



XLIX
CONGRESSO
NAZIONALE
AIEOP

Anemie emolitiche autoimmuni

Quando la terapia di prima linea non funziona

Giovanna Russo

Onco-ematologia Pediatrica
Università di Catania

Bologna, 2 Ottobre 2024



La sottoscritta Giovanna Russo

*ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-
Regione del 5 novembre 2009,*

dichiara

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

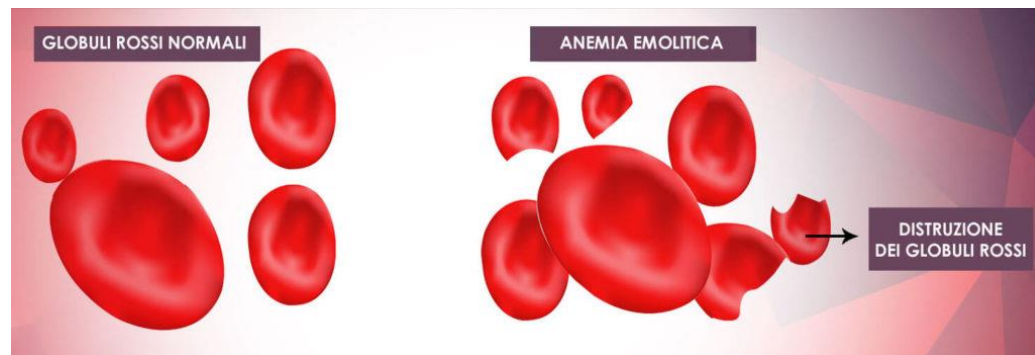
- Vertex
- Junia Pharma



AIHA

Anemia emolitica autoimmune

- Anemia
- Reticolocitosi
- Aumento di bilirubina indiretta e LDH
- Diminuzione di aptoglobina
- Presenza di autoanticorpi





RBCs with IgG (Y) or C3 (C) bound to membrane



Incubation with antibodies to human Ig (X) and C3 (C)



Agglutination (positive direct Coombs' test)

Direct antiglobulin test

D.A.T.



Patient's serum with IgG (Y)



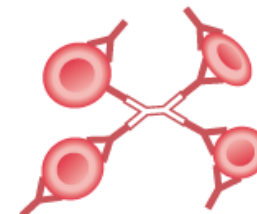
Incubation with reagent RBCs



Binding of any IgG to reagent RBCs



Incubation with antibodies to human Ig (X)



Agglutination (positive indirect Coombs' test)

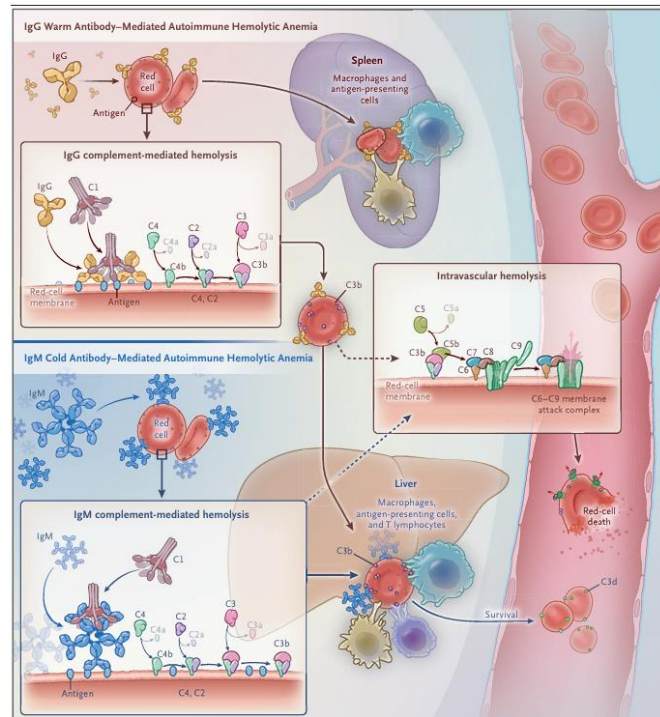
Indirect antiglobulin test

I.A.T.

Caratteristiche delle varie forme classificate in base agli autoanticorpi eritrocitari

Forma clinica	Incidenza	DAT	Classe Ig	Optimum termico (°C)	Avidità e capacità di fissare il complemento	Specificità antigenica	Sede emolisi
Anticorpi caldi	60-70%	IgG+ o IgG+/C3d+	IgG	34-37	-/+	Rh	Extravasale
Anticorpi freddi	20-25%	Neg. o C3d+	IgM	4-27	+++	Anti - i	Extra ed intravasale
Emoglobinuria parossistica a frigore	6-12%	Neg o C3d+	IgG bifasica	fissaz. 4-27 lisi 34-37	+++	Anti P	Intravasale
AEA Mista	< 5%	IgG+ o IgG+/C3d+ o C3d+	IgG/IgM	IgG 34-37 IgM 4-27	++	Anti Rh Anti-i	Extra ed intravasale

Raccomandazioni AIEOP 2013



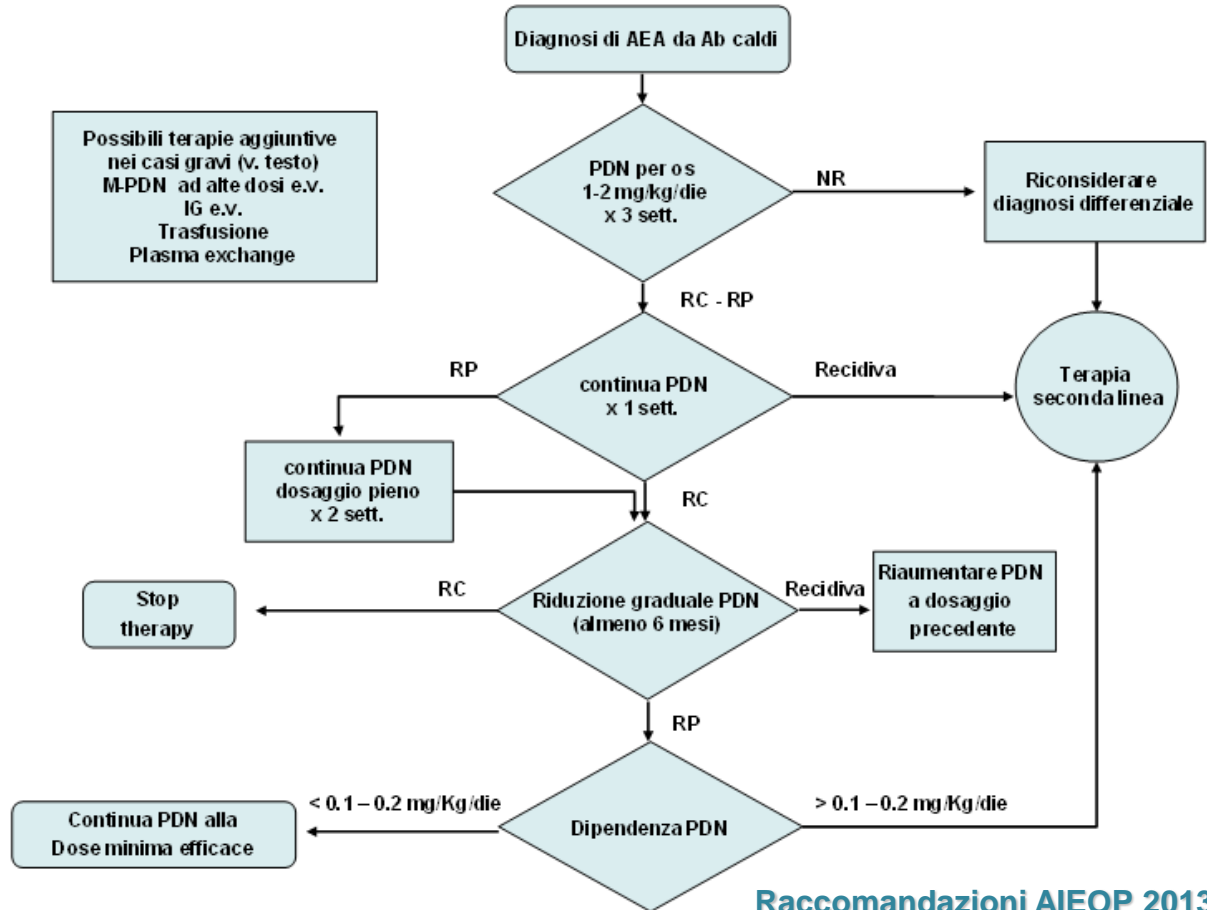


- AEA PRIMITIVA
- AEA SECONDARIE
 - Infezioni
 - Vaccinazioni
 - Piastrinopenia (sindrome di Evans)
 - Malattie autoimmuni
 - Immunodeficienze Primitive
 - Farmaci
 - Emopatie
 - Neoplasie
 - Trapianto di Cellule Staminali Emopoietiche



Warm AIHA

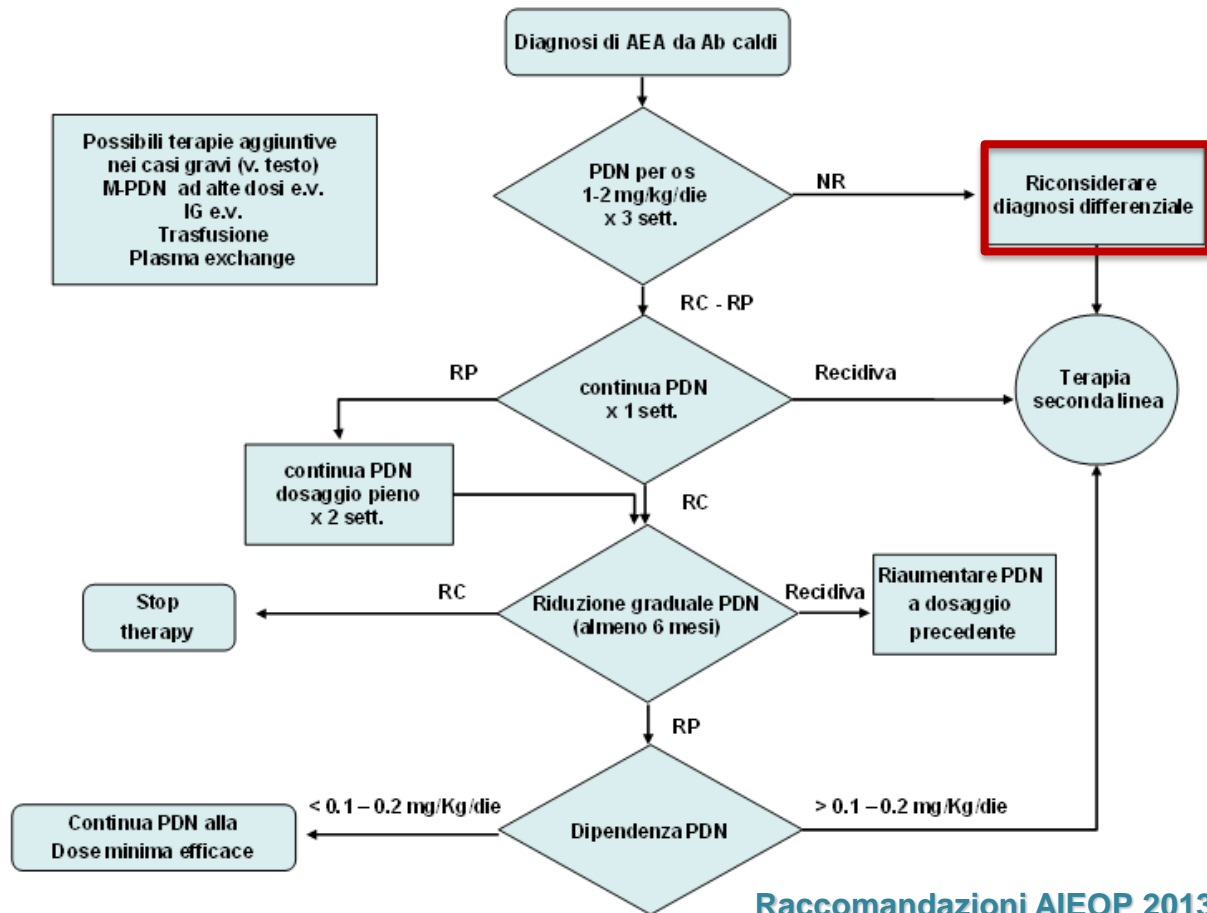
Terapia di prima linea

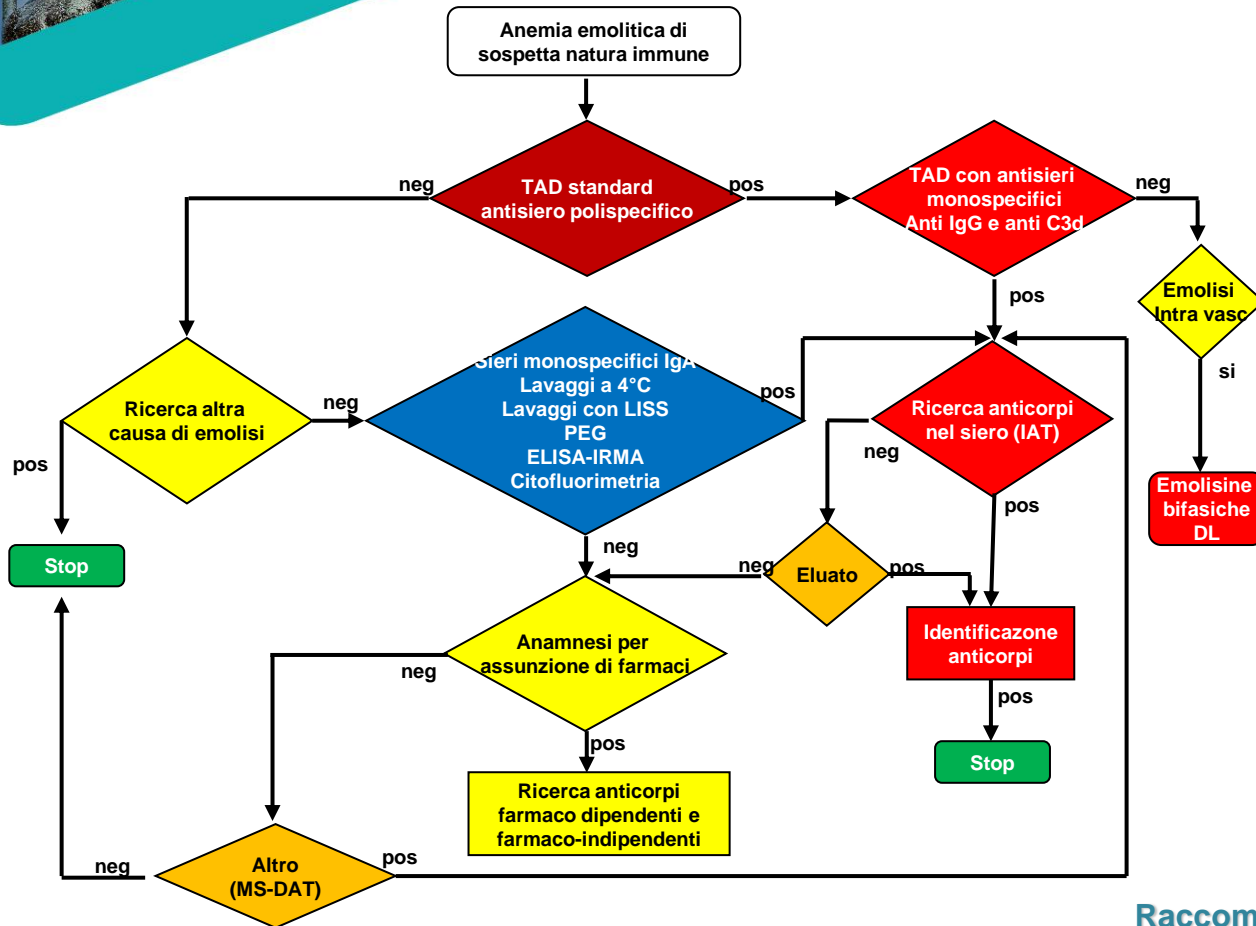




Warm AIHA Terapia di prima linea

Possibili terapie aggiuntive
nei casi gravi (v. testo)
M-PDN ad alte dosi e.v.
IG e.v.
Trasfusione
Plasma exchange







DAT – Insidie interpretative

Falsi positivi:

sindrome da antifosfolipidi,
marcata ipergammaglobulinemia
Infusione recente con immunoglobuline ad alte dosi

Falsi negativi

Motivi tecnici: lavaggio incompleto delle emazie, eccessiva agitazione del preparato al momento della lettura

DAT positivo non vuol dire necessariamente AEA e DAT negativo non esclude la diagnosi.

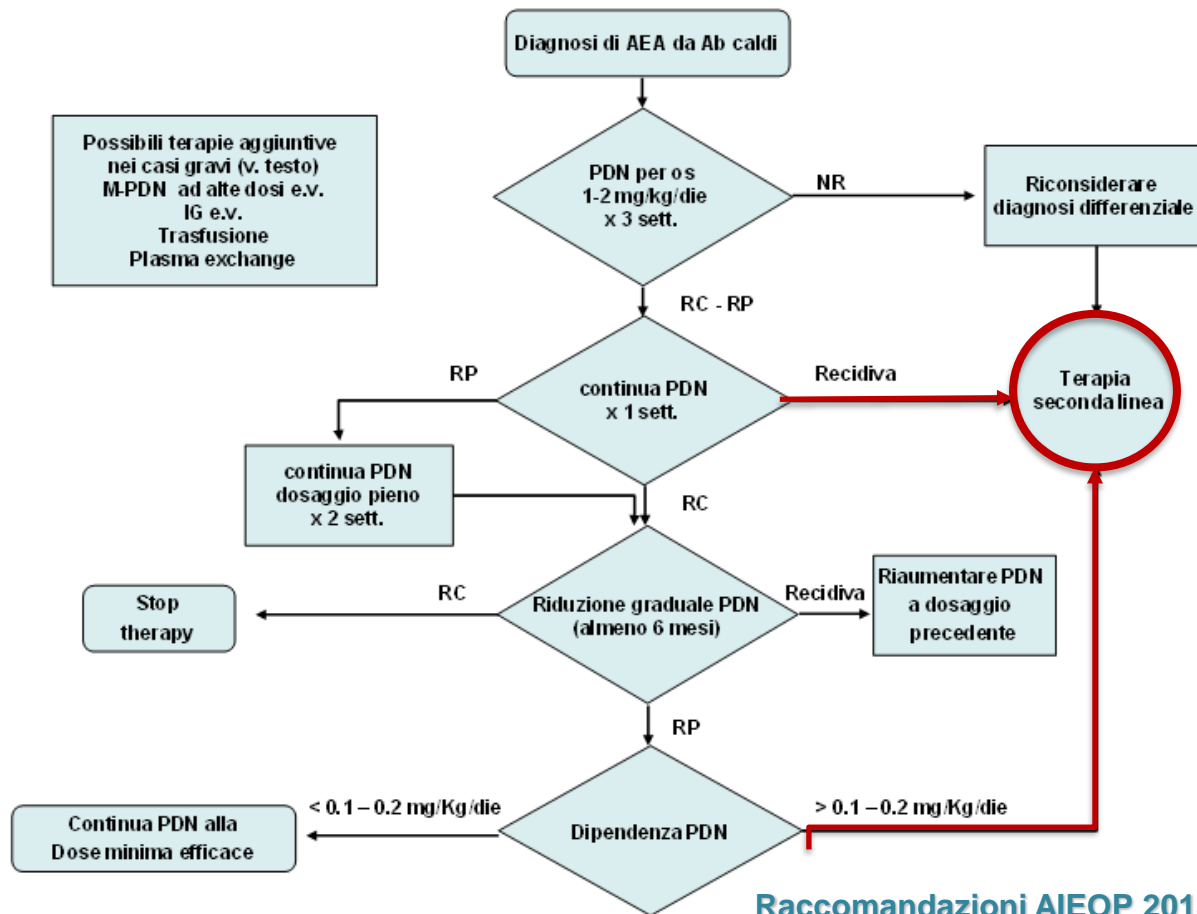


Anemie emolitiche non immuno-mediate

Forme congenite	<ul style="list-style-type: none"> • sferocitosi e altri difetti delle proteine di membrana eritrocitaria • deficit enzimi eritrocitari • anemie diseritropoietiche • emoglobinopatie • malattia di Wilson
Anemie emolitiche da cause meccaniche	<ul style="list-style-type: none"> • valvole cardiache sintetiche, emoglobinuria da marcia, bypass cardiopolmonare
Anemie emolitiche da danno vascolare	<ul style="list-style-type: none"> • AE microangiopatica • porpora trombotica trombocitopenica • sindrome uremico emolitica • coagulazione intravascolare disseminata • malformazioni arterovenose
Anemie emolitiche da danno termico	<ul style="list-style-type: none"> • ustioni estese
Anemie emolitiche da cause chimiche	<ul style="list-style-type: none"> • agenti chimici, solventi, cloruro di metile, piombo, idrogeno arsenicale • veleno di alcuni serpenti
Anemie emolitiche da agenti infettivi	<ul style="list-style-type: none"> • Batteri (Mycoplasma Pneumoniae, Clostridium Welchii) • Virus (Cytomegalovirus, Herpes Virus) • Protozoi (Plasmodi)



Warm AIHA Terapia di prima linea





The choice of new treatments in autoimmune hemolytic anemia: how to pick from the basket?

Sigbjørn Berentsen^{1*}, Bruno Fattizzo² and Wilma Barcellini³

When to add rituximab in the first line?

What to do in emergencies?

When to consider inclusion in a clinical trial?

When to use investigational therapies in wAIHA?

When to use intravenous immunoglobulin in wAIHA?

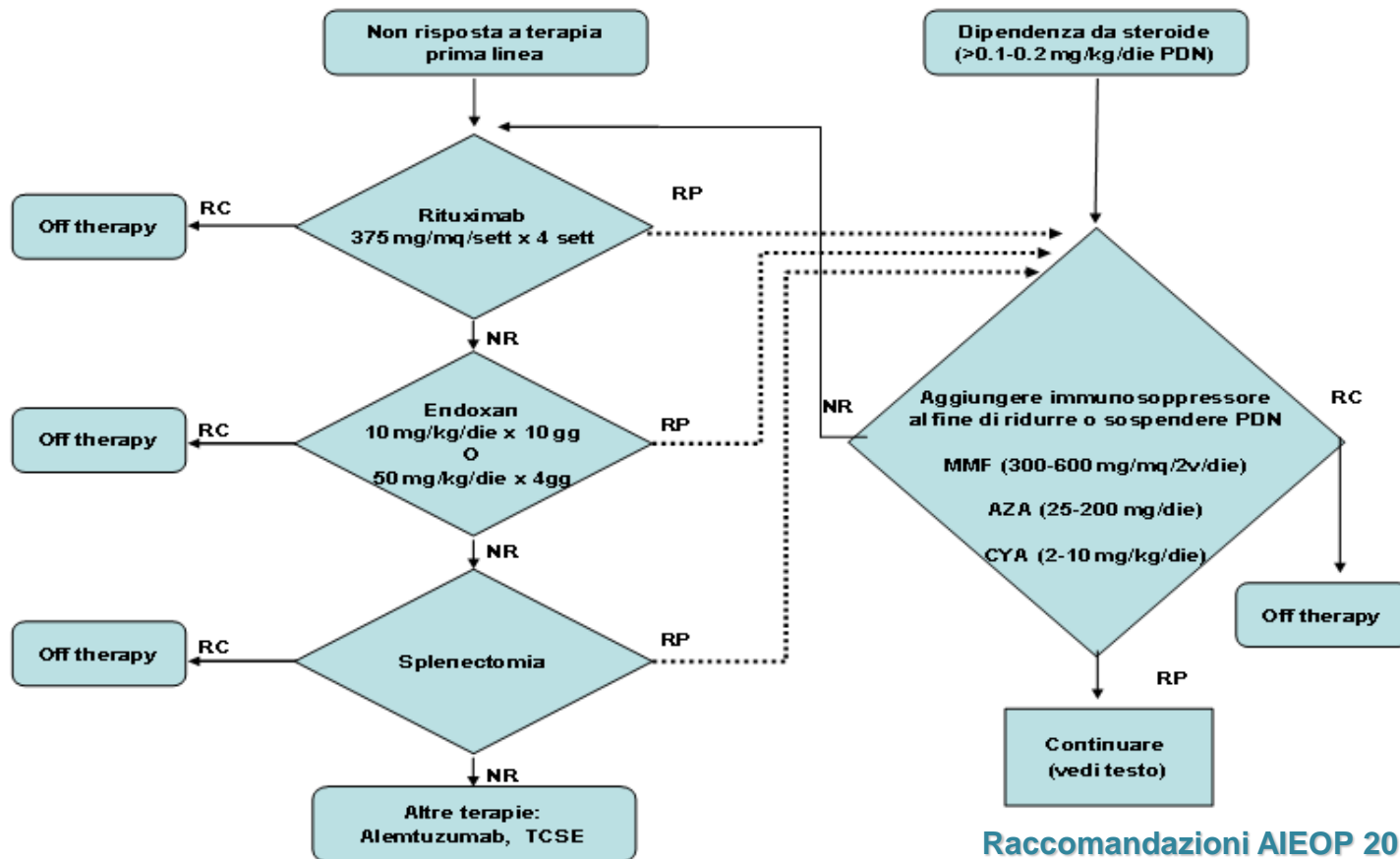
When to recommend splenectomy?

When to use erythropoiesis-stimulating agents?

B-cell or complement directed therapy?



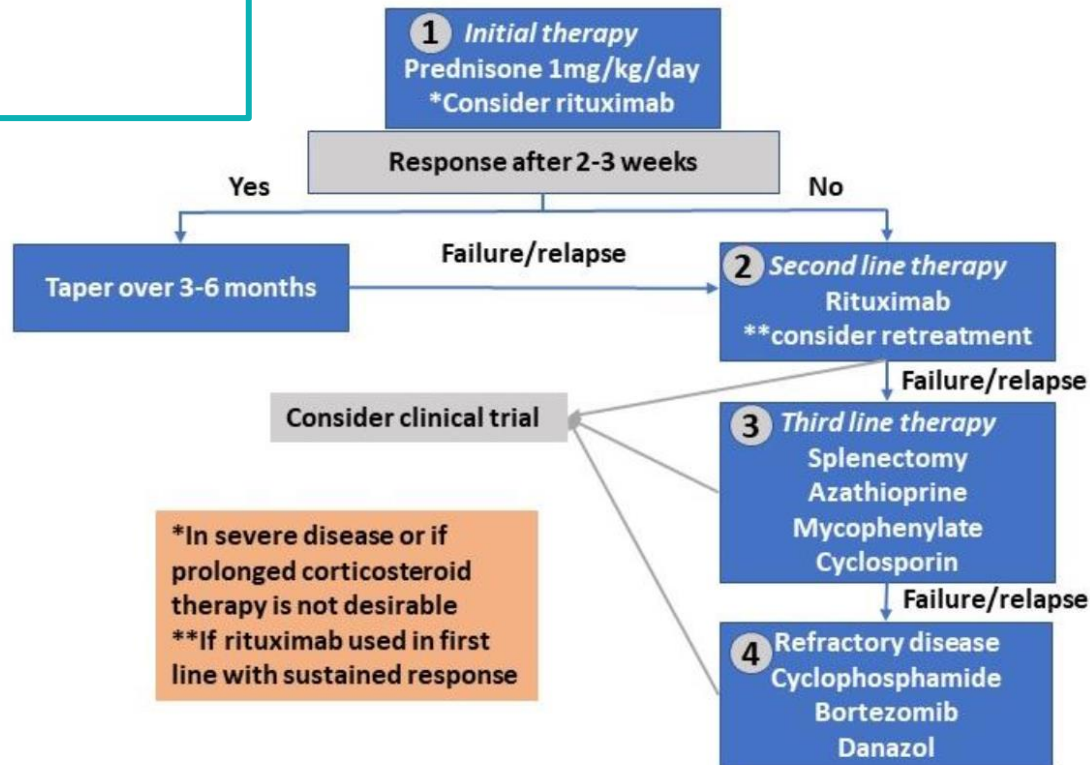
Warm AIHA Terapia di seconda linea





Rituximab Use in Warm and Cold Autoimmune Hemolytic Anemia

Irina Murakhovskaya





Efficacy and safety of rituximab in auto-immune hemolytic anemia: A meta-analysis of 21 studies

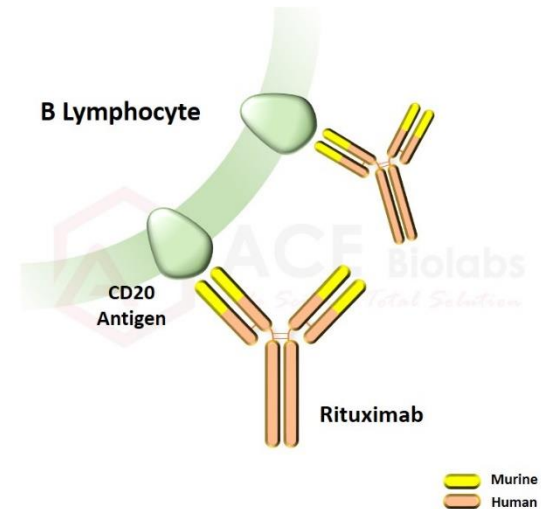


Quitterie Reynaud ^{a,*}, Isabelle Durieu ^{a,d}, Marine Dutertre ^a, Stanislas Ledochowski ^b, Stéphane Durupt ^a, Anne-Sophie Michallet ^c, Denis Vital-Durand ^a, Jean-Christophe Lega ^{a,d}

Table 1
characteristics of the 21 studies included in our meta-analysis.

21 Studies 409 Patients	WAIHA 11 Studies 183 Patients	CAD 7 Studies 118 Patients	ND 5 Studies 108 Patients
Primary 14 Studies 208 Patients	7 Studies 72 Patients Quartier, 2001 Zecca, 2003 Narat, 2005 D'Arena, 2007 Penalver, 2009 Barcellini, 2013 Maung, 2013	6 Studies 100 Patients Berentsen, 2001 Berentsen, 2004 Berentsen, 2006 Schollkopf, 2006 Penalver, 2009 Barcellini, 2013	Cabrera, 2004 Rao, 2008 Dierickx, 2009
Secondary 12 Studies 132 Patients	7 Studies 47 Patients Quartier, 2001 Trape, 2003 Zaja, 2003 Zecca, 2003 Narat, 2005 Penalver, 2009 Maung, 2013	4 Studies 18 Patients Berentsen, 2001 Zaja, 2003 Schollkopf, 2006 Penalver, 2009	Cabrera, 2004 D'Arena, 2006 Dierickx, 2009
ND 4 Studies 69 Patients	Bussone, 2009 Ansari, 2011 Birgens, 2013		Shanafelt, 2003

CAD: cold agglutinin disease, ND: not determined, WAIHA: warm autoimmune hemolytic anemia.





Quality assessment of the 21 studies included in our meta-analysis.

Study	Prospective	Retrospective	Randomized	Individual data	Type of article
Berentsen, 2001	+			+	
Quartier, 2001	+			+	Letter
Trape, 2003	+			+	Letter
Zaja, 2003	+			+	
Zecca, 2003	+			+	
Shanafelt, 2003		+			Abstract
Berentsen, 2004	+				
Cabrera, 2004		+			Abstract
Narat, 2005		+		+	Letter
Berentsen, 2006		+			
D'Arena, 2006	+			+	
Schollkopf, 2006	+			+	
D'Arena, 2007	+			+	
Bussone, 2008		+		+	
Rao, 2008	+				
Dierickx, 2009		+			
Penalver, 2009		+			
Ansari, 2011	+			+	Letter
Barcellini, 2013	+				
Birgens, 2013			Multicentric, randomized, open label, phase 3		
Maung, 2013		+			

Table 5

ORR and CR rates depending on AIHA types acquired in our meta-analysis of RTX efficacy in AIHA.

	<i>n, N</i>	Model	ORR	<i>n, N</i>	Model	CR
CAD	6, 109	Fixed	57% (47–66%)	7, 118	Random	21% (6–51%)
WAIHA	11, 154	Random	79% (60–90%)	11, 154	Random	42% (27–58%)
Primary AIHA	10, 161	Random	67% (49–81%)	11, 176	Random	32% (17–51%)
Secondary AIHA	8, 66	Fixed	72% (60–82%)	9, 87	Random	46% (30–62%)
Primary WAIHA	4, 50	Random	78% (37–95%)	5, 60	Fixed	44% (31–58%)

CAD: cold agglutinin disease, CR: complete response; *n*: number of studies; *N*: number of patients; ORR: overall response rate, WAIHA: warm autoimmune hemolytic anemia.

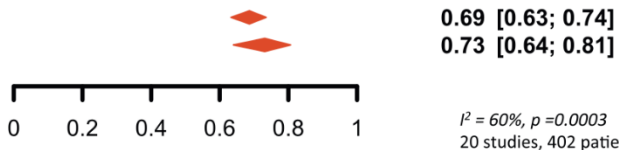
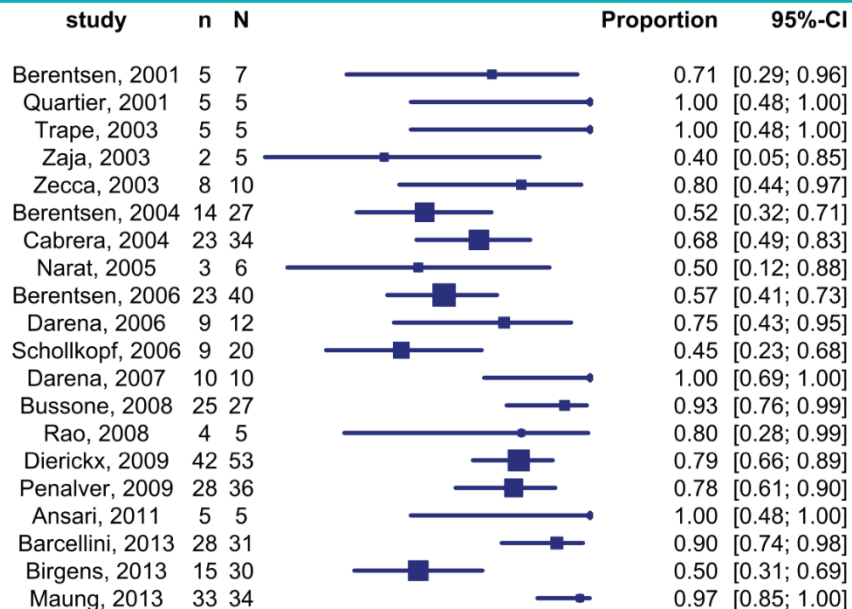


Fig. 4. Global ORR forrest plot.

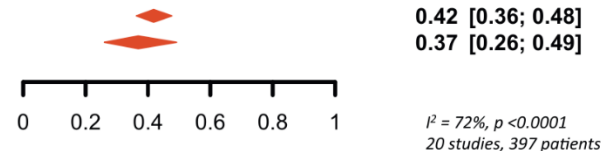
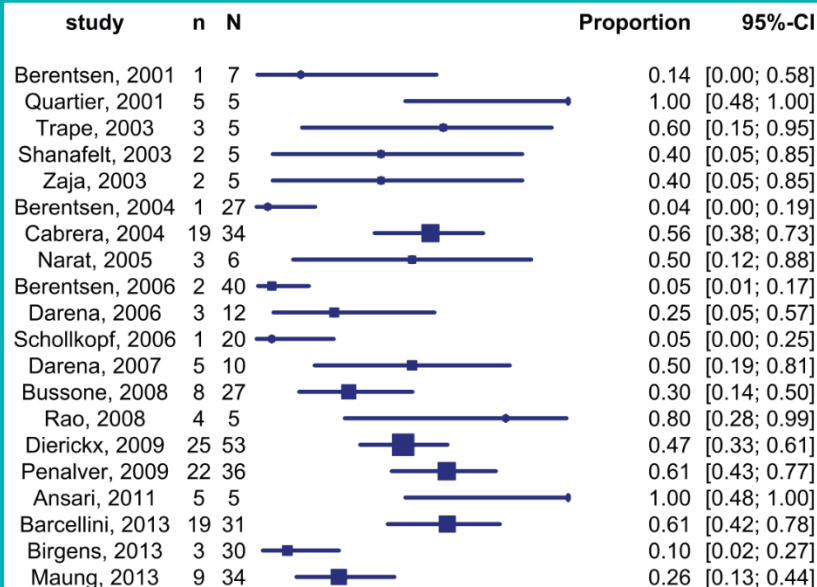


Fig. 5. Global CR forrest plot.



Take-home messages

- This meta-analysis confirms the high short-term benefit/risk ratio of RTX in case of failure or contra-indication of splenectomy in AIHA. Maintenance therapy with low-dose of RTX merits to be investigated further, ideally in prospective trials.
- RTX challenged splenectomy as the preferred second line option therapy in WAIHA.
- In CAD, RTX may be proposed as a first-line treatment before cytostatic agents.



- La più comune terapia di seconda linea
- Elevato overall response rate (ORR)



- Ipogammaglobulinemia
- Frequenti ricadute
- Non indicato in pazienti con ALPS (bassa percentuale di risposta, rischio di infezioni e ipogammaglobulinemia prolungata)



Mycophenolate mofetil and Sirolimus as second or further line treatment in children with chronic refractory Primitive or Secondary Autoimmune Cytopenias: a single centre experience

Maurizio Miano,¹ Maria Scalzone,¹
Katia Perri,¹ Elena Palmisani,¹ Ilaria
Caviglia,² Concetta Micalizzi,¹ Johanna
Svahn,¹ Michaela Calvillo,¹ Laura
Banov,¹ Paola Terranova,¹ Tiziana
Lanza,¹ Carlo Dufour¹ and Francesca
Fioredda¹

British Journal of Haematology, 2015, **171**, 247–253

Diagnostic categories	Patients with cytopenias (n = 58)	Patients needing upscale therapies (n = 39)	Response to MMF (n = 34)	Response to Sirolimus (n = 16)
ALPS	12	11	11/11 (100%)	–
ITP	1	1	1/1	–
ITP + AIHA	1	0	–	–
ITP + Leucopenia/Neutropenia	4	4	4/4	–
AIHA	1	1	1/1	–
AIHA + Leucopenia/Neutropenia	0	–	–	–
Trilineage cytopenia	5	5	5/5	–
ALPS-related syndrome	24	13	5/10 (50%)	5/7 (71%)
ITP	12	8	3/8	3/5
ITP + AIHA	4	3	1/1	1/1
ITP+ Leucopenia/Neutropenia	2	0	0	0
AIHA	1	1	0	1/1
AIHA + Leucopenia/Neutropenia	1	1	1/1	0
Leuko/Neutropenia	4	0	–	–
Trilineage cytopenia	0	–	–	–
PAC	22	15	6/13 (46%)	7/9 (77%)
ITP	14	11	6/11	3/5
ITP + AIHA	3	0	–	–
ITP + Leucopenia/Neutropenia	0	0	–	–
AIHA	5	4	0/2	4/4
AIHA + Leucopenia/Neutropenia	0	0	–	–
Trilineage cytopenia	0	0	0	–

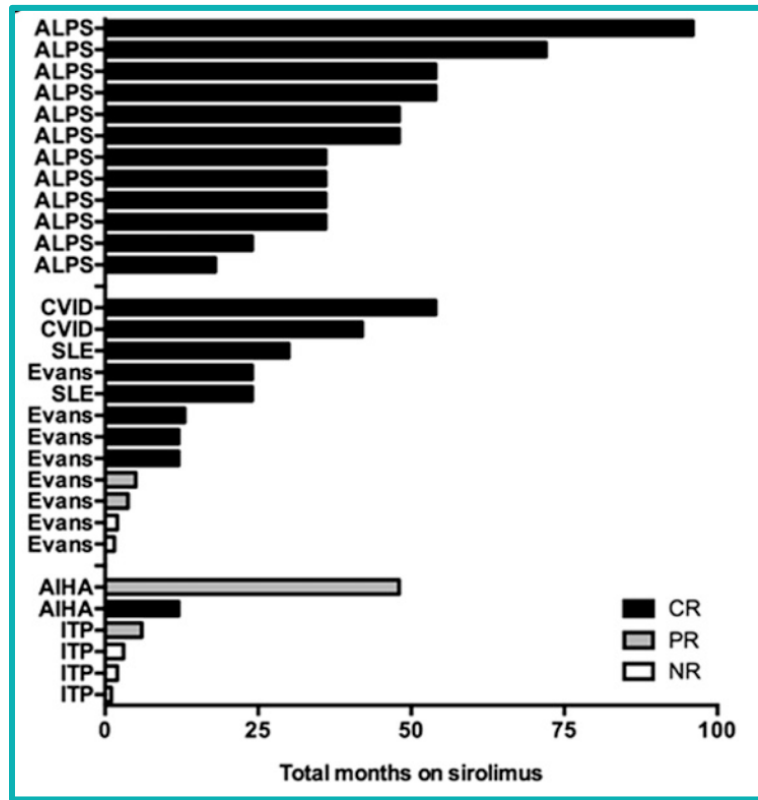
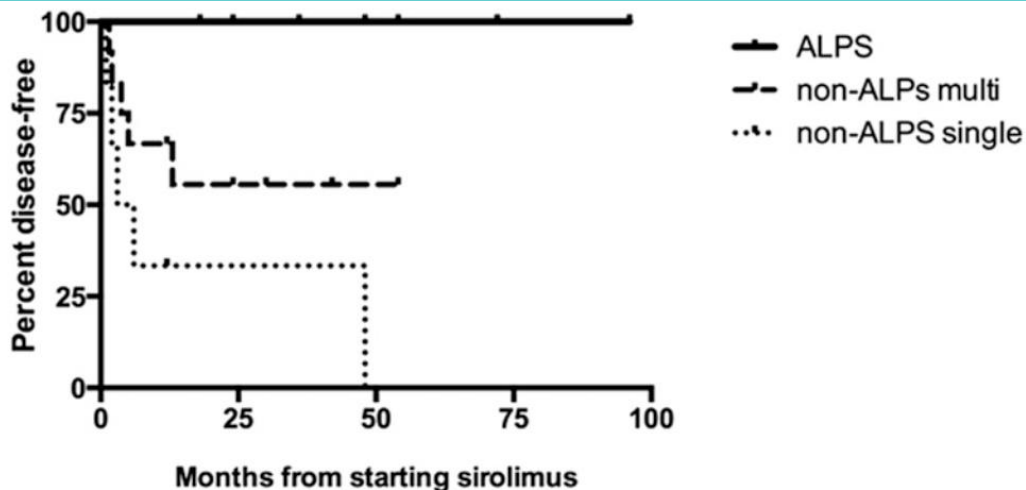
22/34 (65%) risposta al MMF
11/11 (100%) ALPS

12/16 (75%) risposta
Sirolimus inclusi 8 pz NR a
MMF

Sirolimus is effective in relapsed/refractory autoimmune cytopenias: results of a prospective multi-institutional trial

2024

Karen L. Bride,^{1,2} Tiffaney Vincent,^{1,2} Kim Smith-Whitley,^{2,3} Michele P. Lambert,^{2,3} Jack J. Bleesing,⁴ Alix E. Seif,^{1,2} Catherine S. Manno,⁵ James Casper,⁶ Stephan A. Grupp,^{1,2} and David T. Teachey^{1,2}



Sirolimus is effective for primary relapsed/refractory autoimmune cytopenia: a multicenter study

2024

Hongmin Li^a, Jiang Ji^a, Yali Du^a, Yuzhou Huang^a, Hao Gu^b, Miao Chen^a, RunHui Wu^b, and Bing Han^a

Experimental Hematology 2020;89:87–95

Table 2. Patient response at different follow-up times, trough level of sirolimus, and adverse events

Patient no.	Disease	Response during follow-up (mo)				Trough sirolimus (ng/mL)	Adverse event		
		3	6	12	End		Manifestation	Grade	Outcome
1	AIHA	PR	PR	CR	CR	6.7 (4.1–8.8)			
2	AIHA	PR	PR	PR	PR	4.2 (2.5–8.1)			
3	AIHA	CR	CR	CR	CR	4.9 (3.0–5.7)			
4	AIHA	PR	PR	PR	PR	7.3 (6.0–8.4)			
5	AIHA	CR	CR	CR	CR	5.2 (5.0–7.9)			
6	AIHA	CR	CR	CR	CR	4.2 (2.3–6.1)			
7	AIHA	PR	PR	PR	CR	4.5 (3.4–6.1)			
8	AIHA	CR	CR	CR	CR	2.7 (0.3–4.8)			
9	AIHA	CR	CR	CR	CR	10.7 (7.3–13.1)			
10	AIHA	NR	NR	NR	NR	6.3 (1.7–9.4)			
11	AIHA	PR	CR	CR	CR	8.9 (5.6–11.3)	Mucositis	1	Recovery without medication
12	AIHA	NR	NR	NR	NR	7.4 (4.3–9.2)			
13	AIHA	NR	PR	PR	PR	9.7 (6.8–10.5)	Mucositis	1	Recovery without medication
14	AIHA	PR	PR	PR	PR	5.8 (4.6–7.2)	Upper respiratory infection	2	Stable
CR rate (%) of AIHA		35.7	42.9	50.0	57.1				
OR rate (%) of AIHA		78.6	85.7	85.7	85.7				



Received: 18 September 2023

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DOI: 10.1111/sji.13376

ORIGINAL ARTICLE

SCANDINAVIAN JOURNAL OF
Immunology
SCANDINAVIAN JOURNAL

WILEY

Sirolimus is effective and safe in childhood relapsed-refractory autoimmune cytopenias: A multicentre study

Sultan Okur Acar¹ | Neryal Tahta¹ | Işık Odaman Al¹ | Melek Erdem¹ |
Salih Gözmen¹ | Tuba Hilkay Karapınar¹ | Burcu Kılınç² | Tiraje Celkan² |
Serap Kirkiz³ | Ülker Koçak³ | Hale Ören⁴ | Ayşen Türedi Yıldırım⁵ |
Esra Arslantaş⁶ | Aylin Canbolat Ayhan⁷ | Yeşim Oymak¹

17 pz

5 pz con AIHA.

80% CR

6 pz con s. Evans.

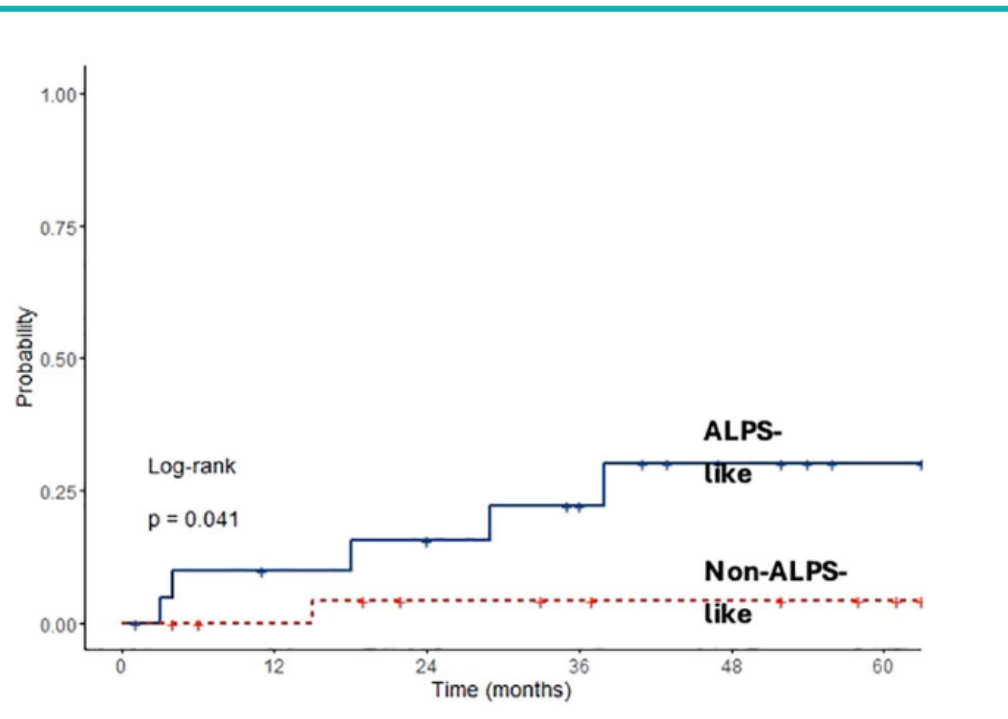
83% CR

Tempo medio di risposta 2.7 mesi



Infection risk in patients with autoimmune cytopenias and immune dysregulation treated with mycophenolate mofetil and sirolimus

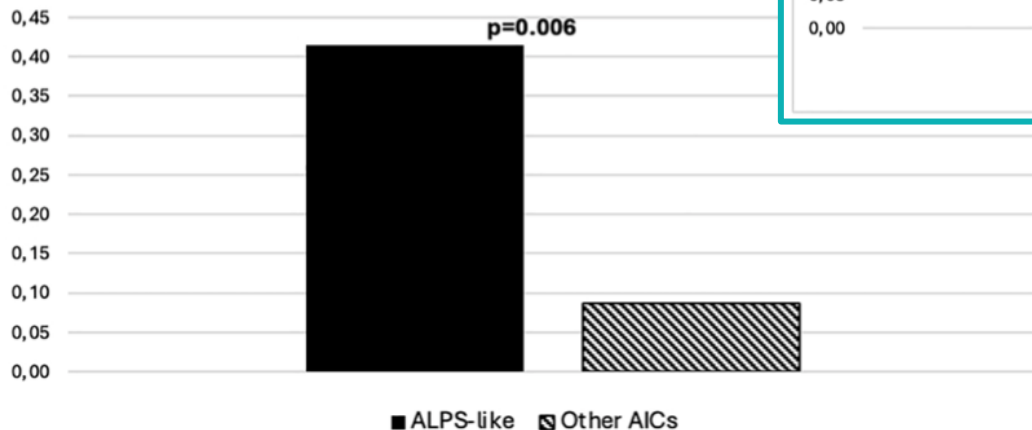
Mattia Comella^{1,2†}, Elena Palmisani^{1†}, Marcello Mariani³, Gianluca Dell'Orso¹, Maria Licciardello², Maria Carla Giarratana¹, Luca Arcuri¹, Sara Pestarino¹, Alice Grossi⁴, Marina Lanciotti¹, Giorgia Brucci⁵, Daniela Guardo¹, Giovanna Russo², Carlo Dufour¹, Francesca Fioredda¹, Elio Castagnola³ and Maurizio Miano^{1*}





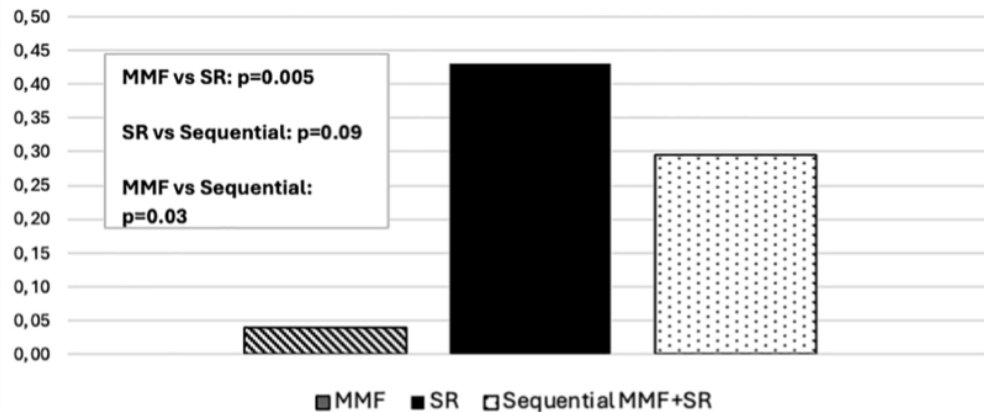
A

SIE incidence rate (*100 p/m/r)



B

SIE incidence rate (*100 p/m/r)

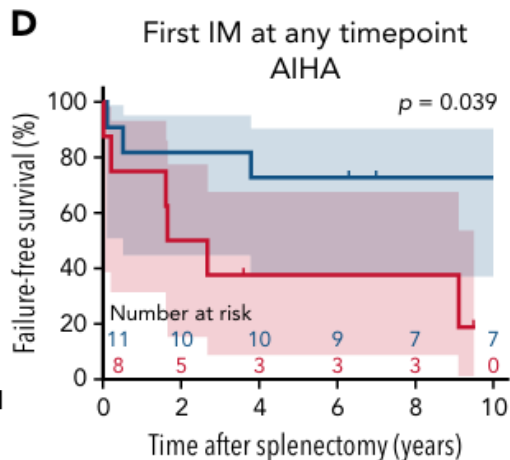
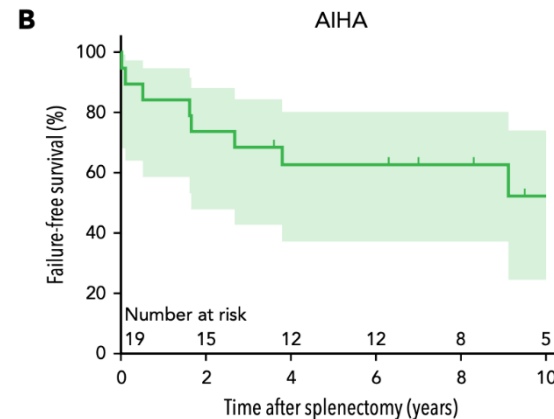




- Terapia di terza linea, dopo rituximab e ciclofosfamide



- Spesso controindicata in pediatria per età
- Remissione di lunga durata nel 20% dei casi



Maggiore efficacia nelle forme primitive



Received: 28 October 2020 | Accepted: 10 February 2021

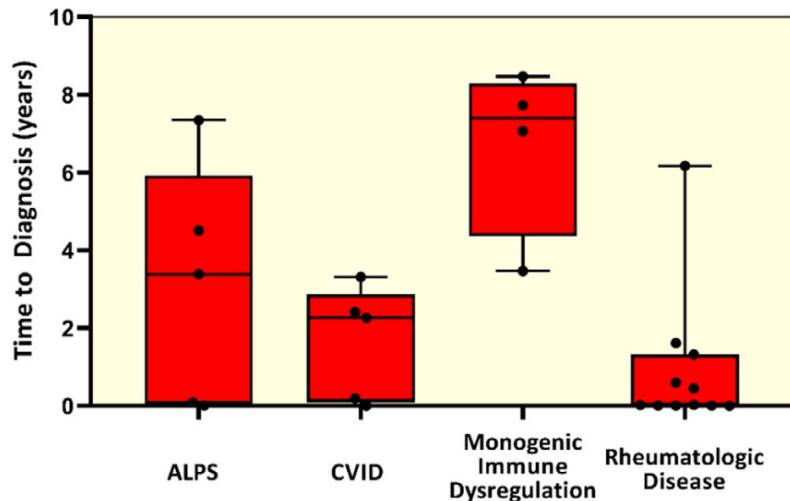
DOI: 10.1111/ehp.13600

ORIGINAL ARTICLE

Journal of
Haematology WILEY

Refractory autoimmune cytopenias in pediatric Evans syndrome with underlying systemic immune dysregulation

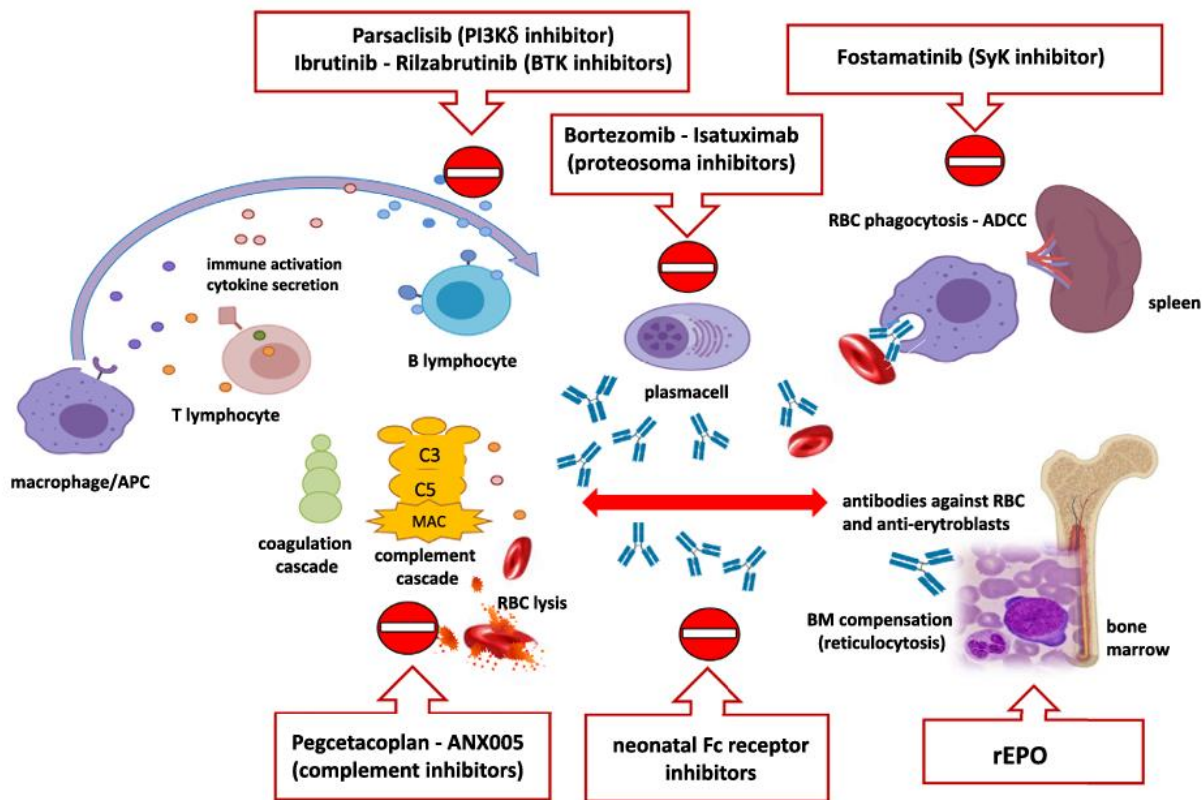
Amanda B. Grimes^{1,2} | Taylor O. Kim^{1,2} | Susan E. Kirk^{1,2} | Jonathan Flanagan^{1,2} | Michele P. Lambert^{3,4} | Rachael F. Grace^{5,6} | Jenny M. Despotovic^{1,2}



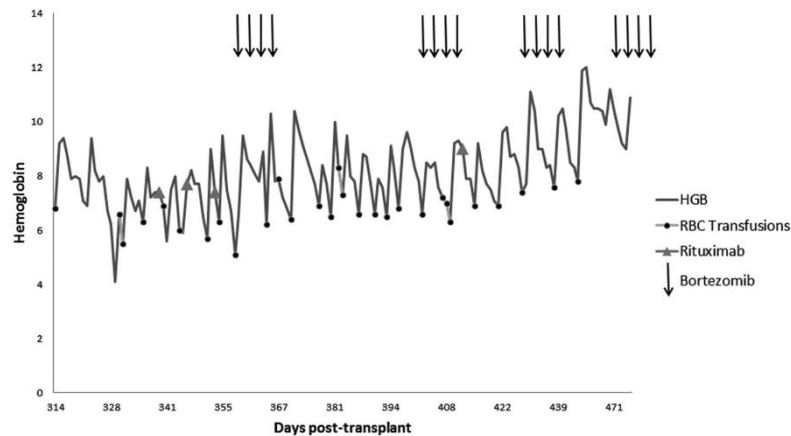
	Number diagnosed (%)	Median time to diagnosis (Range)	Median number of treatments (Range)
Rheumatologic disease			
Systemic Lupus Erythematosus (8)	11 (18%)	0.03 years (0-6.17)	5 (3-8)
SLE/Antiphospholipid antibody syndrome (1)			
SLE/Sjogren's (1)			
Antiphospholipid antibody syndrome (1)			
Autoimmune lymphoproliferative syndrome	5 (8%)	3.39 years (0.01-7.35)	4.5 (2-9)
Common variable immunodeficiency	5 (8%)	2.27 years (0-3.32)	5 (3-7)
Monogenic immune dysregulation			
CTLA-4 haploinsufficiency (2)	4 (7%)	7.4 years (3.47-8.47)	4 (2-9)
NFKB1-related disorder (1)			
A20 Haploinsufficiency/ TNFAIP3 loss (1)			
Idiopathic (No systemic immune dysregulation disorder identified)	35 (58%)	N/A	3 (0-12)

Abbreviations: ALPS, Autoimmune Lymphoproliferative Syndrome; CTLA-4, Cytotoxic T Lymphocyte Antigen-4; N/A, Not Applicable; NFKB1, Nuclear Factor Kappa B Subunit 1; SLE, Systemic Lupus Erythematosus; TNFAIP3, Tumor Necrosis Factor Alpha Induced Protein 3.

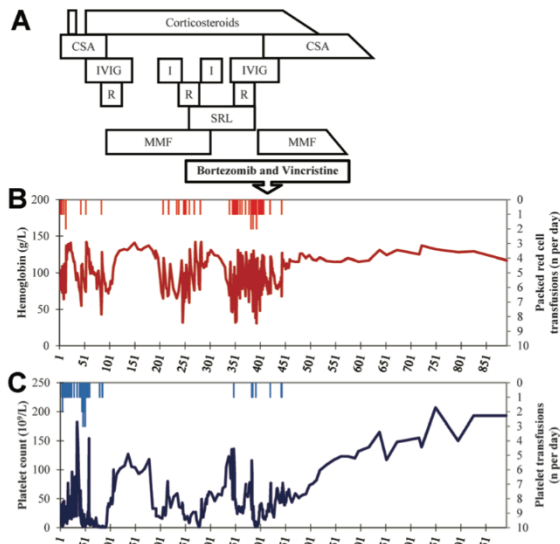
Nuovi farmaci



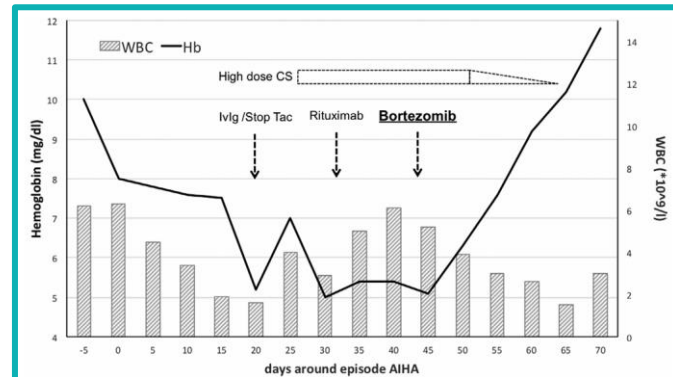
Bortezomib



Pediatr Blood Cancer 2014;61:2324–2325



Pediatr Blood Cancer 2014;61:2112–2114

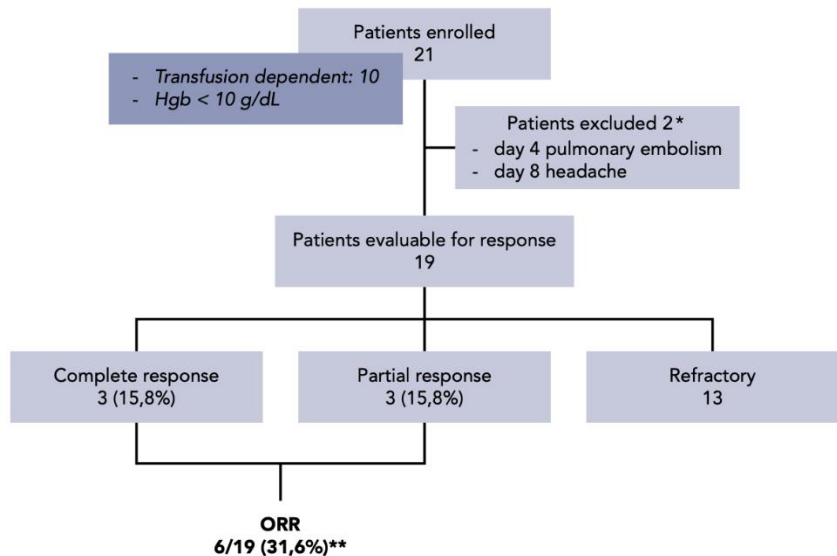


Knops et al. Pediatric Transplantation. 2020

Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study

blood® 2 AUGUST 2018 | VOLUME 132, NUMBER 5

Giuseppe Rossi,¹ Doriana Gramegna,¹ Francesca Paoloni,² Bruno Fattizzo,³ Francesca Binda,³ Mariella D'Adda,¹ Mirko Farina,¹ Elisa Lucchini,⁴ Francesca Romana Mauro,⁵ Flavia Salvi,⁶ Monia Marchetti,⁷ Paola Fazi,² Francesco Zaja,⁴ and Wilma Barcellini³



Response criteria

- ✓ **Complete response (CR):** absence of anemia and hemolysis, complete resolution of clinical symptoms,
- ✓ **Partial response (PR):** stable increase in Hgb level by at least 2.0 g/dl, improvement of clinical symptoms and transfusion independency.
- ✓ **No response (NR):** failure to achieve CR or PR.

Response in 32% of patients (16% complete)

Median duration of response of 16 months

Possibility to repeat cycles

Acceptable toxicity

* one patient actually achieved transfusion independence in spite of treatment stop

** four of six achieved transfusion independence

Received: 24 May 2023 | Revised: 18 September 2023 | Accepted: 12 October 2023

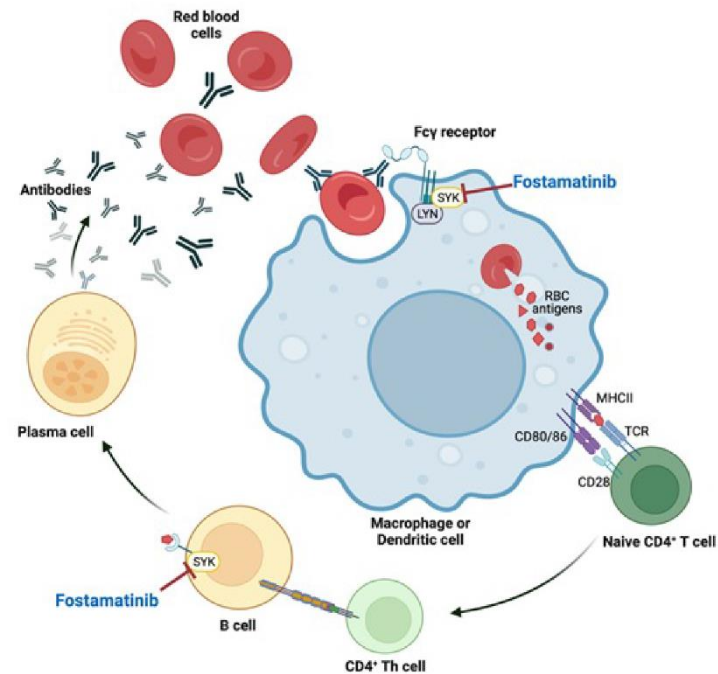
DOI: 10.1002/ajh.27144

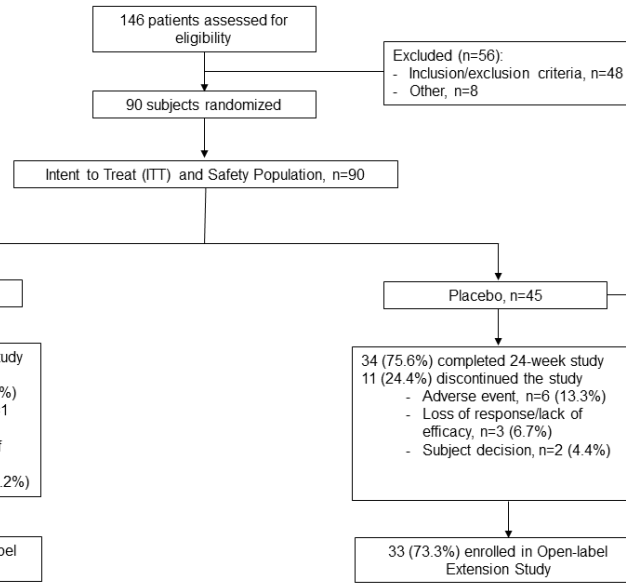
RESEARCH ARTICLE



Fostamatinib for warm antibody autoimmune hemolytic anemia: Phase 3, randomized, double-blind, placebo-controlled, global study (FORWARD)

David J. Kuter¹ | Caroline Piatek² | Alexander Röth³ | Asif Siddiqui⁴ |
Robert P. Numerof⁴ | Wolfgang Dummer⁴ | on behalf of the FORWARD study group

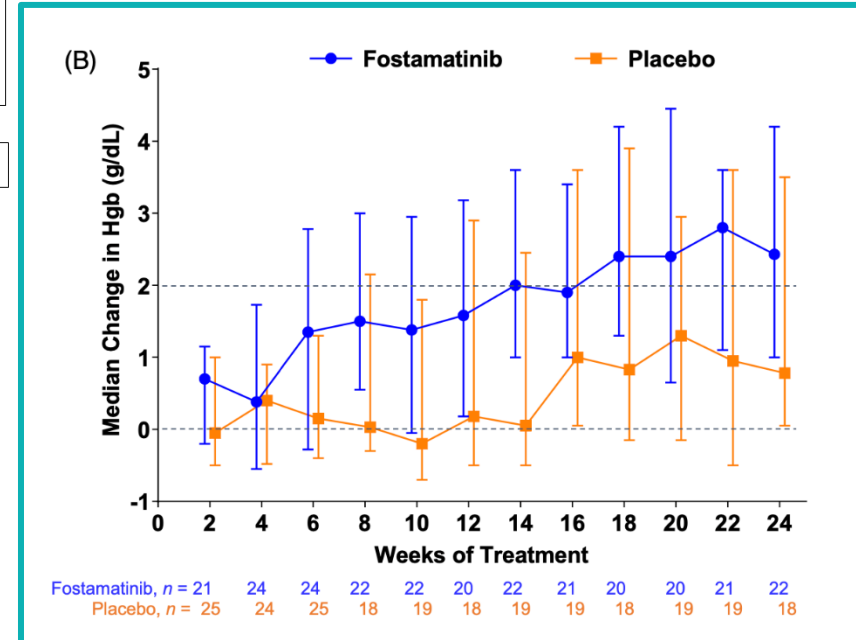




90 pz
Età 29-87
Precedenti linee terapia
una 22
due 32
tre 40

Fosfamatinib
100-150 mg BID

Steroidi, Rituximab, Azatioprina,
Splenectomi, MMF, Ivlg,
Ciclofosfamide, Ciclosporina

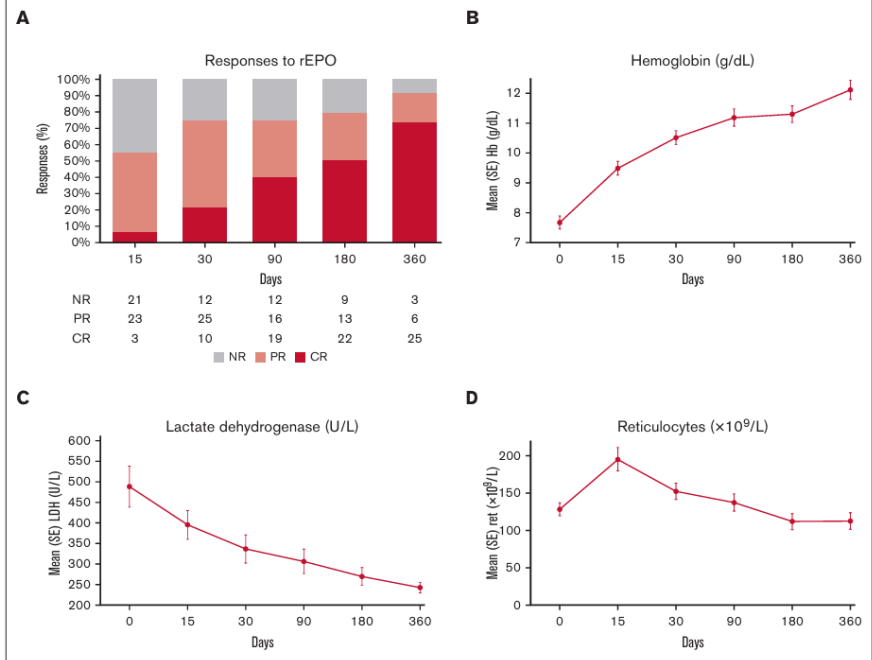


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Recombinant erythropoietin in autoimmune hemolytic anemia with inadequate bone marrow response: a prospective analysis

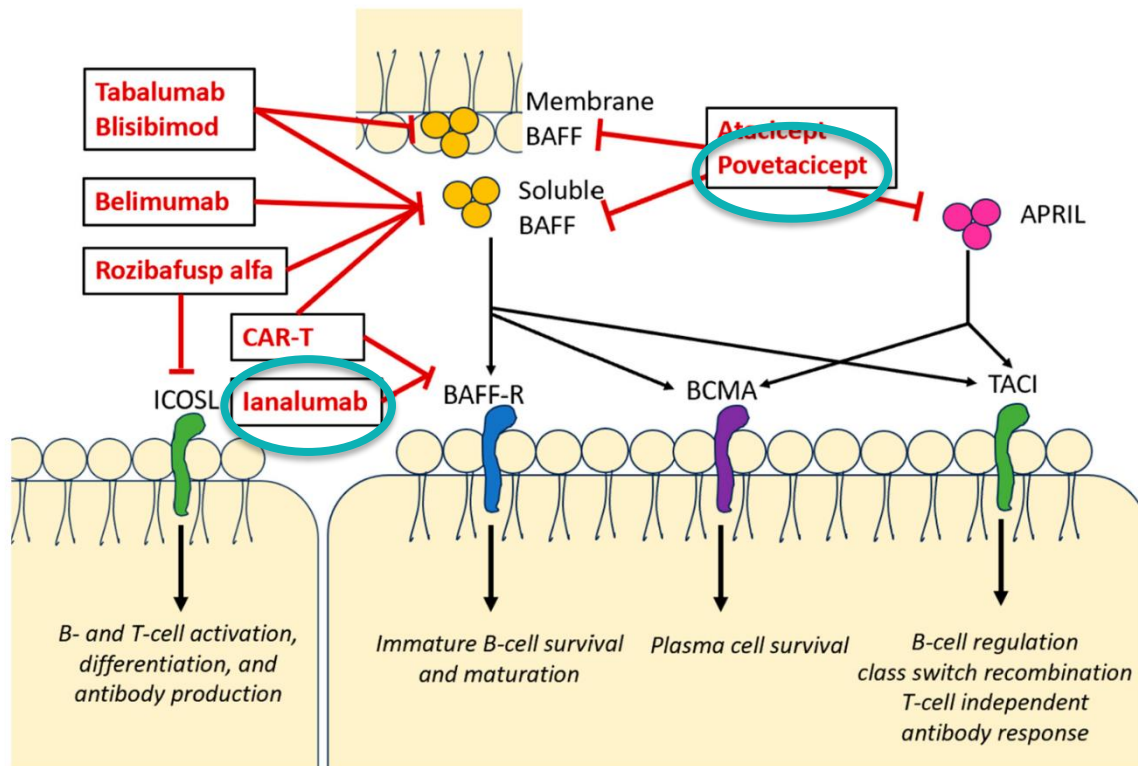
Bruno Fattizzo,^{1,2} Giacinto Luca Pedone,^{1,2} Caterina Brambilla,^{1,2} Loredana Pettine,¹ Anna Zaninoni,¹ Francesco Passamonti,^{1,2} and Wilma Barcellini¹

- Studio prospettico su 47 pazienti
 - EPO 40.000 U /week
 - Overall response di 55% a 15 giorni, 74% a 1 mese, 74% a 3 mesi, 80% a 6 mesi, e 91% a 12 mesi.
 - Aumento medio Hb 1.4 a 15 gg
 - Diminuzione trasfusioni dal 30 al 9%
 - Effetti collaterali simili a quelli di pazienti non trattati con rEpo, rare trombosi.
- Auto anticorpi anti eritroblasti
 - BM in «shock» incapace di rispondere durante la fase acuta
 - Malattia ematologica e/ infettiva sottostante



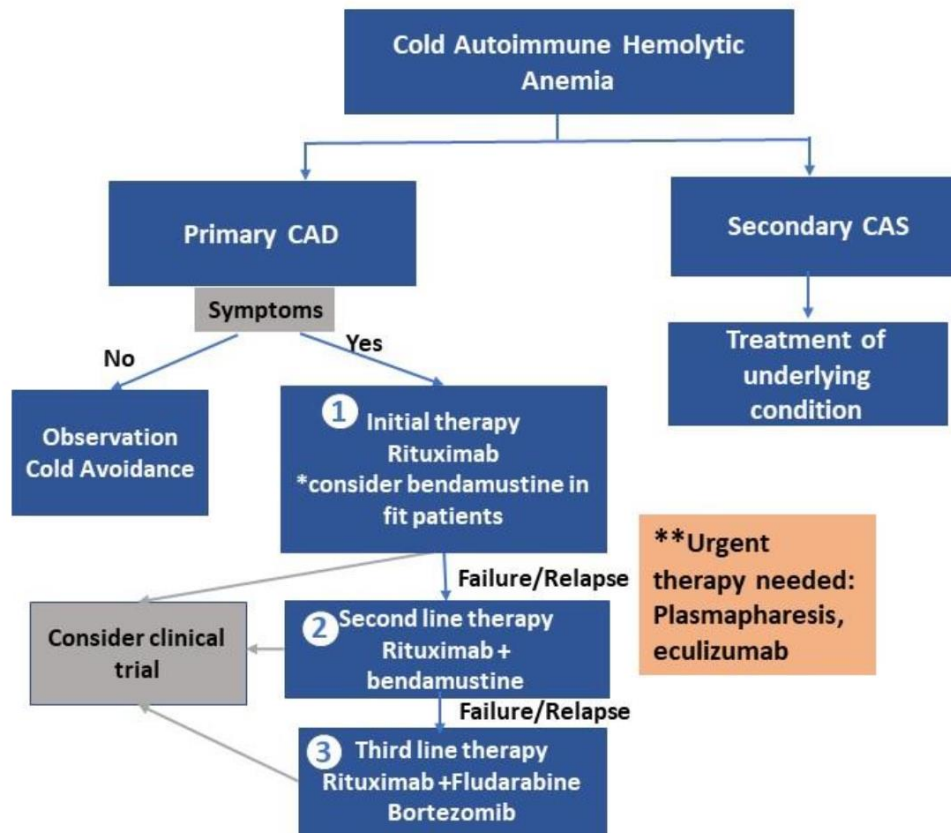
Anti-B-Cell-Activating Factor (BAFF) Therapy: A Novel Addition to Autoimmune Disease Management and Potential for Immunomodulatory Therapy in Warm Autoimmune Hemolytic Anemia

Biomedicines **2024**, *12*, 1597.

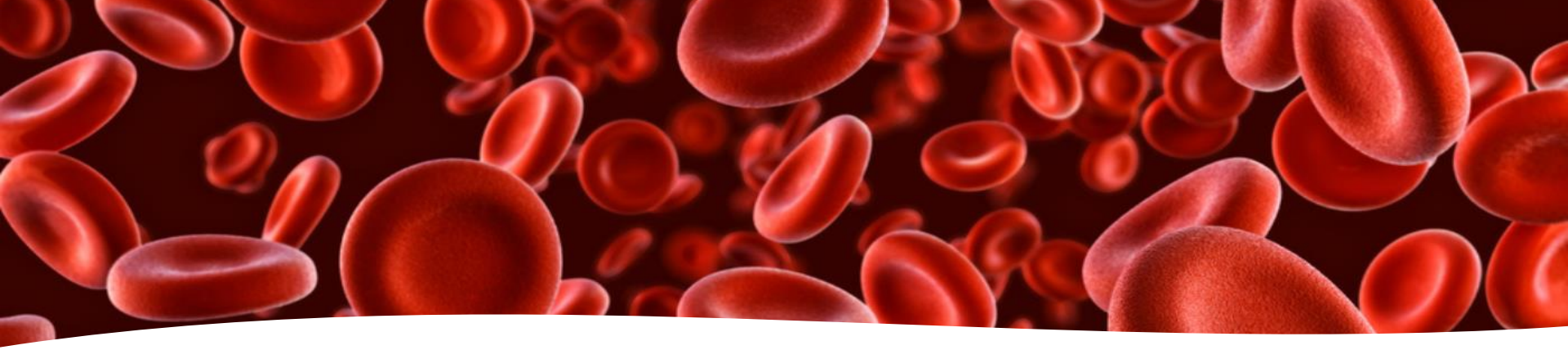


Ianalumab: Phase II, Phase III trials in ITP, phase III RCT VAYHIA in WAIHA

Povetacicept: Phase I-II in ITP and WAIHA



****Urgent therapy needed: Plasmapheresis, eculizumab**



Take home messages

- Le anemie emolitiche sono condizioni rare in età pediatrica che necessitano di terapie mirate.
- Non sempre la terapia di prima linea è efficace nella remissione a lungo termine
- Necessaria una terapia di seconda linea che possa essere personalizzata in base alle caratteristiche cliniche e immunologiche del paziente
- Numerosi nuovi farmaci sono in fase di studio negli adulti ma potranno aprire la strada a nuove prospettive anche nella popolazione pediatrica