAIHA) is a partially complement-mediated disorder, depending on the subtype of wAIHA and the extent of complement activation. The pathophysiology, clinical presentation, and current therapies for these diseases are reviewed in this article. Novel, complement-directed therapies are being rapidly developed. Therapeutic terminal complement inhibition using eculizumab has revolutionized the therapy and prognosis in PNH but has proved less efficacious in CAD. Upstream complement modulation is currently being investigated and appears to be a highly promising therapy, and two such agents have entered phase II and III trials. Of these, the anti-C1s monoclonal antibody sutimlimab has shown favorable activity in CAD, while the anti-C3 cyclic peptide pegcetacoplan appears to be promising in PNH as well as CAD, and may also have a therapeutic potential in wAIHA.

Meccanismi di emolisi complemento mediata nell'anemia emolitica autoimmune

Therapeutic Advances in Hematology Review

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Jager U. Blood 2019; 133:893-901 primo studio pubblicato. In corso due studi di fase III in pazienti con CAD (NCT03347396-NCT03347422)

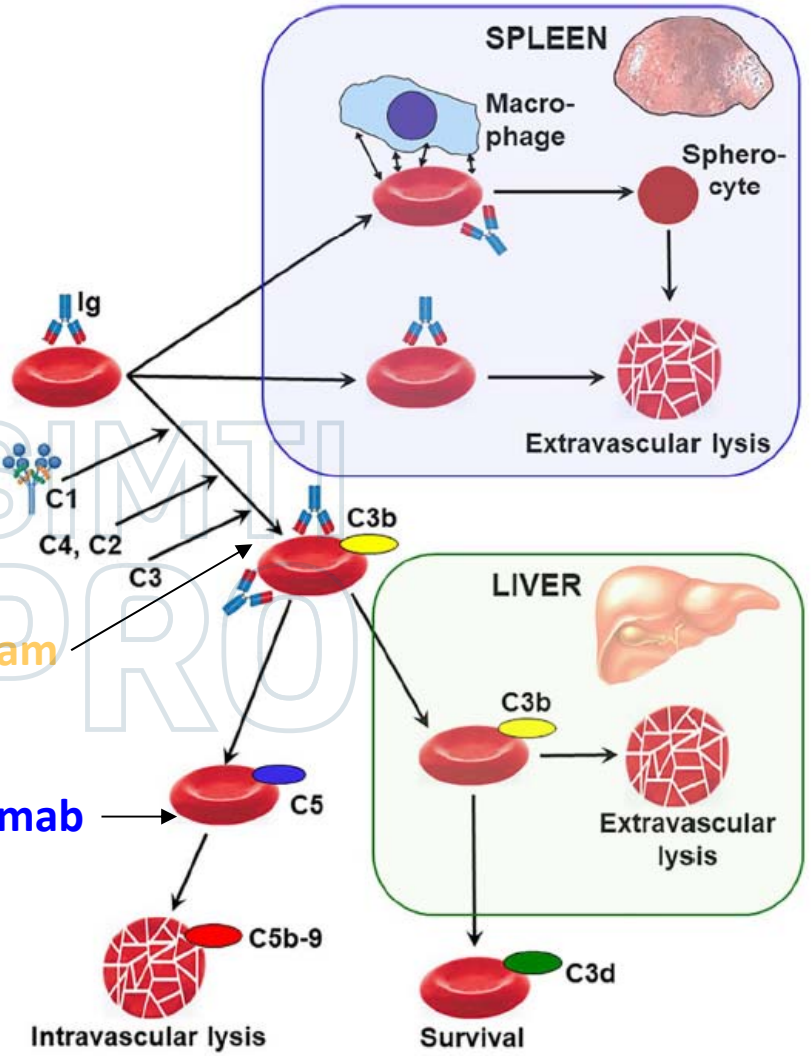
Sutimlimab

Composto peghilato a somministrazione sottocutanea inibisce sia la via Classica che la via alternativa del complemento. Studi clinici di fase II hanno dimostrato l'efficacia sia nell'EPN sia nelle AEA sia da Ab caldi che CAD (Grossi F., Blood 2018; 132 suppl 1: 3623. Blood 2018 132, Suppl 1 : 2314 Wong RSM et al)

Pegcetacoplam

Eculizumab

Studio DECADE, prospettico bicentrico non randomizzato, fase II. Roth A. Blood Adv 2018; 2:2543-49



U.S. National Library of Medicine
ClinicalTrials.gov

A Study to Assess the Efficacy and Safety of BIVV009 (Sutimlimab) in Participants With Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion (Cardinal Study)

Study Description

Sutimilimab Studio di fase III nelle CAD

Brief Summary:

The purpose of Part A is to determine whether sutimlimab administration results in a greater than or equal to (>=) 2 gram per deciliter (g/dL) increase in hemoglobin (Hgb) levels or increases Hgb to >= 12 g/dL and obviates the need for blood transfusion during treatment in participants with primary cold agglutinin disease (CAD) who have a recent history of blood transfusion.The purpose of Part B is to evaluate the long-term safety and tolerability of sutimlimab in participants with CAD.

Condition or disease	Intervention/treatment	Phase
Agglutinin Disease, Cold	Drug: Sutimlimab	Phase 3

Study Design

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	20 participants
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 3, Pivotal, Open-label, Multicenter Study to Assess the Efficacy and Safety of Sutimlimab in Patients With Primary Cold Agglutinin Disease Who Have a Recent History of Blood Transfusion
Actual Study Start Date:	March 5, 2018
Estimated Primary Completion Date:	September 2020
Estimated Study Completion Date:	September 2020

Arms and Interventions

Arm	Intervention/treatment
Experimental: Sutimlimab Participants will receive an intravenous (IV) infusion of sutimlimab. Participants who complete Part A per protocol through the end of treatment visit (Day 182) will participate in Part B, and continue to receive sutimlimab up to 1 year after last patient out (LPO) in Part A.	Drug: Sutimlimab Sutimlimab will be administered as IV infusion.

Therapeutic Advances in Hematology Review

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Ther Adv Hematol
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Pegcetacoplan Studio di fase II nelle CAD

Normalizzazione dei valori di Hb entro 56 giorni nella maggior arte dei pazienti e in tutti entro 84 giorni

Normalizzazione dei livelli di bilirubina entro 1-2 settimane in tutti i pazienti

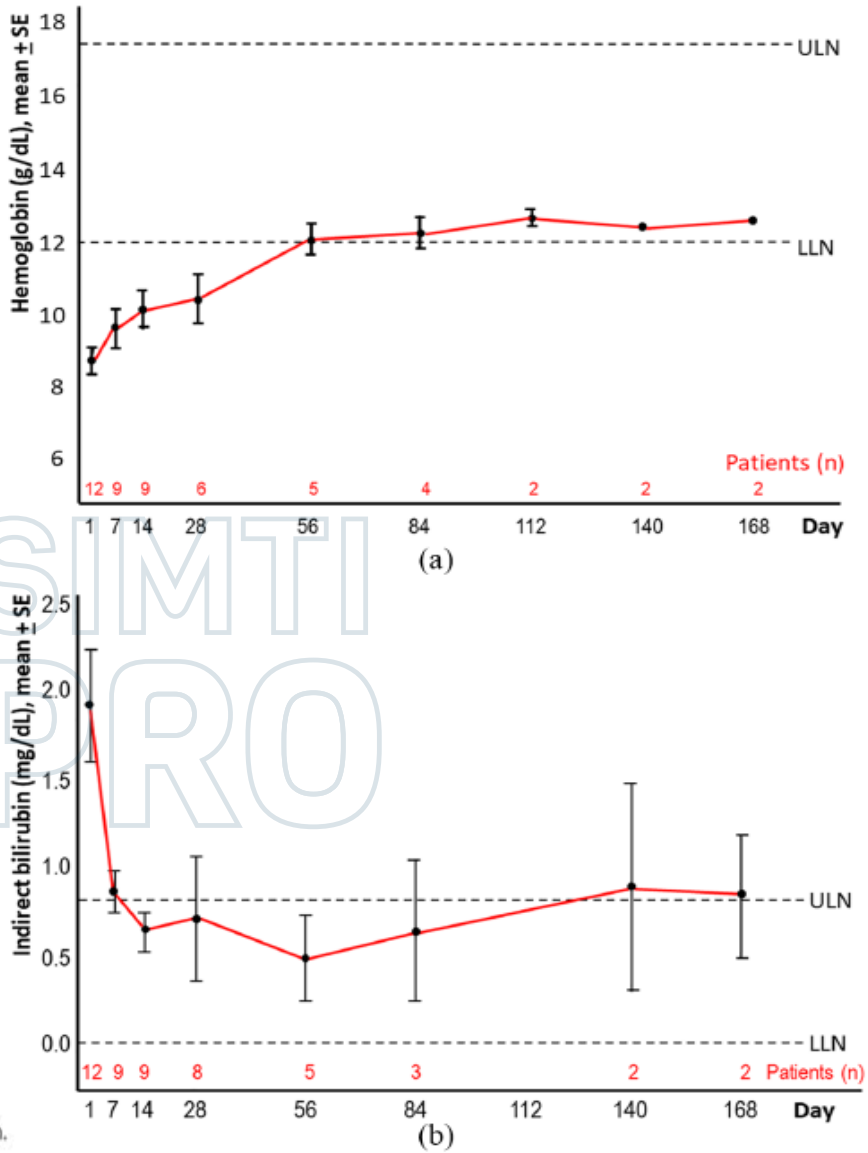

Figure 4. Effect of pegcetacoplan in cold agglutinin disease (CAD). Data from a phase II study, showing normalization of hemoglobin levels within 56 days of medication in the majority of patients and within 84 days in all patients (a). Normalization of indirect bilirubin levels within 1–2 weeks in all patients (b).
LLN, lower limit of normal; ULN, upper limit of normal. Originally presented by F. Grossi and colleagues.[124] at the 60. Annual Meeting of the American Society of Hematology, 2018, reproduced with permission. Courtesy of F. Stout and A. Shen.

Transfusion Medicine Reviews 33 (2019) 256–265

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

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https://www.journals.elsevier.com/transfusion-medicine-reviews/

Eculizumab and Beyond: The Past, Present, and Future of Complement Therapeutics

Christopher J Patriquin [a,b,*], Kevin H.M. Kuo [a,b]

ABSTRACT

Dysregulation of the complement system underlies the pathophysiology of many diseases. Renewed interest in complement occurred with the recognition that its therapeutic inhibition was possible. Terminal complement blockade with the anti-C5 monoclonal antibody eculizumab significantly changed management and clinical outcomes of patients with paroxysmal nocturnal hemoglobinuria, and served as a proof of concept for other complement-mediated diseases. Eculizumab is also approved for atypical hemolytic uremic syndrome and myasthenia gravis. Multiple new disease indications have been identified, and novel complement inhibitors are in various stages of development, with several currently in human trials. Beyond C5, these new drugs block proximal complement, pathway-specific targets, convertase activity, and anaphylatoxin function. Though monoclonal antibodies are still common, peptides, RNAi, and small molecule inhibitors provide the opportunity for different administration routes and schedules. Several challenges still exist or will soon present themselves, including mitigation of infection risk, effective monitoring strategies, and how to choose between therapeutics when more than one is available. In this review, we will describe the lessons learned from the "eculizumab era," present many of the novel therapeutics currently or soon to be in trials, and highlight some of the challenges that will require attention as the field progresses.

REGULAR ARTICLE blood advance

ECULIZUMAB Studio di fase II nelle CAD (DECADE)

Eculizumab in cold agglutinin disease (DECADE): an open-label, prospective, bicentric, nonrandomized phase 2 trial

Alexander Röth,[1] Martin Bommer,[2] Andreas Hüttmann,[1] Dörte Herich-Terhürne,[1] Nils Kuklik,[3,4] Jan Rekowski,[4] Veronika Lenz,[5] Hubert Schrezenmeier,[6,7] and Ulrich Dührsen[1]

[1]Department of Hematology, University Hospital, Essen, Germany; [2]Department of Internal Medicine III, University Hospital, Ulm, Germany; [3]Center for Clinical Studies Essen, University of Duisburg-Essen, Essen, Germany; [4]Institute for Medical Informatics, Biometry and Epidemiology, and [5]Institute of Transfusion Medicine, University Hospital, Essen, Germany; [6]Institute of Transfusion Medicine, University of Ulm, Ulm, Germany; and [7]Institute for Clinical Transfusion Medicine and Immunogenetics, German Red Cross Blood Transfusion Service Baden-Wurttemberg-Hessen and University Hospital, Ulm, Germany

Key Points

- DECADE is the first prospective trial to investigate the effect of complement inhibition by eculizumab in CAD.
- Eculizumab reduced hemolysis and transfusion dependency in the majority of patients but had no impact on cold-induced circulatory symptoms.

Table 2. Impact of eculizumab on indicators of hemolysis in 13 patients with CAD

Laboratory test	Normal range	Week 0	Week 26	*P*
Lactate dehydrogenase, U/L	120-247	572 (534-685)	334† (243-567)	.0215*
Free hemoglobin, mg/dL	<22	46.2 (18.2-124.0)	30.0 (19.5-80.6)	.8438
Bilirubin, μmol/L	5.1-20.5	46.0 (34.2-68.4)	43.0 (20.0-61.6)	.0117
Haptoglobin, g/L	0.3-2.0	0.04 (0.03-0.05)	0.03 (0.02-0.05)	.8438
Hemopexin, g/L	0.5-1.2	0.47 (0.18-0.58)	0.85 (0.45-1.09)	.0127
Hemoglobin, g/dL	11.6-16.1	9.35 (8.80-10.80)	10.15 (9.00-11.35)	.0391
Reticulocytes, $\times 10^9$/L	22-76	160.2 (99.1-185.5)	111.7 (67.4-142.6)	.0625

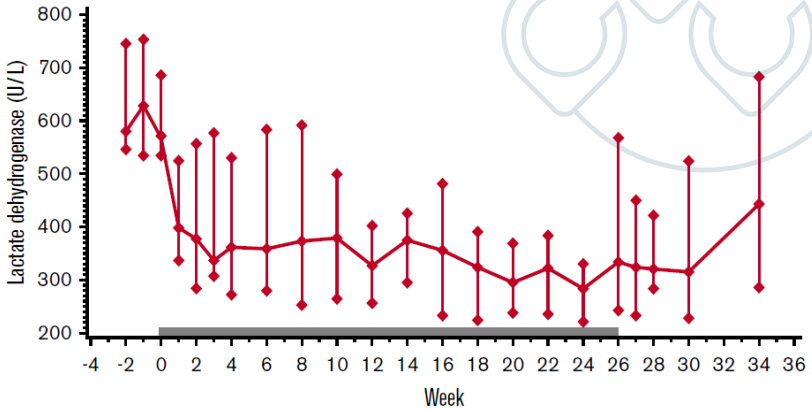

Figure 1. Therapy-related changes in lactate dehydrogenase levels. Lactate dehydrogenase levels before (weeks −2 and −1), during (weeks 0 through 26; solid bar), and after eculizumab treatment (weeks 27 through 34) in 13 patients with CAD (median ± IQR).

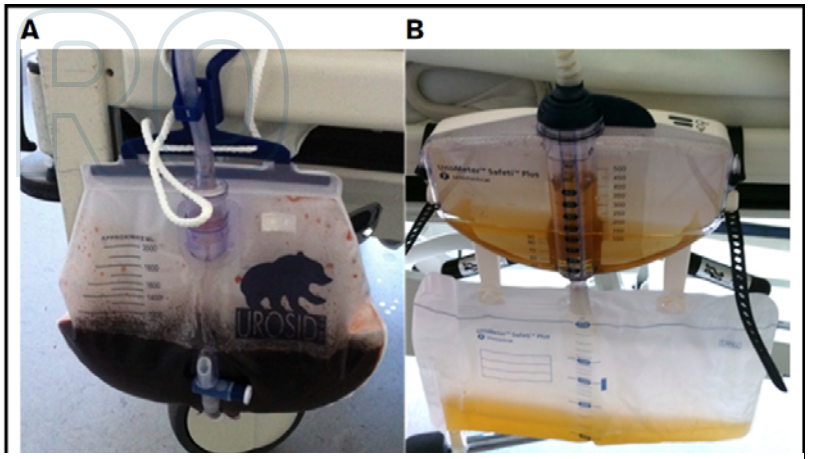

Figure 3. Eculizumab response in a patient with an acute CAS. Urine of patient 5 with severe intravascular hemolysis and hemoglobinuria immediately before (A) and 24 hours after (B) the first dose of eculizumab.

Grazie per l'attenzione!