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Commentary

Sickle cell Anaemia: The Need for Increased Drug Development in Africa

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Abstract

Sickle cell anaemia is a life-threatening genetic disease that causes damage to red blood cells by polymerisation of deoxygenated haemoglobin. It is highly prevalent in Africa especially in regions with high prevalence of malaria. Over the years, hydroxyurea had been the only promising drug used in the management of sickle cell anaemia; however, it has been found to be unaffordable and not readily available to the affected poor people in rural areas. Several challenges face drug development efforts in Africa yet there remains a significant need for the development and standardisation of newer, cheaper, and effective anti-sickling drugs that would be readily affordable and available to meet the needs of the African populace.

Keywords Sickle, cell, disease, anaemia, drug, development, Africa

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Introduction

Sickle cell disease (SCD) is the most prevalent genetic disease in sub-Saharan Africa [1]. Under the umbrella of SCD exists many subgroups, which include; Sickle cell anaemia (SCA), haemoglobin SC disease (HbSC), and haemoglobin sickle-beta thalassemia (beta-thalassemia positive or beta-thalassemia negative) [2]. SCA is the most common form of SCD. It causes a series of debilitating systemic symptoms of which are characterised by acute painful episodes [3], chronic anaemia [4], organ infarction and chronic organ damage [5]. It is also characterised by a significant reduction in life expectancy [6]. The sickle haemoglobin (HbS) is a known structural

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variant of the normal haemoglobin (HbA). This occurs as a result of the cell mutation that involves the replacement of the amino acid glutamine (negatively charged) with the amino acid valine (positively charged) at the sixth position of the beta globin chain [7]. The HbS molecule is susceptible to conversion into rigid elongated polymers when deoxygenation occurs. Initially, the sickle-red blood cells change shape frequently from sickle to the normal biconcave and vice-versa as oxygenation and deoxygenation alternate respectively. However, there comes a time when the sickle shape of the red blood cells become irreversible thereby increasing the risk of haemolysis, anaemia and other vaso-occlusive crises [8].

Africa carries the burden of disease of SCA yet the development of drugs for its management has faced major challenges over the years. Challenges such as; limited financial capacity and also, lack of adequate facilities to aid advancements in the design and development of new and effective anti-sickling medications. Plants whose anti-sickling properties have been proven are abundant in Africa, harnessing them and standardising them into effective therapies is the next major step that needs to be taken [1].

Epidemiology in Africa

Every year, about 300,000 children are born with SCA into the world, of which sub-Saharan Africa makes up about 75% of them [2]. The number of babies estimated to be born with SCA in Africa ranges from about 120,000 to 200,000 [9]. SCA has an estimated prevalence of about 5 to 40% in Western, Eastern and Central Africa while it is less common in Northern and Southern Africa [2]. It has a higher frequency in populations that have historically been living in wet, low-lying locations with a high prevalence of malaria, which has popularly been referred to as the sicklemic belt [9]. An accurate data for the number of children born yearly with SCA is yet to be achieved. Only estimates as stated above are available as new-born screening cannot be accessed in most low-income countries that carry the highest predicted burdens of the disease [10]. It has however been predicted that the annual new-borns with SCA will exceed 400,000 by the year 2050 [9]. The majority of these children die undiagnosed in early childhood [11] from diseases that can be prevented such as malaria [12] severe anaemia and several other bacterial infection complications [7]. This makes SCA responsible for up to 6% of all childhood deaths in sub-Saharan Africa [13]. However, the use of hydroxyurea in both children and adults has been found to significantly reduce the incidence of vaso-occlusive events, infections, malaria, transfusions, and death [14].

Pharmacotherapy of Sickle cell anaemia in Africa

Up until 2008-2013, hydroxyurea, a drug that is useful in the management of SCA [15] by its induction of haemoglobin F was the only promising drug in the treatment of SCA [3] yet hydroxyurea has been proven to be useful only in patients who meet certain criteria which include:

1. More than 3 episodes of moderate to severe pain in a 12-month period,
2. History of stroke and a contraindication to chronic transfusions,
3. Children with history of acute chest syndrome or chronic anaemia,
4. Infants and children 9 months of age or older who are asymptomatic or have infrequent pain episodes [16].

Even though hydroxyurea has been proven to be highly effective in the management of SCA, only few studies on the drug have been performed so far in Sub-Saharan Africa which bears the highest burden of the disease [17]. Hydroxyurea has also been shown to be expensive and relatively unaffordable to most of the people who need it especially poor affected people in rural areas [1]. These above limitations prove the need for the discovery and development of newer anti-sickling drugs that are effective, accessible, affordable and well-studied in the African population. There are definitely several other drugs and interventions for the management of SCA of which include Butyrate, Nitric oxide, Blood transfusion and Gene therapy [3] but these are also mostly unaffordable and inaccessible to the greater part of the affected people in Africa.

Africa bears the burden of disease of SCA so it is only appropriate that steps towards developing drugs for its management be taken in Africa itself. Other countries such as China and India make use of herbal medications as first line in the treatment of diseases due to availability, affordability and widespread acceptance by the citizens of these countries [18].

Herbal drugs developed in Africa would show more promise in terms of accessibility and affordability [1]. Africa is rich in natural plants that have been proven to be useful in the treatment of SCA. Plants like *Cajanus cajan* [18,19], *Eugenia caryophyllata*, *Piper guineense* [20], *Aframomum melegueta*, *Sorghum bicolor* [21], *Pterocarpus osun* that possesses anti-sickling properties have all been proven to be useful in the management of SCA [22]. Niprisan was developed from herbal sources in Nigeria and approved for the management of SCA [23]. More herbs are available that are effective but require standardization through series of clinical trials that would largely involve African people and registration by authorities in order to be made available to people [23].

Challenges

Limited investment from the pharmaceutical industry: Due to inadequate financial capacity, companies in Africa make little or no investments in research and developing and protecting their intellectual property. There is also the problem of inadequate human resource capacity as there has been an increase in brain drain of seasoned researchers from Africa.

Nature of the disease: The treatment of sickle cell disease is branching beyond anti-sickling to molecules that prevent sickle cell interaction. Sickle cells do not act in isolation, the red blood cells stick together and also cause the white blood cell, platelets and cells on blood vessel walls to stick to each other leading to blocked blood vessels and inflamed tissues. This in turn worsens the disease and causes a complication called vaso-occlusive crisis (VOC). VOC leads to intense pain that requires hospitalization and over time causes permanent organ damage [24]. According to Paul Frenette, director of the Gottesman institute for Stem Cell and Regenerative Medicine Research at Albert Einstein College of Medicine in New York City, there is still no specific therapy for VOC which is responsible for most of the symptoms of SCD [24].

Limited trial enrolment: Beyond finding a potential drug, a major problem in getting promising therapies tested and approved for SCA is patient recruitment. Several clinical trials have been stopped in Africa due to low enrolment of participants [24].

Limited Data about frequency, clinical course or mortality: Data is difficult to generate about the prevalence of SCA in Africa due to the unavailability of new-born screening and appropriate documentation. Without this information, it will be difficult to persuade any African government or external donor groups about the burden of this disease [25].

Prospects

Plants which are effective in the management of SCA are abundant and readily available in Africa [1]. Over the years, drug development from natural sources have led to the discovery of several ground-breaking effective drugs, examples include anticancer drugs like Vincrinstine, Epirubucin, Taxols, etc. Exploration of natural sources for newer anti-sickling drugs holds high prospects in the effective management of SCA in Africa [26]. The problem of developing medications from natural sources lies in the lack of appropriate funding to carry out research work [27] and this can be mitigated by government involvement in facilitating drug development efforts. This also includes provision of support through allocation of funds and sponsorship from several donor groups.

There is also the huge problem of lack of standardisation of the herbs used in managing SCA. This problem unfortunately results from the lack of success of clinical trial attempts as people hardly enrol for clinical trial in Africa [28]. Lack of trust in the system can be said to be a major factor against enrolment, hence a more developed health care system and detailed orientation of people about the clinical trial could be a step towards ensuring the conduct of successful clinical trials [16]. Also, researchers should relate with the patients with open-mindedness and not ignore their opinions, beliefs and suggestions especially in rural communities with strong cultural practices, they however should look towards working hand in hand with them to achieve results. Questions presented by the patients should always be answered in a detailed, true and understandable manner. Clinical trial participants should be made to feel like they are an important part of the process as even the most promising treatments cannot be approved without patients willing to test them. [24]

Conclusion

Efforts towards the development of newer medications for the management of sickle cell anaemia are necessary to be taken in Africa, where appropriate clinical trials can be conducted using the affected population. This in turn would allow for the development of readily available and affordable drugs especially from the largely abundant natural sources.

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