WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Malaria and Sickle Cell Disease (SCD)-Chemoprophylaxis and Treatment for Sickle Cell Disease Patients: A Mini-Review

K.K. Sha'a [a]; O.S. Elkanah [a]; S.G. Ishaya [a]*; I.K. Auta [b]

[a] *Department of Biological Sciences, Faculty of Science, Taraba State University, Jalingo, Nigeria*
[b] *Department of Biological Sciences, Faculty of Science, Kaduna State University, Kaduna, Nigeria*
DOI: https://doi.org/10.55248/gengpi.4.723.49251

A B S T R A C T

Malaria is an infectious disease that may result from infection by any protozoan parasite of the genus *Plasmodium*. Malaria is one of the prevailing human parasitic diseases, ranking first in terms of its socioeconomic and community health burden in tropical and subtropical areas. Malaria infection cuts across people of all ages, sexes and occupations, but is most common among categories of people referred as 'the high risk group, which include sickle cell disease patients.Sickle cell disease occurs more commonly among people of African, Mediterranean, middle eastern and Indian sub-continent origin, where malaria is or was common. Malaria is a leading cause of morbidity and mortality among SCD patients have been proven by researsh undertaken to determine the incidence of malaria in sickle cell patients. On the other side Sickle cell Disease carriers enjoy a relative immunity against malaria. This review looked into the close relationship of malaria and sickle cell disease, the scientific basis for relative immunity against malaria enjoyed by sickle disease carriers, and the place of malaria chemoprophylaxis in the prevention of crises due to malaria. The review also looked into Hydroxyurea as the drug for SCD treatment and the need to make it available to patients in Africa and other malarious regions.

Keywords: Malaria, Sickle Cell Disease (SCD), Chemoprophylaxis, Treatment, Mosquitoes

1.0 Introduction

Malaria is an infectious disease that may result from infection by any protozoan parasite of the genus Plasmodium. Five species of malaria parasites are known to infect humans. They are *Plasmodium falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi*. The disease is transmitted to humans through the bite of the female Anopheles mosquitoes**.** Malaria is one of the prevailing human parasitic diseases, ranking first in terms of its socioeconomic and community health burden in tropical and subtropical areas, a major contributor to morbidity and mortality of under five children with sickle cell anaemia (SCA) in malaria endemic regions (Oyetunji *et al*., 2020). The World Health Organization (WHO) estimated that there were 241 million malaria cases in 2020 in 85 malaria endemic countries (including the territory of French Guiana), with most of this increase coming from countries in the WHO African Region (World Malaria Report, 2021).

Malaria infection cuts across people of all ages, sexes and occupations, but is most common among categories of people referred as 'the high-risk group' (Najera *et al*., 1992; FMOH, 1991; Maartens and Ellis, 1990). They include children aged 6 months to 5 years, pregnant women, non-immune immigrants and travelers from non-endemic countries and sickle cell disease (SCD) patients. This review principally looked at the complex relationship between malaria and SCD, one of the malaria high risk groups.

Sickle-cell disease (SCD) refer to a group of inherited blood disorders typically inherited from an individual's parents. People who have this disease condition normally inherit two abnormal genes, one from each parent. When a person has two haemoglobin S genes (H SS), it is called sickle cell anaemia, the most common and often most severe form of SCD (SCD, 2018).The condition leads to an abnormality in the oxygen-carrying protein haemoglobin (Haemoglobin S) found in red blood cells. This leads to a rigid, sickle-like shape under certain circumstances. Sickle cell disease is indeed a chronic hereditary haemoglobinopathy and the most common life-threatening genetic disorder in the world (Sins *et al*., 2017; Uyoga *et al*., 2022). Other forms of sickle cell disease include: Hemoglobin SC (Hb SC), Hemoglobin $S\beta^0$ thalassemia, Hemoglobin $S\beta^+$ thalassemia, Hemoglobin SD and Hemoglobin SE (NIH, 2016).

Nearly all symptoms of sickle cell disease are the direct result of the abnormally shaped sickled red blood cells blocking the flow of blood that circulates through the tissues of the body (Shiel Jn, 2021). In effect tissues with impaired circulation suffer damage due to lack of oxygen. Such damage to tissues and organ can cause severe disability in patients with SCD. However, major features and symptoms of SCD include pain crises, swelling and inflammation of the hands and feet, fatigue and anaemia, sudden pulling of blood in the spleen and liver congestion, lung and heart injury, leg ulcers, septic necrosis and bone infections (Shiel Jn, 2021).

1.1 Epidemiology of Sickle Cell Disease

Sickle-cell disease occurs more commonly among people of African, Mediterranean, middle eastern and Indian sub-continent origin, where malaria is or was common. Where malaria is common, carrying a single sickle-cell allele (trait) confers a selective advantage; in other words, being a heterozygote is advantageous. Specifically, humans with one of the two alleles of sickle-cell disease show less severe symptoms when infected with malaria (Wellems *et al.*, 2009).There is a good evidence to suggest that malaria endemicity in tropical Africa, particularly falciparum malaria, is largely responsible for the persistence of high frequency of HbS gene in the region. This is in view of the fact that the possession of the sickle cell trait confers a relative protection against *P. falciparum* (Luzzatto and Pinching, 2012).

A World Health Organization (2010) report estimated that around 2% of newborns in Nigeria were affected by sickle cell anaemia, giving a total of 150,000 affected children born every year in Nigeria alone. The carrier frequency ranges between 10% and 40% across equatorial Africa, decreasing to 1–2% on the north African coast and <1% in South Africa (WHO, 2010).There have been studies in Africa that show a significant decrease in infant mortality rate, ages 2–16 months, because of the sickle-cell trait. This happened in predominant areas of malarial cases (Aidoo *et al*, 2002). In the United States of America, about 70,000 African Americans are diagnosed with SCD and additional 2.5 million African Americans are living with SCT (Gallo *et al*., 2010).

As established by field studies from different malarious regions, carriers of the sickle cell disease enjoy a relative immunity against malaria infection. The mechanism of protection is still not clear. We looked into the presented mechanisms in the literature but cannot conclusively approve any reasons/mechanism for protection. Malaria chemoprophylaxis is often recommended for SCD patients, eventhough the effectiveness of the strategy is based on a few studies conducted in a few malarious regions prior to widespread antimarial drugs resistance. Hydroxyurea has been used in non-malarious regions with great success. The challenge in the use of the drug is that little is known about its effects in malaria regions. In addition, the cost of affording the drug, particularly in Africa south of the Sahara is a major bridge to cross.

2.0 Incidence Of Malaria Among Sickle Cell Disease Patients

Malaria as a major cause of crisis among SCD patients have been proven by researsh undertaken to determine the incidence of malaria in sickle cell patients. Molta *et al*. (2005) conducted a research on malaria and malaria therapy among SCD patients in North-east Nigeria. Their work revealed that 40% of cases of crises among patients were partly or wholly due to malaria infection. However, low parasitaemia was observed among the patients, and was attributed to the effect of proguanil prophylaxis. Eleonore *et al*. (2020) conducted a similar research on malaria in sickle cell anaemia patients in Languitinae Hospital Cameroon. Their work revealed that the incidence of malaria is lower among children with SCD (23.5%) than it was among children without SCD 44.9%. Likewise among SCD patients with a positive microscopy, the parasite density was significantly lower among children with SCD than it was among children without SCD. They concluded that, eventhough the SCD population has a lower mortality related to malaria compared to non-SCD population, SCD patients admitted for malaria are twice likely to die than those admitted for other pathologies/diseases. Low parasitaemia in SCD patients in Eleonore *et al.* (2020) corroborates with Molta *et al*. (2005).

Recently, Uyoga *et al*. (2022) worked on Sickle Cell Anaemia and Severe malaria. Secondary analysis of transfusion and treatment of African children trial, revealed that malaria has a major contribution to mortality among children with Scickle cell anaemia, also, malaria prevalence among SCA patients was significantly lower. They however, opined that even low-level infection can precipitate severe anaemic crises that would likely prove fatal without rapid access to blood transfusion services.

2.1 Malaria Protection in SCD Patients

Malaria as a major determinant of mortality and morbidity is SCD in most parts of Sub-Saharan Africa (Fleming, 1989), is apparently related or connected to the haemoglobin S gene and intimately connected, being that they have similar geographic distribution (Piel *et al.* 2010). In heterozygous state, the sickle gene confers immunity/protection against malaria (Ashley-Kosh *et al*., 2000; Aidoo *et al*., 2002; Ayi *et al*., 2004). The sickle cell trait (Hb AS) is estimated to reduce malaria admission rates by 70%, and is 90% protective against severe malaria (William *et al.*, 2005). In additon, sickle trait reduce severe malarial anaemia by 60% (Aidoo *et al*., 2002). The mechanism by which the Hb AS gene protects is still not very well known. Some authors suggest that the mechanism by which it protects against malaria include; increased splenic phagocytosis, premature haemolysis and parasite death (Luzzatto *et al*., 1970; Roth *et al*., 1978), reduced parasite invasion, and retarded development of *P falciparum* in Hb S erthrocytes at reduced xygen tension, and the development of antibodies to the band of protein (Ayi *et al.*, 2004; Kennedy, 2010). In recent times various reason have been suggested. According to Intituto Gulbenkian de Ciencia (2011), that Ferreira Ana, through a series of genetic experiments, showed that the main player in the protective effect is haeme oxygenaze-1(HO -1), an enzyme whose expression is strongly induced by sickle haemoglobin, This enzyme that produces the gas carbonmonoxide, had been previously shown by laboratory of Miguel Soares to confer protection against celebral malaria. Futher more, this mechnism of protection, Ana Ferreira demonstrated that when produced in response to sickle heamoglobin, the same gas carbon monoxide, protected the infected host from succumbing to cerebral malaria without interfering with the life cycle of the parasite inside its red blood cells. According to Instituto gulbenkian de Ciencia (2011),this research findings would open the way to new therapeutic interventions against malaria.

Aidoo *et al.* (2002) showed that Hb AS provides significant protecetion against all-cause mortality, severe malarial anaemia and high-density parasitaemia. They reported that the significant reduction in mortality was detected between ages of 2 and 16 months, the highest risk of malaria in the research area. They concluded that their findings are important in the maintenance of sickle cell disease.

Williams *et al.* (2005) reported that the protection is unclear, but may be due to changes in the way that people with Hb AS develop immumity to malaria. They looked at 1054 people in Kenya with age range from birth up to 84 years, but predominantly aged less than 10 years, who either had Hb AS or normal haemoglobin (Hb AA). They found that protection of Hb AS against mild malaria increased with age from 20% in the first two years of life to a maximum of 56% by the age of 10 years and then decreased to 30% in people older than 10 years. They concluded that it is not yet known whether these results are also true for protection against severe malaria,and in any case the protection is only parital.

2.2 Malaria Chemoprophylaxis in SCD Patients

It is a fact that malaria is a common precipitating cause of crisis in sickle cell disease in malaria endemic countries (Eke, 2003; Molta *et al*., 2005; Oniyangi and Omari, 2006). Life long chemoprophylaxs is often recommened for people with SCD living in malarious areas. Malaria chemoprophylaxis is widely used in SCD patients because of the associated morbidity and mortality. Policies recommended phrophylaxis have been based on case reports, observational studies and concensus (Oniyangi and Omari 2006). As it is, there is inadequate evidence to support or refute given routine antimalarial chemoprophylaxis in areas where malaria is endemic.

Relevant studies have been conducted to assess the efficacy of malaria prophylaxix in the setting of SCD comparing with non-prophylaxis. One recent study was that of Diof *et al*. (2011) in Senegal. The result demonstrated a reduction in the need for blood transfusion in patients with SCD on Sulfadoxine/ Pyreimethamine combination compared to those who received placebo. No differences were seen in the rates of vaso-occlusive crises, although their ability to detect end-points may have been limited by sample size of the sixty subjects followed for atleast four months (Aneni *et al*., 2013). Similarly, Eke and Anochie (2003) conducted a research in which they used daily proguanil or weekly pyrimethamine compared with placebo.. The chemoprophylaxis was effective in reducing malaria parasite density and the need for blood transfusion in patients with SCD. The two studies indicates that malaria chemoprophylaxis offers some protection against malaria in SCD and reduction in blood transfusion needs.

In another study on Proguanil as malaria chemoprophylaxis in sickle cell anaemia: the controversies, problems and the future, Enato and Israel-Aina (2021) reported that malaria chemoprophylaxis seems to be more useful in young children than in adults. They also reported that proguanil chemoprophylaxis is less efficacious in reducing malaria induced morbidity and mortality in SCA, compared to IPT using sulphadoxine/pyrimethamine (SP) or mefloquine/artesunate (MQAS).

From studies conducted on prophylaxis in SCD patients, chemoprophylaxis generally appear to offer reduction in anaemia, clinical malaria, malaria parasite levels, sickle related events and malaria related hospitalisation (Aneni *et al*., 2013).

As stated earlier, many authorities recommend life-long malaria prophylaxis for people with homozygous sickle cell disease, however, several factors needs be considered when starting life-long chemoprophylaxis. Poor adherence may occur, as it is difficult to take drugs regularly. Adverse effects may occur or develop, such as hair loss and mouth ulcers with proguanil and neuropsychiatric reactions with mefloquine (WHO, 2001). Another thing to consider is that, the development of natural immunity to malaria (particularly in children) could be impaired by chemoprophylaxis with the potential risk of severe malaria on stopping the the treatment (Oniyangi and Omari, 2006). In addition, drug resistance may develop, thereby incresaing the cost of treatment, since newer antimalarials are more expensive (WHO, 1990). It is therefore important to assess the benefits and harms of this life-long interventions carefully (Oniyangi and Omari, 2006). Antimalarial drugs used for chemoprophylaxis are proguanil, pyrimethamine and mefloquine (Molta *et al*., 2005; Frimpong *et al*., 2018). From the point of view of Public health and WHO, children with SCD in malaria endemic regions should be protected from malaria by placing them on appropriate prophylaxis (Luzzatto, 2012; WHO, 2010).

3.0 Treatment Of SCD With Hydroxyurea

Hydroxyurea is a chemical compound with a chemical formula $CH_4N_2O_2$. It was first synthesized in a series of experiments attempting to extract the derivatives of urea (Rees, 2011). Hydroxyurea was first used as an anticancer drug to treat myoloproliferative syndrome; leukamia, melanoma and ovarian cancer (Agrawal *et al*., 2014). Hydroxyurea was found to be an effective drug for reducing the frequency of painful crisis in sickle cell disease patients, and also raises the level of faetal haemoglobin and haemoglobin. It is known to decrease the episodes of painful crises and blood transfusion by 50% in adults (Agrawal *et al*., 2014). Hydroxyurea was also associated with significantly fewer SCA related clinical events, specifically vaso-occlusive crises, dactylitis, and hospitalizations. Other laboratory outcomes of long-term clinical importance for children with SCA, including increases in hemoglobin concentration and HbF, as well as decreases in leukocyte, neutrophil, and reticulocyte counts, were all more favorable in children receiving hydroxyurea than placebo, further supporting the drug's efficacy in this studypopulation (Opoka *et al*., 2017).

Eventhough recent progress have been made in the development of new therapies that target specific parts of pathophysiology of sickling, nontheless hydroxyurea remains the only carefully studied and widely available and clinically effective therapy for SCD (Mc Gann and Ware, 2015). The drug was initially reserved only for adults SCD patients, but now being recommended that it be utilised much more broadly, including infants with SCD from 9 months of age, regardless of clinical severity (Yawn, 2014).

The exact machanism of action by which hydroxyurea induces HbF and ameorates the pathophysiology of SCD remains incompletely understood, depsite decades or research documenting laboratory and chimical benefits for SCD patiants (Lebensburger *et al.*, 2010). Current evidence suggests that several potential mechanism of action by hydroxyurea may be relevant for patients with SCA which leads to HbF induction. Perhaps the most important mechanism of action is the inhibition of reboncleotide reductise, the enzyme involve in transforming ribonucleosides into deoxyribonucleotides that

serveas building blocks for DNA synthesis (Agrawal *et al*., 2014; Elford, 1968.) In addition,The American Society of Hematology (ASH, 2019) reported that Hu makes the red blood of SCA patients bigger, helps it to stay rouder and more flexible and makes less likely to turn into sickle shape.

Hydroxgorea is readily absorbed oral administration with peack plasma lerch 1-4 hours after oral administration dose. The drug distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water,with over 50% of an oral dose undergoing conversion through metabolic pathways that are not fully characterised (Agrawal *et al*., 2014). In other words, Hu has excellent bioavailability in its oral form and is rapidly cleared from the circulation with half life of 2-3 hours in most adults and children (Ware *et al*., 2011; de Montalembert *et al*., 2006). The medicine does that by increasing a special kind of heamoglobin called HbF.The more HbF a pateient has the less are to cause problems.(ASH, 2022). In addition to thebenefits of Hydroxyurea, side effects of the drug in SCD patients are usually mild, most children tolerate it without difficulty (Agrawal *et al*., 2014). Hepatic and renal dysfunction from Hydroxyurea treatment has not been reported yet. Clinical experience shows that most common short term Hydroxyurea toxicity in SCD patients is transient and reversible myolosuppression, primarily neutropenia (Kinney *et al*., 1999).

Hydroxyurea as a drug for sickle cell disease has been widely used in non-malarious areas, however, little is known about its effect in malaria endemic areas or on malaria related outcomes (Aneni *et al*., 2013). It has been demonstrated that hydroxyurea increases the level of foetal haemoglobin which is protective against malaria, but its effect should go beyound that. This review suggests that studies that will include longer duration of Hydroxyurea in malaria endemic areas should be conducted. This will help determine optimal drug dosing, range of adverse effects and malaria incidence in in areas with higher malaria transmission (Opoka *et al*., 2017).

3.1 Hydruxyurea and Malaria

Hydroxyurea has no antimalarial activity, and malaria infection is a predesposing factor in SCD crisis. The question is, how would the drug alleviates crisis due to malaria infection? Also, recent concern was raised over using Hydroxyurea in the treatment of SCD in areas endemic for malaria, because Hydroxyurea up-regulates the endothelial surface expression of ICAM- major receptor for *P. falciparum*-infected erythrolytes in the brain. Pino *et al*. (2006) evalauted the interaction of Hu with malaria parasites and demonstrated that HU pretreatment increased the number of infected red blood cells adhercing to the endotheluim but did not increase endothelial apoptosis. In addition, using an experimental cerebral malaria model, Hu pretreatment was found to prevent significantly mice from developing neurological syndrome by inhibiting parasite growth, thereby opening therapentic avenues. It is a fact that HU cannot be considered as an anti-malarial drug, but man should consider it as this molecule has the ability to enhance foetal haemoglobin (HbF) production and influence indirectly parasite growth. Indeed it has been demonstrated that Plasmodium parasites invade more quickly erythrocytes that contain HbF but cannot digest it properly to complete their development (Pino *et al*., 2006; Opoka *et al*., 2017). Eventhough Hydroxyurea doesn't exhibit antimalarial activity, its use in malaria endemic regions should be encouranged since it can reduce painful crisis and also reduce hospital admission.

4.0 Conclusion

Sickle cell disease is chronic blood disease affecting millions of people, especially those living in sub-Saharan Africa, people of African decent, mediterranean, middle eastern and Indian sub-continent region where malaria is endemic or very common. Furtheremore, malaria is a leading cause of crises, morbidity and mortality among people living with disease. We therefore recommend that appropriate life long chemoprophylasis be administered to sickle cell disease patients. Hydroxyurea as a treatment drug is known to reduce the frequency of painful crisis in sickle cell disease patients, and also raises the level of faetal haemoglobin and haemoglobin. It is also known to decrease the episodes of painful crises and blood transfusion by 50% in adults (Agrawal *et al*., 2014). We suggest that large scale trials to ascertain its efficacy be carried out in malaria endemic regions. We also appeal that Hydroxyurea be provided to Sickle cell global community, as it's most needed to contend with menace of the disease.

5.0 Conflict of Interest

All authors declare that they have no conflicts of interest

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