Webinars for patients

Sickle Cell Disease

Topic on Focus EuroBloodNet

New Therapies for Sickle Disease Patients

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Director of the Reference labelled Constitutive Red blood cells
and Eythropoieisis disorders center
at Robert-Debré University Hospital
APHP and MCGRE labelled network
ERN-EuroBloodNet subnetwork: Red Blood Cell
Paris– France
31 of January 2022

Co-funded by
the Health Programme
of the European Union

Investigator Post label registry (Addmedica)

Learning objectives

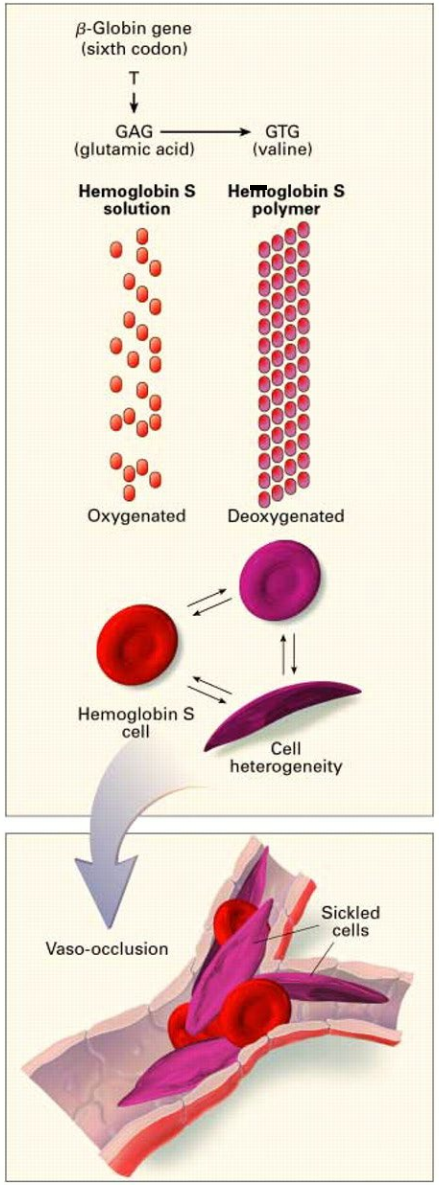
1. Introduction to SCD
2. Disease modifying therapies
3. Curative Approach
4. Comprehensive SCD center
5. Take home messages
6. Discussion

1. Introduction to SCD new therapies

1.Introduction to SCD

2.Targets

Introduction to SCD (1): a Most frequent Monogenic Disease



(Steinberg NEJM, 1999)

- Single nucleotide mutation: β globin 6th codon
  - Transversion A →T
  - -6thAA Glu → Val: Hb A→S:
  - = HbS Polymerise upon deoxygenation

-Symptoms

Chronic hemolytic anemia

Vaso-occlusion

Functionnal Asplenia : high susceptibility to encapsulated bacterial infections

-Diagnosis:

-Adult: Hb electrophoresis

-newborn: isoelectric focalisation HPLC or MS

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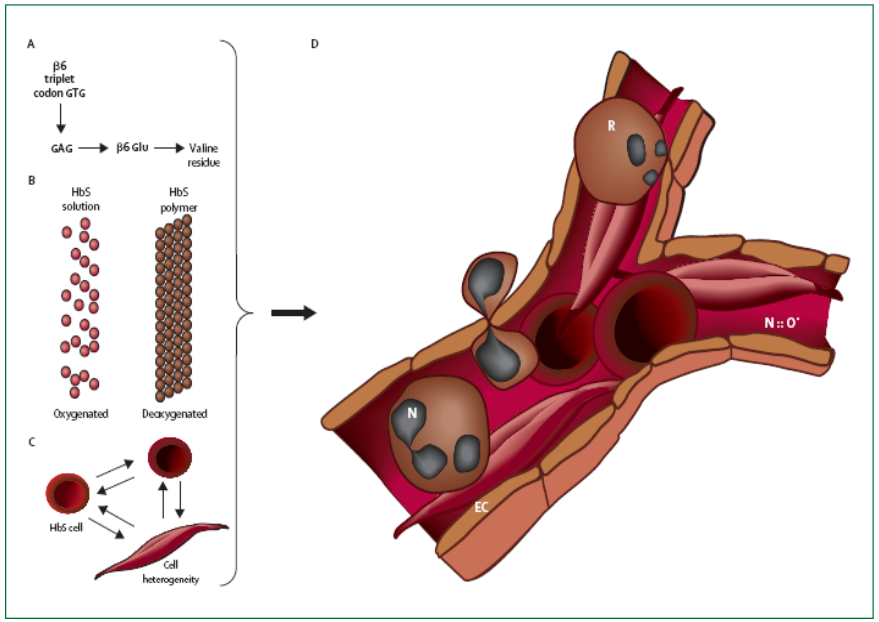
Introduction to SCD (2) : A wide biological and clinical variability

- **For example: Pain in sickle cell disease**
  (Platt OS et al NEJM 1991)

- 2412 patients with homozygous SCD (Inclusions from 1979 to1986)
- No neonatal screening nor implemented care after neonatal screening
- Patients with pain symptoms/year
  - No pain : 39%
  - >6 épisods : 1%
  - 3 à 10 episods : 5.2% responsibles for 32.9% of pain events

  – No individual prognostic factor



(Stuart MJ, Nagel RL. *Lancet* 2004)

Response to stress:
oxydative,
inflammatory,
Hypoxia-reperfusion:

→Driven by microcirculation partners and tissue polymorphisms

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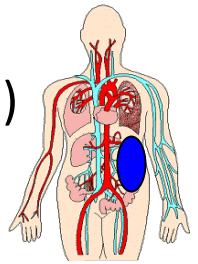
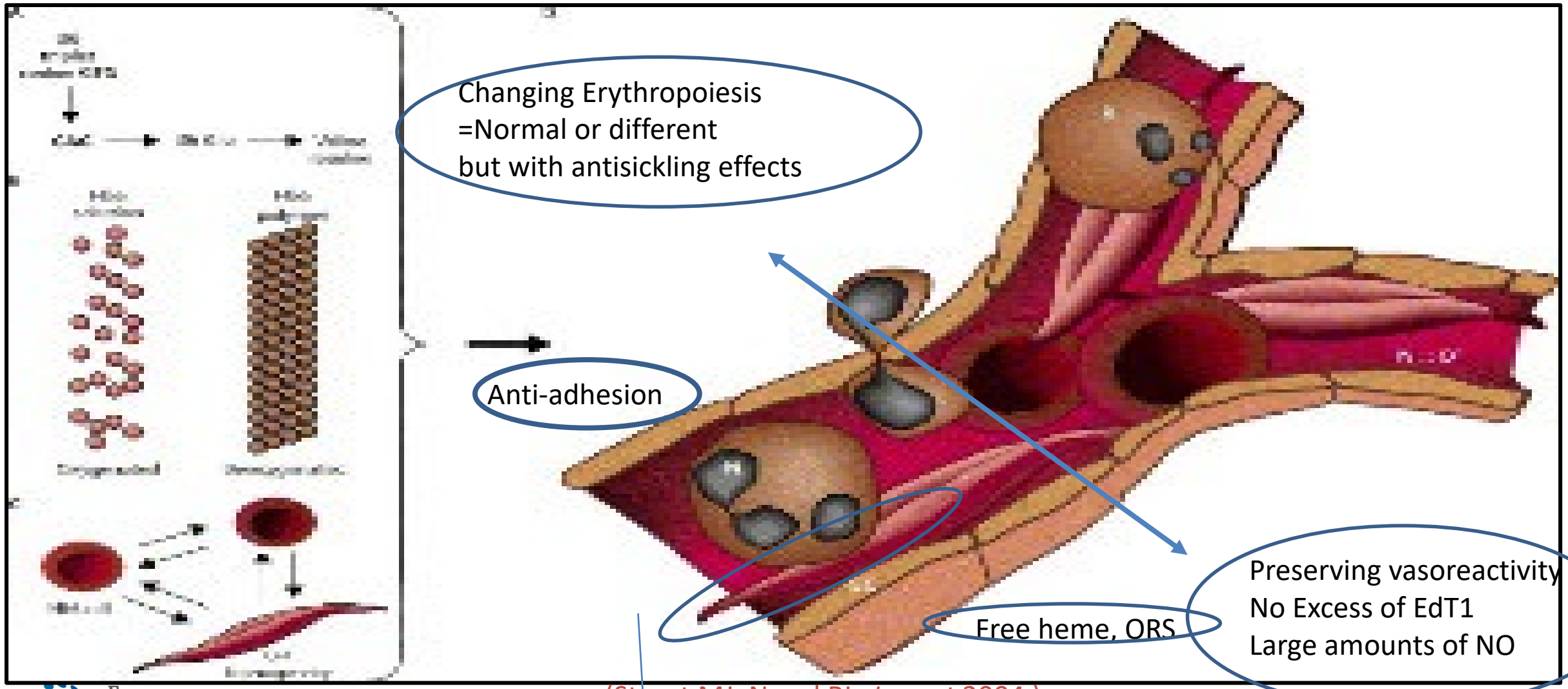
Introduction to SCD (3): Very early mortality and morbidity

- Without care or in low income countries : very severe disease
  - Early and unpredictable Mortality
    - 50 à 80% before 5 years of age (peak between 6 to 18 mo)
      - 50% Infectious (2/3pneumoccocal)
      - 45% Acute Anaemia (mainly ASS)



- ***Prevention:*** ***Drastic decrease of mortality (and morbidity) before 5 years of age between 0 and 5%*** *(Gill FM Blood 1995; Lee BMJ, 1995, Telfer Hematologica 2007, Quinn CT Blood 2010, Bernaudin F Blood 2011, Couque N BJH 2016)*
  - Neonatal screening, organised health and social network
    - Peni V, anti-pneumococcal, meningococcal vaccines, parental and referent adult education (Fever, Pain, Pallor, treatments), folic acid , support to ttt compliance, TCD…, regular outpatient and annual review)
    - Early Intervention whenever needed: TP, Hydroxycarbamide, HSCT, other disease modifying or curative therapies.

Introduction to SCD new therapies : TARGETS (1)



(Stuart MJ, Nagel RL. *Lancet* 2004)

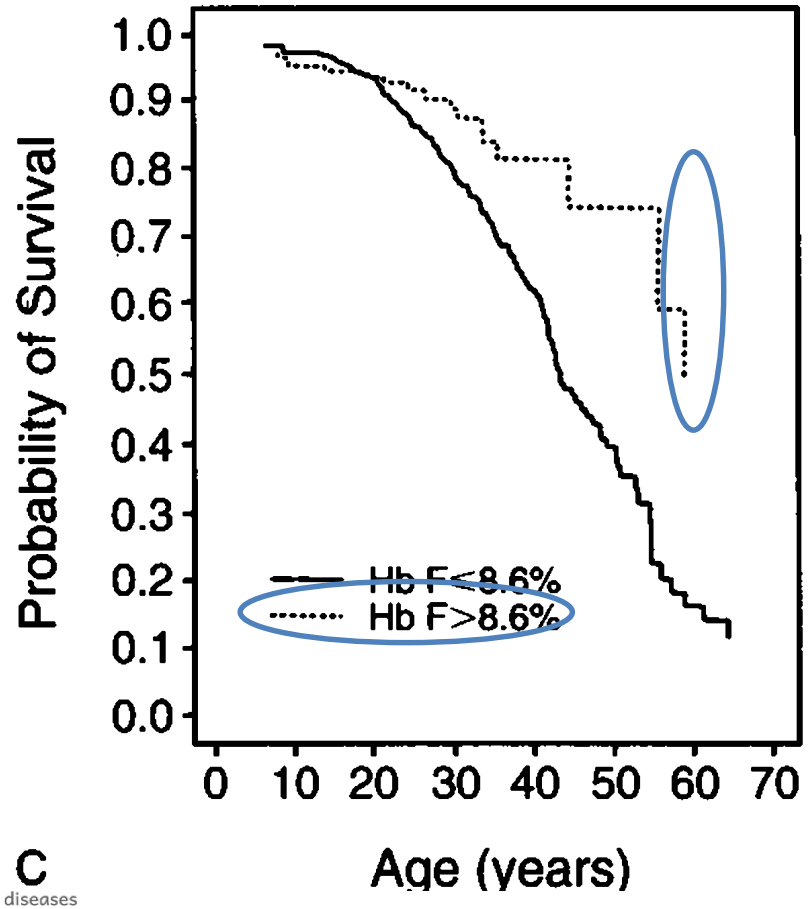
Introduction to SCD new therapies : TARGETS(2)

MORTALITY IN SICKLE CELL DISEASE

Life Expectancy and Risk Factors for Early Death

ORAH S. PLATT, M.D., DONALD J. BRAMBILLA, PH.D., WENDELL F. ROSSE, M.D., PAUL F. MILNER, M.D., OSWALDO CASTRO, M.D., MARTIN H. STEINBERG, M.D., AND PANPIT P. KLUG, M.D.

(N Engl J Med 1994;330:1639-44.)



- CSSCD: 2542 SS patients included between1978 and 1988
- No neonatal screening nor implemented care after neonatal screening
- Life expectancy: 42 y for men and 48 y for women, improved when ↑ **HbF**

2.Disease modifying therapies

1. Antisickling agents
2. Antidhesion therapies
3. Optimising oxygenation.
4. Increasing Hb F expression
5. Substitutive therapy
6. Empowerment
7. Prevention

Antisickling agents(1): Maintaining OXY Hb

- **GBT-440 (VoxelatorR) maintains HbS in oxyform by binding covalently alpha genes**
  - **Lowers polymerisation**
  - **Increase in Hb and decrease in hemolysis parameters**
  - **Hopekids II trial: 2-12 y kids with conditionnal TCD/placebo**

Antisickling (2): Increasing HbS Affinity and RBC repair

- Pyruvate Kinase Activator (FT-4202 Etavopivat)
  - Decreases 2-3DPG And Increases ATP

- Increases Hb Affinity for O2 (less deoxy HbS) and improves Red blood cell repair
  - SCD trials showed
    - increased Hb
    - an decreased Hemolysis
  - Hibiscus phase II/III trials ongoing for kids with 2 or more VOC drug/placebo

2. anti-adhesion

- Anti p-selectin

DOI: 10.1002/ajh.25308

RESEARCH ARTICLE

Effect of crizanlizumab on pain crises in subgroups of patients with sickle cell disease: A SUSTAIN study analysis

Abdullah Kutlar[1] | Julie Kanter[2] | Darla K. Liles[3] | Ofelia A. Alvarez[4] | Rodolfo D. Cançado[5] | João R. Friedrisch[6] | Jennifer M. Knight-Madden[7] | Andreas Bruederle[8] | Michael Shi[9] | Zewen Zhu[9] | Kenneth I. Ataga[10]

Am J Hematol. 2019;94:55–61.

-40% reduction in VOC rate
-2 IVLx2/month then once a month
-Do not need every day compliance
-Team and adult centres experience: Interesting in patients compliant to HU remaining symptomatic
No evidence of effect for those needing HU and not taking it

3. Optimising oxygenation preventive strategy

- *Identifying new risk factors with adapted statistical methods*
  - *Longitudinal biological and clinical data on newborn cohort*
  - *for macrovascular disease*
    - *Risk factors : ENT and bronchial obstruction, reticulocyte count*
    - *Protective factor : Increase of HbF*
    - ***Easy factors to target***

bjh research paper

British Journal of Haematology, 2016, 172, 966–977

Clinical and haematological risk factors for cerebral macrovasculopathy in a sickle cell disease newborn cohort: a prospective study

Sommet J et al

Children 2021, 8, 143. https://doi.org/10.3390/children8020143

Variability of Prognostic Results Based on Biological Parameters in Sickle Cell Disease Cohort Studies in Children: What Should Clinicians Know?

Sommet J et al

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4.Re-expressing HbF: Gene therapy (Inhibiting BCL11A)

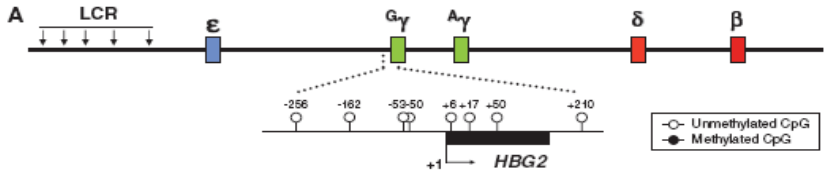
CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernytsky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

N ENGL J MED 384;3 NEJM.ORG JANUARY 21, 2021

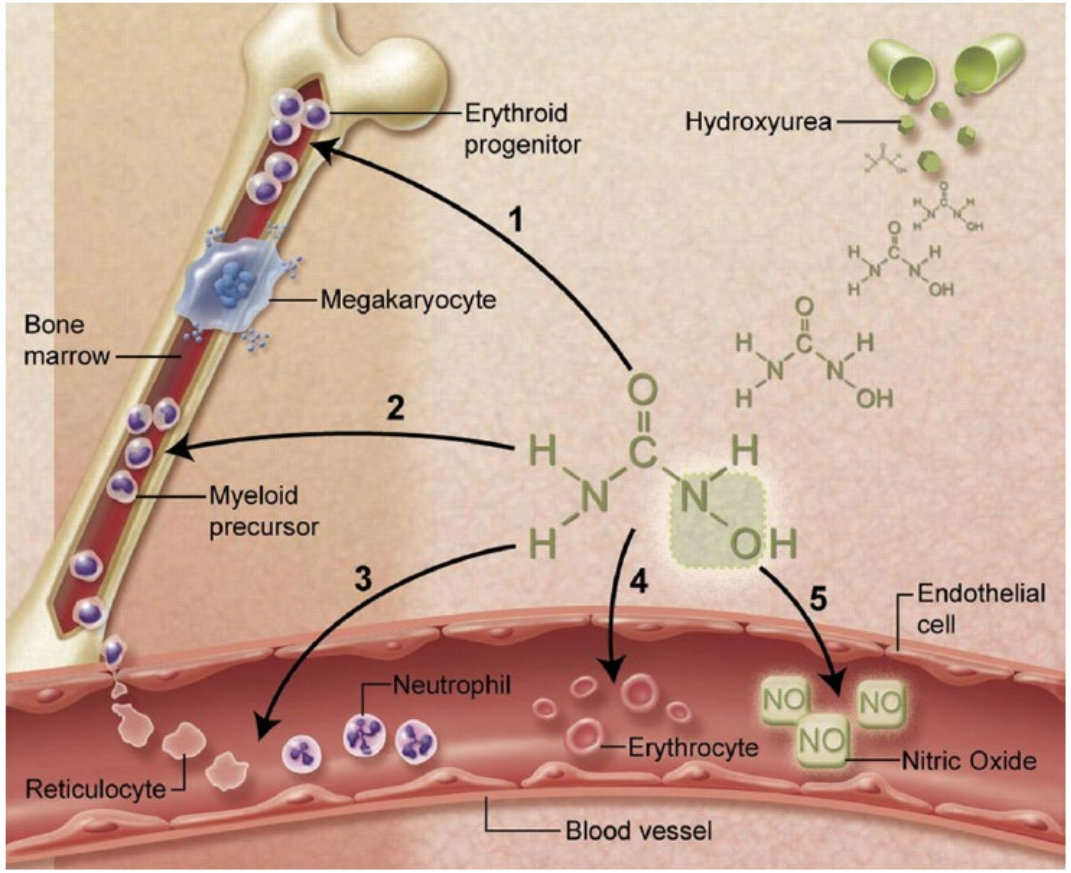
1 patient with Beta0/beta+ thal TD and
1 with SCD with frequent VOC
Pre apheresis TP
Apheresis x3 of mobilized STC
Myeloablative conditionning regimen
SCD patient is free of symptoms with more than a year follow-up
HbF rose from 9.1% to 43,2%
HbS decrease from 74% to 52.3%, 100% of F cell

BCL11A is silencing gamma globin genes during devellopment: HbF → HbA or HbS
silencing specifically its expression activates gamma globin gene again

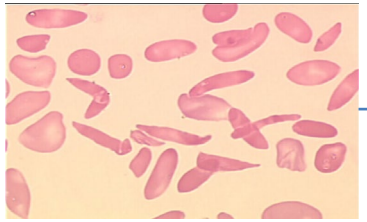


Old dog New tricks (1-2-4 VR) Hydroxycarbamide

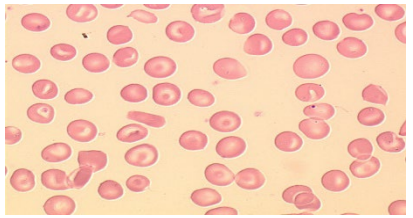
- Ribonucleotid reductase inhibitor
- Beneficial pleiotropic effects



Ware RE, Blood 2010



→ after 6mo of HC



1- ↑Σ HbF

2- ↓ Production adherent cells
PMN, Reticulocytes, Platelets

3- ↓ adhesion molecules on Reticulocytes, PMN
- ↓Endothelin 1 (vasoconstrictor)
- ↓ Endothelial injuries

4- Macrocytosis:
- ↑ red blood cell hydratation: ↓[HbS]
- ↑deformability
- ↓Haemolysis

5- ↑NO (vasodilation)

Terribly under utilized, 40% or less patients with VOC or anemia< 7g/dl are treated with HC *Couque N BJH 2016)*

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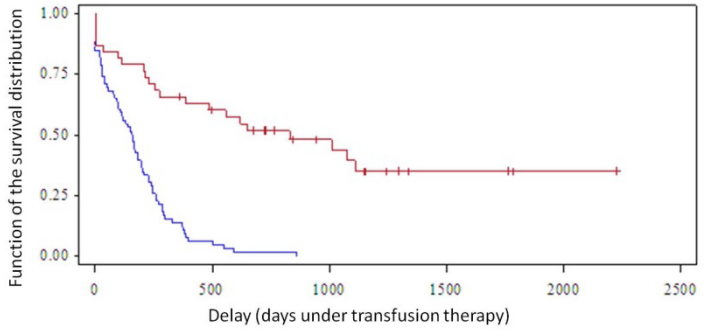
Old dog New tricks 5. Substitutive therapy Exchange transfusion



Survival curve (Kaplan-Meier estimation) of ferritinemia functions of the duration of transfusion therapy in the two groups

STRATA: Red Cells Transfusion group — Exchange Transfusion group

Survival curve with Ferritinemia<1000µg/l
Continous manual exchange=Erythrapheresis
B Koelh et al **TRANSFUSION** 2016;56;1121–1128

- Monthly National neuroradiology expertise meeting
  Thousands images and charts review since 1998
- Coordinated by our neuro-radiologists and our team
- Preventing erroneous TP and safely resuming TP

Exchange transfusion therapy without iron overload TCD and ARM normalisation
Safe switch to HC after 5 y

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6. Support and empowerment

- Psychological (support, self esteem, stress control)
- Mediation
- Treatment adherence, educated health-care provider, parent and patient expert
  - **oral medications work if taken**
  - **only for personal goals that change with time (play with friends, football, “white eye”….)**
  - **Had to be encouraged**
  - **Discouragement is acceptable**
  - **Therapy has to be quickly at the best dosage**

- Adolescent and young adult support through a smartphone application connected to a dedicated nurse platform (Applidrep)

7. prevention and empowering existing preventive strategies

- ***Prevention:***

bjh research paper

Improvement of medical care in a cohort of newborns with sickle-cell disease in North Paris: impact of national guidelines

British Journal of Haematology, 2016, 173, 927–937

Couque N et al

3. "Curative" therapies

1.Bone marrow transplant

2. Gene therapy

Curative Therapies(1) « Allogenic Bone Marrow transplant »

Allogeneic transplantation strategies including haploidentical transplantation in sickle cell disease

Eliane Gluckman[1]

[1]*Eurocord, Hospital Saint Louis, Assistance Publique–Hôpitaux de Paris, Université Paris-Diderot, Paris, France*

Hematology 2013

ASH 370-376

- HLA Identical donor
- Myeloablative conditionning regimen (ALS, Busulfan Cyclophosphamide, IS regimen 1Y post transplant
- >1000 in the world
    - 25 to 30% of paediatric patients have a matched donor
    - Mortality 4 to 5%
    - Chronic morbidity (cGVH) 12.6%,
    - Toxicity to be decreased

Our department coordinates an international Multi-professional consultation meeting / 2 months

– Consensus indications (PNDS et NIH 2010):

– Severe forms no responding to HC or confirmed cerebrovascular damage

Curative Therapies(2) « Allogenic Bone Marrow transplant »

The impact of pre-existing HLA and red blood cell antibodies on transfusion support and engraftment in sickle cell disease after nonmyeloablative hematopoietic stem cell transplantation from HLA-matched sibling donors: A prospective, single-center, observational study

EClinicalMedicine 24 (2020) 100432

Robert Sheppard Nickel[a,b,*], Willy A. Flegel[c], Sharon D. Adams[c], Jeanne E. Hendrickson[d], Hua Liang[e], John F. Tisdale[f], Matthew M. Hsieh[f]

- HLA Identical sibling
- Non myeloablative Conditionning Regimen (Alemtuzumab 5days, TBI 3GY, Cy 100mg/kg, sirolimus 1 year at least
- ≈10% rejection in the first year, partial chimerism….. Long term outcomes?

Curative Therapies(3) « Allogenic Bone Marrow transplant »

- HLA Haplo-Identical donor
- Myeloablative Conditionning Regimen

New curative SCD therapies: Gene-Therapy

Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial

NATURE MEDICINE | VOL 28 | JANUARY 2022 | 81–88

Elisa Magrin[1,2,26], Michaela Semeraro[3,4,26], Nicolas Hebert[5,6,26], Laure Joseph[1], Alessandra Magnani[1,2], Anne Chalumeau[7], Aurélie Gabrion[1,2], Cécile Roudaut[1,2], Jouda Marouene[3], Francois Lefrere[3], Jean-Sebastien Diana[1], Adeline Denis[7], Bénédicte Neven[8], Isabelle Funck-Brentano[8], Olivier Negre[9,10,27], Sylvain Renolleau[11], Valentine Brousse[12], Laurent Kiger[5], Fabien Touzot[1,2], Catherine Poirot[13,14], Philippe Bourget[15], Wassim El Nemer[16], Stéphane Blanche[8], Jean-Marc Tréluyer[3,4], Mohammed Asmal[10,27], Courtney Walls[10], Yves Beuzard[5,6], Manfred Schmidt[17], Salima Hacein-Bey-Abina[1,2], Vahid Asnafi[18], Isabelle Guichard[19], Maryline Poirée[20], Fabrice Monpoux[21], Philippe Touraine[22], Chantal Brouzes[23], Mariane de Montalembert[12], Emmanuel Payen[5], Emmanuelle Six[7], Jean-Antoine Ribeil[1,2,10,27], Annarita Miccio[7,28], Pablo Bartolucci[5,6,28], Philippe Leboulch[9,24,28] ✉ and Marina Cavazzana[4,225,28] ✉

-3 SCD with VOC under HU and TP, no HLA identical donor
-bone marrow harvest with CD34+ purification
-Cultivated in presence of lentiviral vector with modified Beta globin gene insulated targeted to beta globin locus
-Myeloablation with Busulfan followed by infusion of transfected STC 10 days after
-40 to 50% expression of the transgene
-2/3 patients cured with median follow-up of 4.5 y

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4.Comprehensive SCD centers

Mandatory

WHY???

Comprehensive patient approach Network

Labelled reference SCD center
multiprofessional team
Hospital based
←Coordination→

AEH

Regional
« handicap » houses

2 levels Written communication

Expertise
Referral

Proximity Hospital based
Labelled Competence Center

Written communication

School doctor
+Teachers
+ educative psycho-social

↕ Family doctor
+ other health care providers

Written communication

Written communication

Maternal and child health care system with psycho-social

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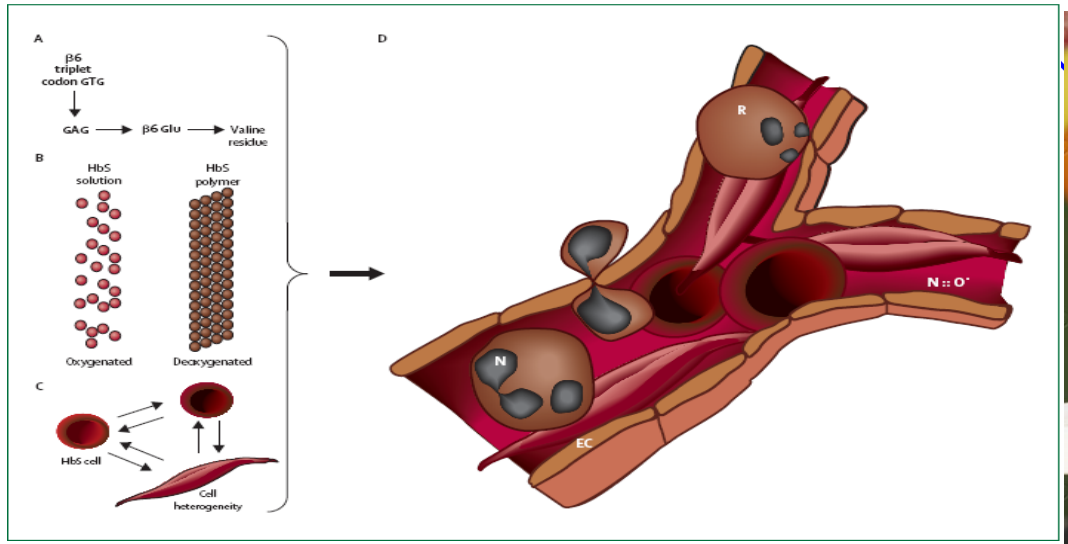
From research to care

Better disease control,

Optimize prevention and cure with known tools
Research for new disease modifying drugs
Access to international trials
New statistical tools for defining early risk factors (ie ENT and bronchial obstruction)J Sommet BJH 2016)

↓



Stuart MJ, Nagel RL. *Lancet* 2004

Real time evaluation

NEODREP
Regional Monthly meeting on paediatric "complex situations"

Have fun, living well with sickle cell disease

Therapeutic education *EDUDREP, JEUDREP, Applidrep*

↓ progressive empowerment toward adulthood
↓ Life project (mediation) MEDIADREP
↓ Pain control (PCA)
↓

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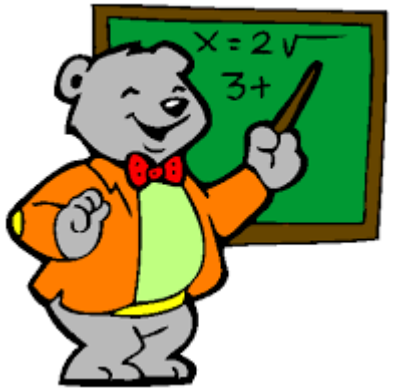
Medical issues of the diagnostic announcement:

Building the therapeutic alliance for life



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Take-home message

1. **Collaboration between all health care providers, parents, children, patients:**
2. **Advocacy for referral centres and networking**
3. **Huge progresses in the past five years**
4. **Tailored therapy with combination of approaches following need of patient for quality of life**

Sickle Cell Disease National Référence Center, Robert-Debré University Hospital, Paris France

•André Baruchel et Jean-Hugues Dalles (MD-PHD)
•Berengère Koelh, MD, PHD,
•Valentine Brousse (MD,PHD,) Florence Missud, Laurent Holvoet, Gislaine Ithier (MDs)
•Angele Mouopouondo, Valèrie Rigaux (Psychologists)
•Sylvie Vernois, Kagny Traore, Arouny Kehoavong (Head Nurse and educational as well as coordinating Nurses)
•Sabrina Lecerf (social worker)
•Zinedine Haouari (MD data base manager)
•Celine Vivier (Teacher, N E S)

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•Monique Elmaleh
•Suzanne Verlhac

Neonatal screening and molecular biology,

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•Bichr Allaf
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All collaborators both on site and of site

French Blood Bank

Emmanuelle Lesprit
Anne Arnould
France Noizat-Pirenne

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UMR 1163

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Thank You Very Much!

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Discussion