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What the Expert Says

Treatment of sickle cell disease: Beyond hydroxyurea

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ABSTRACT

India is home to a large number of patients with sickle cell disorders. We do not have any clear data on its prevalence and incidence but can surmise that it remains an area of concern from several single-center data and regional papers. It roughly correlates in distribution with tribal populations and affects a large population with basic medical access, poor infant mortality rates, and life expectancy. Therefore, it has remained unrecognized as a public health problem in this country. Hydroxyurea remains the cornerstone of sickle cell management by pharmacological means and does change the natural history of the disease. There remain barriers to the widespread use of this drug, most commonly due to a fear of teratogenicity. It does not reduce the risks and effects of long-term organ damage. An understanding of the mechanisms behind the phenotypic presentation of the disease has opened research into several medications targeting different mechanisms. This review looks at the newer drugs that have been approved for sickle cell disease in addition to reviewing the data on hydroxyurea.

Keywords: Sickle cell disease, Hydroxyurea, Novel therapy

INTRODUCTION

Sickle cells were first described in the scientific literature by James Herrick in 1910. These were seen on the blood smear of a young West Indian dentist, Walter Clement Noel by Herrick's intern, Ernest E Irons.[1] Pauling *et al.*, in 1949, established for the 1st time the molecular basis for a disease.[2] The molecular defect in hemoglobin S is characterized by the inversion of one base pair (A with T at codon 6 of the beta globin chain). This changes the sixth codon of the beta globin chain from (GAA) to (GTA), thereby replacing a single amino acid, glutamic acid, and by valine.

Deoxygenated red cells with HbSS are prone to polymerization. This polymerization imparts the characteristic sickle cell shape. These manifest as vaso-occlusive pain crisis. The vaso-occlusive episodes and resultant ischemic damage releases inflammatory cytokines and upregulation of adhesive molecules which aggregate neutrophils and platelets causing further vaso-occlusion.

In addition, the red cells with HbSS are stiff, even when they are normally shaped in an oxygenated environment.[3] This stiffness makes them prone to hemolysis. The hemolysis releases heme products into the circulation that scavenges nitric oxide and results in vasoconstriction and endothelial damage. This, then, causes vascular events such as priapism, leg ulcers, and chronic organ damage involving the renal, cerebrovascular, and cardiopulmonary systems.

These represent the two phenotypes of sickle cell disease (SCD), either hemolysis/vaso-occlusion or more commonly a mixture of both. They are modified by several genetic and environmental modifiers. Among the genetic modifiers, populations with the Arab/India genotype are consistently associated with higher HbF levels and, thereby, a milder phenotype.[4] HbF is not

affected by the sickle cell mutation and the rise in HbF is associated with reduced polymerization of sickle cells in the deoxygenated state. The benefits of a raised HbF are both due to dilution and the inability of the HbF tetramer ($\alpha 2\beta^S\gamma$) to enter the deoxy polymer phase associated with HbS. Affected newborns are protected from sickling by the HbF and manifest disease by 6 months to 2 years of age when they attain adult HbF levels.

HbF does not protect from the hemolytic effects of SCD. It ameliorates the vaso-occlusive crisis (VOC) and pain episodes. These are not entirely prevented though, as the HbF is not uniformly distributed through all the erythrocytes.[5] This would explain later on in this review why hydroxyurea alone might not completely change the natural history of the disease. Patients with compound HbS/HPFH are protected by uniformly distributed HbF on account of the associated HPFH (gene deletion variety and not the non-deletional HPFH which has the usual sickle phenotype).[4]

Frequent VOCs, besides affecting the quality of life, predict mortality.[6] Chronic organ dysfunction is the major cause of death in adults. Cerebrovascular, renal, cardiopulmonary events, and the acute chest syndrome predict shortened survival.[6] Therapeutic interventions would aim to resolve both the hemolytic and vaso-occlusive mechanisms:

1. Inhibition of polymerization
    a. Induction of fetal hemoglobin
    b. Increasing the oxygen affinity.
2. Prevention of RBC and white blood cell adhesion
3. Modulators of oxidative stress.

INDUCTION OF FETAL HEMOGLOBIN

5-azacitidine augments HbF production in animal models. It inhibits the methylation of deoxycytidine 5' to the gamma gene. It's cytotoxic activity interferes with dividing cells in S phase.[7] This limits the use of this chemotherapeutic agent in benign disorders.

Hydroxyurea has reversible bone marrow cytotoxicity and has demonstrated long-term mutagenic potential. The mechanism of HbF potentiation is not entirely clear. It has no direct effect on the methylation of deoxycytidine but has been shown *in vivo* to result in hypomethylation of sites 5' to the gamma globin genes[7] resulting in increased HbF. This rise comes from an increase in the number of BFU-E cells rather than the increased HBF content of individual BFU-E cells.[7]

Hydroxyurea was approved by the FDA in 1998 for use in adults after the encouraging results of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia.[8] It takes 8–24 weeks for therapy to raise HbF levels and correlated with the time taken to reduce VOCs (begins at 2 months with demonstrable benefits by 4 months). Hydroxyurea reduced the mean annual rate of painful crises by 44%. This study could not demonstrate any benefit on the incidence of death, stroke, or hepatic sequestration. Just about half, of the study subjects, achieved the maximally tolerated dose (MTD) of 35 mg/kg/day.[8] The BABY-HUG trial (median age 13.6 months) with a fixed dose of 20 mg/kg[9] and an Indian study with a fixed dose of 10 mg/kg/day also had similar benefits.[10]

While a starting dose of 15–20 mg/kg is recommended for all with dose titration as per the blood counts (target absolute neutrophil count to 1500–3000/cumm), the maximal dose of 30–35 mg/kg/day is perhaps not essential for benefit. Most patients tolerate a MTD of 22.5 mg/kg/day.[11]

Hydroxyurea's mechanism is poorly understood. In addition to raising HbF levels, effects on the adhesiveness of erythrocytes and leukocytes to the activated endothelial surface as also beneficial effects of the myelosuppression on reducing the inflammation are posited.[12]

Hydroxyurea prolongs life. Hydroxyurea is the only known drug intervention to change the natural course of the disease. The LaSHS study from Greece demonstrated a 10 years survival of 86% for hydroxyurea arm as compared to 65% for the non-hydroxyurea arm ($P = 0.001$).[13]

Observational studies showed the benefits of hydroxyurea in renal function (reduced proteinuria and renal hypertrophy),[14] retinopathy,[15] and splenic sequestration.[16] The Stroke With Transfusions Changing to Hydroxyurea (SWiTCH trial) failed to show any benefit as compared to chronic transfusion in the prevention of secondary stroke (5.6 recurrent strokes per 100 patient-years compared to none in the transfusion arm).[17]

A subsequent phase three trial (TWiTCH-TCD With Transfusions Changing to Hydroxyurea) studied the role of hydroxyurea/phlebotomy in the prevention of primary stroke. It found non-inferiority in the prevention of the primary stroke among children with a transcranial Doppler velocity of 200 cm/s provided they received 1 year of transfusions along with hydroxyurea and the MRI did not demonstrate any vasculopathy.[18]

HYDROXYUREA: WHERE ARE WE TODAY?

Hydroxyurea remains underutilized. An estimated 30% of eligible patients are actually on hydroxyurea.[19] It is FDA approved for use in infants above the age of 9 months. There is no evidence that the long-term use of hydroxyurea predisposes to malignancies and given the data from the TWiTCH study which has equivalent data for chronic transfusion and hydroxyurea in preventing the first stroke, hydroxyurea use should be encouraged from childhood. The Belgian study reported that adequately treated patients on hydroxyurea survived longer than patients who received

stem cell transplants (SCT).[20] A reduced HbF response attributed to marrow exhaustion has been noted over a period of time.[21]

Hydroxyurea reduces pain frequency and intensity. It reduces the rates of acute chest syndrome and transfusion requirements thereby translating to improved survival.[8,10] There is no data supporting hydroxyurea toward reductions in long-term organ damage.[8,22] Benefits from a reduction in VOC and transfusion requirement improve survival but have not translated to a reduction in morbidity due to chronic organ damage.[23] Thus, despite the spectacular benefits of hydroxyurea, there remains an unmet need for the prevention of long-term chronic organ damage, to be fulfilled by the newer molecules, perhaps in combination with hydroxyurea.

NEED FOR DRUGS BESIDES HYDROXYUREA

The central and western parts of India, with predominantly tribal populations and poor medical access, have the highest prevalence of SCD. An estimated 20% of SCD patients in these regions died by the age of 2 years and 30% died before adulthood (2012 data).[34] With improvements in childhood health and vaccination strategies, the overwhelming majority of children in developed countries now survive to adulthood. This shifts the burden of morbidity/mortality to adulthood. The US reported the median age at death for patients with SCD as 38 and 42 years for females and males, respectively (2005).[35] Poor compliance and delayed hydroxyurea use are cited for poorer outcomes. Even so, we need medications to prevent chronic organ damage and improve the quality of life until such time curative options such as gene therapy are more widely available (star trek medicine as eloquently described in Telen's review).[6]

DRUGS TARGETING THE INHIBITION OF POLYMERIZATION BY INCREASING OXYGEN AFFINITY

Voxelotor was one among several candidate molecules such as 5-hydroxymethylfurfural and tucaresol that reversibly bind oxygen to HbS without affecting the tissue transfer of oxygen. Increased affinity of oxygen to HbS prevents polymerization. The phase 3 HOPE (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization) trial studied oral voxelotor in patients (age group 12–65 years) with SCD.[24] The primary endpoint was an improvement in hemoglobin by 1 g/dl at 24 weeks. The secondary endpoints were improvement in hemolytic biochemical parameters (lactate dehydrogenase, reticulocyte count, and indirect bilirubin levels) and reduction in VOC. Two doses were studied, 900 mg and 1500 mg with significantly better improvements at the later dose.

The 1500 mg dose was associated with the achievement of the primary endpoint in 51% of cases (as opposed to 33% in the 900 mg group and 7% in placebo). The interbention reduced the reticulocyte count (19.9% reduction with 1500 mg vs. 4.5% with placebo) and indirect bilirubin (29.1% with 1500 mg vs. 3.2% with placebo). These changes were evident within 2 weeks. There were no improvements in lactate dehydrogenase. There is a theoretical possibility of increased VOCs at higher hemoglobin. The study demonstrated that higher hemoglobin was associated with a greater reduction of VOC.[24] In the 72 week analysis of the HOPE study, patients who achieved the greatest improvements in hemoglobin developed fewer VOC as compared to placebo and those with lower levels of hemoglobin. The improvements were seen across the complete range of hemoglobin levels with the highest benefits seen in the group of patients achieving Hb >10 g/dl.[25]

There were numerically fewer VOC in the voxelotor group as compared to placebo even after discontinuation of treatment. Venous thromboembolism has been reported on voxelotor.[26] Voxelotor could potentially interfere with the results of the hemoglobin HPLC. The US FDA approved this drug at a dose of 1500 mg for SCD on the basis of its benefits on anemia in November 2019 for adults and children older than 12 years of age. It was approved for children older than 4 years in December 2021after data on 45 children, 4–11 years of age, was presented in the 2021 EHA.[27] Abdominal symptoms are the main side effects of the medication.

INHIBITION OF ADHESION

P-selectin is a cellular adhesion molecule that is stored within alpha granules of platelets and endothelium. It gets transported to the surface of the activated platelets and the endothelium in response to injury. P-selectin on the surface the activated platelets attracts neutrophils and monocytes which, in turn, get activated. These platelet-neutrophil-erythrocyte aggregates block the small vessels and cause VOC.[28]

Therapies targeted at selectins and other adhesion targets are the subject of study including P-selectin-directed monoclonal antibodies (Crizanlizumab), E-selectin (Rivipansel), MAC-1 (intravenous immunoglobulin), platelet glycoprotein Ibα (CCP224), and mitogen-activated-protein-kinase inhibitors (MEK inhibitors).[29]

Crizanlizumab is approved in patients older than 16 years and non-responsive to hydroxyurea and/or L-arginine. It was FDA approved at a dose of 5 mg/kg/day every 4 weeks in 2019 based on the SUSTAIN data.[30] The SUSTAIN trial is a randomized multicenter phase 2 study that enrolled 198 patients. The annual rate of sickle cell pain crisis was reduced by 45.3%. It significantly increased the time to first and second crisis and was effective in patients receiving

hydroxyurea (32.1% lower) as well as those without (50% lower). It was effective in other compound sickle states. Expectedly, it did not reduce hemolysis (reticulocyte count, LDH, haptoglobin, hemoglobin, and indirect bilirubin). There were no significantly different side effects compared to placebo and no antibodies to the monoclonal antibody were detected.[30]

The adhesive process mediated through P-selectin is an essential first step in the recruitment of leukocytes to sites of tissue injury. This P-selectin mediated regulation plays a major role in tissue repair by leukocyte mediated removal of dead senescent cells. An animal model study on p-selectin deficient SCD mice showed the absence of VOC in the hepatic sinusoids. However, this did not prevent liver damage and iron overload. This study by Vats *et al.*[31] demonstrated higher circulating levels of aged neutrophils and monocytes and delayed migration of neutrophils to sites of inflammation. They also demonstrated higher levels of senescent cells and reduced epithelial cell proliferation in the liver. Thus, despite the reduction in VOC, crizanlizumab did not reduce chronic liver damage.

MODULATORS OF OXIDATIVE STRESS

Sickle cells have reduced capability to withstand oxidative stress as compared to normal red blood cells. HbS is unstable hemoglobin and easily undergoes autoxidation in a hypoxic environment. This releases reactive oxygen species and depletes glutathione and nicotinamide adenine dinucleotide (NAD) which maintain structural integrity. This puts the red blood cell under further stress and predisposes it to lysis. RBC lysis releases free heme which scavenges nitric oxide and affects vascular tone.[32] The ROS incites inflammation, endothelial dysfunction, and surface expression of adhesion molecules such as P-selectin and VCAM-1.[29]

Glutamine is an essential precursor to the synthesis of NAD which along with its reduced form, NADH is essential to maintain the redox balance. Glutamine is also the precursor for glutathione and arginine which also protect the RBC from oxidative damage. Thus, the replacement of glutamine is an attractive target in preventing oxidative stress.[32]

L-glutamine was approved by the FDA in 2017 for children and adults with SCD based on the results of the phase 3 trial of L-Glutamine (Endari) in children and adults, age range 5–58 years.[33] It is administered in a dose of 0.3 g/kg orally twice per day limited to a maximum daily dose of 30 g. The mechanism of L-glutamine is not clearly understood but possibly involves the correction of the NAD-NADH redox balance. Glutamine was associated with fewer pain crises (3 vs. 4), fewer acute chest syndromes (8.6 vs. 23.1%), and fewer hospitalizations (2 vs. 3). L-glutamine was associated with longer time to first (84 days vs. 54) and second (212 vs. 133) hospitalizations. This was effective irrespective of hydroxyurea use. This, however, did not translate into improvements in markers of hemolysis – hemoglobin, reticulocyte count, and LDH.[33]

Endari as a proprietary medication is 20 times more expensive than hydroxyurea in developed countries.[32] Over the counter, preparations of glutamine are available but have not been studied as generic variants of the trial drug.

OTHER NOVEL DRUGS

There have been several candidate drugs in various phases of the study. Senicapoc and magnesium which improved RBC volume and prevented dehydration were terminated for lack of benefit. Pomalidomide, decitabine, and panobinostat have effects on improving HbF, but there are concerns of secondary malignancies. Yet others failed to show benefits in phase 3 studies (prasugrel- platelet inhibitor, L-arginine, and N -acetylcysteine), lack of benefit in phase 2 studies (inhaled NO, and sildenafil), and several others with limited efficacy data.[36] A special mention must be made of Nicosan. This is a plant product patented by Nigerian scientists and showed promise as a natural plant-derived product. This phytomedicine reduced the frequency of the most severe forms of pain crisis.[37] However, its production has been hampered mainly by a lack of local expertise in scaling up production.

STEM CELL REPLACEMENT THERAPIES:

The only curative options to reverse the SCD phenotype are SCT or gene therapy. It is estimated that just about 20% donor myeloid chimerism[42] is sufficient for the purpose. The overall survival rate is reported at 93% with greater survival rates in children below the age of 16 (95% vs. 80% 5-year survival).[43] The 2-year survival in recipients of matched unrelated donors is 79%. The STRIDE trial, using a reduced toxicity regimen with busulfan, fludarabine, and ATG regimen in young adult recipients, achieved 3 years event-free survival of 82% with both fully matched related and unrelated donors.[38]

Taking advantage of the ability to reverse the phenotype with mixed chimerism, a chemotherapy-free regimen of TBI with alemtuzumab allows the transplant procedure in older children and adults with a fully matched sibling donor, without mortality.[39] We, in our center, have benefited from the availability of alemtuzumab/campath under a patient assistance program and have successfully used this regimen. The only drawback is the prolonged use of sirolimus, possibly lifelong, to maintain the mixed chimerism state. The availability of a matched sibling donor is approximately 25% and in selected cases with significant morbidities attributed to SCD, haploidentical transplant is a valid option.

Gene therapy utilizes autologous stem cells and then genetically modifying them to remove the HbS mutation. In 2017, a 13 years old was cured of the disease through transfer of an antisickling beta globin gene variant (βA-T87Q).[40] Jennifer Doudna received the Nobel prize for the CRISPR-Cas9 technique to edit genome information in 2020. In 2014, this technique was used to edit out the mutant gene in sickle cell recipients and is currently undergoing trials. The technique has also been used to silence a gene that interferes with HbF expression.[41]

CONCLUSION

Stem cell replacement therapies (allogenic SCT or gene therapy) are the only curative options for therapy and are not applicable due to various reasons in the majority of individuals with SCD. There are currently four approved drugs for SCD. They can be used as per the perceived phenotype of an individual patient: Anemia/hemolysis(hydroxyurea, L-Glutamine, and voxelotor), vaso-occlusion (hydroxyurea, L-glutamine, and crizanlizumab), and acute chest syndrome (hydroxyurea, and L-glutamine).[6]

None of the medications so far (perhaps other than hydroxyurea in primary stroke prevention) have proven benefits against the prevention of stroke and chronic organ damage. Hydroxyurea remains the most affordable and effective option of the four with the potential to improve on the benefits in combination with the other agents. Despite its many proven benefits, it remains underutilized. We do have three other drugs and resource constraints aside, one would be interested in trials combining these with hydroxyurea to see if this could provide meaningful and normal lifespans for individuals with SCD.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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