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Editorial

Sickle cell disease: Progress made & challenges ahead

About seven per cent of the world's population is a carrier of globin-gene mutations[1], of which the sickle gene is one of the most common and the most pathogenic [sickle cell disease (SCD)] in its homozygous and compound heterozygous forms. Annually, over 300,000 infants are born with the homozygous form of the disease, about two-thirds of them in Africa; Nigeria, India and the Democratic Republic of Congo shoulder half of the global burden[2]. These numbers are expected to rise above 400,000 per year by 2050[3]. High carrier frequencies up to 35 per cent are found in the sub-Saharan Africa, certain regions of central, southern and western States of India and the Arabian peninsula[3]. In 2006, SCD was recognized as a global health problem by the World Health Organization[4]. Two years later, the 63rd United Nations Assembly designated June 19 as 'World Sickle Cell Day' to be commemorated to raise public awareness of the disease and galvanize stakeholders to mobilize resources aimed at improving outcomes for people living with SCD[4].

With World Sickle Cell Day 2020 now upon us, the question to pose is: what progress have we made in improving patient outcomes? Today, in high-income countries (HICs), over 94 per cent of newborns with SCD would be expected to survive into adulthood, although they face emerging SCD-associated morbidities as they grow older. By contrast, less than half of those born in low-income countries (LICs), mainly in sub-Saharan Africa, live beyond age five years[5]. However, not much information is available on the estimated life expectancy of those with SCD in India[6]. This wide disparity is attributable to the level of implementation of newborn screening and comprehensive care including penicillin prophylaxis, pneumococcal vaccinations and parental education. In HICs, tremendous strides have been made in the use of disease-modifying therapies such as hydroxyurea and regular blood transfusions to mitigate complications such as stroke, recurrent vaso-occlusive pain, acute chest syndrome and severe anaemia. Transcranial Doppler (TCD) screening and prevention of stroke by regular blood transfusion was introduced into care of patients after the findings of the STOP (Stroke Prevention Trial in Sickle Cell Anaemia) in 1998 and has resulted in reduced stroke incidence from 0.67/100 to 0.06/100 patient-years[7]. However, regular blood transfusions are associated with iron overload requiring iron-chelation therapy. By and large, access to regular transfusions is limited in LICs, and even when available, risks of blood-transmitted infections and prohibitive costs of iron-chelation therapies pose insurmountable barriers[8]. Findings from the seminal TWiTCH (TCD With Transfusions Changing to Hydroxyurea) have enabled switching from regular blood transfusions to oral hydroxyurea therapy as a key strategy for maintaining reduced TCD velocities in a large majority of at-risk children[9]. In addition, the Stroke Prevention Trial in Nigeria (SPIN) has demonstrated that hydroxyurea is effective in reducing strokes, providing further support for widespread TCD screening and hydroxyurea therapy for stroke prevention in LICs[10]. A few centres in India have implemented TCD screening and patients with abnormal velocities are offered chronic transfusion therapy or hydroxyurea therapy[11].

Despite evidence for its efficacy in both adults and children, hydroxyurea remains underutilized even in HICs. NOHARM (Novel use Of Hydroxyurea in an African Region with Malaria), a randomized placebo-controlled trial proved that hydroxyurea therapy was not associated with increased incidence of clinical malaria among Ugandan children with sickle cell anaemia[12]. REACH (Realizing Effectiveness

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across Continents with Hydroxyurea), an open-label trial conducted in four African countries, provided strong evidence of the safety and clinical/laboratory benefits of hydroxyurea therapy at a starting dose of 20 mg/kg with dose escalation to maximum tolerated dose (MTD) in African children with sickle cell anaemia[13]. Study (NOHARM-MTD) results showed that among children with sickle cell anaemia in Uganda, dose-escalation of hydroxyurea had superior clinical efficacy to that of fixed-dose hydroxyurea with equivalent safety[14]. Studies in India have reported clinical benefits from fixed low-dose (10-15 mg/kg) hydroxyurea therapy[15]. With these multiple pieces of evidence, hydroxyurea should be made affordable and available to all patients with SCD, particularly in LICs where the need is the most. In India and HICs, where hydroxyurea is accessible, adherence to therapy still remains a barrier to achieving optimal outcomes.

Over the last five years, progress has been made in accelerating SCD research. SCD has been placed higher on the agenda of research funding institutions in India, USA and Europe. Until 2017, only two disease-modifying therapies (hydroxyurea and blood transfusions) for SCD were in wide use. L-Glutamine was approved by the U.S. Food and Drug Administration (FDA) in 2017[16]. Later crizanlizumab, a P-selectin inhibitor, received expedited approval by the FDA, followed by the approval of voxelotor, an oral medication that targets HbS polymerization two weeks later[17,18]. Several other pharmacological agents targeting specific sites in the pathophysiologic pathway of SCD are in the pipeline as drug developers take the advantage of orphan drug designation policies now existing in many countries. Several emerging drugs are being studied both alone and in combination with hydroxyurea, as combination therapies offer the best prospects for optimizing disease outcomes[19].

Haematopoietic stem cell transplantation (HSCT) is currently the only established curative treatment for SCD. However, its use has been limited by the availability of suitably matched sibling donors, procedure-related toxicities and costs[20]. Progress has been made to expand the donor sources by using haploidentical donors and minimizing transplant-related toxicities by employing reduced-intensity conditioning regimens and better graft-versus-host disease prevention/treatment strategies. Though HSCT is widely available in HICs, their accessibility is limited. A step in overcoming the access barrier is the emergence of gene therapy approaches. These strategies include gene addition (mediated by viral vectors) and gene editing (*e.g.*, CRISPR/Cas9) to modify or correct the defective sickle gene or induce high HbF expression. It is likely that regulatory approval for clinical use of one or more of these products will be forthcoming within the next few years.

Although considerable work has been done on SCD in India, the bulk has occurred in a few centres with limited impact at the national level. Many patients in remote rural areas are not adequately managed and are often unable to reach a hospital. The need for collaboration and networking between centres has been realized[21]. Multicentre studies have started the process of systematic documentation of the disease. The Indian National Health Mission is making major contributions with their programmes in Gujarat, Maharashtra, Odisha and Chhattisgarh focused on population screening to determine disease prevalence, establishing newborn screening cohorts and standardizing hydroxyurea therapy[22]. Some programmes also deliver prenatal diagnosis, premarital screening and genetic counselling services[23,24]. The Ministry of Health and Family Welfare has released guidelines for a National Haemoglobinopathy Programme with emphasis on newborn screening and comprehensive care[1]. While celebrating these achievements, we should also remain focused on addressing current and future challenges. There is a need for more public-private partnerships to implement and sustain early diagnosis and interventions to reduce the high under-5 mortality related to SCD in LICs, given their proven cost-effectiveness. A concerted global effort to mobilize political will at high levels of governments in LICs with high disease burden should be paramount. Point-of-care (POC) tests for the detection of SCD have been developed and should help provide rapid, accurate and timely diagnosis when patients seek healthcare. POC tests lend themselves well to being integrated into primary care services such as immunization clinics. How such integration efforts can enhance SCD diagnosis needs to be further explored and studied through implementation research endeavours. Integration of SCD interventions into the existing health systems should occur at all levels to ensure the sustainability of SCD-directed services. With the strength of evidence behind the benefits of hydroxyurea therapy in children and adults with SCD, a coordinated push to disseminate its use in Africa and India should be a top priority. Multi-stakeholder partnerships are needed to make the drug affordable and available to patients in need. Bulk purchasing through government-supported

financing programmes will help alleviate the burden on patients and families who would otherwise have to pay out of pocket. Health professionals in Africa and India need training in the prescription and monitoring of hydroxyurea therapy while government-sponsored protocols based on WHO recommendations should be developed to guide these professionals.

Public awareness raising and SCD education championed by government, non-governmental organizations and advocacy groups need enhancing to counter the stigma and myths associated with SCD. Much of SCD advocacy has in the past been fragmented and not sophisticated enough to exert pressure on governments to deliver on their own promises. This is beginning to change, and effective groups have emerged in some countries; a global alliance of SCD advocacy groups has recently been formed[25]. Initiatives to train current and future SCD advocates will help enhance advocacy skills needed to influence government strategy and plans that result in the design and delivery of SCD services where those are most needed.

Disparities in care occur even within HICs. Lack of insurance coverage for adults with SCD and the low numbers of SCD professionals dedicated to adult care account for the lower quality of care for adults compared with children. These disparities are further accentuated by the increased emergence of morbidities as patients grow older. Centres of excellence with the prerequisite clinical resources to deliver comprehensive care for both adults and children should be established to serve as referral centres linked to secondary and primary care facilities within each country.

We ushered in 2020 with the emergence of the COVID-19 pandemic. Combating the SARS-CoV-2 virus has exerted enormous strain on the health resources of countries worldwide. The WHO has issued several alerts regarding the threat posed by the COVID-19 pandemic to maintaining essential health services such as immunizations, malaria and tuberculosis prevention/treatment and nutrition programmes[26]. SCD-directed care adds to the list of services that could be under threat. Care providers should make every effort to engage their patients to adopt innovative approaches that ensure continuing care while minimizing the risks of COVID-19 exposure. Strategies would include the use of telemedicine consultations, ensuring continued access to disease-modifying therapies such as hydroxyurea and blood transfusion and timely treatment of acute complications of SCD. Data on the influenza H1N1 pandemic in 2009 showed increased susceptibility to virus induced complications among children with SCD[27]. SCD may, therefore, be included in the list of risk factors for severe complications of COVID-19 infection.

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