Short communication

ANNALS OF MEDICINE & SURGERY

OPEN

# Tackling sickle cell crisis in Nigeria: the need for newer therapeutic solutions in sickle cell crisis management – short communication

Ekene Mary Nnagha, MBBCh[a,b], Matthew Kayode Ademola, MBChB[a,c], Eghosa Ann Izevbizua, MD[a,d], Olivier Uwishema, MD[a,e,f], Abubakar Nazir, MBBS[a,g,*], Jack Wellington, MD[a,h]

**Abstract**

Sickle cell disease (SCD) is a group of inherited haematological disorders, which affects the shape of the oxygen-carrying haemoglobin component of erythrocytes, giving it an abnormal sickle-shaped appearance. This disease is one of the most common haematological disorders in Nigeria and is generally characterized by anaemia, painful crises, and multi-organ dysfunction. Recurrent episodes of painful crises account for most of the morbidities and mortalities observed in SCD, particularly sickle cell anaemia. This has been a critical concern in the field of haematology and molecular genetics as several therapeutic solutions have been explored over the past few years to treat symptoms of this disease and alleviate painful crises. However, most of these treatment options are not readily available and affordable to affected patients in lower socioeconomic settings in Nigeria, causing a wider range of complications and end-stage organ failure. To address this issue, this article explores an overview of SCD, management alternatives and the need for newer therapeutic solutions to cover the gaps or inadequacies of effective sickle cell crisis management.

**Keywords:** anaemia, haematology, haemoglobin, haemoglobinopathies, Nigeria

## Introduction

Sickle cell disease (SCD) has been recognized as a public health problem globally by the WHO since 2006 and the United Nations since 2008[1] with studies showing it to be the most frequent and socially significant haemoglobinopathy in the world[2]. It is an inherited haemoglobinopathy characterized by sickle-shaped erythrocytes or red blood cells that differ from the normal biconcave-shaped erythrocytes in the bloodstream.

The global incidence of SCD among neonates is about 300 000–400 000 yearly, and most of these cases are found in sub-Saharan Africa[3]. Africa produces about 240 000 newborns with SCD annually. In the past, most of these cases were unrecorded and undiagnosed mortalities due to inappropriate treatment and lack of newborn screening. As the years have gone by, there has been an improvement in survival cases due to increasing awareness of the disease, more sensitization as well as epidemiologic and economic transition[4]. SCD is an autosomal recessive inherited disorder. The affected individual has likely inherited it from both parents who are each heterozygous for the gene. This means that each parent has one copy of the mutated gene and will show no sign or clinical feature of the disease; they are referred to as carriers. An individual with just one copy of the mutated gene is said to have sickle cell trait (SCT), while an individual with both copies of the mutated gene has SCD, which then manifests as sickle cell anaemia (SCA), amongst other signs and symptoms. When two parents having SCT have a child, there is a 25% probability of that child having the disease, a 50%

### HIGHLIGHTS

- Sickle cell disease (SCD) has been recognized as a public health problem globally by the WHO since 2006 and the United Nations since 2008, with studies showing it to be the most frequent and socially significant haemoglobinopathy in the world.
- Blood transfusion and supplemental oxygen are also very important in the management of SCD. Transfusion is often indicated in sequestration and haemolytic crisis.
- Gene therapy involves the use of a patient's stem cells, thereby avoiding immune-mediated immune rejection and eliminating the need for a haemopoietic stem cell donor.

[a]Oli Health Magazine Organization, Research and Education, Kigali, Rwanda, [b]College of Medical Sciences, University of Calabar, Calabar, [c]Obafemi Awolowo University Teaching Hospital, Ile-Ife, [d]Benjamin S. Carson College of Health and Medical Sciences, Babcock University, Ilishan-Remo, Nigeria, [e]Clinton Global Initiative University, New York, New York, USA, [f]Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey, [g]Department of Medicine, King Edward Medical University, Lahore, Pakistan and [h]Faculty of Medicine, Cardiff University School of Medicine, Cardiff University, Cardiff, UK

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Oli Health Magazine Organization, Research and Education, Kigali, Rwanda. E-mail: abu07909@gmail.com (A. Nazir)



Annals of Medicine & Surgery (2023) 85:2282–2286

Received 27 February 2023; Accepted 6 April 2023

Published online 18 April 2023

http://dx.doi.org/10.1097/MS9.0000000000000696

chance that the child will have only the trait and another 25% that the child will have no mutated gene at all; neither a carrier nor has the disease. This genetic disease occurs as a result of a single-point mutation in the amino acid sequence that codes for the HBB gene that encodes for the beta subunit of normal haemoglobin (Hb) leading to the production of the haemoglobin S (HbS)[2]. There is a substitution of glutamic acid for valine, thus re-arranging the amino acid sequence to have 'GTG' (codon for valine) instead of 'GAG' (codon for glutamic acid). The abnormal Hb produced polymerizes upon deoxygenation causing sickling of the erythrocytes. The fragility, abnormal shape and rigidity of these cells predispose them to haemolysis, occlusion of blood vessels like capillaries, anaemia and other acute clinical sequelae. Studies have shown the presence of inflammation because of active haemolysis leading to the accumulation of Hb and heme in the plasma. The haemolysis causes a reduction in nitric oxide and increased production of reactive oxygen species. Molecules such as erythrocytic danger-associated molecular pattern molecules (eDAMPs) present from the heme can activate inflammation of the endothelium and activate the innate immune complement system and a host of events, thus accounting for the clinical severity of the disease condition.

## Forms of SCD

SCD is an umbrella term for genetically inherited red blood cell dyscrasias that affect the oxygen-carrying Hb molecular component of erythrocytes, as seen in SCA (HbSS), HbSC, HbSD, HbSE, HbSO and Thalassaemia (typically of the beta variant). SCD is also referred to as 'sickle cell disorder' by some authors. Others may refer to SCD as 'HbS disease' or 'HbS associated sickling disorder'. In SCD, the beta chain of the Hb component of red blood cells is affected, where valine replaces glutamic acid at position 6 of the beta-globin chain. This negatively decreases the solubility of the Hb at low oxygen tension, causing hypoxia and sticky sickle-shaped red blood cells, which can result in painful complications and morbidities.

### *Sickle cell trait*

SCT occurs in individuals who have both HbA (normal adult Hb) and HbS (sickle cell Hb) in nearly equal quantities. There is no clinical abnormality or symptoms in this condition. The ratio of HbA to HbS is 3:2. Therefore, the person is heterozygous.

### *Sickle cell haemoglobin disease*

Sickle cell haemoglobin disease (HbS) occurs when valine, which is the normal amino acid in HbA, is substituted for glutamic acid in the 6th position of the amino acid sequence of the β-chain. The individual is homozygous because both β-chains synthesize HbS ($2^{\propto}_{A}2^{\beta}_{S}$).

The Hb in this reduced state is less soluble, and semi-crystalline bodies called tactoids are formed. Molecular aggregation of the Hb occurs. This gelling of Hb inside the cells changes the shape of the red blood cell, making them 'sickle' shaped, instead of disc shaped. The viscosity of blood is increased, and the red blood cells quickly haemolyse due to low oxygen tension. The increased blood viscosity contributes to morbidity and mortality in sickle cell patients. In-vitro sickling is demonstrated by adding a reducing agent (i.e. Na-metabisulphite) to blood.

Sicklers are deficient in glucose-6-phosphate dehydrogenase, which makes them resistant to *Plasmodium malariae* and severe forms of *Plasmodium falciparum*. Their red cells are hypersensitive to lyse and more vulnerable to damage by oxidizing agents.

### *Sickle cell haemoglobin C disease*

Sickle cell haemoglobin C disease (HbC) is an abnormal Hb that is slow-moving and associated with intraerythrocytic crystal formation, target cells and chronic haemolytic anaemia. It may occur together with sickle cell Hb as (HbSC) and may lose water and shrink to become xerocytes. HbC causes HbC disease, which is characterized by target erythrocytes, anaemia, splenomegaly and intraerythrocytic Hb crystals (i.e. part of red cell inclusions).

### *Thalassaemia*

Thalassaemia is due to a defect in the synthesis of the polypeptide chains (α and β) of HbA. There is an increased amount of $HbA_2$ ($\alpha_2\,\delta_2$) and HbF ($\alpha_2\,\gamma_2$), which compensates for a reduced amount of HbA, and abnormal red cells are rapidly haemolysed *in vivo*. Children with β-thalassaemia fail to thrive and die young. There are two types of thalassaemia, α-thalassaemia and β-thalassaemia, but β-thalassaemia is more common.

In thalassaemia, there is no structural abnormality of Hb but a decreased rate of synthesis. A-thalassaemia is produced if α-chain synthesis is inhibited. B-thalassaemia is produced if β-chain synthesis is inhibited. The disease manifests as microcytic hypochromic anaemia.

(1) Thalassaemia major: here, the homozygous β-thalassaemia is evident from early life.
(2) Thalassaemia minor: this is the heterozygous state, which may or may not be accompanied by clinical illness.

## Clinical presentations of SCA

Some of the clinical presentations of SCA include chronic haemolytic anaemia, painful sickling crisis, leg ulceration, recurrent respiratory infection and infarction of the spleen, bones and organs as a result of sickling crisis and obstruction of small vessels by the sickle-shaped cells (Drepanocytes). Patients are also liable to salmonellosis, and the abdomen, bones and joints are affected by the crisis.

## Complications

The complications associated with sickle cell haemoglobinopathy include: acute pain chest syndrome and splenic sequestration; chronic pain; cerebrospinal disease and stroke; pulmonary hypertension; leg ulcers; avascular necrosis of the hips and shoulders; retinopathy; renal failure; blindness; gall stones; organ damage; and frequent infections, amongst others.

## Diagnosis

There are different techniques developed and currently being used in the diagnosis of SCD. These techniques include basic screening tests such as peripheral blood smear, solubility tests and sickling tests, as well as confirmatory diagnostic tests such as Hb electrophoresis, isoelectric focusing (IEF), high-performance liquid chromatography (HPLC) and genetic studies[5].

A peripheral blood smear is a simple screening modality for SCD that can be performed with the aid of a microscope and a glass slide. Blood is smeared on the slide and viewed under the microscope for morphological changes in the red cells. The presence of irreversibly sickle-shaped red cells, target cells, anisopoikilocytes and polychromasia could serve as pointers to SCD[6].

The sickling screening test for SCD is performed based on the sickled changes expected in HbS in its deoxygenated state. A drop of blood is mixed with a drop of freshly prepared 2% sodium metabisulphite, covered with a coverslip and sealed with petroleum jelly. The slide is left to stand at room temperature for 1–4 h and then examined under the microscope for the presence of sickled erythrocytes, which could be a pointer to SCD. The sickling test could give a false positive result if the concentration of sodium metabisulphite is greater than 2%, and a false negative result if the solution is stale, if the coverslip is not properly sealed, and in neonates[7].

The solubility test is based on the insolubility of HbS when compared to HbA in their reduced states. A freshly prepared solution of sodium metabisulphite, potassium dihydrogen phosphate and dipotassium hydrogen phosphate is mixed with the patient's blood, with the mixture spun in a centrifuge. The presence of HbS causes the precipitation of a red opaque band on the surface of the solution. Control samples with HbA, HbS and HbAS are expected to be tested simultaneously with the patient's test. Solubility test gives a false negative result if used in the newborn.

The use of Hb electrophoresis in the screening of SCD is based on the principle of migration of negatively charged Hb molecules towards the positive electrode (the anode) in an electric field. A specific medium is required for the separation and identification of different Hb variants. The rate of migration depends on the mass of the molecule, the strength of the electric field, pH and temperature of the buffer. The two commonly used buffers are cellulose acetate (alkaline) and citrate agar (acidic), operating at a pH of 8.4–8.9 and 6.0–6.2, respectively. The rapid separation of Hb molecules and the ease of buffer preparation are some benefits of the alkaline cellulose acetate Hb electrophoresis (ACAE) over the citrate agar electrophoresis (CAE). The co-migration of HbS, HbD and HbG, as well as HbC, HbE and HbO as single bands, are the drawbacks of the ACAE. The CAE helps to delineate Hb molecules that co-migrate in alkaline pH. It is also suitable for use in diagnosing SCD in newborns[7].

The IEF technique is a high-resolution electrophoretic method that is based on the principle of Hb molecule separation according to their isoelectric point – the point where the net charge of the molecule is zero. IEF is more suitable for larger sample sizes with variant Hb than ACAE due to its ability to identify more Hb variants because of its high resolution[5]. The high-resolution property of IEF depends on the applied voltage, thickness and pH of the gel medium[7]. IEF is considered the gold standard screening modality for SCD in newborns[5].

HPLC is an advanced automated setup that can be used to separate and quantify Hb variants based on their retention time and the shape of the peak[8]. Each variant has a specific retention time, which can be compared to the known Hb fractions[9]. HPLC can detect HbF, HbA2, HbS, HbC, HbBarts and other Hb variants. The need for skilled personnel and the high cost of purchasing and setting up an HPLC are major drawbacks to this technique[10].

DNA analysis is based on PCR or Southern blot analysis with the former gaining more usage in recent times. These techniques are used in diagnosing SCD based on the mutation in the beta-globin gene that leads to the production of sickled Hb. DNA analysis is used mostly in prenatal and pre-implantation diagnosis, and in resolving conflicting results from other methods used in diagnosing haemoglobinopathies.

Despite the volume of literature detailing multiple screening and diagnostic techniques for SCD, there is no structural national policy for diagnosing SCD in Nigeria[11]. ACAE is the most used method of SCD screening in Nigeria. It is, however, prone to errors which could be a result of faulty equipment, poor operation techniques and irregular monitoring of the laboratories where they are carried out. CAE, IEF, HPLC and DNA analysis are all very expensive, electricity-dependent and require specialized personnel training; hence, they are not frequently used in resource-poor countries like Nigeria[12].

In the last decade, point-of-care testing (POCT) kits such as Haemotype SC and Sickle SCAN have been deployed in the screening of SCD across the globe. The POCT kits are portable, affordable, user-friendly and do not require electricity or specialized personnel training. In addition, it provides subjects with the opportunity to have their screening for SCD done by themselves in the comfort of their homes[11]. The POCT kit helps by providing real-time actionable results leading to the initiation of prompt management protocols in patients suspected by healthcare workers to have a diagnosis of SCD[11]. Two multicentre studies conducted in Nigeria and India reported the specificity and sensitivity of Haemotype SC as 99.9 and 93.4%, respectively, for Nigeria, and 99.1 and 98.1%, respectively, for India[13]. A similar multicentre study conducted in the U.S. revealed both the sensitivity and specificity of Sickle SCAN as 99.0%. These multiple studies highlight the accuracy of POCT kits in the screening of SCD. The major drawback of the POCT kit is the inability to identify other Hb variants asides from HbA, HbS and HbC[14].

## Treatment

The treatment options available for SCD patients are aimed at relieving symptoms, avoiding crises, preventing complications and improving their quality of life.

Antibiotics play a key role in the management of SCD with children encouraged to commence the use of penicillin within their first year of life up to at least 5 years. This helps to protect the child against life-threatening infections from encapsulated organisms. Antibiotics are also used in adults to fight several infections caused by different groups of organisms.

Analgesics are also integral to the management of SCD patients particularly in vasoocclusive crises (VOCs). The class of analgesic used depends on the pain severity, with non-steroidal anti-inflammatory agents used for mild-to-moderate pain and opioids used in very severe cases.

Blood transfusion and supplemental oxygen are also very important in the management of SCD. Transfusion is often indicated in sequestration and haemolytic crisis.

Hydroxyurea (HU) is an HbF-inducing agent used in the treatment of SCD. The availability of HbF helps in significantly reducing the severity of SCD, thereby reducing associated morbidity and mortality. HU also contributes to the reduction of chronic inflammatory processes and helps in vasodilation

through an increase in nitric oxide (NO) levels[15–17]. Despite the available literature to back up the efficacy of HU, its level of use is still very low in Nigeria. The unavailability of a national guideline for its use, fear of potential side effects and doubts about its effectiveness have been implicated as leading reasons for the poor utilization of the medication among physicians in Nigeria.

Data obtained from Galadanci *et al*.[18] demonstrate the usage of old therapeutic medications for the management of SCD in about 11 hospitals across Nigeria.

Therapeutic medications used for sickle cell disease management in Nigeria

From the table above, folic acid and HU are the most commonly used therapeutic drugs of choice for SCA in about 11 hospitals in Nigeria. HU demonstrated effectiveness in decreasing the prevalence of painful sickle cell crisis and some of its associated acute complications, particularly Acute anaemia and Acute Chest syndrome, by increasing the synthesis of foetal Hb (HbF) in the red blood cells[18]. Folic acid is commonly used in combination with malaria prophylaxis to manage SCD in the 11 hospitals in Nigeria demonstrated above. Folic acid is given with malaria prophylaxis in SCD patients to reverse the anti-folate effects of the antimalarial therapy, and replete red blood cell stores[19]. There is no sufficient information on the effectiveness of folic acid in managing sickle cell crisis in Nigeria; however, a study carried out at a tertiary hospital in Enugu, Nigeria, from September 2018 to March 2019 demonstrated the observation of lower rates of red blood cells folate levels during sickle cell crisis than in normal or steady state. More research studies are still needed to confirm the correlation between folic acid deficiency and sickle cell crisis[19].

Newer agents have been approved by the FDA within the last 6 years for the treatment of SCD. These include voxelotor, crizanlizumab, and L-glutamine.

Its mechanism of action is by binding specifically to the N-terminus of the alpha subunit of HbS, thereby reducing dehydration and sickling of the red cells[20,21].

Although there is no substantial data to analyse the use of newer therapeutic medications in the management of SCD in Nigeria, one of the newly approved therapeutic medications for the management of SCD – Voxelotor – was approved for use for the treatment of SCD in the U.S. in 2019, and has demonstrated remarkable decrease in the frequency of VOC and transfusion rates in SCD patients, with a marked increase in Hb levels of sickle cell patients observed[22].

Crizanlizumab was approved for therapeutic use in SCD patients in 2019. It is a monoclonal antibody to *P*-Selectin that interferes with the mechanism of adhesion between sickled cells and the endothelium. This ultimately prevents the recruitment of leucocytes and other inflammatory response cells, activation of which could result in a sickle cell crisis. Its mechanism of action was found to be useful in decreasing the frequency of VOC in SCD patients[23].

The characteristic increase in the production of reactive oxygen species (ROS) from free iron and heme in SCD creates a pro-oxidant atmosphere. L-glutamine, one of the newer agents being considered in the treatment of SCD, was approved in 2017, and is an antioxidant actively involved in the metabolism of the reduced form of glutathione – GSH. L-glutamine has not demonstrated any efficacy in resolving the pathophysiology of sickle cell crisis,

| No | Clinic | City | Adult/paediatric | No. of patients | Medical records | Database | Folic acid | Malaria prophylaxis | Penicillin | Hydroxyurea |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ABUTH | Zaria | Adult/paediatric | 1150 | Y | N | Y | Y | N | Y |
| 2 | ABUTH | Zaria | Paediatric | 1700 | Y | Y | Y | Y | Y | N |
| 3 | AKTH | Kano | Adult | 270 | Y | Y | Y | Y | Y | Y |
| 4 | AKTH | Kano | Paediatric | 1300 | Y | Y | Y | Y | Y | Y |
| 5 | FMCA | Asaba | Paediatric | 100 | Y | N | Y | Y | Y | N |
| 6 | FMCA | Asaba | Adult | 15 | Y | Y | Y | Y | N | N |
| 7 | LASUTH | Lagos | Adult | 2200 | Y | Y | Y | Y | N | N |
| 8 | LASUTH | Lagos | Paediatric | 670 | Y | Y | Y | Y | N | N |
| 9 | LUTH | Lagos | Adult | 1000 | Y | Y | Y | Y | Y | Y |
| 10 | LUTH | Lagos | Paediatric | 1500 | Y | Y | Y | Y | Y | Y |
| 11 | MMSH | Kano | Adult/paediatric | 11000 | Y | Y | Y | Y | Y | Y |
| 12 | OAUTHC | Ile-Ife | Adult | 200 | Y | Y | Y | Y | N | N |
| 13 | OAUTHC | Ile-Ife | Paediatric | 145 | Y | Y | Y | Y | N | N |
| 14 | SCF | Lagos | Adult/paediatric | 270 | Y | Y | Y | Y | N | N |
| 15 | UCH | Ibadan | Paediatric | 500 | Y | Y | Y | Y | N | Y |
| 16 | UCH | Ibadan | Adult | 1000 | Y | N | Y | Y | N | N |
| 17 | UNTH | Enugu | Paediatric | 350 | Y | Y | Y | Y | N | N |
| 18 | UATH | Abuja | Adult/paediatric | 350 | Y | Y | Y | Y | Y | Y |

Y represents Yes and N represents No. ABUTH, Ahmadu Bello University Teaching Hospital; AKTH, Aminu Kano University Teaching Hospital; FMCA, Federal Medical Centre, Asaba; LASUTH, Lagos State University Teaching Hospital; LUTH, Lagos University Teaching Hospital; MMSH, Murtala Mohammed Specialist Hospital; OAUTHC, Obafemi Awolowo University Teaching Hospital; SCF, Sickle Cell Foundation; UCH, University College Hospital; UNTH, University of Nigeria Teaching Hospital; UATH, University of Abuja Teaching Hospital.

and has been associated with several adverse effects, including renal failure in SCD[20]. There are also limited studies that support the use of L-glutamine and other related antioxidants; hence the cautious use of L-glutamine in the therapeutic management of SCD is recommended[24,25].

The curative options for SCD include hemopoietic stem cell transplant (HSCT) and Gene Therapy. HSCT from an HLA-matched donor can provide the necessary cure for SCD. However, getting an HLA-matched donor (a sibling or haploidentical family member), as well as graft rejection, are limitations of this curative option[26]. HSCT, if performed below 16 years of age, tends to establish red cell production, reverse the damage and restore function in affected organs in patients with SCD[27]. Gene therapy involves the use of a patient's stem cells, thereby avoiding immune-mediated immune rejection and eliminating the need for a haemopoietic stem cell donor[28].

Despite the abundance of information and giant strides recorded in the treatment of SCD, there is no documented study for the use of any of the newer treatment agents or curative treatment options for SCD in Nigeria.

## Ethical approval

Not applicable.

## Consent

Not applicable.

## Sources of funding

Not applicable.

## Conflicts of interest disclosure

There are no conflicts of interest.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## References

[1] Mburu J, Odame I. Sickle cell disease: reducing the global disease burden. Int J Lab Hematol 2019;41(Suppl 1):82–8.
[2] Pinto VM, Balocco M, Quintino S, *et al*. Sickle cell disease; a review for the internist. Intern Emerg Med 2019;14:1051–64.
[3] Arishi WA, Alhadrami HA, Zourob M. Techniques for the detection of sickle cell disease: a review. Micromachines (Basel) 2021;12:519.
[4] Ford J. Red blood cell morphology. Int J Lab Hematol 2013;35:351–7.
[5] Adegoke SA, Oladimeji OI, Akinlosotu MA, *et al*. HemoTypeSC point-of-care testing shows high sensitivity with alkaline cellulose acetate hemoglobin electrophoresis for screening hemoglobin SS and SC genotypes. Hematol Transfus Cell Ther 2022;44:341–5.
[6] Frömmel C. Newborn screening for sickle cell disease and other hemoglobinopathies: a short review on classical laboratory methods-isoelectric focusing, HPLC, and capillary electrophoresis. Int J Neonatal Screen 2018;4:39.
[7] Pant L, Kalita D, Singh S, *et al*. Detection of abnormal hemoglobin variants by HPLC method: common problems with suggested solutions. Int Sch Res Notices 2014;2014:257805.
[8] Yang X, Kanter J, Piety NZ, *et al*. A simple, rapid, low-cost diagnostic test for sickle cell disease. Lab Chip 2013;13:1464–7.
[9] Nnodu O, Isa H, Nwegbu M, *et al*. HemoTypeSC, a low-cost point-of-care testing device for sickle cell disease: promises and challenges. Blood Cells Mol Dis 2019;78:22–8.
[10] Mukherjee MB, Colah RB, Mehta PR, *et al*. Multicenter evaluation of HemoTypeSC as a point-of-care sickle cell disease rapid diagnostic test for newborns and adults across India. Am J Clin Pathol 2020;153:82–7.
[11] Kanter J, Telen MJ, Hoppe C, *et al*. Validation of a novel point of care testing device for sickle cell disease. BMC Med 2015;13:225.
[12] Emechebe GO, Onyire NB, Orji ML, *et al*. Sickle cell disease in Nigeria – a preview. J Dent Med Sci 2017;16:87–94.
[13] Yawn BP, Buchanan GR, Afenyi-Annan AN, *et al*. Management of sickle cell disease: summary of 2014 evidence based report by expert panel members. JAMA 2014;312:1033–48.
[14] Ofakunrin AOD, Okpe ES, Afolaranmi TO, *et al*. Level of utilization and provider-related barriers to the use of hydroxyurea in the treatment of sickle cell disease patients in Jos, North-Central Nigeria. Afr Health Sci 2021;21:765–74.
[15] Dufu K, Oksenberg D. GBT440 reverses sickling of sickled red blood cells under hypoxic conditions in vitro. Hematol Rep 2018;10:7419.
[16] Patel M, Cabrales P, Dufu K, *et al*. GTx011, an anti-sickling compound, improves SS blood rheology by reduction of HbS polymerization via allosteric modulation of $O_2$ affinity. Blood 2014;124:1370.
[17] Ataga KI, Kutlar A, Kanter J, *et al*. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med 2017;376:429–39.
[18] Galadanci N, Wudil BJ, Balogun TM, *et al*. Current sickle cell disease management practices in Nigeria. Int Health 2013;6:23–8.
[19] Nnajekwu UC, Nnajekwu CO, Onukwuli VO, *et al*. Folate levels in children with sickle cell anaemia on folic acid supplementation in steady state and crises at a tertiary hospital in Enugu, Nigeria: a prospective, comparative study. Malawi Med J 2022;34:132–7.
[20] Niihara Y, Miller ST, Kanter J, *et al*. A phase 3 trial of l-glutamine in sickle cell disease. N Engl J Med 2018;379:226–35.
[21] Niihara Y, Tran L, Razon R, *et al*. A phase 3 study of L-glutamine therapy for sickle cell anemia and sickle b0-thalassemia. Blood 2014;124:86.
[22] Shah N, Lipato T, Alvarez O, *et al*. Real-world effectiveness of voxelotor for treating sickle cell disease in the US: a large claims data analysis. Expert Rev Hematol 2022;15:167–73.
[23] Quinn CT. l-Glutamine for sickle cell anemia: more questions than answers. Blood 2018;132:689–93.
[24] Gluckman E, Cappelli B, Bernaudin F, *et al*. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 2017;129:1548–56.
[25] Esrick EB, Bauer DE. Genetic therapies for sickle cell disease. Semin Hematol 2018;55:76–86.
[26] Orkin SH, Bauer DE. Emerging genetic therapy for sickle cell disease. Annu Rev Med 2019;70:257–71.
[27] Leonard A, Tisdale JF. Stem cell transplantation in sickle cell disease: therapeutic potential and challenges faced. Expert Rev Hematol 2018;11:547–65.
[28] Morgan RA, Gray D, Lomova A, *et al*. Hematopoietic stem cell gene therapy: progress and lessons learned. Cell Stem Cell 2017;21:574–90.