Use of Hydroxyurea in Children with Sickle cell Disease

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Outline

- Pathophysiology of SCD .
- Treatment options for SCD
- Mechanisms of Action of Hydroxyurea
- Indications for Hydroxyurea use
- Dosing and monitoring of Hydroxyurea
- Fertility and Hydroxyurea

Objectives

- Understand the mechanism of action of hydroxyurea
- Discuss the indications for hydroxyurea use
- Initiate and monitor patients on hydroxyurea
- Discuss the side effects of hydroxyurea

Background – SCD Epidemiology

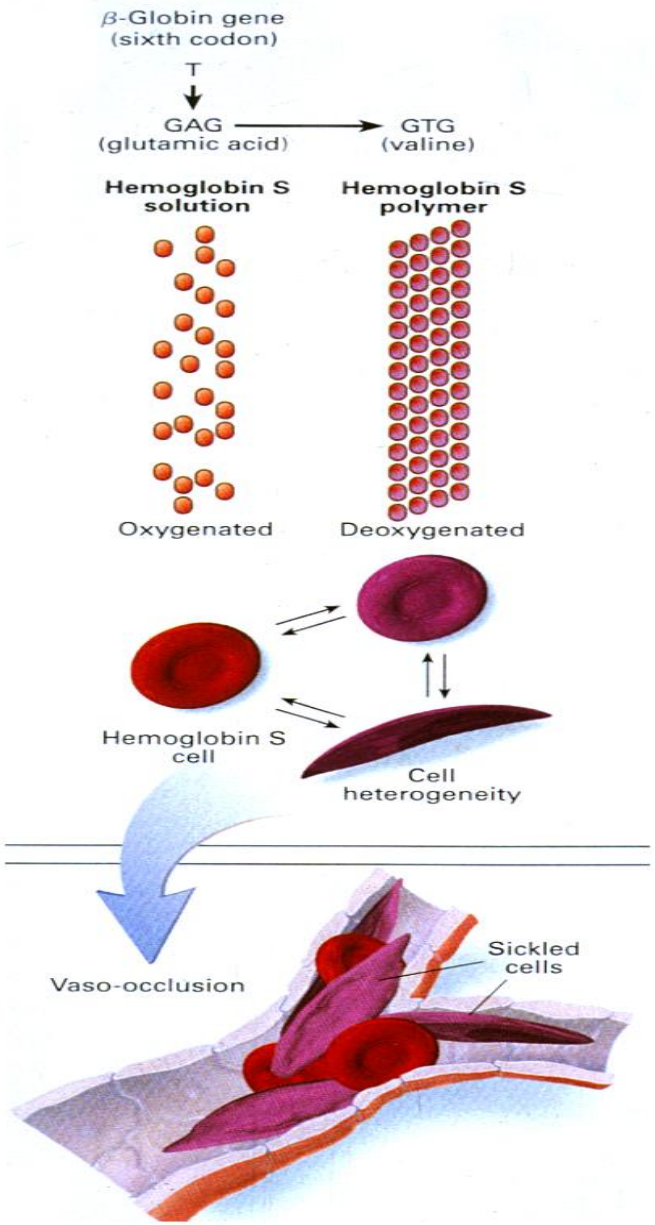
- Sickle cell disease (SCD) is a group of inherited blood disorders caused by an abnormal hemoglobin- hemoglobin S (HbS).

- HbS results from point mutation in the B –globin genes, resulting in the substitution of valine for glutamic acid at position 6 of the B-globin chains. SCA (HBSS) is the most common and most severe form

- An estimate of over 300,000 babies annually are born globally with SCD and 80% are from sub-Saharan Africa (SSA)

- In Uganda, 20,000 babies are born with SCA annually, and it is estimated that 80% die before their fifth birthday .

Back Ground – SCD Pathophysiology



Upon deoxygenation, the HbS molecule polymerizes within the RBC leading to shape changes

Sickled RBC are rigid and adhesive, so obstruct small blood vessels and lead to tissue ischemia

Vaso-occlusion is a complex event, involving WBC, reticulocytes, sickled cells, and endothelium

Hemolysis and endothelial vasculopathy also contribute to organ dysfunction

Care and Treatment of children with SCD

Cure
Bone marrow
Transplant
Gene therapy

Health Maintenance

1. Education
2. Penicillin and malaria prophylaxis
3. Immunisation
4. Screening for chronic complications

Treatment of acute and chronic complications

1. Pain management
2. ACS
3. Treatment of fever

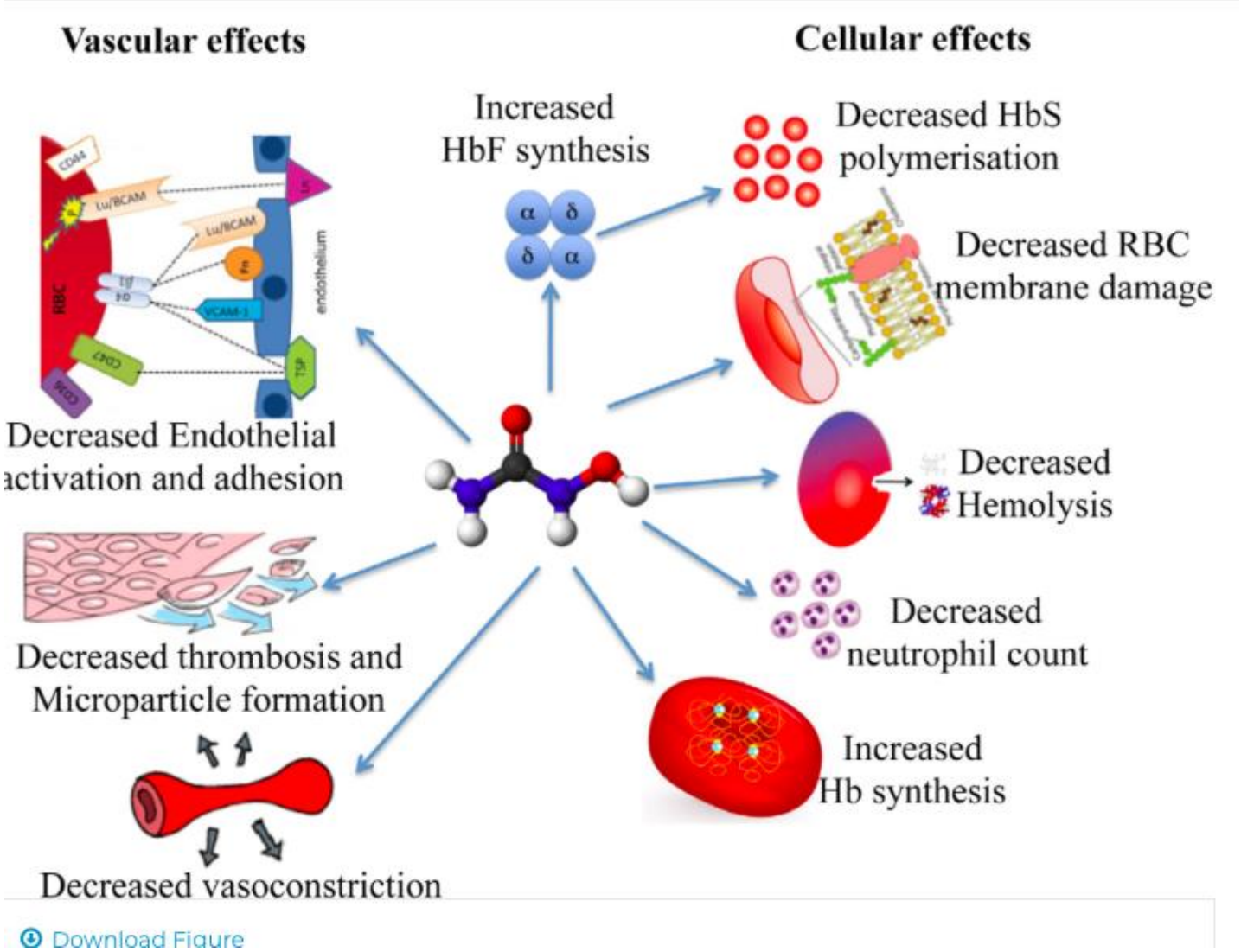
Disease Modifying Treatments

1. Hydroxyurea
2. Chronic blood transfusion
3. L. Glutamine
4. Voxelotor

Role of Hydroxyurea in the treatment of SCD

- Hydroxylated analog of urea originally synthesized in 1869
- First animal studies in 1928 for leukopenia, macrocytosis, anemia, death
- First tested in SCD in 1984. Was approved for use in the USA in 1998.
- Principal mechanism of cytotoxicity is the inhibition of DNA synthesis (Ribonucloetide Reductase inhibitor)- causing intermittent suppression of erythroid progenitors
- Spontaneous recovery of the enzyme occurs when hydroxyurea is removed
- Resistance and tolerance have not been described to occur

Hydroxyurea: Multiple Mechanisms of Action with Multiple Benefits to Patient



- HbF induction
- Myelosuppression
- ↓RBC adhesion to endothelium
- Better rheology
- Increase in levels of nitric oxide

Hydroxyurea is Efficacious in Children and Adolescents with SCD

- Reduces pain episodes by 50%
- Reduces need for blood transfusion
- Decreases trans cranial doppler velocities ,reduces risk of primary and secondary stroke
- Decreases the rates of acute chest syndrome
- Reduces rates of hospitalization
- Preserves splenic function in infants and improves growth and development

Opoka et al, Ware et al, Jayabose et al, wang et al.

The MSH trial showed the effectiveness of hydroxyurea in adults 25 years ago

ORIGINAL ARTICLE

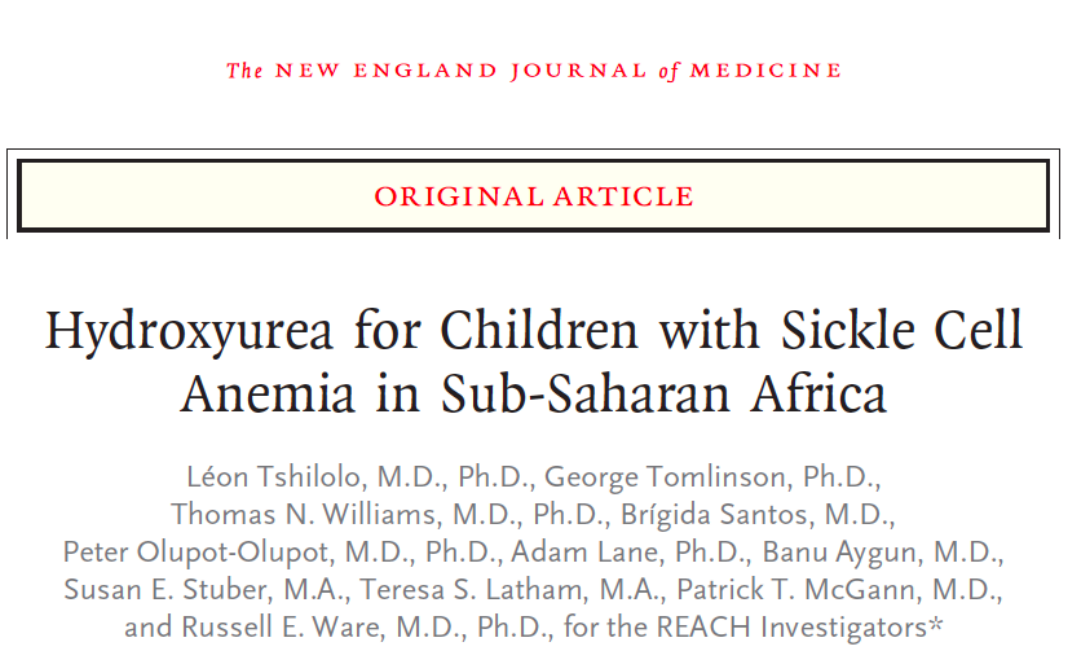
Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia

Samuel Charache, M.D., Michael L. Terrin, M.D., Richard D. Moore, M.D., George J. Dover, M.D., Franca B. Barton, M.S., Susan V. Eckert, Robert P. McMahon, Ph.D., Duane R. Bonds, M.D., and the Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia*

May 18, 1995
N Engl J Med 1995; 332:1317-1322
DOI: 10.1056/NEJM199505183322001

Abstract

Hydroxyurea is Safe and Does not Increase Malaria Risk in African Children

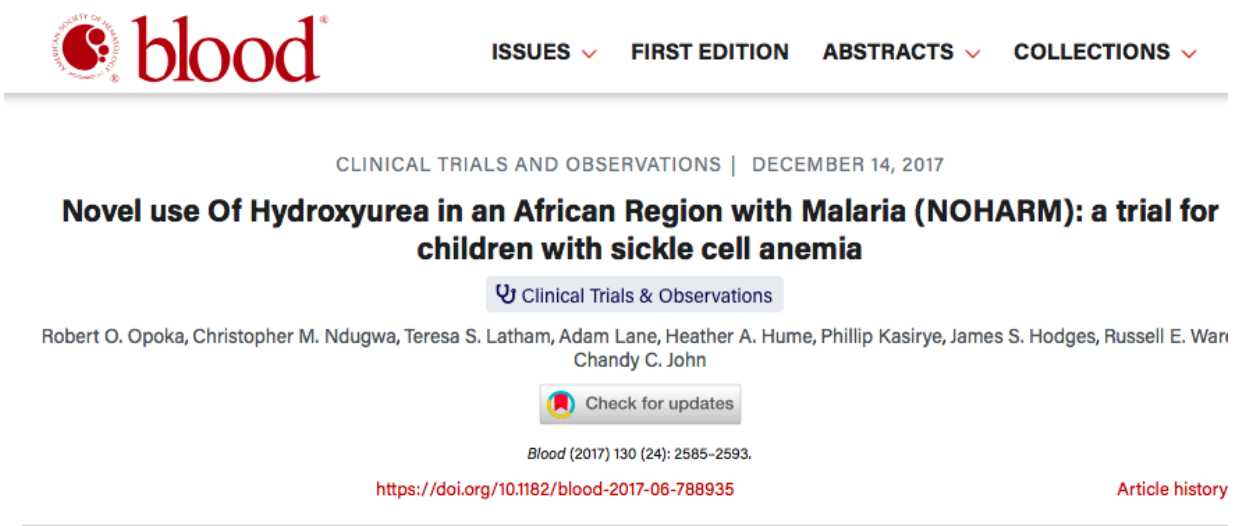


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa

Léon Tshilolo, M.D., Ph.D., George Tomlinson, Ph.D., Thomas N. Williams, M.D., Ph.D., Brígida Santos, M.D., Peter Olupot-Olupot, M.D., Ph.D., Adam Lane, Ph.D., Banu Aygun, M.D., Susan E. Stuber, M.A., Teresa S. Latham, M.A., Patrick T. McGann, M.D., and Russell E. Ware, M.D., Ph.D., for the REACH Investigators*



blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS

CLINICAL TRIALS AND OBSERVATIONS | DECEMBER 14, 2017

Novel use Of Hydroxyurea in an African Region with Malaria (NOHARM): a trial for children with sickle cell anemia

Clinical Trials & Observations

Robert O. Opoka, Christopher M. Ndugwa, Teresa S. Latham, Adam Lane, Heather A. Hume, Phillip Kasirye, James S. Hodges, Russell E. Ware, Chandy C. John

Check for updates

Blood (2017) 130 (24): 2585–2593.

https://doi.org/10.1182/blood-2017-06-788935 Article history

Indications and Contraindications for Hydroxyurea Use

- Frequent pain crises ,>5 in a year
- Stroke or history of stroke
- Abnormal TCD velocities> 200cm/sec
- Low baseline Haemoglobin,<6g/dL
- History of/admission for acute chest syndrome

Contraindications

- Pregnancy or sexually active and not willing to use contraception
- Active liver disease
- Hypersensitivity to Hydroxyurea
- Significant non compliance to therapy

- ***Offer Hydroxyurea to all children older than 9 months – National Heart, Lung and Blood Institute***

Dosing and Monitoring

- Baseline investigations
- CBC with differential and reticulocyte count
- Quantitative HB electrophoresis – Help in monitoring response
- Creatinine and Urea – Should be in normal range
- Liver function – AST/ALT- Should be <2 times the upper limit

Prior to Initiating Hydroxyurea Therapy

- Complete history and physical exam.
- Discuss the rationale and potential adverse effects of hydroxyurea with patient and family members.
- Document that family agrees to have regular clinic monitoring.
- Document diagnosis of SCD
- Patient must meet initial blood count and chemistry criteria: ANC > 1,500/µl, platelet > 100,000/ul, and ALT< X2 the upper limit of normal, and normal creatinine .

Parental/Patient Education on use of Hydroxyurea

- Key is to emphasize that hydroxyurea is not a cure
- Effectiveness of hydroxyurea depends on adherence dosing schedule
- Do not double doses if one misses
- Do not share drugs among siblings

Dosing and Monitoring

- Start at 20mg/kg /day
- Monitor CBC every month for 3 months, then every 3-6 months
- Monitor for toxicity and clinical and laboratory response
- Aim for mild myelosuppression of ANC 2,000-4,000/µL
- Maintain platelet count >= 80,000/ /µL

Monitoring

- At each monitoring visit, assess
  - Interim clinical events
  - Adherence; check WBC, ANC, ARC on CBC which should reduce while

    haemoglobin level , HBF and MCV should increase
  - Reweigh the patient and check dose against weight
  - CBC: Stop Hydroxyurea if ANC <1500 **OR** Hb<6 AND ARC <80,000 **OR** platelets <80,000

Dosing and Monitoring

- Monitor WBC weekly after holding hydroxyurea. Restart at a dose 5mg/kg/day lower when counts recover
- Clinical response may take 3- 6 months
- Lack of increase in HBF or MCV is not an indication to stop therapy
- Do not discontinue therapy due to uncomplicated fever or hospitalization

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- ***What is the optimal dose of hydroxyurea in children with SCD ?***

Hydroxyurea at MTD is Safe and Superior to Fixed Dose

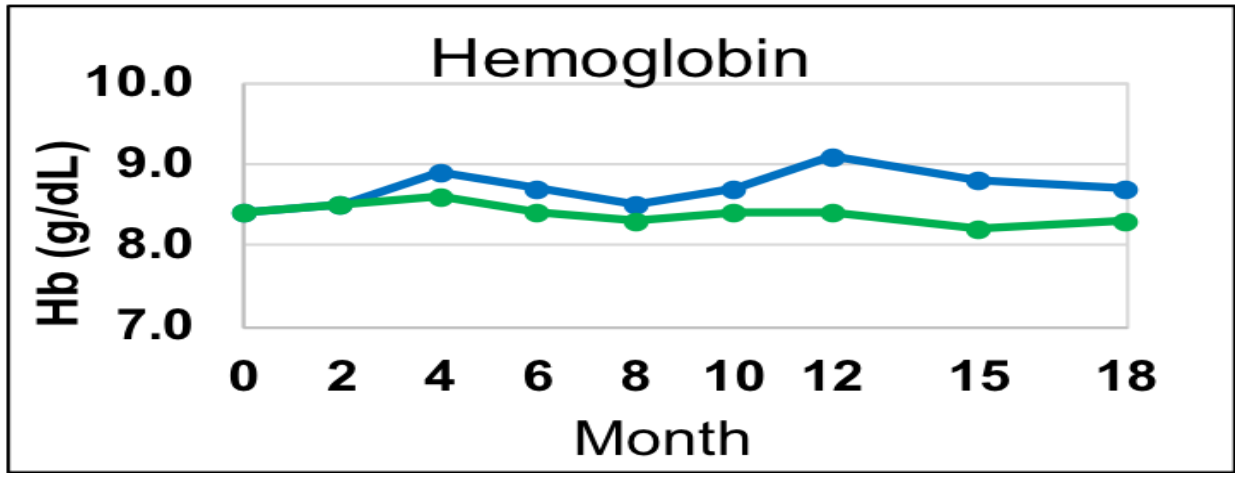
The NEW ENGLAND JOURNAL of MEDICINE

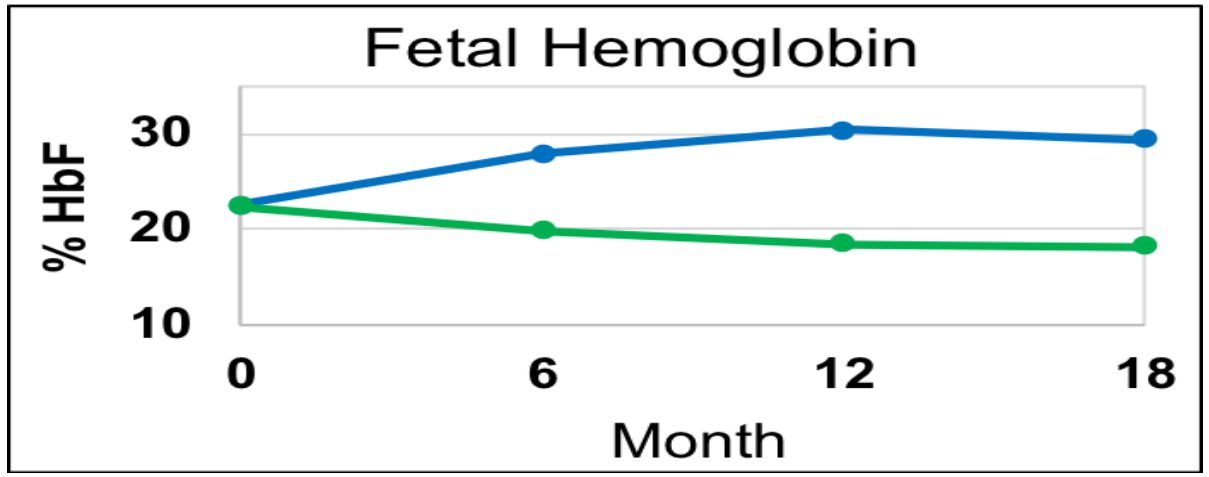
ORIGINAL ARTICLE

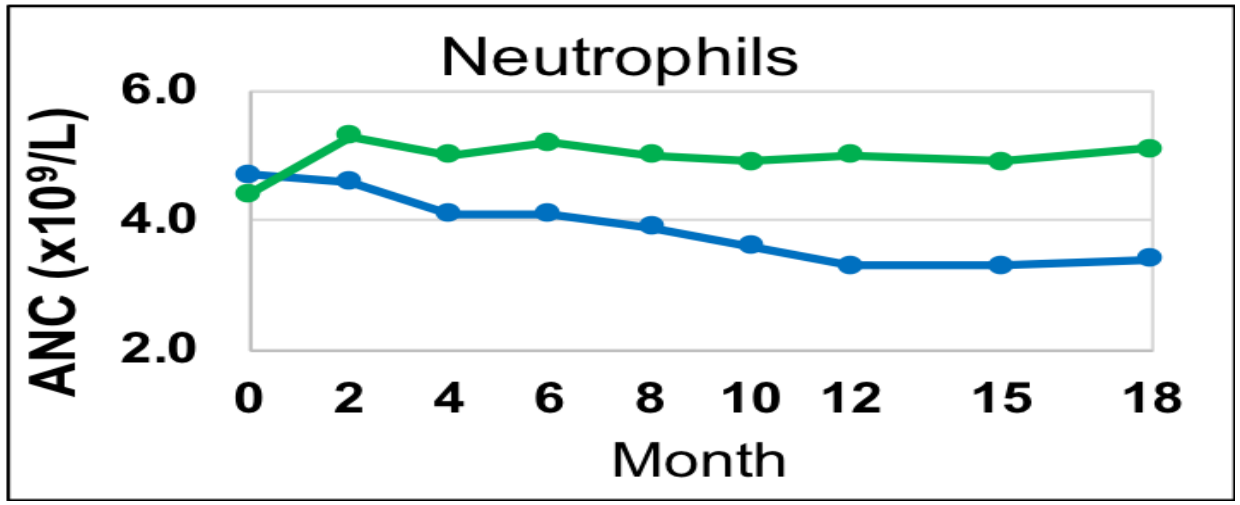
Hydroxyurea Dose Escalation for Sickle Cell Anemia in Sub-Saharan Africa

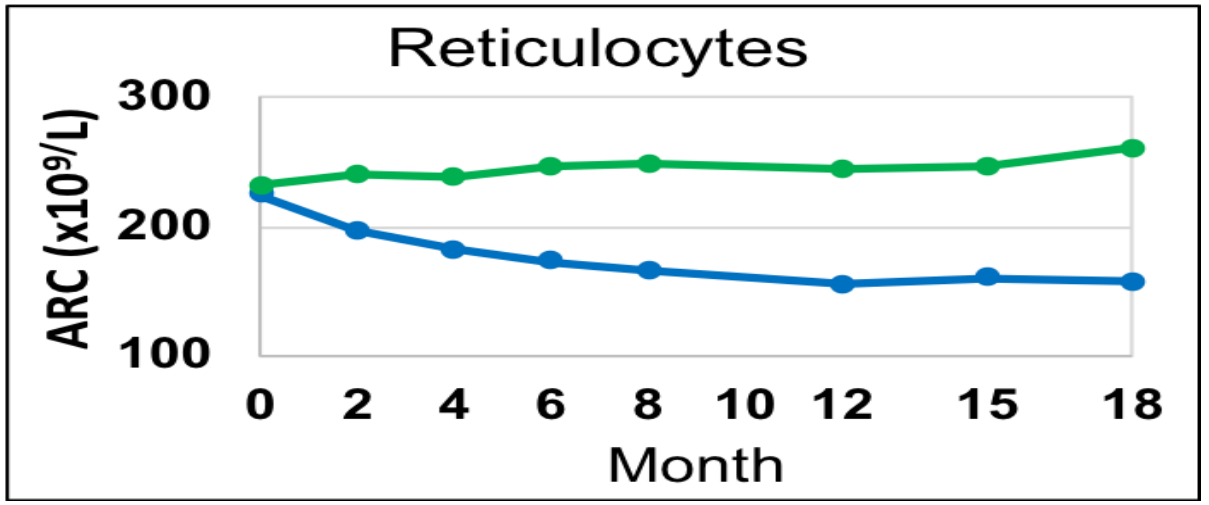
Chandy C. John, M.D., Robert O. Opoka, M.Med., Teresa S. Latham, M.A., Heather A. Hume, M.D., Catherine Nabaggala, M.B., B.S., Phillip Kasirye, M.Med., Christopher M. Ndugwa, M.Med., Adam Lane, Ph.D., and Russell E. Ware, M.D., Ph.D.

Laboratory Effects of MTD vs. Fixed Dose









Adapted from John et al

Dose escalation to MTD

Escalate dose as indicated: Abnormal TCD, stroke, ANC>6,000 /µL, no clinical response

Escalate by 5mg/kg/day every 6-8 weeks up to 30mg/kg/day

Maximum Tolerated Dose : Mild myelosuppression- ANC 2-4,000/uL without toxicity

At the Mulago Hospital sickle cell clinic ,mean dose is 25-32mg/kg/day

Monitor CBC, with differentials and (reticulocyte count) at each dose escalation

Challenges with Hydroxyurea therapy in Clinical Practice

Formulations : 250 and 500 mg capsules

Calculate total dose for a week and divide by 500!

- E.g. for 15 kg child, daily dose at 20mg/kg/day =20x15=300mg
- Total weekly dose =7x300= 2100mg
- So the child would need 2100/500 (4 capsules of 500mg a week)
- Give a capsule on Monday, Wednesday, Friday and Sunday

Fertility and Hydroxyurea

BRIEF REPORT | FEBRUARY 11, 2021

Effect of hydroxyurea exposure before puberty on sperm parameters in males with sickle cell disease

Clinical Trials & Observations Brief Report

L. Joseph, C. Jean, S. Manceau, C. Chalas, C. Arnaud, A. Kamdem, C. Pondarré, A. Habibi, F. Bernaudin, S. Allali, M. de Montalembert, B. Boutonnat-Faucher, J.-B. Arlet, B. Koehl, M. Cavazzana, J.-A. Ribeil, F. Lionnet, I. Berthaut, V. Brousse

Blood (2021) 137 (6): 826–829.

https://doi.org/10.1182/blood.2020006270 Article history

1. Some studies suggest reduction in sperm count with male subfertility
2. Men who participated in the multi center trail on hydroxyurea have successfully have children

Hydroxyurea, Conception and Pregnancy

RESEARCH ARTICLE | Free Access

Pregnancy outcomes with hydroxyurea use in women with sickle cell disease

Barbara L. Kroner, Jane S. Hankins, Norma Pugh, Abdullah Kutlar, Allison A. King, Nirmish R. Shah, Julie Kanter, Jeffrey Glassberg, Marsha Treadwell, Victor R. Gordeuk ... See all authors

First published: 10 February 2022 | https://doi.org/10.1002/ajh.26495 | Citations: 13

In this study on self reported pregnancy outcomes, hydroxyurea use during conception and pregnancy was associated with increased odds of miscarriage

Does Long term Hydroxyurea use increase cancer risk?

DECEMBER 6, 2014

Long-Term Safety of Hydroxyurea in Sickle Cell Anemia and Other Benign Diseases: Systematic Review and Meta-Analysis

Ali H. Algiraigri, MBBCh,FRCPC, Mansoor Radwi, MD

Blood (2014) 124 (21): 560.

https://doi.org/10.1182/blood.V124.21.560.560

The use of Hydroxyurea in treating patients with hemoglobinopathies does not appear to be associated with increase risk of secondary malignancies nor myelodysplastic syndromes despite being used for relatively long-term courses.

Conclusions

- Hydroxyurea is safe and efficacious in children with SCD
- Wider use should be encouraged for children with SCD
- Long-term follow up studies needed to answer questions on long term side effects

THANK YOU

Q & A