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Pharmacotherapy of Sickle Cell Disease

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Summary:

Sickle cell disease (SCD) is a potentially devastating condition that is caused by an autosomal recessive inherited hemoglobinopathy which results in the vaso-occlusive phenomena and hemolysis. The severity of the complications that occur with this disorder are widely variable, but overall mortality is increased and life expectancy decreased when compared to the general population.

Care of patients with sickle cell disease is largely supportive with hydroxyurea representing the only widely used drug which modifies disease pathogenesis. Painful vaso-occlusive events are the most common complication experienced by both children and adults with sickle cell disease and there are few treatment options to prevent the development of these events. Most are managed with traditional supportive care measures (i.e. aggressive hydration, anti-inflammatory and narcotic analgesics) that have not changed in decades and which are adequately met by the current World Health Organization (WHO) Essential Medicines List (Table 1).

Table 1. Pharmacotherapeutic agents utilized in the treatment of sickle cell disease which are currently on the Essential Medicines List and the Clinical Use of Blood Handbook.

Disease Modifying Agents
hydroxycarbamide (hydroxyurea)*****

Supportive Care Agents
Analgesics
paracetamol
ibuprofen
codeine
morphine

Antibiotics
phenoxymethylpenicillin
cefotaxime

Pertinent Vaccines
pneumococcal vaccine

Systemic Treatments
Parenteral 5% glucose, 0.45% sodium chloride
Red blood cell transfusion
(http://www.who.int/bloodsafety/clinical_use/en/Handbook_EN.pdf)

Iron Chelators
Deferoxamine

*****On list for treatment of cancer not sickle cell disease; also not on essential medicines list for children

Sickle Cell Disease: Background

Etiology and Epidemiology

Sickle cell disease (SCD) is a potentially devastating condition that is caused by an autosomal recessive inherited hemoglobinopathy, which results in the hallmark clinical sequelae of vaso-occlusive phenomena and hemolysis. The genetic abnormality is due to a substitution of the amino acid valine for glutamic acid at the sixth position on the beta globin chain and was first described over one hundred years ago.[1-2] Hemoglobin S (HbS), the hemoglobin that is produced as a result of this defect, is a hemoglobin tetramer (alpha2/beta S2) that is poorly soluble and polymerizes when deoxygenated.[3] Overall, the incidence of sickle cell disease exceeds that of most other serious genetic disorders, including cystic fibrosis and hemophilia.[4-5] It is seen worldwide but occurs most frequently in Africans and less commonly in those of Mediterranean, Latino, East Indian, and Arab descent.[6] It is estimated that 16% of the population in Africa has a sickle hemoglobinopathy which is the highest proportion worldwide. The Americas and the East Mediterranean region represent the next highest proportion of sickle cell hemoglobinopathy as delineated by the World Health Organization.[6]

SCD results from any combination of the sickle cell gene with any other abnormal β-globin gene and there are many types of SCD. The most common types include sickle cell anemia (Hb SS), the sickle beta-thalassemias (Hb $S\beta^0$ and Hb $S\beta^+$), hemoglobin SC disease (Hb SC) and sickle cell disease with hereditary persistence of fetal hemoglobin (S/HPFH). HbSS is the most common form of sickle cell disease. Patients with Hb SS and Hb $S\beta^0$, in general, have the most severe forms of SCD including lower hemoglobin levels and more frequent vaso-occlusive and hemolytic complications. Sickle-C (Hb SC) disease is the second most common form of SCD. Patients with this type of SCD generally have a more benign clinical course than do patients with Hb SS or sickle β^0-thalassemia. Likewise, patients with Sickle β^+-thalassemia and S/HPFH also generally have a more benign clinical course and patients with S/HPFH may actually have hemoglobin levels that are or approach normal.

Adults with sickle cell disease who live in the United States have a decreased life expectancy with the odds of surviving beyond the 7th decade of life reported to be less than 30%.[7] Historically, Platt et al. reported a large number of adults with sickle cell disease who died during acute sickle cell related complications such as pain, acute chest syndrome, and stroke.[7] In this era, the most common causes of death in adults from sickle cell disease reported are pulmonary hypertension, sudden death of unknown etiology, renal failure, and infection.[8] With regard to children with SCD, in the developed world, the mortality rate is estimated to be as low as 0.5-1.0 per 100,000 children. This is in contrast to higher rates in developing countries such as the Republic of Benin which recently reported a mortality rate of 15.5 per 1,000 children (or 1,550 per 100,000 children).[9] The most common causes of death in childhood from sickle cell disease are infection, acute chest syndrome and stroke.[10-11]

Pathophysiology

There is a large amount of heterogeneity in the expression of sickle cell disease which is not fully explained by the single mutation or different variants of hemoglobin S. This variability is manifest by a wide spectrum in both frequency and intensity of painful vaso-occlusive crises as well as highly variable degrees of organ dysfunction. The pathophysiologic processes that lead to sickle cell disease related complications result from a combination of hemolysis and vaso-occlusion. Hemolysis occurs as a result of repeated episodes of hemoglobin polymerization/depolymerization as sickle red blood cells pick up and release oxygen in the circulation. Red blood cell membranes become abnormal from this process and red blood cells have a shortened lifespan. Hemolysis can occur both chronically and during

acute painful vaso-occlusive crises and also results in the release of substantial quantities of free hemoglobin into the vasculature. This resultant free ferrous hemoglobin likely consumes significant quantities of nitric oxide (NO),[12] which in turn, leads to abnormal regulation in vascular homeostasis.[12-14]

In addition to hemolysis, intermittent episodes of vascular occlusion cause tissue ischemia, a major morbid component of the disorder which results in acute and chronic multi-organ dysfunction,[15] and which is characterized by chronic inflammation and ischemia-reperfusion injury.[16-18] Data suggest that neutrophils play a key role in the tissue damage which occurs as both neutrophil numbers are increased and evidence suggests that they are abnormally activated and adherent.[19] Likewise, recent data suggest that sickle red cells induce adhesion of lymphocytes and monocytes to the endothelium such that these may contribute to the pathogenesis of vascular occlusion.[20]

Common Morbid Complications

Vaso-occlusion

Vaso-occlusive painful events are the most common morbidity seen in patients (both children and adults) with sickle cell disease. Vaso-occlusion not only results in recurrent painful episodes, but also a variety of serious organ system complications that can lead to life-long disabilities and/or early death. For example, based on data from the Cooperative Study of Sickle Cell Disease (CSSCD), in which the circumstances of death were examined in 209 patients who were over 20 years of age when they died, 22% of deaths occurred during a pain episode. Acute chest episodes were temporally related to hospitalization for pain in 77% of patients who had them, and individuals older than 20 years of age with a higher rate of painful episodes had an increased risk of premature death when compared to those with a lower rate of pain.[7, 21-22]

Painful events are unpredictable and often severe resulting in repeated hospitalizations, missed days of school or work, and very poor health-related quality of life as well as an increased mortality rate.[7, 23-26] Furthermore, recent data suggest that nearly every day, children, adolescents and adults with sickle cell disease all suffer from pain that is intense enough to disrupt day to day functioning.[23, 27-29] Despite how common and widespread this complication is, there are few treatment options to prevent the development of these events and most are managed with traditional supportive care measures that have not markedly changed in decades. The pain which occurs can be acute or chronic, it varies among individuals in its frequency and intensity, and it is the primary cause of hospitalization in patients with SCD. Common triggers for vaso-occlusive crises include dehydration, infection, extreme temperature, and emotional stress. However, often no identifiable cause is found and pain often occurs without warning.

Bacteremia/Sepsis

Children with sickle cell disease are at increased risk for bacteremia that can result in sepsis and death; due in large part to functional asplenia that develops over time in these children. In developed countries and recently in Africa, the most common organisms involved include *Streptococcus pneumoniae*, Salmonella species, and *Haemophilus influenza*.[30-31]

Acute Chest Syndrome

The specific definition of what constitutes acute chest syndrome (ACS) varies but usually refers to a new pulmonary infiltrate accompanied by fever and/or symptoms or signs of respiratory disease in a patient with sickle cell disease (SCD).[21, 32] It is a relatively common

cause of frequent hospitalizations and death and a common indication for transfusion and treatment with hydroxyurea.[32-34] Several studies suggest that the case fatality rate is lower in children (1.1–1.5%) than adults (4.3–9%), but ACS accounts for a significant proportion of mortality in both groups. [7, 21, 34-35] Over half of the patients who developed ACS were hospitalized for another reason prior to developing ACS, usually a vaso-occlusive painful crisis.[21] The etiology of ACS is multi-factorial and not completely understood. Previous studies have shown that infection, fat emboli, and pulmonary infarction are all commonly associated with the development of ACS but many episodes of ACS develop without an obvious cause.[21, 32] Treatment usually involves antimicrobials to cover both common causes of pneumonia such as S*treptococcus pnuemoniae* and *Chlamydia pneumoniae* as well as atypical pathogens such as mycoplasma.[21] If there is a history of asthma, bronchodilators and corticosteroids may be used during an acute chest syndrome event. However, use of corticosteroids may prolong hospitalization or lead to readmission.[34] In addition to these measures, red blood cell transfusion is often used as supportive treatment during an acute chest syndrome event.

Pulmonary Hypertension

The prevalence of pulmonary hypertension in adults with sickle cell disease is 25-32% in both the United States and Africa.[36-37] The use of echocardiogram to detect high tricuspid regurgitant velocity as a marker of increased systolic pulmonary artery pressure has been increasingly used over the last 5 years leading to the recognition that pulmonary hypertension is common in sickle cell disease and is associated with an increased risk of death.

Central Nervous System Disease

Central nervous system disease is common in sickle cell disease and usually manifests as stroke and/or vasculopathy in those with the disease. Overt stroke occurs in up to 10% of children with the disease and usually involves large cerebral vessels that affect large regions of the brain.[38] Without treatment, there is a high risk of recurrence. With transfusion therapy, this risk remains substantial at 22%.[39] Silent stroke, defined as an infarct on imaging studies with a normal neurological examination, occurs in at least 22% of those with sickle cell disease.[40] Over the last decade much has been learned about cerebral vasculopathy given the advent of newer imaging modalities. Ten years ago, Adams et al.[41] described how elevated transcranial Doppler (TCD) velocities detected in large intracerebral vessels were associated with an increased risk of an overt stroke occurring. For patients who received chronic red blood cell transfusions to decrease the concentration of hemoglobin S, the risk was significantly decreased and this therapy has now been accepted as standard of care for patients with elevated TCD velocities. The morbidity related to stroke is not insignificant. Children suffer cognitive impairment from stroke that impacts their academic achievement.[42] In addition, they may suffer physical limitations related to the stroke such as hemiparesis.

Priapism

Priapism is another vaso-occlusive event that occurs in patients with sickle cell disease. Priapism is not uncommon for males with sickle cell disease with a probability of having at least one episode by age 20 of 89% and an average age of 12 years for the first episode. The frequency in adults with sickle cell disease ranges from 30-45%.[43-45] Treatment varies and consists largely of supportive measures with intravenous fluids, non-steroidal anti-inflammatory medication and opioids. A urological consultation for aspiration and irrigation of the corpora is warranted for persistent priapism and has been effective. There are few randomized trials comparing treatment options and preventive measures especially in pediatric patients.[46]

Renal Effects

Microalbuminuria and albuminuria are common in the more severe genotypes of sickle cell disease and can occur in up to 80% of patients resulting in a glomerulopathy.[47-48] Approximately 15% of patients will advance to end stage renal disease by their third decade of life. About 25% of patients with hemoglobin SS disease have renal insufficiency defined as a reduced creatinine clearance of < 90 ml/min.[49] Currently, there are no identified treatments that have been shown to be effective in preventing the development of end stage renal disease in patients with sickle cell disease who show evidence of kidney disease early on. However, treatment with an angiotensin-converting enzyme inhibitor may decrease microalbuminuria and proteinuria.[50-51]

Avascular Necrosis

Avascular necrosis is one of the few complications that is more common with Hb SC than Hb SS and its prevalence has been reported to be as high as 41% of adults with sickle cell disease. With the advent of newer imaging such as magnetic resonance imaging, however, true prevalence remains unknown.[52] Surgical treatment with coring and osteotomy and joint replacement have both been used for severe disease.[53-54]

Sickle Cell Disease: Pharmacotherapy (Disease Modifiers and Supportive Care)

Disease Modifiers

Hydroxyurea

Hydroxyurea represents the only major breakthrough in pharmacotherapy of sickle cell disease within the past 20 years and is the only drug that is approved by the U.S, Food and Drug Administration (FDA) for treatment of adults with sickle cell disease. It also represents the only currently available agent that is capable of modifying disease pathogenesis and its use has transformed the treatment of sickle cell disease.[55-57] Treatment with hydroxyurea has not only been shown to significantly decrease the incidence of painful crises but also, to be effective in the treatment of acute chest syndrome,[58] priapism,[59] and in reducing overall mortality in adult patients.[58] Hydroxyurea has also been shown to be cost effective in the treatment of adults with sickle cell disease[60] and to be of value for treatment of SC disease.[61] For all of these reasons, hydroxyurea is available to be a part of standard of care for patients with severe sickle cell (SS) disease in the United States. Studies have also shown, however, that patients with sickle cell disease have a variable response to hydroxyurea,[62-63] which in some instances, may limit its utility. The mechanisms responsible for this variability remain unknown and may include adherence to therapy as the medication is dosed on a daily basis and treatment requires regular follow up.

Hydroxyurea increases HbF in sickle cell anemia through its cytotoxic effects which cause erythroid regeneration. It also causes myelosuppression which leads to decreased leukocyte counts and less inflammation which likely result in decreases in both hemolysis and vaso-occlusion.[64] Although the clinical improvement observed following treatment with hydroxyurea has been attributed to increased levels of HbF, hydroxyurea also reduces the number of poorly deformable dense sickle cells, highly adhesive sickle reticulocytes, and leukocytes, and improves hemoglobin levels, any one of which may also alter disease severity. And, while hydroxyurea is potentially mutagenic and carcinogenic, there are no definitive data to suggest that the incidence of malignancy is increased in patients who receive

hydroxyurea for therapy related to sickle cell disease. Given that the risk of death from the complications of adult sickle cell disease appears to be substantially greater than the potential for hydroxyurea induced leukemia, the risk benefit ratio of treatment appears to favor treating patients with sickle cell disease. Despite the fact that hydroxyurea is a well known drug with proven efficacy for sickle cell disease, its utilization in the United States and elsewhere is limited.[65-67]

Despite lack of FDA approval for use in children, hydroxyurea is also utilized for treatment of children who exhibit signs of severe disease. Therapeutic studies of hydroxyurea have been performed in children including investigations that have documented hematologic response and lack of significant toxicity,[68-69] decreases in vaso-occlusive episodes,[68, 70-74] and possible prevention of secondary strokes.[75] An additional study in children has also shown that hydroxyurea decreases resting energy expenditure and may curtail the hypermetabolic state observed in sickle cell disease.[76] Importantly, recent data also suggest that administration of hydroxyurea in infants with sickle cell disease is feasible, well tolerated, demonstrates efficacy as measured by hematologic and biochemical parameters and may delay functional asplenia.[77] In longer term studies of hydroxyurea in children, the treatment effects were sustained in some patients for more than 5 years without any clinically important toxicity.[69, 78-80] Interestingly, pediatric patients appear to exhibit a more robust hemoglobin F response than adults.[69, 81-83] The reasons for this phenomenon (e.g., age-associated differences in pharmacokinetics, concentration-effect response as pertains to increasing NO availability) remain unknown.

Supportive Care Agents

Analgesia

There are no evidence-based guidelines for the treatment of SCD-associated acute pain episodes, either in the hospital or at home. Only a small number of high quality studies of analgesics have been performed with small numbers of patients suffering from acute SCD related pain and there are no studies performed which address the management of chronic pain.[84] Reasonable strategies for patient care management can be employed based on established principles of pain management such as the World Health Organization's "ladder" for the treatment of cancer-related pain (http://www.who.int/cancer/palliative/painladder/en/index.html). Rational and effective management SCD related pain relies on thorough assessment and individualization of therapy coupled with the use of both non-pharmacologic and pharmacologic approaches. Non-pharmacologic approaches include the use of heat or ice packs, relaxation, distraction, music, massage, vibration, prayer, therapeutic exercises, menthol cream rub, self-hypnosis, acupressure, acupuncture, transcutaneous electrical nerve stimulation (TENS), and biofeedback. While there are few controlled trials which evaluate the efficacy of these modalities, anecdotal reports from patients and providers attest that these approaches are often effective in relieving mild pain and decreasing the amount of opioid consumption for more severe pain.[85] Unfortunately, multiple studies show that a large number of patients with SCD in many countries including the United States do not seek medical attention for the treatment of pain and, instead cope with pain at home or in the community.[26, 86-88]

Mild pain can be treated at home and is usually adequately treated with general nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and ketorolac or other non-opioid analgesics like paracetamol. However, given the compromise of renal blood flow in patients with SCD and the risk of acute renal failure, NSAIDs should be utilized based on a case-by-case basis, should be avoided in those with renal involvement, and probably should not be used beyond five days.[22] For more severe pain, oral opioids should be considered as first-line

treatment in acute pain crises unless there is clinical evidence that the patient cannot take or absorb oral medications. For children, sustained-release oral opioids, coupled with readily available rescue analgesia, appear to be an effective alternative to parenteral opioids.[84] Codeine in combination with other analgesics appears to be the most common first-line oral opioid treatment and plays an essential role in home pain management regimens.[4, 87, 89-91] However, there are a multitude of alternative opioid drugs that are commonly used to treat SCD related pain which include hydrocodone/acetaminophen combinations, oxycodone, morphine, and hydromorphone, and fentanyl. The choice of an opioid, its dose, and route of administration should be individualized based on past history and experience and severity of the pain. No one opioid constitutes an effective treatment for all patients or even a given patient at different times. The general trend currently is to avoid the use of meperidine and to administer opioids orally for mild pain and intravenously or subcutaneously for severe pain and to avoid the intramuscular route if possible. Considerations of drug metabolizing enzyme polymorphisms (e.g. CYP2D6, UGT2B7) and drug-drug interactions must be taken into account.[85]

In addition to analgesic drug treatment, acute pain episodes may also be treated with hydration (oral or intravenous) as increased plasma osmolarity from a reduced plasma volume can worsen a vaso-occlusive crisis by causing intracellular dehydration, hemoglobin polymerization and further sickling. Patients with sickle cell disease also have isosthenuria, which leads to difficulty in excreting a sodium load. Therefore, fluids should be administered in a quantity sufficient to correct existing deficits and replace ongoing losses in order to maintain a euvolemic state. If tolerated, oral rehydration should be used in patients with milder vaso-occlusive crises. The parenteral route of rehydration is indicated in patients with severe pain, vomiting or volume depletion.[92-93]

Iron Chelators

Chronic red blood cell transfusion is used for a variety of indications in patients with sickle cell disease including for the treatment of stroke, acute chest syndrome and refractory pain. The goal of chronic red blood cell transfusion therapy is to decrease the percentage of sickle hemoglobin (often to less than 30%) rather than to raise the hemoglobin level. This treatment has been shown to be quite effective, but leads to the development of iron overload when administered for long periods of time. Iron overload results in premature death due to iron deposits in the liver and heart, most commonly, resulting in end organ damage and death from liver cirrhosis or heart disease.

Historically, deferoxamine has been used to treat iron overload and this medication requires parental administration, usually subcutaneously, over several hours 5-7 days a week. Recently, effective oral iron chelators such as deferasirox have become more widely used and are approved for use in the United States and by the European Medicines Agency (EMA). Deferiprone, another oral iron chelator, is not approved for use in the United States but is approved for use in the European Union. It is thought to be effective at removing cardiac iron but may not be as effective in removing liver iron.[94] These medications have the potential to revolutionize the treatment of iron overload as they are easy to administer, and may help improve compliance.

Treatment for Pulmonary Hypertension

To date there are no curative or “best” treatments defined and there are clinical trials underway to discover new drugs effective in treating pulmonary hypertension. For pulmonary hypertension that is not related to hemolytic anemia, new treatments have resulted in clinical responses and improved survival. Prostacyclin analogues, endothelin-1–receptor antagonists, phosphodiesterase inhibitors, and thromboxane inhibitors, along with anticoagulants and

calcium channel blockers, are currently available or are the subject of ongoing clinical trials. Encouraging pilot studies have shown that infusions of prostacyclin analogues reduce pulmonary-artery pressures during cardiac catheterization in patients with sickle cell disease. These therapeutic agents most likely have a role in the treatment of pulmonary arterial hypertension associated with hemolysis.[21] However, studies for therapy focused on the pulmonary hypertension associated with sickle cell disease are greatly needed due to the unique pathophysiology that exists. For example, sildenafil is approved by the FDA and EMA for use in patients with pulmonary hypertension. In general, the drug treats pulmonary hypertension by relaxing the blood vessels in the lungs to allow blood to flow more easily. Since sildenafil was not FDA-approved to treat pulmonary hypertension in patients with sickle cell disease, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health sponsored but then stopped a clinical trial testing sildenafil for pulmonary hypertension in adults with sickle cell disease due to safety concerns. In an interim review of safety data from 33 participants who completed 16 weeks of treatment, researchers found that, when compared to participants on placebo, participants taking sildenafil were significantly more likely to have other serious complications such as vaso-occlusive crises related to their sickle cell disease (http://www.medicalnewstoday.com/articles/159196.php. Accessed 14June2010).

Preventive Pharmacotherapeutic Agents

Penicillin

Once it was realized that *Streptococcus pneumonia* was a common pathogen that causes bacteremia in children with sickle cell disease, a randomized, controlled trial was conducted that showed a decreased incidence of infection in those receiving penicillin prophylaxis therapy.[31] Recently, it has been shown that the organisms causing bacteremia in African children with sickle cell anemia are the same as those in developed countries such that there has been a push to begin similar therapy in this continent.[30]

Folate

Several countries in the developed world fortify food with folate such that folate deficiency is rare and folate supplementation is not warranted. However in the developing world, when there are cases of malnutrition or undernutrition, folate supplementation may need to be considered in patients with sickle cell disease.

Vaccines

Due to the increased risk of bacteremia with *Streptococcus pneumoniae*, it is recommended that children with sickle cell disease receive pneumococcal vaccines with both the recent 13-valent pneumococcal conjugate vaccine and the pneumococcal polysaccharide vaccine. In the United States and other developed countries, this has led to a significant reduction in the incidence of infection from this organism.[95] In fact, use of the 7-valent pneumococcal conjugate vaccine over the last nine years is the likely reason why the mortality rate for children less than four years of age has decreased so significantly.[9]

Other Treatment Modalities

Red Blood Cell Transfusion

Chronic red blood cell transfusion is utilized to suppress hemoglobin S production and is the mainstay of secondary prevention of overt stroke in patients with sickle cell disease. For the first three years after an overt stroke, the goal of red blood cell transfusions is to suppress

hemoglobin S levels to 30% or less. After 3 years, the goal becomes to maintain hemoglobin S levels to 50% or less. For those with high TCD velocities, chronic red blood cell transfusions are recommended to decrease the risk of an overt stroke occurring.[41] Treatment to suppress hemoglobin S is recommended indefinitely.

There is currently no recommended standard treatment for prevention of silent stroke. An ongoing multi-center trial is presently underway to determine if chronic red blood cell transfusions are effective in preventing recurrent silent stroke.[96] In addition, a multi-center trial to determine the efficacy of hydroxyurea compared to chronic red blood cell transfusions in preventing recurrent overt stroke was recently underway but stopped prematurely (Stroke with transfusions changing to hydroxyurea.[97] Further data on the findings from this study will help inform future therapy of stroke.

Many centers also perform pre-operative transfusions with the aim of reducing the complications of surgery and anesthesia.[98] The largest study to examine the role of transfusion in the pre-operative management of sickle cell anemia was a randomized study that compared exchange transfusion (with a goal of achieving a Hb of > 10 g/dL and Hb S of <30%) versus simple transfusion (to achieve a Hb of > 10 g/dL).[98-99] This study concluded that not only was simple transfusion as effective as exchange transfusion in preventing perioperative complications, it also provided a significantly lower rate of transfusion related complications.[100] The question of which procedures are safe to carry out in children with SCD without pre-operative transfusion remains controversial as there is a lack of randomized controlled trials to answer this question. However, simple transfusion to increase the Hb level to 10g/dL for major procedures, blood replacement for both profound anemia of less than 5 g/dL and intraoperative hemorrhage appear appropriate.[99] Several studies suggest that minor procedures can possibly be safely undertaken without transfusion.[98, 101-102] Alloimmunization can be minimized by giving antigen matched blood (matched for K, C, E, S, Fy, and Jk antigens).[4] Regardless of transfusion status, strong multidisciplinary collaboration is vital throughout the perioperative period.

Pharmacotherapeutic Agents under Investigation

There are a multitude of therapeutic agents under investigation for disease modifying treatment of sickle cell disease,[103] but as stated previously, hydroxyurea is the only agent that is currently widely available. Investigational agents include:

Drugs designed to increase hemoglobin F (i.e. decitibine which causes hypomethylation of the γ-globin gene promoter).

Short chain fatty acids (i.e. phenylbyturate) which inhibit histone deacetylase causing histone hyperacetylation and changes in chromatin structure and resultant enhancement of γ-globin gene expression.

Medications to prevent sickle red blood cell dehydration (i.e. oral magnesium which inhibits erythrocyte K+-Cl– co-transport and ICA 17043 which is a Gardos channel inhibitor.)

Anti-adhesion agents which target the abnormal interactions among erythrocytes, endothelial cells, leukocytes and platelets that are part of the pathophysiology of the disease process.

Both endothelium dependent (i.e. atorvastatin) and independent (i.e. nitric oxide) vasodilators.

It is important to note that these agents are in various stages of testing and are not proven to be of clinical benefit in patients with sickle cell disease.[103]

Conclusion

Sickle cell disease is a chronic, debilitating disorder with a myriad of symptoms that make disease treatment challenging. While there is a need for new treatments for sickle cell disease, especially for disease modifying agents, there is also a need to explore new approaches for improving treatment with existing modalities.

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