VIIÈ CURS D'ERITROPATOLOGIA

DE LA SOCIETAT CATALANA D'HEMATOLOGIA I HEMOTERÀPIA

Actualització en malalties amb afectació eritrocitària i anèmies poc freqüents

21 i 28 de novembre de 2019- **Hotel Cristal Palace**

Coordinadors del curs:

Dr. Albert Altés Hernández

Cap de Servei Hematologia, Fundació Altahia

Dr. David Benéitez Pastor

Unitat Eritropatologia, Servei Hematologia, Hospital Universitari Vall d'Hebrón

Dr Beneitez Pastor, David
Servicio de Hematología Clínica
Unidad de Eritropatología y Patología Congénita Serie Roja

dbeneitez@vhebron.net
dbeneitez@vhio.net

ERN-EuroBloodNet Center (RBC and BMF disorders subnetworks)
Centro CSUR en Síndromes de Fallo Medular Congénitos
Unidad Clínica de Confirmación del Cribado Neonatal de ECF en Cataluña
Unidad del Programa de Eritropatología Hereditaria HUVH
Unidad miembro de Orphanet y TIF

@beneitez_david
@Hemato_Vhebron

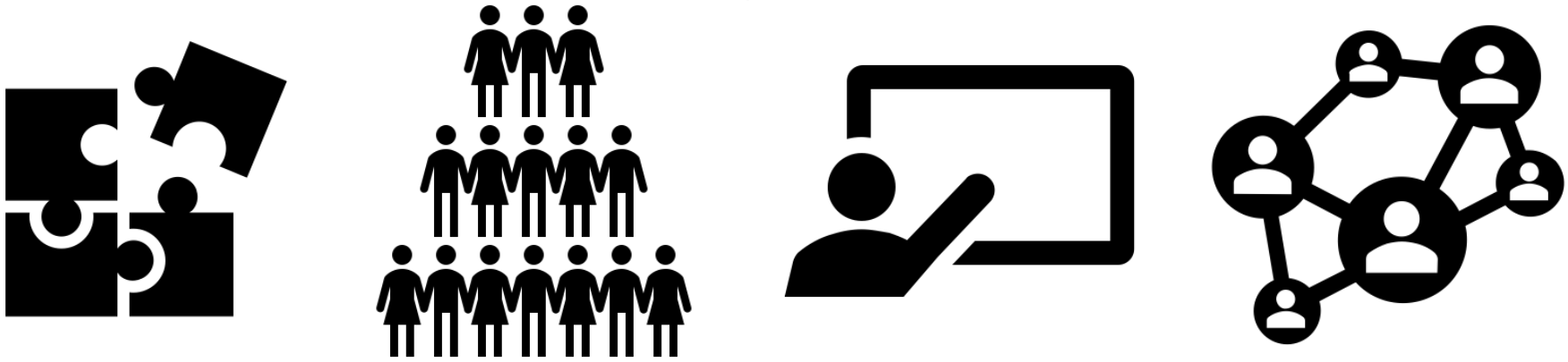
INDEX:
Eritropatologia: actualitat

1. Introducció

-Abans pocs professionals implicats, però bons (eritropatòleg, “raros”)

-Dificultats diagnòstiques, entitats rares, poc habitual diagnòstic genètic
*clínica compartida, transfusions, inestabilitat hematies
-Pocs tractaments específics per les malalties (hidroxiurea, acfol, transfusió,...)

-Poca col·laboració amb els pacients, poca formació continuada



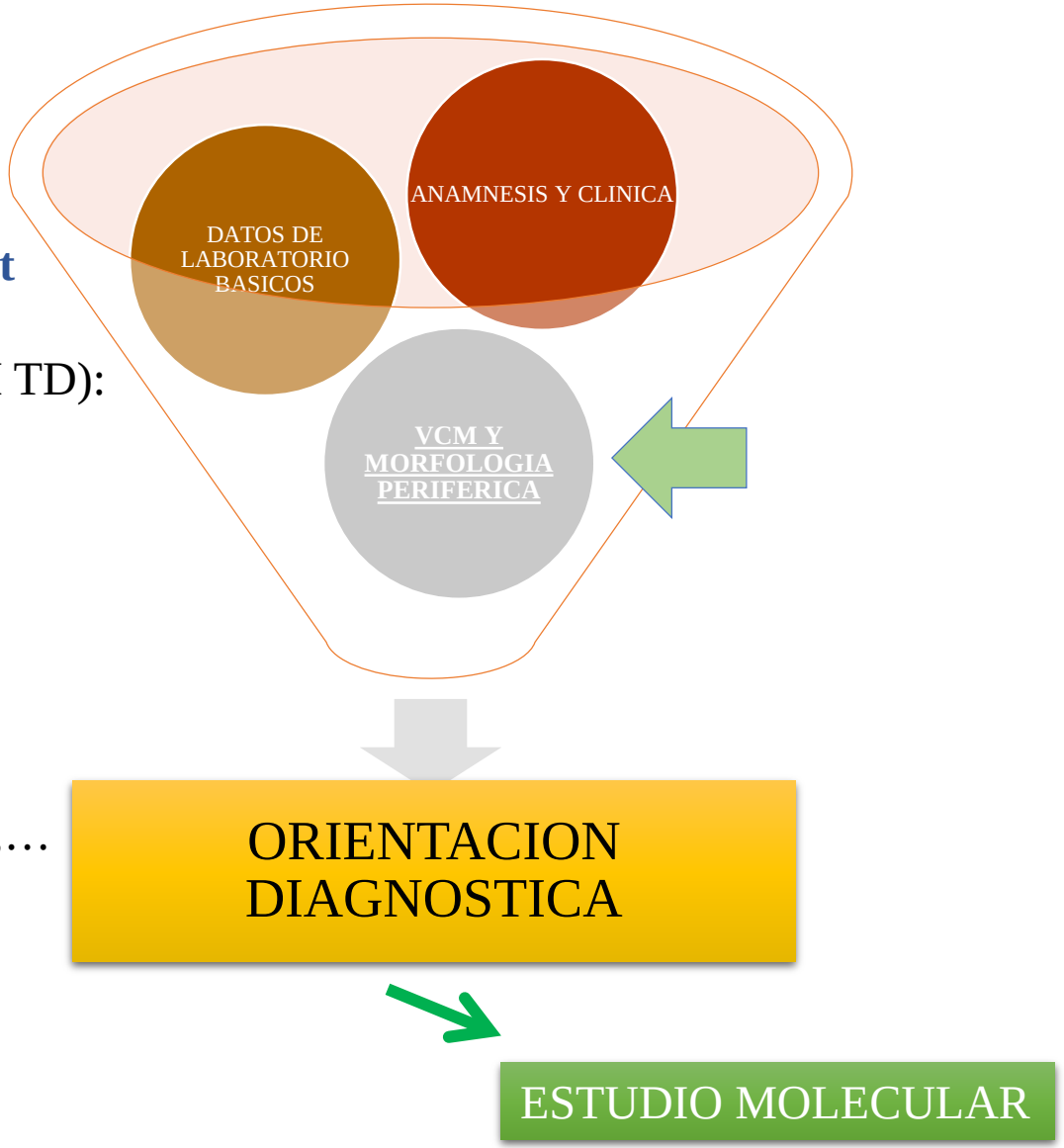
2. Diagnòstic

-Història Clínica, part i postpart

-Estudi pares a ser possible (AH TD):
- HG, indexs eritrocitaris

(*experimentals)
- Reticulòcits (IRF, Hb Ret)
- Morfologia Perifèrica

-Altres estudis
- Activitat enzimàtica
- Test d'EMA, fragilitat osmòtica,…



2. Diagnòstic

Red Blood Cell Enzyme Disorders

Rachael F. Grace, MD, MMSc[a,*], Bertil Glader, MD, PhD[b]

Pediatr Clin N Am 65 (2018) 579–595

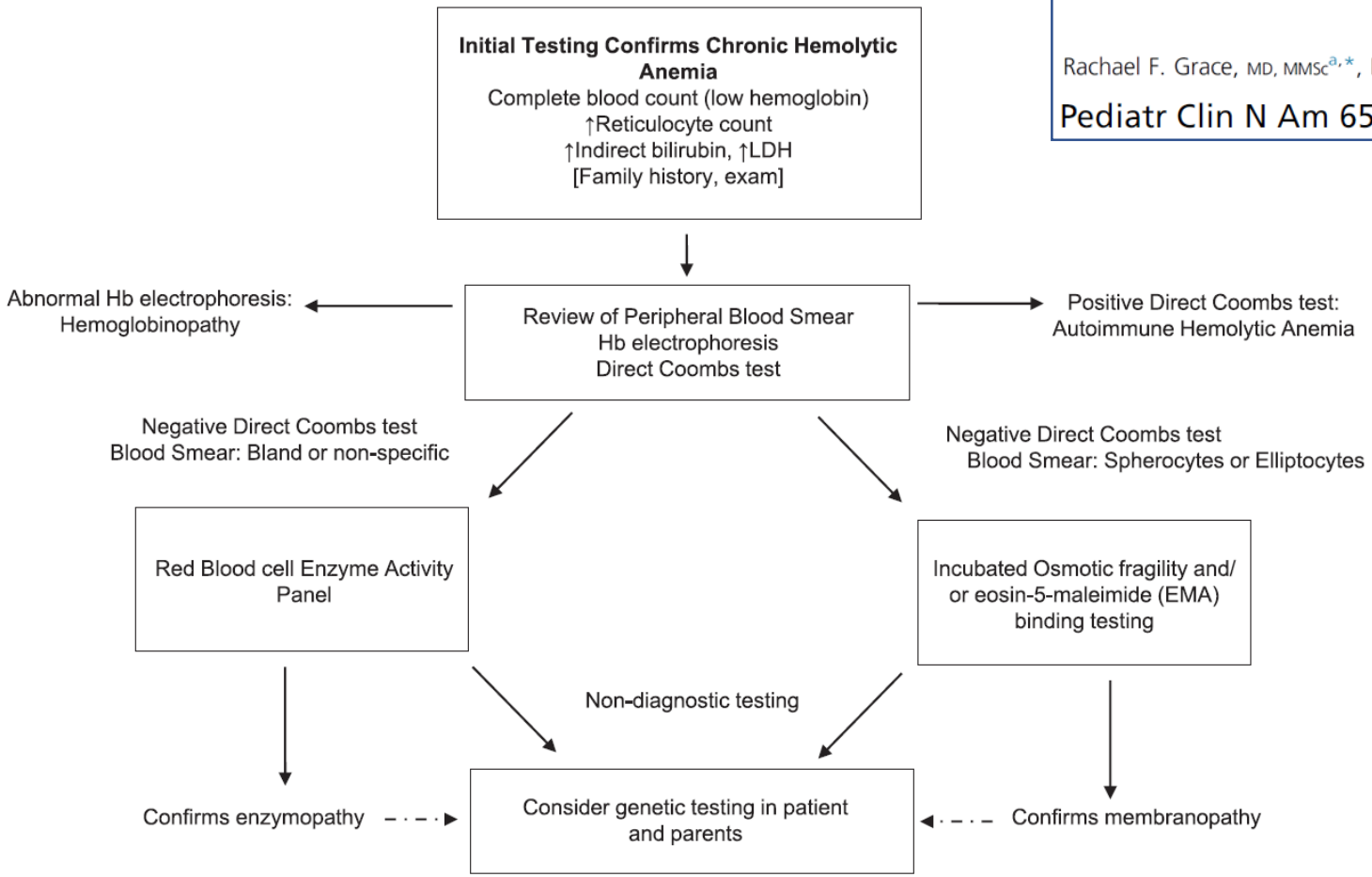


Fig. 2. Evaluation of chronic hemolytic anemia.

2. Diagnòstic

ANAMNESIS
HIST FAMILIAR

ESTUDIO INICIAL

HEMOLISIS (con/sin anemia)

Morfología periférica → **Puede ser Sugestiva o Inespecífica**

Microcitosis → Estudio mediante HPLC, electroforesis,… → **Talasemias, hemoglobinopatías estructurales**

Macrocitosis o Normocitosis → Test de COOMBS

- CD positivo → **AHAI, antecedente transfusional**
- CD negativo
  - Hemolisis aguda → **HPN, drepanocitosis, parásitos, G6PDH, sepsis, fragmentación eritrocitaria**
  - G6PDH? C HEINZ
  - Hemolisis moderada → **Esferocitosis, eliptocitosis, enzimopatías, hepatopatías**

OTROS

EMA

- Déficit B12
- SMD

ACTUALITAT

2. Diagnòstic

- ✓ Període Neonatal
- ✓ Infància
- ✓ Adults

No hi ha novetats diagnòstiques*

Unes consideracions

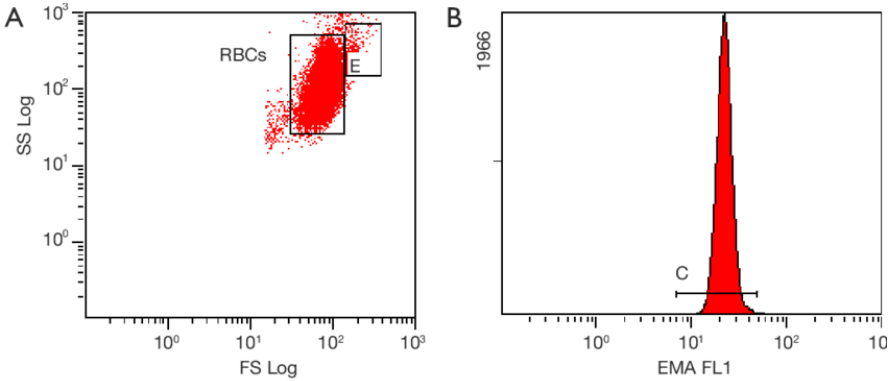
TEST UNIÓ EMA

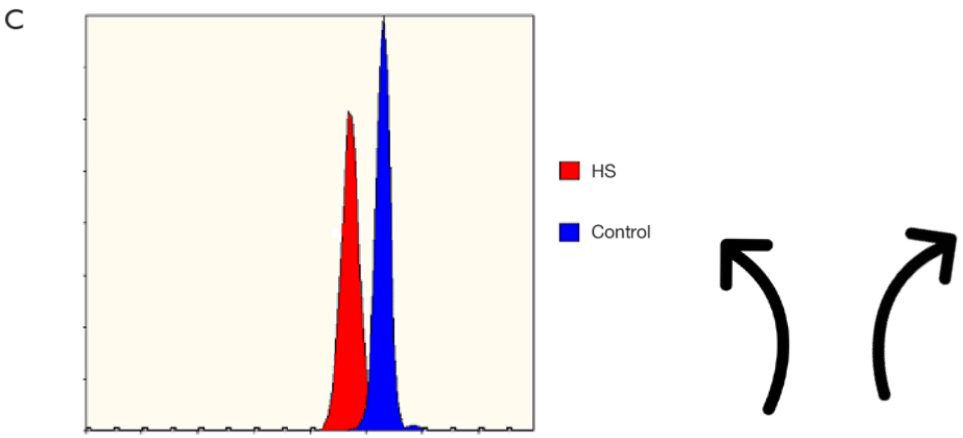
ECTACITOMETRIA

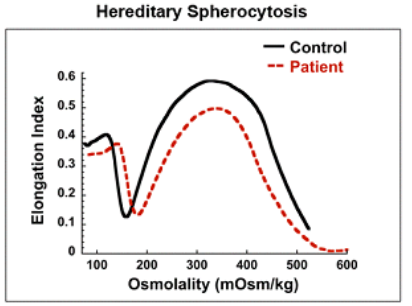
NGS

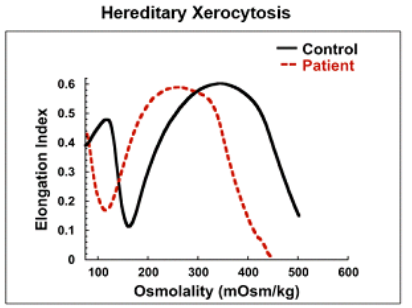
2. Diagnòstic

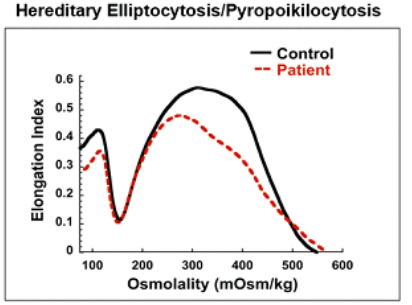
Test EMA / Ectacitometria

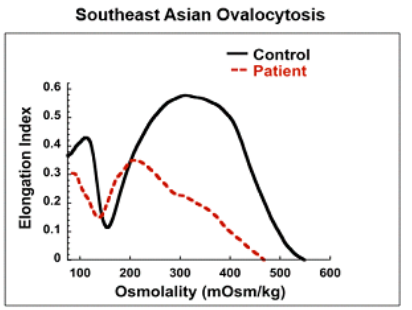












CONTROLS

CONTROLS: SEXE I EDAT, I VCM

2. Diagnòstic

Test EMA

Ann Hematol (2015) 94:1277–1283
DOI 10.1007/s00277-015-2377-0

ORIGINAL ARTICLE

Mean corpuscular volume of control red blood cells determines the interpretation of eosin-5′-maleimide (EMA) test result in infants aged less than 6 months

Olga Ciepiela[1] · Anna Adamowicz-Salach[2] · Weronika Bystrzycka[3] · Jan Łukasik[3] · Iwona Kotuła[1]

EMA binding test is used as a screening test to diagnose HS [3, 7–16]. The result of the test is calculated as a decrease in the fluorescence of EMA-bound red blood cells of patients compared to EMA fluorescence of six healthy reference samples.

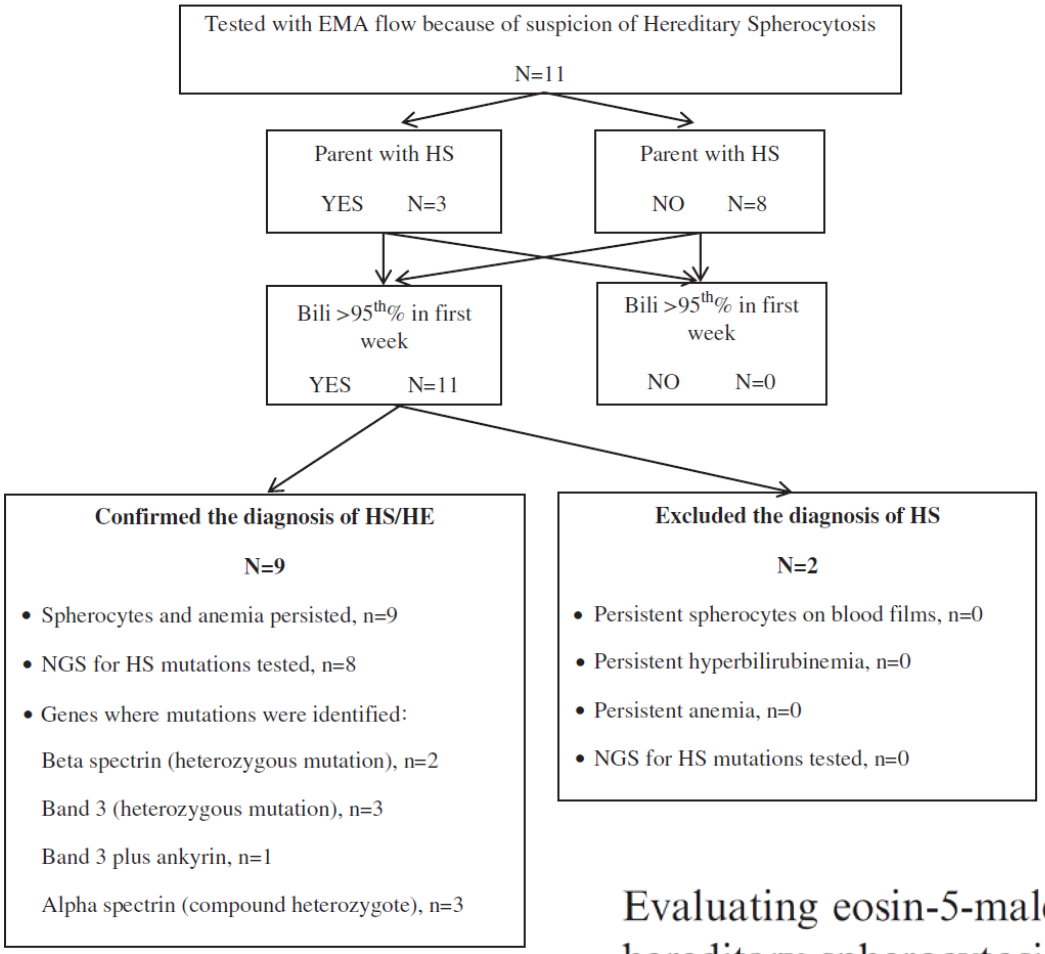
The problem of low sensitivity of EMA test in newborns may be associated with the choice of reference samples as a control for the test. The reference values for mean corpuscular volume of red blood cells for children aged 0–1 months are 88–125 fL, while reference values for adults are significantly lower (77–94 fL) [24].

1) Controls adequats (VCM)
2) Estandardització
3) <6m, resultat negatiu no exclou

2. Diagnòstic

Test EMA

31 neonates; 20 healthy term newborns and 11 who were suspected

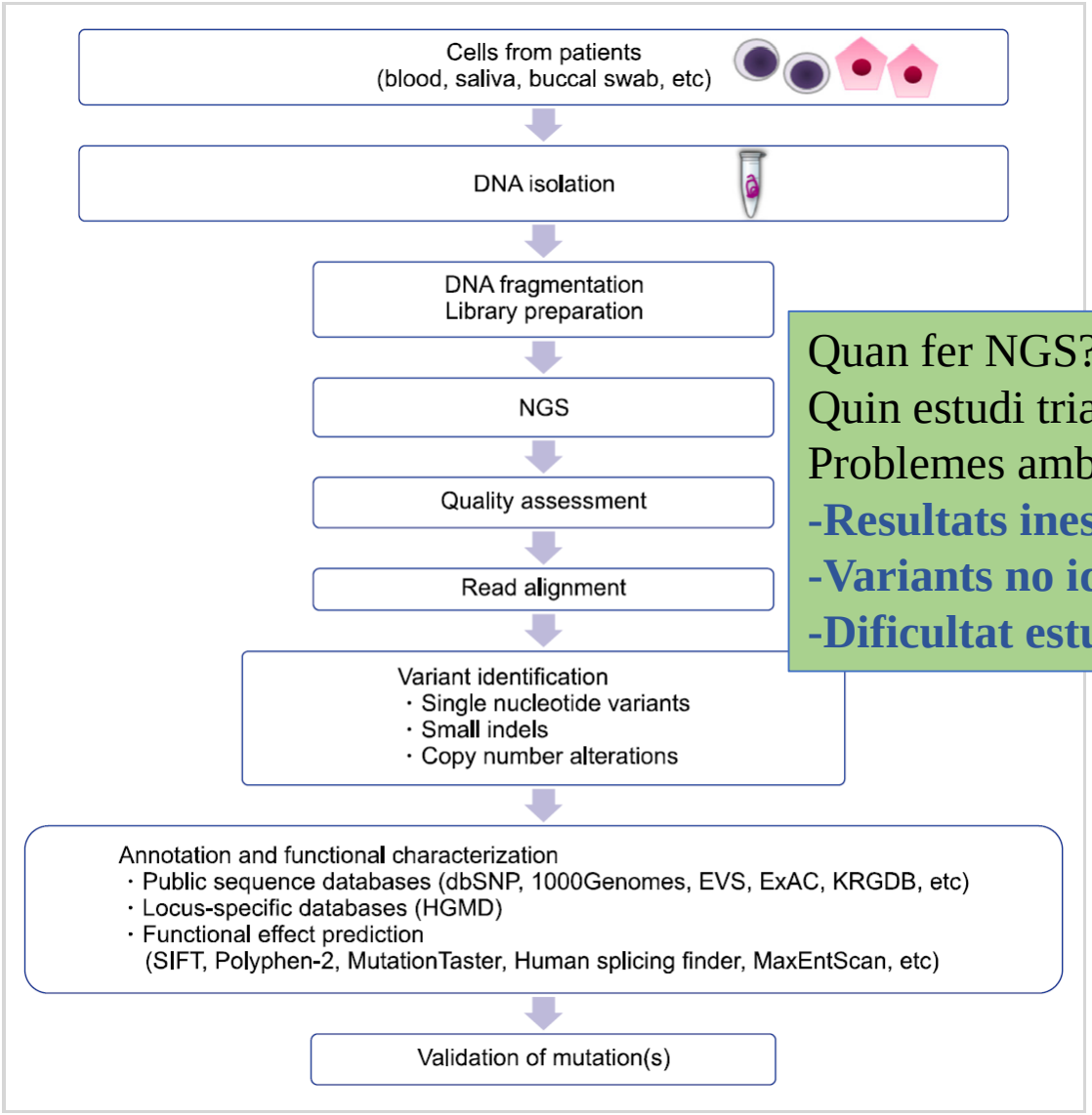


Evaluating eosin-5-maleimide binding as a diagnostic test for hereditary spherocytosis in newborn infants

RD Christensen[1,2,3], AM Agarwal[4,5], RH Nussenzveig[4], N Heikal[4,5], MA Liew[4] and HM Yaish[3]

Journal of Perinatology (2015) 35, 357–361

2. Diagnòstic



Quan fer NGS? Quan SANGER?
Quin estudi triar dins NGS?
Problemes amb les noves metodologies:
-Resultats inesperats
-Variants no identificades
-Dificultat estudis funcionals

2. Diagnòstic

NGS

Malalties amb heterogeneïtat genètica

Malalties per gens grans

- PIEZO1,...

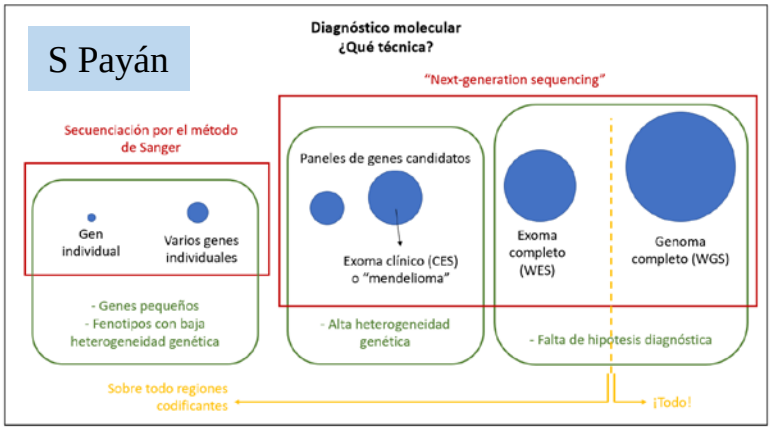
Quan fer NGS

Fenotips sobreposats

- CDA, Esferocitosi hereditària

2. Diagnòstic

NGS



Whole Genome

Whole Exome

22000 gens

Reg codificant

1%genoma

85%mutacions malaltia

No hipòtesi diagnòstica

Panell Gens

Grup de malalties

Alta heterogeneïtat

Nombre limitat de gens

Gens únics o pocs

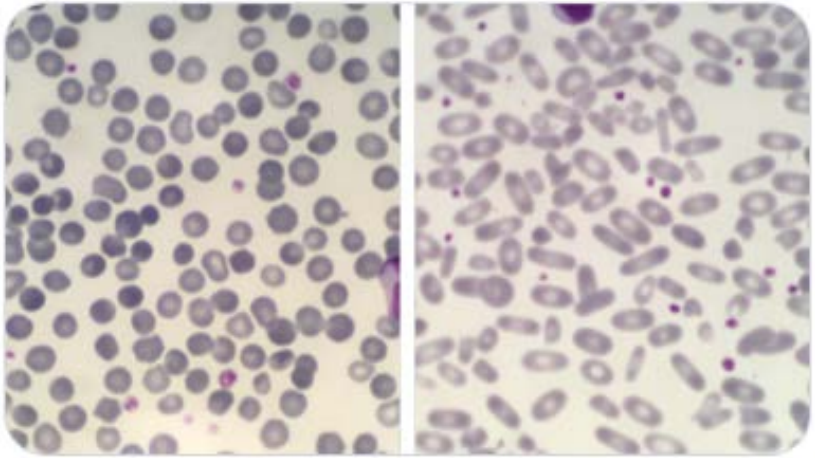
Malalties específiques

Poca heterogeneïtat

Gens petits

Quin estudi triar dins NGS?

In this time of exciting molecular advances, we must not forget to see the peripheral morphology and interpret correctly the CBCs:
Two RBC disorders afecting erythrocyte membrane
*Second image, courtesy of Dra Montserrat (Hematimetry Unit)
@Hemato_Vhebron @vallhebron



3. Registres

Locals

CATSALUT / MMMM, XUECs

Nacionals

Pediàtrics/adults

Ministeri / CSURs

Internacionals

Pediàtrics/adults

EU / ERNs

Grupo Español de ERITROPATOLOGÍA

SEHH Sociedad Española de Hematología y Hemoterapia

SEHOP
SOCIEDAD ESPAÑOLA DE HEMATOLOGÍA Y ONCOLOGÍA PEDIÁTRICAS

European Commission

European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

3. Registres

Enfermedad de células falciformes	Talasemias mayor e intermedia y Hb H	Otras hemoglobinopatías con relevancia clínica: Hb C, D, O homocigota, y otras	
Anemia diseritropoyética	**Anemia sideroblástica**	**Xerocitosis**	**Déficit de PK, G6PDH**

Hematología pediátrica y de adultos	**Elena Cela / Eduardo Bardón**	**Coordinadores del REHem**

Sociedad Española de Hematología y Hemoterapia

Grupo Español de ERITROPATOLOGÍA

SEHOP SOCIEDAD ESPAÑOLA DE HEMATOLOGÍA Y ONCOLOGÍA PEDIÁTRICAS

3. Registres

Disease Specific Arms

RADeep is being implemented in different phases through disease specific arms. For each disease specific arm, a scientific committee will be established including experts on the prevention, diagnosis and clinical care of the disease, researchers, and national coordinators for data gathering.

RADeep Phases of implementation (foreseen):

1. PKDeep - 1st phase of implementation on pyruvate kinase deficiency
2. Sickle Cell Disease
3. Thalassaemia
4. Congenital dyserythropoietic anaemias (CDA)
5. Hereditary erythropoietic failure or aplasia: Diamond Blackfan anaemia (DBA) and Fanconi Anaemia (FA)
6. Membrane disorders and other enzymopathies
7. Hereditary sideroblastic anaemias
8. Hereditary non-sideroblastic anaemias due to iron defects

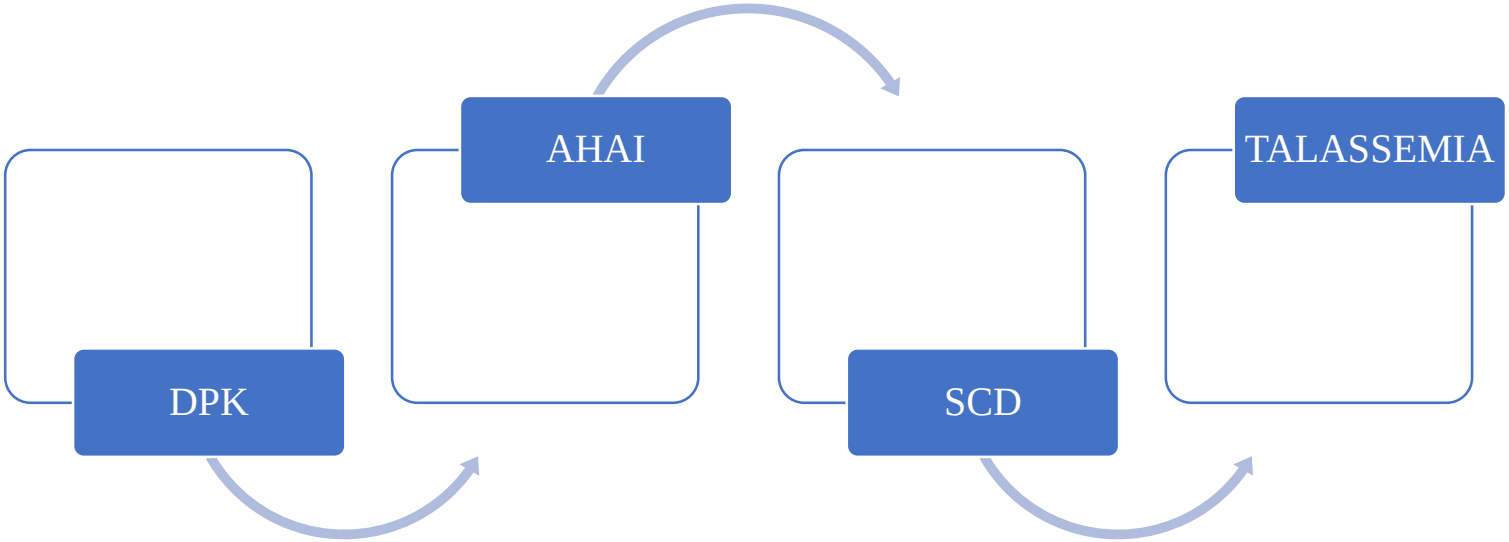
European Reference Network
for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

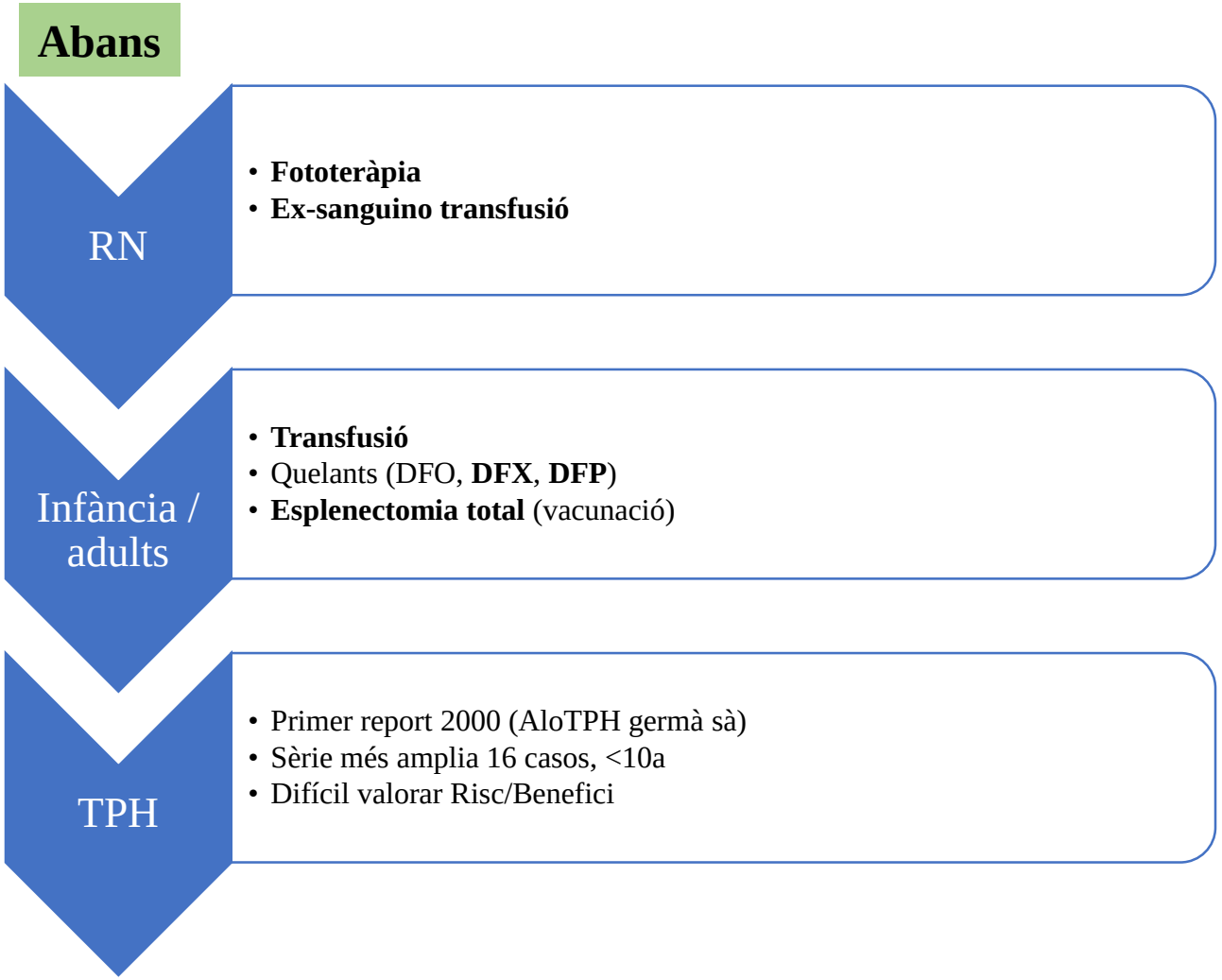
4. Novetats en tractament

FANCONI → DPK → SCD → TALASSÈMIA TD → ABD → CDA II

- TERÀPIA GÈNETICA
- EDICIÓ GÈNICA
- APC
- Eritropoiesi ineficaç



4. Novetats en tractament



4. Novetats en tractament

Actualment, 2019

Transfusió

- Depèn de pacient i clínica, no tant de la Hb (**personalitzada**)
- Quelants orals (**deferasirox, deferiprona**)

Esplenectomia

- Si transfusió regular o anèmia severa, esperar a partir dels 5a, vacunació, risc TVE 10%

TPH

- Sèries curtes, no criteris clars, esplenectomia vs TPH

Noves Teràpies

- **AG348** (act enzimàtic), assatjos clínics actuals (Fase III)
- **Teràpia genètica**, assaig clínic Fase I aprovat sept 2019

4. Novetats en tractament

FASE I

Gene Therapy for Pyruvate Kinase Deficiency (PKD): A Phase I Clinical Trial to Evaluate the Safety of the Infusion of Autologous CD34+ Cells Transduced With a Lentiviral Vector Carrying the Codon Optimized Red Cell Pyruvate Kinase (coRPK) Gene in Adult and Pediatric Subjects With PKD

Initial safety evaluation will occur in an adult cohort (n=2) patients, followed by pediatric patients ages 12-17 (n=2), and pediatric patients ages 8-11 (n=2
Abierto septiembre
RP-L301
RECLUTANDO
NCT04105166

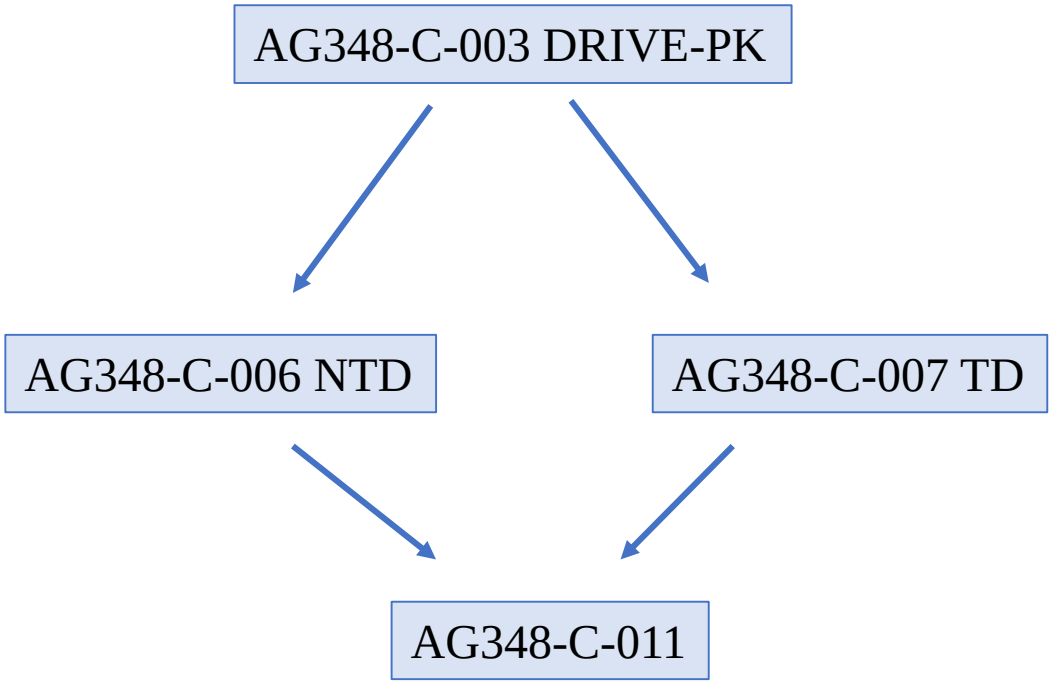
RP-L301 (gene therapy product), autologous genetically modified CD34+ HSC

Severe transfusion-dependent anemia:
At least 6 RBC, 12-month period, or at least 3 RBC/year 2 prior years
(in the absence of precipitating events)
& Hb levels <9.5 g/dL in the previous 12 months despite prior splenectomy

4. Novetats en tractament

AG348 o MITAPIVAT

AG-348 fue evaluado en dos ensayos farmacológicos completados en sujetos sanos (AG348-C-001 [single ascending dose study (SAD)] y AG348-C-002 [multiple ascending dose study (MAD)]).
Un Fase 2, multicéntrico, randomizado, open-label, eficacia y seguridad de AG-348 en adultos con DPK (AG348-C-003, DRIVE-PK)



4. Novetats en tractament

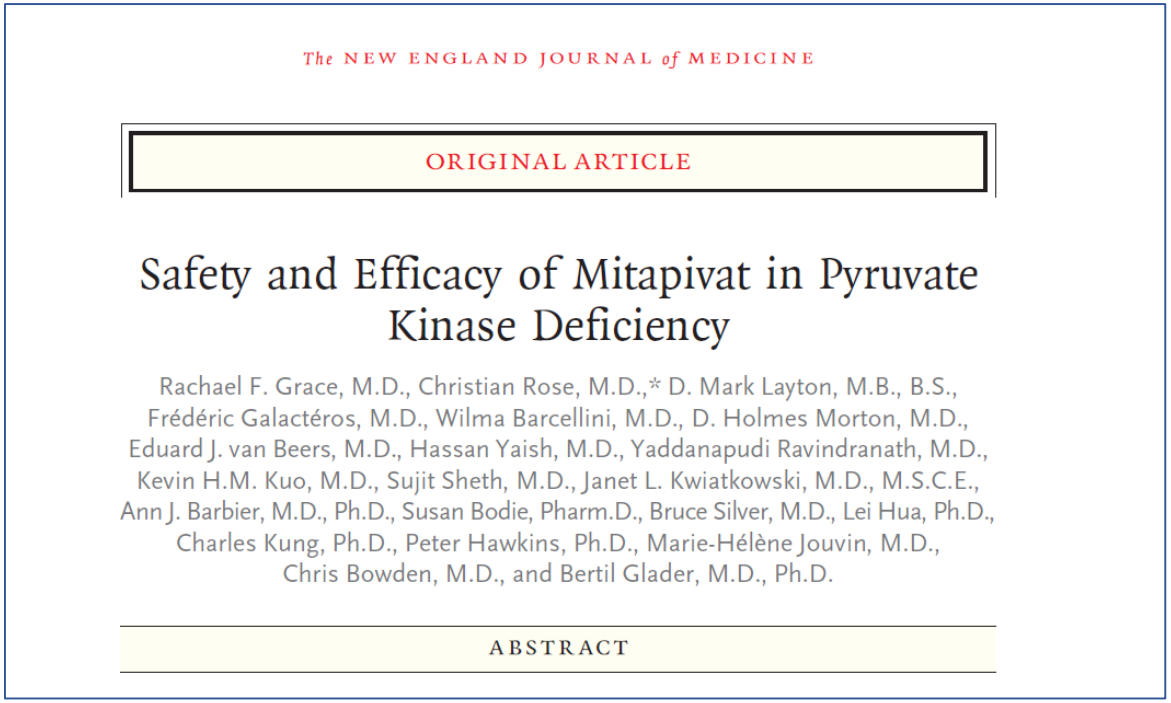
FASE II

Study AG348-C-003

Multicenter study designed to evaluate the safety and efficacy of different dose levels of AG-348 in patients with PK deficiency.

A Phase 2, Open Label, Randomized, Dose Ranging, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of AG-348 in Adult Patients With Pyruvate Kinase Deficiency

NCT02476916



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Mitapivat in Pyruvate Kinase Deficiency

Rachael F. Grace, M.D., Christian Rose, M.D.,* D. Mark Layton, M.B., B.S., Frédéric Galactéros, M.D., Wilma Barcellini, M.D., D. Holmes Morton, M.D., Eduard J. van Beers, M.D., Hassan Yaish, M.D., Yaddanapudi Ravindranath, M.D., Kevin H.M. Kuo, M.D., Sujit Sheth, M.D., Janet L. Kwiatkowski, M.D., M.S.C.E., Ann J. Barbier, M.D., Ph.D., Susan Bodie, Pharm.D., Bruce Silver, M.D., Lei Hua, Ph.D., Charles Kung, Ph.D., Peter Hawkins, Ph.D., Marie-Hélène Jouvin, M.D., Chris Bowden, M.D., and Bertil Glader, M.D., Ph.D.

ABSTRACT

N ENGL J MED 381;10 NEJM.ORG SEPTEMBER 5, 2019

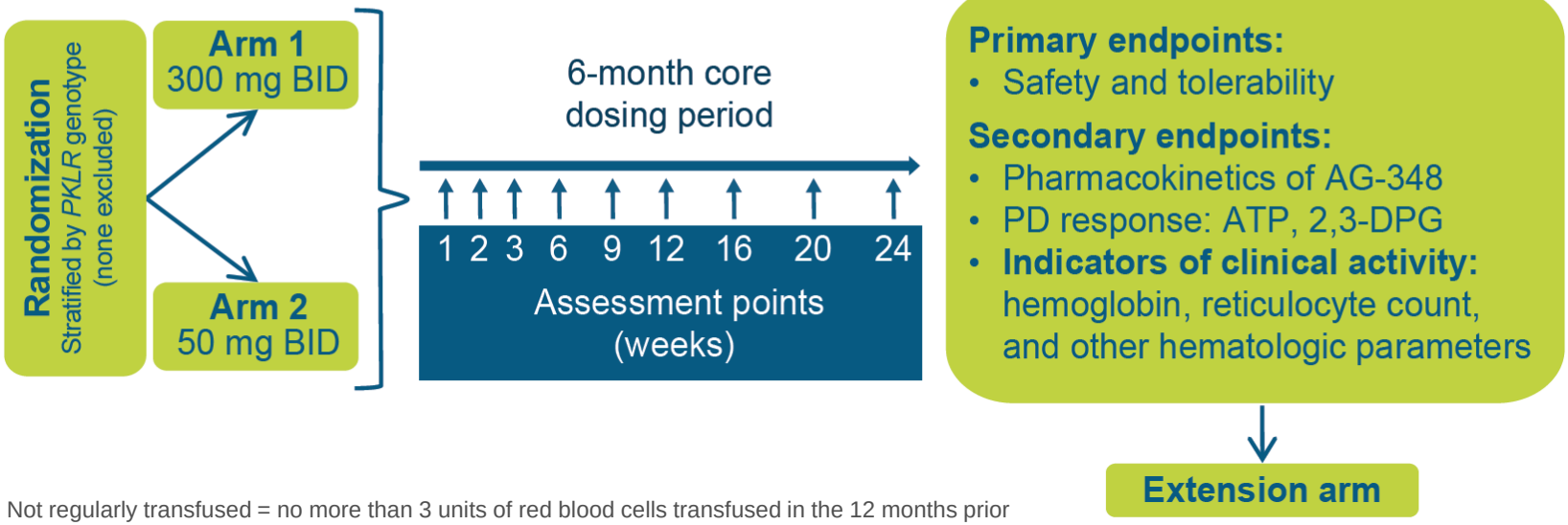
4. Novetats en tractament

Study design

DRIVEPK

Open-label, global, phase 2 study: 14 centers in the US, Canada, and EU

PK-deficient adults who are not regularly transfused
(ClinicalTrials.gov NCT02476916)



Not regularly transfused = no more than 3 units of red blood cells transfused in the 12 months prior to the first day of study dosing and no transfusions within 4 months of the first day of study dosing
All patients provided written informed consent
2,3-DPG = 2,3-diphosphoglycerate; BID = twice daily; PD = pharmacodynamic

4. Novetats en tractament

- Ages ≥18 years
- Confirmation of diagnosis of PK deficiency by:
  - Low red cell PK activity
  - Two *PKLR* mutations
- Hb ≤ 12.0 g/dL (male) or ≤ 11.0 g/dL (female)
- Patients not receiving regular transfusions:
  - No more than 3 units of RBCs in the preceding 12 months
  - No transfusions in the preceding 4 months

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Mitapivat, 50 mg Twice Daily (N = 27)	Mitapivat, 300 mg Twice Daily (N = 25)	All Patients (N = 52)
Sex — no. (%)			
Female	9 (33)	11 (44)	20 (38)
Male	18 (67)	14 (56)	32 (62)
Median age (range) — yr	28 (18–58)	40 (20–61)	34 (18–61)
Race — no. (%)†			
White	22 (81)	21 (84)	43 (83)
Asian	2 (7)	1 (4)	3 (6)
Not reported	2 (7)	1 (4)	3 (6)
Other	1 (4)	2 (8)	3 (6)
PKLR mutation type — no. (%)			
Missense/missense	15 (56)	17 (68)	32 (62)
Missense/non-missense	6 (22)	4 (16)	10 (19)
Non-missense/non-missense	6 (22)	4 (16)	10 (19)
Median hemoglobin (range) — g/dl	9.6 (6.9–12.3)	8.6 (6.5–12.0)	8.9 (6.5–12.3)
Splenectomy — no. (%)‡	23 (85)	20 (80)	43 (83)
Cholecystectomy — no. (%)	19 (70)	19 (76)	38 (73)
Chelation therapy before enrollment — no. (%)	14 (52)	11 (44)	25 (48)
Median ferritin (range) — ng/ml	723 (41–3254)	775 (346–2518)	764 (41–3254)
Osteoporosis — no. (%)	5 (19)	3 (12)	8 (15)
Completion of 24-wk core period — no. (%)§	21 (78)	22 (88)	43 (83)

Safety & AEs

- Majority of AEs were:
  - Grade 1 or 2
  - Non-serious events
  - Transient
  - Self-limiting

Table 2. Adverse Events.*

Adverse Event	Core Period			Core Period plus Extension Phase
	Mitapivat, 50 mg Twice Daily (N=27)	Mitapivat, 300 mg Twice Daily (N=25)	All Patients (N=52)	All Patients (N=52)
Summary of adverse events — no. of patients (%)				
At least one adverse event	26 (96)	25 (100)	51 (98)	52 (100)
At least one adverse event of grade ≥3	4 (15)	7 (28)	11 (21)	19 (37)
Grade 3	3 (11)	6 (24)	9 (17)	16 (31)†
Grade 4	1 (4)	1 (4)	2 (4)	3 (6)‡
At least one serious adverse event	5 (19)	3 (12)	8 (15)	15 (29)
At least one adverse event leading to treatment discontinuation	2 (7)	2 (8)	4 (8)	6 (12)§
Most common adverse events — no. of patients (%)				
Headache	9 (33)	14 (56)	23 (44)¶	24 (46)
Insomnia	5 (19)	16 (64)	21 (40)‖	22 (42)
Nausea	10 (37)	10 (40)	20 (38)	21 (40)
Nasopharyngitis	7 (26)	2 (8)	9 (17)	16 (31)
Hot flush	2 (7)	7 (28)	9 (17)**	9 (17)
Arthralgia	5 (19)	3 (12)	8 (15)	9 (17)
Fatigue	4 (15)	4 (16)	8 (15)	9 (17)
Vomiting	2 (7)	5 (20)	7 (13)	9 (17)
Diarrhea	3 (11)	3 (12)	6 (12)	9 (17)
Influenza	6 (22)	1 (4)	7 (13)	9 (17)
Cough	4 (15)	4 (16)	8 (15)	8 (15)
Dizziness	5 (19)	2 (8)	7 (13)	8 (15)
Oropharyngeal pain	3 (11)	4 (16)	7 (13)	8 (15)
Pyrexia	1 (4)	5 (20)	6 (12)	8 (15)

4. Novetats en tractament

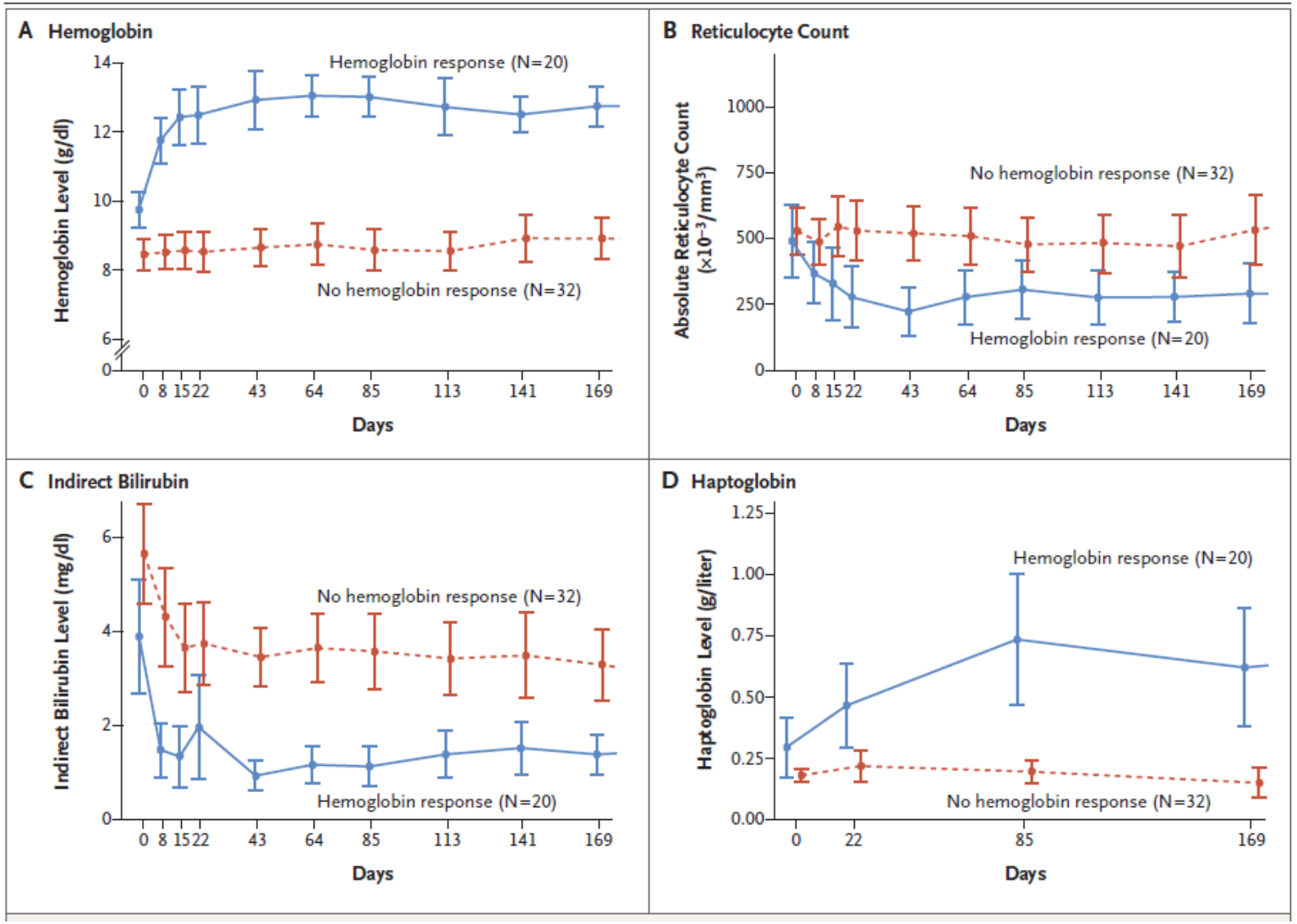
- **50% (26/52) of patients had an increase from baseline of more than 1.0 g/dL in Hemoglobin (Hb) level**
  - Mean maximum increase in the Hb was 3.4 g/dL (range 1.1 – 5.8 g/dL)
  - Median time until first observed increase of >1.0 g/dL in Hb was 10 days (range 7 to 187 days)
  - 77% (20/26) had an increase from baseline of >1.0 g/dL at more than 50% of the assessments in the core period
  - Hb response maintained in the 19 patients who were continuing treatment in the extension phase, all of whom had at least 21.6 months of treatment

4. Novetats en tractament

- All patients <u>who had an increase had at least one missense mutation</u>
  - None of the 10 patients with two non-missense mutations and none of the 5 patients homozygous for R479H had a Hb response
    - After removal of the 10 patients with two non-missense mutations, a Hb response occurred in 20/42 (48%). Further removal of the 5 homozygous R479H patients, a Hb response occurred in 20/37 (54%)

- No definitive relationship apparent between the randomly assigned dose and the likelihood of Hb response
  - Actual dose received by 80% of the patients with Hb response was ≤50mg BID
  - 15% of patients with Hb response received actual dose of 300mg BID
  - Supports that responses can be achieved with a low dose

4. Novetats en tractament



MITAPIVAT en SCD i Talassèmia!!!!
VIIIè Curs Eritropatologia SCHH-Nov 2020 ???

Mitapivat es va associar a un ràpid i clínicament significatiu increment de la Hb al 50% aprox de pacients tractats

L'estudi estableix la prova de concepte d'una teràpia molecular dirigida al defecte enzimàtic subjacent d'una enzimopatia hereditària.

Sembla que el perfil de seguretat permet l'administració a llarg termini del medicament

4. Novetats en tractament

Expert Review of Clinical Immunology

Current and emerging treatment options for autoimmune hemolytic anemia

Wilma Barcellini, Bruno Fattizzo & Anna Zaninoni

To cite this article: Wilma Barcellini, Bruno Fattizzo & Anna Zaninoni (2018) Current and emerging treatment options for autoimmune hemolytic anemia, Expert Review of Clinical Immunology, 14:10, 857-872, DOI: 10.1080/1744666X.2018.1521722

ABSTRACT

Introduction: Autoimmune hemolytic anemia (AIHA) is a heterogeneous disease mainly due to auto-antibody-mediated destruction of erythrocytes but also involves complement activation, dysregulation of cellular and innate immunity, and defective bone marrow compensatory response. Several drugs targeting these mechanisms are under development in addition to standard therapies.

Areas covered: The following targeted therapies are illustrated: drugs acting on CD20 (rituximab, alone or in association with bendamustine and fludarabine) and CD52 (alemtuzumab), B cell receptor and proteasome inhibitors (ibrutinib, bortezomib), complement inhibitors (eculizumab, BIVV009, APL-2), and other drugs targeting T lymphocytes (subcutaneous IL-2, belimumab, and mTOR inhibitors), IgG driven extravascular hemolysis (fostamatinib), and bone marrow activity (luspatercept).

Expert opinion: Although AIHA is considered benign and often easy to treat, chronic/refractory cases represent a challenge even for experts in the field. Bone marrow biopsy is fundamental to assess one of the main mechanisms contributing to AIHA severity, i.e. inadequate compensation, along with lymphoid infiltrate, the presence of fibrosis or dyserythropoiesis. The latter may give hints for targeted therapies (either B or T cell directed) and for new immunomodulatory drugs. Future studies on the genomic landscape in AIHA will further help in designing the best choice, sequence and/or combination of targeted therapies.

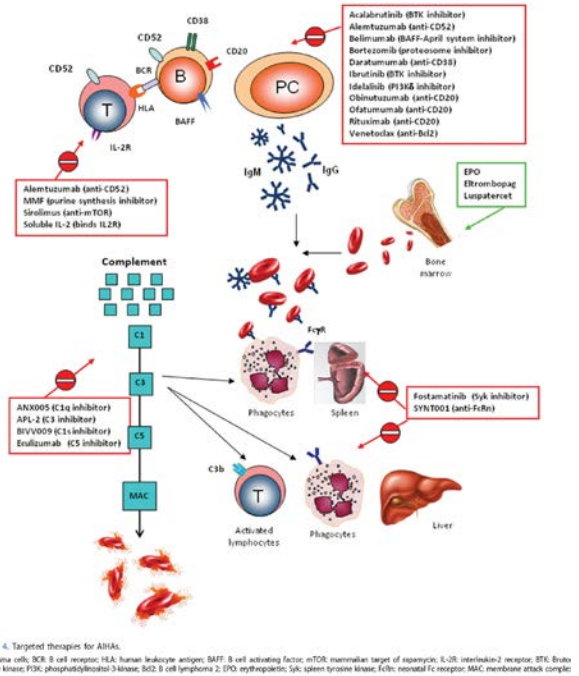


Figure 4. Targeted therapies for AIHAs.

PC: plasma cells; BCR: B cell receptor; HLA: human leukocyte antigen; BAFF: B cell activating factor; mTOR: mammalian target of rapamycin; IL-2R: interleukin-2 receptor; BTK: Bruton tyrosine kinase; PI3K: phosphatidylinositol-3-kinase; Bcl2: B cell lymphoma 2; EPO: erythropoietin; Syk: spleen tyrosine kinase; FcRn: neonatal Fc receptor; MAC: membrane attack complex

4. Novetats en tracta

Expert Review of C

Current and emerging tre
autoimmune hemolytic a

Wilma Barcellini, Bruno Fattizzo & Ann

To cite this article: Wilma Barcellini, Bruno Fattiz
treatment options for autoimmune hemolytic anem
857-872, DOI: 10.1080/1744666X.2018.1521722

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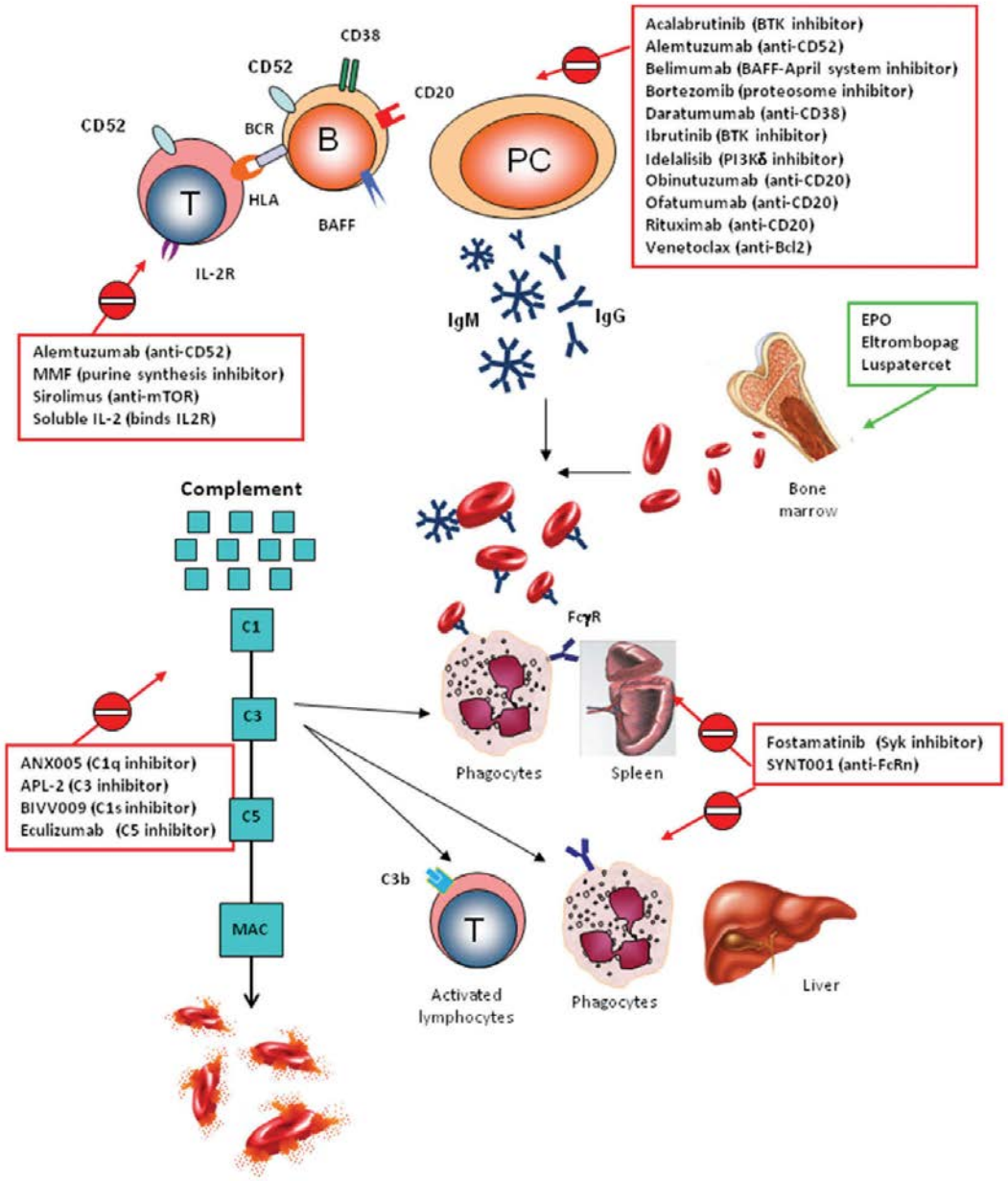

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4. Novetats en tractament

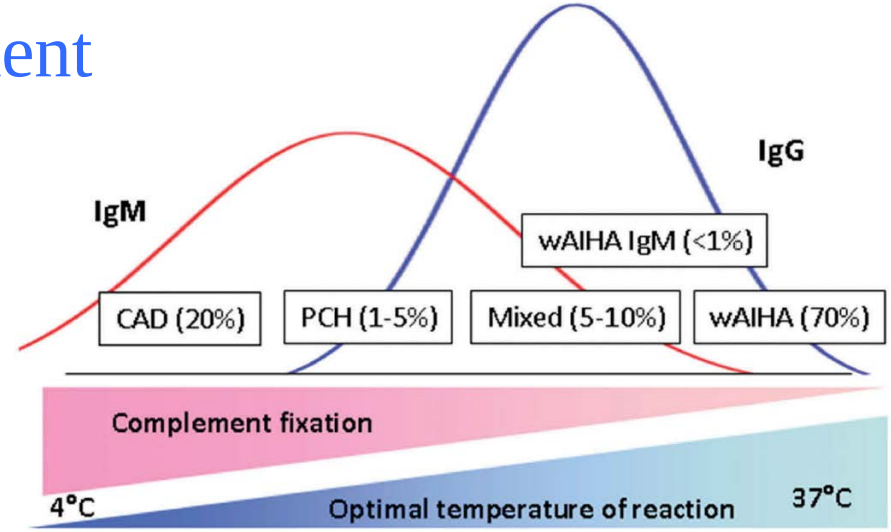


Table 1. Current non-targeted therapies for warm AIHA (wAIHA) and cold agglutinin disease (CAD).

	Response rates (%)			
Treatment	wAIHA	CAD	Pros	Cons
Steroids	75–80	15–30	Response in 15–30 days Orally available Long-term efficacy in most wAIHA	Curative effect only in 20–30% Long-term tapering Short-term side effects (mood swings, agitation) Long-term side effects (diabetes, hypertension, osteoporosis, Cushingoid syndrome)
Azathioprine	60–70	–	Steroid-sparing agent, orally available	Myelosuppression, infections, secondary malignancy, hepatic dysfunction
Cyclophospamide	60–70	–	Steroid-sparing agent, orally available	Myelosuppression, infections, urotoxicity, secondary malignancy, fertility problems/teratogenic
Cyclosporin A	50	–	Orally available, possible dose adjustment	Hypertension, arrhythmia, myelosuppression, infections, nephrotoxicity, urotoxicity
Mycophenolate mofetil	80–100	–	Good safety profile	Mild myelosuppression, infections
Splenectomy	80	0–20	Potentially curative in wAIHA	Unsuitable for elderly Surgical procedural risk Thrombotic risk Life-long immune suppression Infection prophylaxis required

wAIHA: Warm AIHA; CAD: cold agglutinin disease.

4. Novetats en tractament

Table 2. New drugs in AIHA.

	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
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	–	–

4. Novetats en tractament

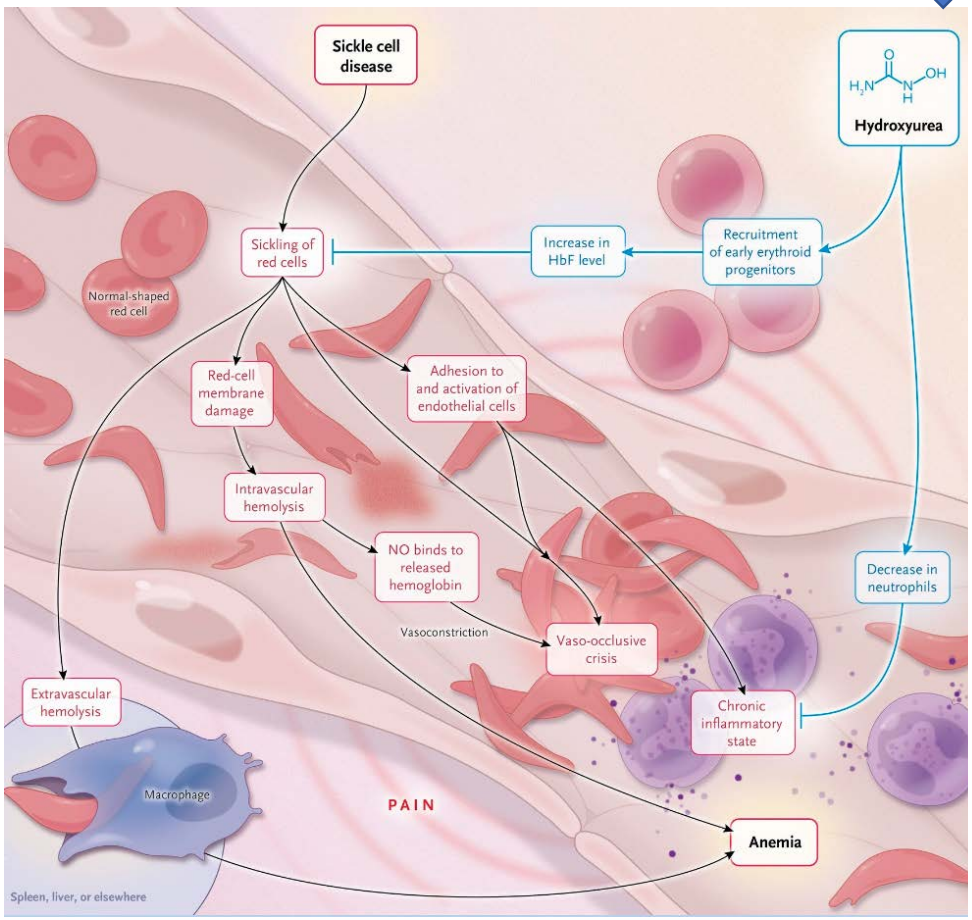
AHAI

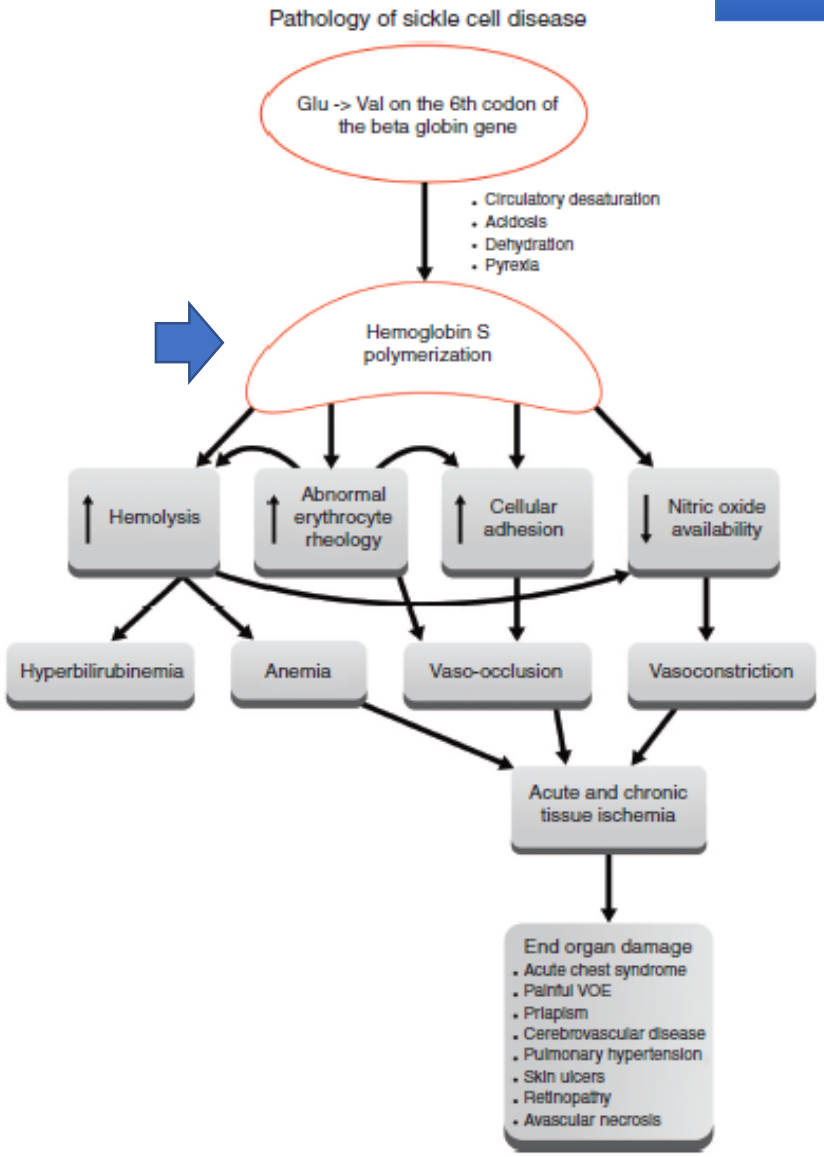
VIIIè Curs Eritropatologia SCHH-Nov 2020

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]
Complement inhibitors					
Eculizumab	C5i	IV	Case reports	CAD/Mixed AIHA	Gupta N, Ann Hematol 2014
TNT003/BIVV009	Anti-C1s MoAb	IV	Phase 1b	CAD	Jaeger U, Blood 2017 [48]
TNT003/BIVV009	Anti-C1s MoAb	IV	Phase 3	CAD	https://clinicaltrials.gov NCT03347422 https://clinicaltrials.gov NCT03347396
APL-2	C3/C3bi	SC	Phase 1/2	CAD/wAIHA	Grossi FV, Blood 2016 [49] https://clinicaltrials.gov NCT03226678
T-cell-directed therapies					
Soluble IL-2	Treg stimulation	SC	Phase 2	wAIHA	https://clinicaltrials.gov NCT02389231
Sirolimus	mTORi	Oral	Case series	Evans'/Secondary AIHA	Park JA, Transfus Med Rev 2016 [61] Jasinski S, J Ped Hematol Oncol 2017 [62]
Mycophenolate mofetil	Purine synthesis inhibitor	Oral	Case series	wAIHA/CAD/Secondary AIHA/ Evans'	Howard J, Br J Haematol 2002 [20] Kotb R, Eur J Hematol 2005 Miano M, Br J Haematol 2016 [21]
IgG-mediated phagocytosis inhibitors					
Fostamatinib	Syki	Oral	Phase 2	wAIHA	https://clinicaltrials.gov NCT02612558
SYNT001	FcRn MoAb	IV	Phase 1b	wAIHA	https://clinicaltrials.gov NCT03075878

CTX: Cyclophosphamide; BTKi: brutus tyrosine kinase inhibitor; Bcl2: B-cell lymphoma 2; δPI3Ki: phosphatidylinositol-4,5-bisphosphate 3-kinase delta-type inhibitor; mTORi: mammalian target of rapamycin inhibitor; Syki: spleen tyrosine kinase inhibitor; FcRn: neonatal crystallizable fragment receptor; wAIHA: Warm AIHA; CAD: cold agglutinin disease; Treg: regulatory T cells; Mo Ab: monoclonal antibody.

4. Novetats en tractament





Pediatric RESEARCH Volume 81 | Number 1 | January 2017

Avances en el manejo:

Diagnóstico temprano**, CN ECF**

Profilaxis con penicilina

ECO Doppler TC

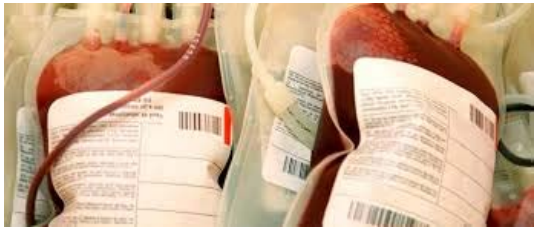
Educación Sanitaria

Avances en el tratamiento:

Hidroxiurea

TPH

Transfusión

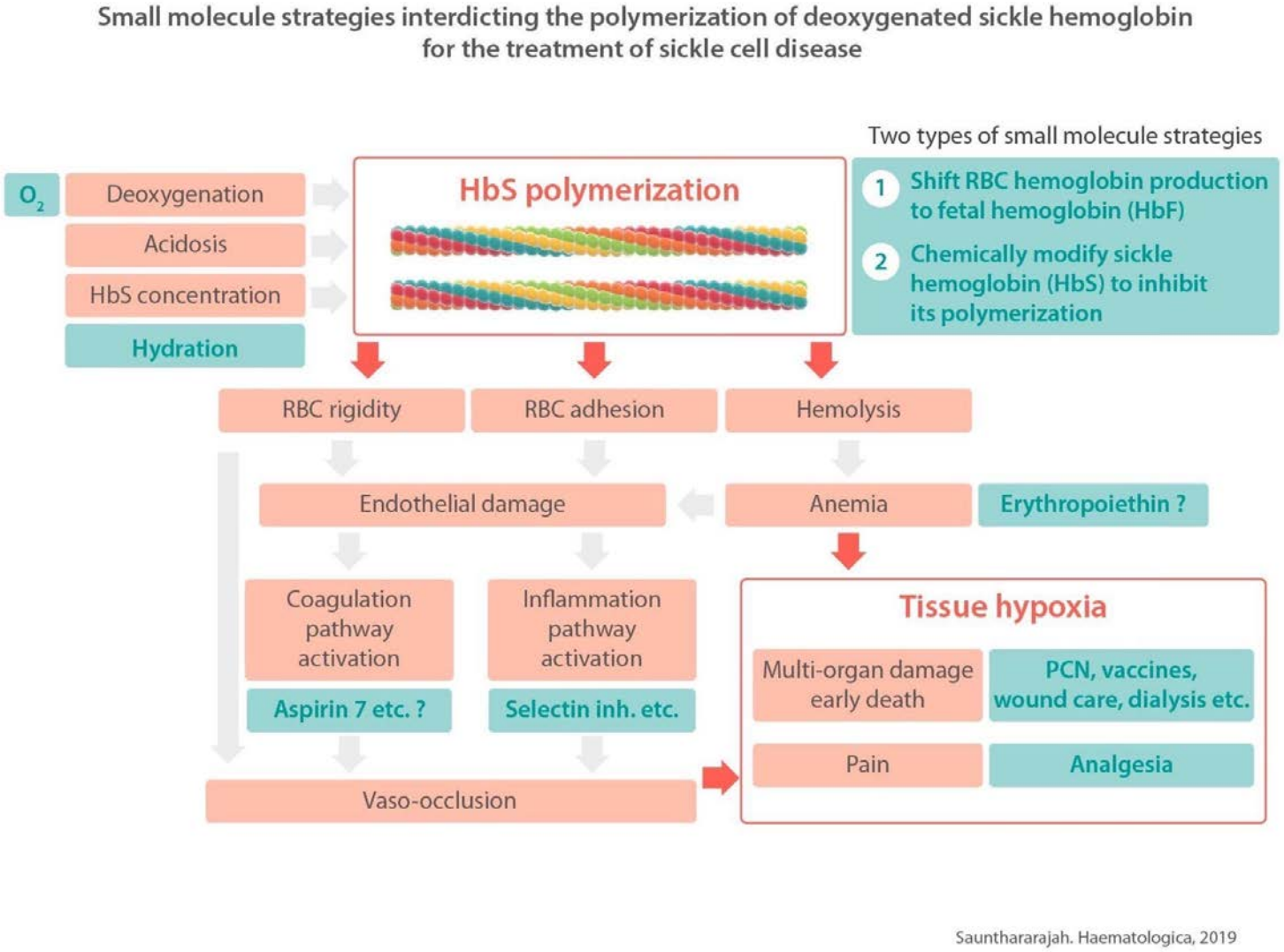


Eritrocitoaferésis

Nuevos fármacos en estudio

Terapia génica

4. Novetats en tractament



4. Novetats en tractament
- CVO en la MCF

Name	Clinical effect	Stage of development
Crizanlizumab	Humanized monoclonal antibody that binds to P-selectin with high affinity and specificity[1]	Fase II PED Fase III *Fase II adults renal
Endari™ (L-glutamine powder)	Increases availability of reduced glutathione, improving nicotinamide adenine dinucleotide (NAD) redox potential and reducing oxidative damage in sickle RBCs[5]	Approved in the USA (July 2017) to reduce the acute complications of SCD in adult and paediatric patients ≥5 years old[5]
Rivipansel	Glycomimetic E-selectin antagonist (with partial L- and P-selectin inhibition) that reduces cell adhesion and improves blood flow[6]	Phase III for the treatment of acute SCD pain crises (due for completion July 2018)[7]

1. Ataga KI *et al. N Engl J Med* 2017;376:429–439; 2. Clinical Concept Sheet CSEG101A2202; 3. Clinical Concept Sheet CSEG101B2201 4. Clinical Concept Sheet CSEG101A2301; 5. Endari™ (L-glutamine) prescribing information https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208587s000lbl.pdf; 6. Chang J *et al. Blood* 2010;116:1779–1786; 7. ClinicalTrials.gov NCT02187003

4. Novetats en tractament
- CVO en la MCF

Name	Clinical effect	Stage of development
GBT440	Prevents HbS polymerization in hypoxic conditions, prolonging RBC half-life[1]	Phase III for the treatment of acute SCD pain crises (due for completion June 2019)[2]
Sevuparin	Inhibits adhesive interactions via P-selectin[3]	Phase II for the treatment of acute SCD pain crises (due for completion December 2017)[4]
LentiGlobin	Autologous CD34+ cells transduced with BB305 lentiviral vector, encoding β-globin with a single point mutation (A^{T87Q}) designed to give anti-sickling properties[5]	Phase I/II trial in β-thalassemia major and SCD (due for completion February 2019)[6] Phase I trial for severe SCD (due for completion August 2020)[7]

1. Oksenberg D *et al. Br J Haematol* 2016;175:141–153; 2. ClinicalTrials.gov NCT03036813; 3. Telen MJ *et al. Br J Haematol* 2016;175:935–948; 4. ClinicalTrials.gov NCT02515838; 5. Kanter J *et al. Blood* 2017;130:527; 6. ClinicalTrials.gov NCT02151526; 7. ClinicalTrials.gov NCT02140554

4. Novetats en tractament

SCD

198 Pacients SCD:
45% reducció dolor respecte placebo
SUSTAIN

En tan sols 2 setmanes, la FDA ha aprovat dos fàrmacs per la MCF:
- **Crizanlizumab** (ADAKVEO), infusió ev mensual
- **Voxelotor** (OXBRYTA) (vo diària (>12a)

Una nova era pels pacients amb MCF

274 Pacients SCD:
92 placebo, 90 1500mg, 92 900mg
51.1% van augmentar Hb (1500mg)
6,5% placebo

Fase I/II Edició Gènica CRISPR/cas9 CTX001
-B-Talassèmia TD
-MCF
Vector Lentiviral BT87Q globin

La FDA ha aprovat per la B-TALASSÈMIA TD:
- **Luspatercept** (REBLOZYL)

Una nova era pels pacients amb Talassèmia

336 Pacients BT-TD, 112 placebo
21% van reduïr 33% transfusions
4-5% placebo

4. Novetats en tractament, Crizanlizumab

- Ac monoclonal frente a p-selectina
- Ensayo fase II, randomizado , doble ciego, (3 ramas: crizanlizumab dosis alta, crizanlizumab dosis baja, placebo)
- 198 pacientes, EF,16 a 65 años, con 2-10 crisis de dolor en los 12 meses previos
- Objetivo primario: tasa anual de crisis de dolor

Variable	High-Dose Crizanlizumab	Low-Dose Crizanlizumab	Placebo
Primary end point: annual rate of crises in the intention-to-treat population			
No. of patients	67	66	65
Median rate of crises per year (IQR)	1.63 (0.00–3.97)	2.01 (1.00–3.98)	2.98 (1.25–5.87)
Difference from placebo — %	−45.3	−32.6	—
P value	0.01	0.18	—
No. of patients with crisis rate of zero at end of trial	24	12	11
Annual rate of crises in the per-protocol population			
No. of patients	40	44	41
Median rate of crises per year (IQR)	1.04 (0.00–3.42)	2.00 (1.00–3.02)	2.18 (1.96–4.96)
Difference from placebo — %	−52.3	−8.3	—
P value	0.02	0.13	—
No. of patients with crisis rate of zero at end of trial	15	7	5

Ataga KI, N Engl J Med 2017

4. Novetats en tractament

Clinical Trial Protocol CSE

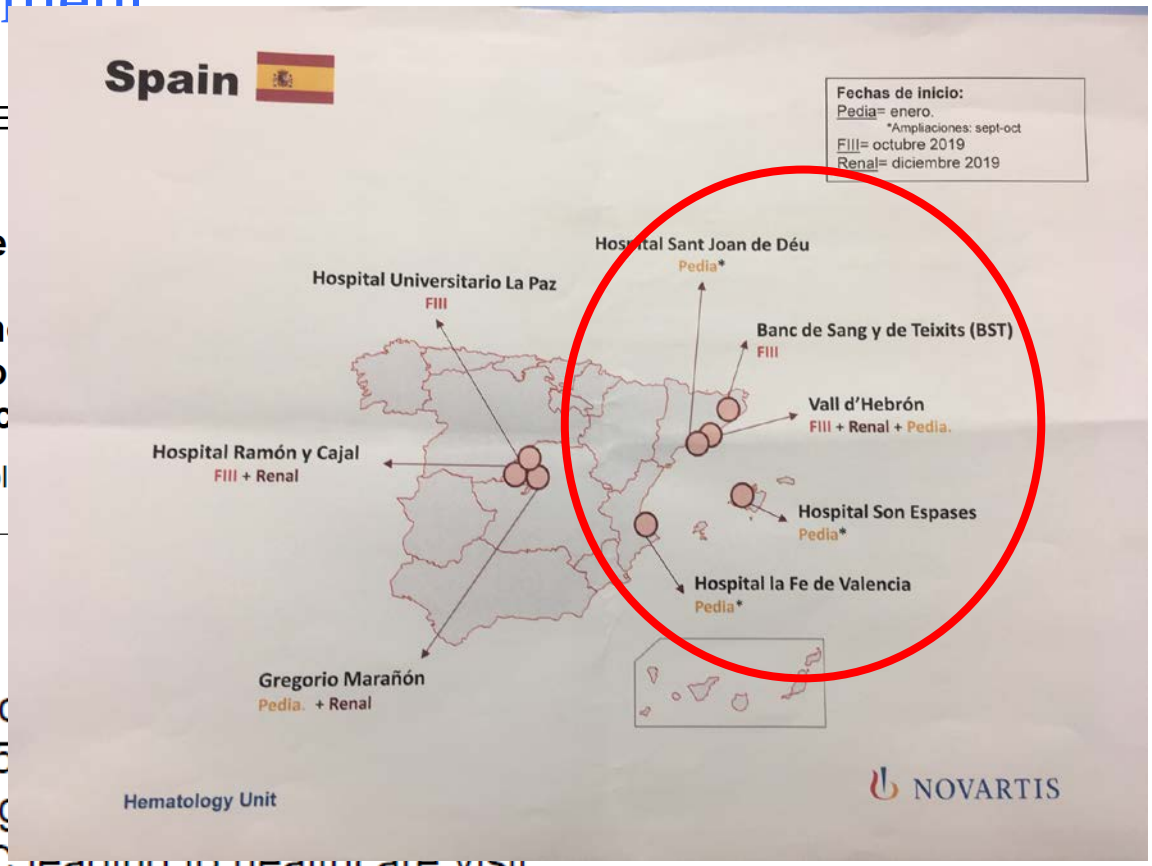
A phase III, Multicenter, Randomize
Assess Efficacy and Safety of Two
versus placebo, with or with
Hydroxycarbamide Therapy, in Ado
Cell Disease Patients with Vaso-Oc

Study of two doses of crizanlizumab versus pl
cell disease patients

Novartis

Phase III

Phase 3, randomized, placebo-c
crizanlizumab (5.0 mg/kg and 7.5
care that subjects might be taking
SCD patients with history of VOC leading to healthcare visit.



dbeneitez@vhebron.net
dbeneitez@vhio.net

Key Inclusion criteria

1. Written informed consent must be obtained prior to any screening procedures
2. Male or female patients aged 12 years and older on the day of signing informed consent. Adolescent include patients aged 12 to 17 years old and adults ≥ 18 years and older
3. Confirmed diagnosis of SCD by Hb electrophoresis or high performance liquid chromatography (HPLC) (performed locally). All SCD genotypes are eligible, genotyping is not required for study entry
4. Experienced at least 2 VOCs leading to healthcare visit within the 12 months prior to screening visit as determined by medical history. Prior VOC leading to healthcare visit must include:
    a. Pain crisis defined as an acute onset of pain for which there is no other medically determined explanation other than vaso- occlusion
    b. a visit to a medical facility and/or healthcare professional,
    c. and receipt of oral/parenteral opioids or parenteral nonsteroidal anti-inflammatory drug (NSAID) analgesia

    As well as other complicated crises, such as ACS, priapism, and hepatic or splenic sequestration
5. If receiving HU/HC or erythropoietin stimulating agent or L-glutamine, must have been receiving the drug for at least 6 months prior to Screening visit and plan to continue taking at the same dose and schedule until the subject has reached one year of study treatment

Key Exclusion criteria

1. History of stem cell transplant.
2. Participating in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) and/or planning on undergoing an exchange transfusion during the duration of the study; episodic transfusion in response to worsened anemia or VOC is permitted.

4. Novetats en tractament
Tractaments anteriors i actuals

- Acfol, Anticoagulantes, hidroxiurea, transfusiones (simple o régimen hipertransfusional), quelantes orales del hierro, *TPH
- No diagnóstico prenatal
- No diagnóstico pre-implantacional

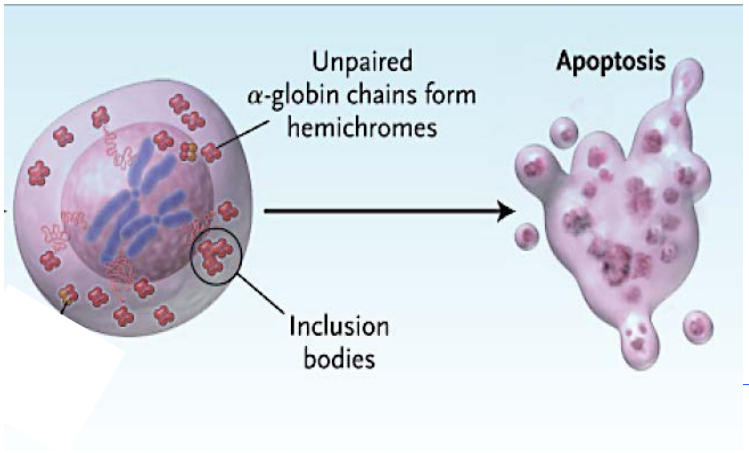
RETOS EN LA CEXT
-prevención
-manejo multidisciplinar
-consejo genético (prenatal,preimplantacional)
-Opciones terapéuticas varias (TPH s/n, hidroxiurea, nuevos ttos en EECC)

- Suplementos Acfol
- Anticoagulantes si precisa
- Hidroxiurea
- Transfusiones con fenotipo ampliado, selección donantes (simple, régimen hipertransfusional, eritrocitoaféresis), quelantes orales del hierro (deferasirox, deferiprona)
- TPH (hermano HLA idéntico, *haploidéntico)
- Terapia Genética
- L-Glutamina
- Crizanlizumab
- Rivipansel
- Voxelotor
- Diagnóstico prenatal
- Diagnóstico pre-implantacional
- TRANSICION

4. Novetats en tractament

- β-thalassemia is an inherited anemia due to defective synthesis of β-globin
  - Excess unpaired α-globin chains lead to **ineffective erythropoiesis**
- Ineffective erythropoiesis is characterized by expanded RBC proliferation and elevated GDF11 and other TGF-β superfamily ligands and Smad 2/3 signaling

Erythroid Precursors in Bone Marrow



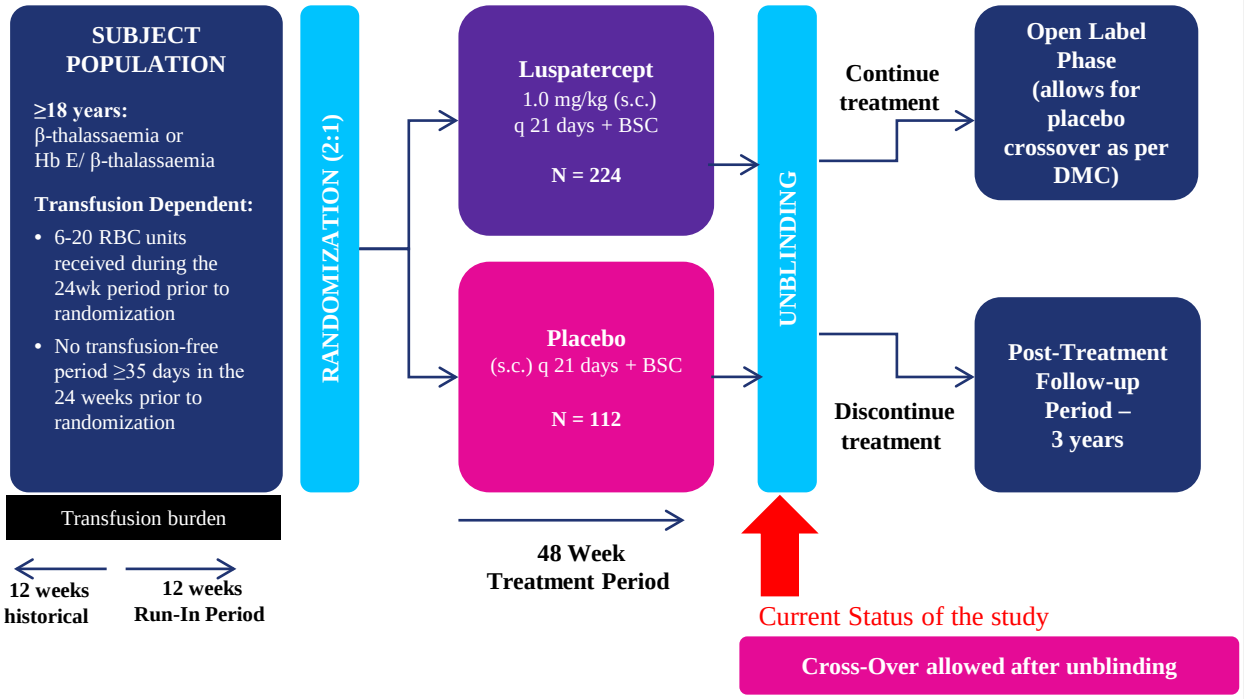
Rund D, Rachmilewitz E, NEJM 2005

From Piga et al, ASH 2015 oral presentation

4. Novetats en tractament

The BELIEVE Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept in Adult Beta-Thalassemia Patients Who Require Regular Red Blood Cell (RBC) Transfusions

Data Cutoff: May 11, 2018 Includes Last Subject Randomized + 48 weeks



EFFICACY ENDPOINTS

1º Endpoint:

Proportion of patients achieving ≥ 33% reduction in RBC transfusion burden of ≥ 2 units (13 to 24 weeks)

Key 2º Endpoints:

- ≥ 33% reduction in RBC transfusion (week 37 to 48)
- ≥ 50% reduction in RBC transfusion (week 13 to 24)
- ≥ 50% reduction in RBC transfusion (week 37 to 48)
- Mean Δ in RBC transfusion burden (week 13 to 24)

Other 2º Endpoints:

- Mean Δ liver iron concentration
- Mean Δ iron chelating therapy use
- Mean Δ ferritin

4. Novetats en tractament

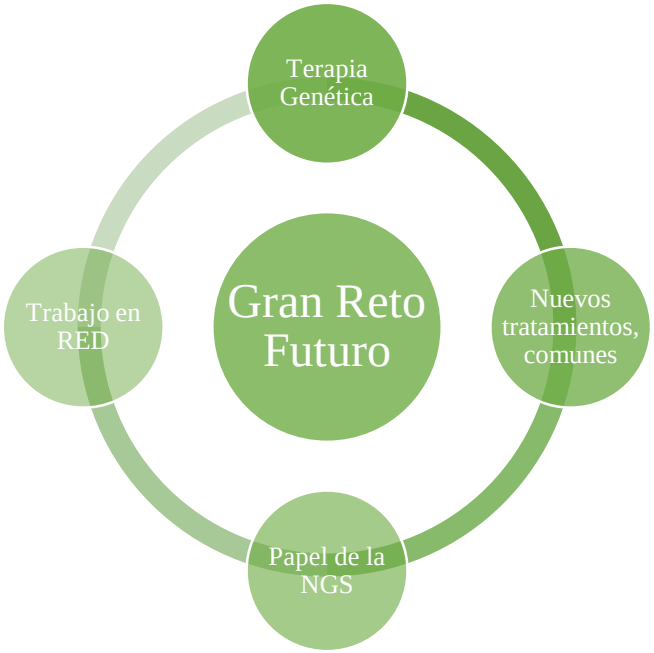
	Luspatercept (n = 224)	Placebo (n = 112)	OR	*P* Value
Primary (≥ 33% transfusion burden reduction from Weeks 13–24), n (%)	48 (21.4)	5 (4.5)	5.79	< 0.0001
Key Secondary				
≥ 33% transfusion burden reduction from weeks 37–48, n (%)	44 (19.6)	4 (3.6)	-	< 0.0001
≥ 50% transfusion burden reduction from weeks 13–24, n (%)	17 (7.6)	2 (1.8)	-	0.0303
≥ 50% transfusion burden reduction from weeks 37–48, n (%)	23 (10.3)	1 (0.9)	-	0.0017
Mean change in baseline transfusion burden (luspatercept vs placebo) from Weeks 13–24	−1.35		-	< 0.0001
Additional secondary[a]	158 (70.5)	33 (29.5)		< 0.0001
≥ 33% transfusion burden reduction over any 12 consecutive weeks on study				

- AEs were generally consistent with previously reported phase 2 data
- TEAEs leading to dose delay or dose reduction were similar between treatment arms
- No patient deaths were reported for those treated with luspatercept

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

[a] Statistically significant differences were also noted for all other transfusion burden reduction endpoints.
Abbreviations: AE, adverse event; OR, odds ratio; TEAE, treatment-emergent adverse event.

Conclusiones



- TENEMOS UN GRAN RETO POR DELANTE

- La **mejora del conocimiento** de la fisiología y fisiopatología en SR y Met Hierro, ha abierto nuevas posibilidades terapéuticas

- Diferentes **enfermedades comparten similar fisiopatología**, potencial de ampliar indicaciones en nuevos tratamientos (MITAPIVAT, LUSPATERCEPT, VOXELOTOR, …)

-Dispondremos de nuevas estrategias terapéuticas y deberemos **desarrollar algoritmos de tratamiento basados en la evidencia**

-Importante poder **trabajar en RED** (**PEDIATRÍA-ADULTOS**), papel de los REGISTROS, participar en EECC e implicar a los propios PACIENTES

LARGA VIDA AL CURSO ERITROPATOLOGIA

Vall d'Hebrón Campus

HOSPITAL UNIVERSITARI VALL D'HEBRÓN (HUVH)

SERVICIO DE HEMATOLOGÍA CLÍNICA

UNIDAD DE ERITROPATOLOGÍA Y DIAGNÓSTICO INTEGRADO

- David Beneitez (VHIO)
- Ana Ortuño
- Adoración Blanco
- Barbara Tazón (VHIO)
- LABORATORIO HEMATOLOGÍA

SERVICIO DE ONCOLOGÍA Y HEMATOLOGÍA PEDIATRICAS

- Cristina Diaz de Heredia (VHIR)
- Pablo Velasco (VHIR)
- Thais Murciano
- Mari Luz Uría
- Maribel Benítez
- Laura Murillo
- Laura Alonso

INSTITUT D'INVESTIGACIÓ VALL D'HEBRÓN (VHIR)

RECERCA TRANSLACIONAL EN CÀNCER EN LA INFÀNCIA I L'ADOLESCÈNCIA - RECERCA EN ANÈMIES MINORITÀRIES

- María del Mar Mañú Pereira
- Victoria Gutiérrez Valle
- Valeria Rizzuto

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

Vall d'Hebron Barcelona Hospital Campus

Vall d'Hebron Hospital | Vall d'Hebron Institut de Recerca | VHIO Vall d'Hebron Institute of Oncology | Cemcat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