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New ASH initiatives to improve patient care in the long-overlooked sickle cell disease

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Because of the unique biology of sickle cell disease (SCD) as well as the societal disadvantages and racial inequities suffered by these patients, individuals with SCD have not benefited from the same remarkable advances in care and therapeutics as those with other hematologic disorders. Life expectancy of individuals with SCD is shortened by ~20 years even with optimal clinical care, and infant mortality continues to be a major concern in low-income countries. As hematologists, we must do more. The American Society of Hematology (ASH) and the ASH Research Collaborative have instituted a multipronged initiative to improve the lives of individuals living with this disease. Here, we describe 2 components of this ASH initiative, the Consortium on Newborn Screening in Africa (CONSA) to improve the early diagnosis of infants in low-resource countries and the SCD Clinical Trial Network to accelerate the development of more effective therapeutics and care for those with this disorder. The combination of SCD-focused initiatives, ASH Research Collaborative, CONSA, and Sickle Cell Clinical Trials Network has enormous potential to dramatically alter the course of SCD worldwide. We believe that the timing is ripe to embark on these critical and worthwhile initiatives and improve the lives of individuals with this disease.

Introduction

Over the course of our careers, we have witnessed remarkable growth in novel therapeutics for almost all disorders cared for by hematologists. In fact, we are proud to state that hematologists have often paved the way for other fields of medicine by developing innovative strategies to create new treatments that have, time and again, been replicated and used to treat nonhematologic diseases. Sadly, for various reasons that are related to both the unique biology of sickle cell disease (SCD) and the racial inequities suffered by these patients, individuals with SCD have not benefited from the remarkable advances in care and therapeutics that have been experienced by individuals with other medical disorders.

Sickle cell anemia was first described by James B. Herrick in 1910 and further characterized as a molecular disease by Linus Pauling in 1949 when he showed that it was caused by a biochemically abnormal hemoglobin. SCD is one of the most common and clinically severe inherited human diseases in the world, estimated to affect from 3 to 6 million people. More than 90% of individuals who are affected live in Africa and India, with very limited access to appropriate health care and where misinformation about and stigma related to the disease are not uncommon. Although recent efforts have led to some progress in the care of SCD, significant and substantial gaps remain in the effective prevention, management, and cure of this complex human disease. These gaps are of particular concern in low-resource countries, where the majority of patients with SCD live. Life expectancy of individuals with SCD is shortened by ~20 years, even with optimal clinical care, and in low-income countries, infant mortality continues to be a major concern.[1,2] As the clinical manifestations of SCD progressively worsen with age, it is critical that there be early detection of SCD, and newborn screening is an essential strategy for effective clinical management of SCD. Although such a strategy has been implemented in several well-resourced countries, it is very sparse or is not being pursued at all in low-resource regions of the world.

In addition to identifying children with SCD at a young age, we desperately need more therapeutics. Although underused for 3 decades, hydroxyurea shows proven efficacy at reducing painful crisis and other complications of this disease. In recent years, the Food and Drug Administration has also approved L-glutamine, crizanlizumab, and voxelotor for the treatment of this disease. Today, there are more than 25 potential new therapeutics for SCD in various stages of development. We never thought that we would see the day when we could say that we are optimistic about new therapeutic strategies for the treatment of SCD, yet, here we are. Hematopoietic stem cell transplantation is effective and curative, but its use is limited to a small subset of patients in high-resource settings. Various forms of gene therapy and gene editing, which can also be curative, are currently being explored. It is possible that gene therapy–based approaches will eventually become the treatment of choice. However, technical and economic issues are likely to limit their availability globally for at least the next decade, if not longer.

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Therefore, we can and must do even more. There is a continued need for identifying and developing effective and inexpensive new oral drugs that can be used alone or in combination with existing agents to prevent sickling and for providing more robust therapeutic responses. To achieve this, access to a well-developed, high-quality clinical trial network that is designed to evaluate the safety and effectiveness of promising drugs in the pipeline is essential. This issue has been a long-standing and persistent problem in drug development for SCD. As these therapies are developed, patients around the world must receive a diagnosis and be offered access to these medications. To directly improve the care, treatment, and outcomes for people with this disease, the American Society of Hematology (ASH) launched a multifaceted, patient-centric SCD initiative focused on access to high-quality care, research, policy, and global challenges.[3] To address the need for therapeutics, through this initiative ASH has made serious commitments to both the early diagnosis in low-resource countries and the development of an SCD Clinical Trial Network.

CONSA

Newborn screening and early diagnosis are seen as essential first steps in preventive care. However, widespread screening and early diagnosis are not currently universally available in any of the countries in sub-Saharan Africa. As a result, a majority of infants with SCD born in sub-Saharan Africa die of potentially preventable causes without having received a diagnosis of SCD. A recent study performed in 5 African countries estimated a 36.4% mortality for children younger than 5 years with SCD.[4] Although this represents a marked improvement from earlier reports of ~50% to 90% mortality, such mortality rates are far from acceptable.[5] To narrow this critical gap, ASH established the Consortium for Newborn Screening in Africa (CONSA).[6] The goals of CONSA include the following: to expand access to early (within the first 3 months of life) diagnostic screening for SCD; to model the cost of universal early diagnosis that can be applied to other sub-Saharan African countries; and to evaluate the effectiveness of early diagnosis and early clinical interventions in reducing childhood mortality attributable to SCD. While acknowledging that India and countries in the Middle East share similar challenges, CONSA was established in Africa with an additional goal of facilitating regional partnerships in hematology among these African nations, sharing the best practices and eventually building the capacity to implement clinical trials as the initiative matures. CONSA is dedicated to ensuring the long-term sustainability of these newborn screening and early intervention services by working with ministries of health, local health systems, health care providers, community-based organizations, industry partners, and other stakeholders. By establishing these partnerships at the outset, CONSA partners will also ensure that lifelong high-quality care is available locally after early diagnosis.

CONSA was established with the following 7 member countries: Ghana, Kenya, Liberia, Nigeria, Tanzania, Uganda, and Zambia. In addition to diagnosing SCD early in a child's life, the members of CONSA also address several other important needs through several subcommittees. For example, the Family Education and Counseling Committee provides resources for training and education for clinical staff at all levels of the health care system, along with resources for families and communities. The committee also looks to destigmatize beliefs about SCD among families and communities by showing that children can thrive if they receive care. The Laboratory and Diagnostics Committee leverages industry partnerships, including with PerkinElmer, to ensure availability of screening tools and connects experts within CONSA with other ASH experts to share knowledge and provide training support for diagnosis. The Data Collection Committee facilitates patient tracking and communication of diagnosis and will ultimately be responsible for the final analysis of the impact of this effort. The Publications Committee identifies research questions and works within CONSA to build the capacity for research planning and writing. Overall, CONSA aims to support the screening of at least 76 000 newborns per year for the duration of this 5-year effort. We estimate that we will diagnose between 800 and 1500 children per year who would otherwise be overlooked until a later stage of their lives or remain undiagnosed. The vast majority of these children will have HbSS or HbS/β0-thalassemia and should have access to disease-modifying therapy.

Although newborn screening and parental education alone can help reduce early morbidity and mortality, disease-modifying therapies that have been transformative in high income countries are desperately needed in low- or middle-income countries (LMICs). Hydroxyurea is an ideal therapy for LMICs because of its relative low cost and oral administration. In the last decade, several studies have demonstrated that hydroxyurea is safe and effective to use in the African setting.[4,7-9] Laboratory monitoring significantly adds to the cost of the therapy. However, multiple models are currently under investigation, which would decrease the need for frequent laboratory monitoring. Hydroxyurea is not currently widely available in the African continent because it has not yet been placed in the local essential medicines list in many African countries, which is a crucial first step in facilitating a national import plan. Currently, hydroxyurea is largely imported by private pharmacies or small manufacturers. Therefore, hydroxyurea remains prohibitively expensive, with a daily dose of 1000-mg tablets ranging in price from $0.18 in Tanzania[10] to $0.80 in Nigeria.[11] At these current costs, the use of the medication is unimaginable for most families. As CONSA has evolved, there has been an increased focus on improving access to hydroxyurea. Through partnerships with pharmaceutical companies, such as Novartis Pharmaceuticals, and supply chain distribution partners, CONSA is facilitating discussions to provide low-cost access to hydroxyurea throughout Africa. Although these discussions are urgent and crucial to ensure the provision of hydroxyurea, the methods and practices established will prove critical for the expansion of newer disease-modifying therapies across the African continent as approvals are gained and costs decline.

ASH RC Clinical Trials Network

Despite the impressive advances in our understanding of the science of globin gene expression and the pathophysiology of SCD-induced pain crisis and end organ damage, translating these findings into therapeutic applications has been frustratingly slow. However, the rich pipeline of novel therapeutics to treat this disease positions us to make a profound difference in the lives of individuals with SCD. As part of ASH's commitment to improve the lives of individuals living with SCD, in 2018, it created the ASH Research Collaborative (ASH RC), designed to enable large-scale

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collaborative research focused on improving the care of patients with SCD (along with other blood disorders). After a summit comprising representatives from academia, patient groups, governmental partners, and industry, ASH concluded that a national Sickle Cell Clinical Trials Network should be assembled. This network is designed to enable investigators to conduct sickle cell clinical trials in a coordinated and consistent fashion, and it will offer more patients the opportunity to participate in research studies affordably. In addition to the Clinical Trials Network, an accompanying data registry (ASH RC Sickle Cell Data Hub) provides analysis of real-world data to compare the effectiveness of different therapeutics. The goal of the ASH RC is to provide people with SCD a voice and better opportunities to receive not only the latest but the best treatments.

Over the past couple of years, the ASH RC has labored to develop this new SCD Clinical Trials Network. Its mission is not only to hasten the evaluation of potential new therapeutics for the treatment of this disease but also compare existing treatments, determine which combinations of therapies work best, and design new ways to overcome barriers to implementing beneficial treatment modalities. This Clinical Trials Network provides an infrastructure that promotes collaborations between clinical investigators and sites, sponsors of trials, and the SCD community. These components, in conjunction with the data hub, are the essential ingredients in our secret sauce that is designed to make this effort highly effective.

Since the beginning, we pledged to build this network with the community rather than for the community. We believe that the most important component of this Clinical Trials Network is its alignment and relationship with the community with SCD, which is composed of individuals living with SCD, their families, and care givers. In this way, we bring the voice of the community to the table so that trials can be designed in a way that is meaningful to this group. We have confidence that this approach will also improve enrollment in trials. To accomplish this goal, every clinical trial unit in the network has a local community advisory board that meets regularly to advise investigators and develop ways to best engage and hear the concerns of the community. Each local community advisory board additionally elects 2 representatives to participate in the National Community Advisory Board, which in turn reviews protocols and educates the steering committee on what will be appealing or problematic if a potential trial uses the network.

Currently, 20 clinical trial units are participating in the network, and they are distributed throughout the United States in a way that overlaps well with the geographic distribution of people with SCD. All clinical trial units have a deep culture of cooperative research and are situated at institutions with the infrastructure to efficiently perform clinical research. Each of these 20 clinical trial units is composed of multiple clinical research sites, resulting in 98 research sites that have an affiliation with this Clinical Trials Network. In total, these sites care for ~41 000 people with SCD. Stated alternatively, >1 out of every 3 individuals in the United States with SCD receive care at one of the Clinical Trials Network sites.

One advantage of the Clinical Trials Network is its close alignment with the ASH RC SCD Data Hub. This is a registry that imports a limited data set of clinical information on the care of individuals at the clinical trial sites. To date, it has collected and has begun to analyze data of more than 10 000 individuals, a number that continues to grow rapidly. When fully operational, this registry of real-world data will allow us to support clinical trials in several ways. Firstly, it will provide the clinical sites with more up-to-date natural histories of SCD for studies. Secondly, it will be helpful for rapidly screening individual sites for the number of eligible participants who meet inclusion and exclusion criteria in potential trials. Additionally, it could be used to develop contemporaneous control groups, which could be used in a fashion by which each trial may not need to enroll its own control arm. For example, in this scenario, the outcomes of patients receiving a novel therapeutic could be compared with the outcomes of patients in a contemporaneous control group.

It should be noted that finding ways to fund clinical trials that compare Food and Drug Administration–approved therapeutics or different combinations of approved therapeutics has always been a significant challenge. Comparative studies are usually not supported by competing pharmaceutical companies. We believe that the Clinical Trials Network will facilitate individual investigators to obtain funding for these types of studies. The network can help improve trial designs and grant applications by providing rigorous peer review of study proposals before they are submitted for consideration of funding. In addition, this coalition of collaborative sites has access to large numbers of patients that will enable the enrollment of sufficient numbers of participants for trials. Therefore, we believe that the already assembled ASH RC Clinical Trials Network provides the infrastructure that will best situate individual investigators to compete for federal funding for drug comparison studies.

We are excited because of the rich potential of this Clinical Trials Network. We also firmly believe that galvanizing this community of patients, investigators, and sponsors of trials through our clinical trial network, along with our newly formed data registry, will help us overcome long-standing existing barriers to care of these patients. It will also build trust, maximize the efficiency of trials, and dramatically change the course in the management of care while additionally improving the quality of life for people with SCD.

Other initiatives

Finally, it should be stated that the vast majority of care for individuals with SCD is not performed by hematologists with expertise in the management of this disorder. Instead, care of these individuals is assumed by many other types of health care professionals, including nurses, emergency medicine personnel, hospitalists, oncologists, and primary care physicians. To help address the education of this broader community of care providers, ASH has developed practice guidelines, pocket guides, podcasts, and teaching slides that can be accessed online.[12] Additional resources are available for patients and their families.[13] ASH also offers practical experience to physicians in training with Sickle Cell Away Rotations.[14] Through a cooperative effort involving individuals with SCD, caregivers, and clinicians, ASH is piloting a learning community to improve the quality of care. ASH also formed the SCD Coalition to amplify the voice of the community with SCD. The SCD Coalition unites stakeholders, including public health, research, and provider organizations; patient groups; faith-

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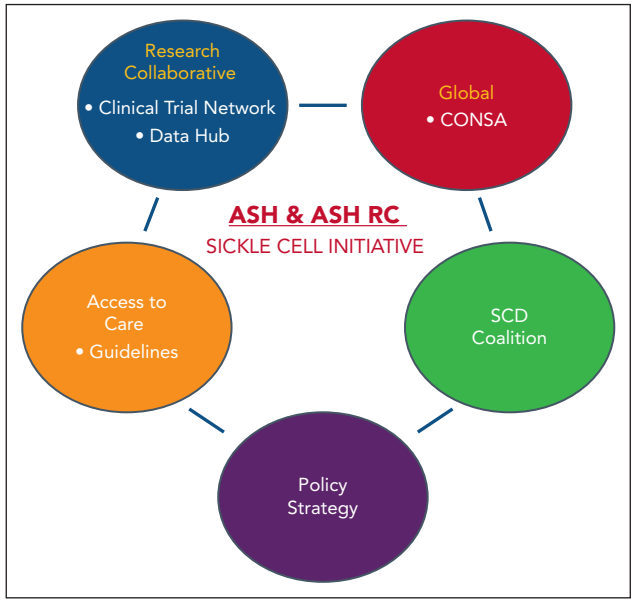

Figure 1. ASH and the ASH Sickle Cell Initiative. Shown is the multipronged initiative to improve the lives of people living with sickle cell anemia. ASH established its Research Collaborative, which developed the SCD Clinical Trials Network and Data Hub. ASH has also created CONSA as part of its global initiative. CONSA is a consortium of African hematologists who are working to demonstrate the effectiveness of newborn screening and early intervention for infants with SCD. ASH founded the SCD Coalition, composed of more than 100 organizations that amplify the voice of the community with SCD. In addition, ASH has developed educational material on SCD to enhance access to high-quality care and worked with the US government to boost SCD research, training, and services as well as to improve the reimbursement for SCD care.

based organizations; US government entities; industry; and private foundations to partner in improving the outcomes for persons with SCD (Figure 1).

In addition to the ASH SCD initiatives, 2 other non-ASH initiatives are currently underway that should be mentioned. The first initiative is the Cure Sickle Cell Initiative, a National Heart, Lung, and Blood Institute–led collaborative research effort that began in 2018, with the aim of developing curative strategies by focusing on genetic therapies that modify hematopoietic stem cells (HSCs). HSCs are engineered by either introducing the normal hemoglobin gene into the HSCs or correcting the mutation in the abnormal hemoglobin gene. The modified progenitor cells are subsequently transplanted back into the patient. These genetic therapy approaches are in the early stages of testing, and 1 clinical trial has already opened for enrollment.

The second initiative is the Global SCD Network, which is an independent community of clinicians and scientists who are committed to providing effective clinical care for people with SCD globally. Because of the gap in clinical care, research efforts and education about the disease in LMICs are essential. The Global SCD Network engages SCD experts around the world through a network that supports growth in these areas, particularly in LMICs that shoulder the heaviest burden of SCD. The objective of this network is to reduce the burden of SCD globally by becoming a platform of educational resources for caregivers of SCD in LMICs.

Metrics

CONSA has already demonstrated the effective implementation of cost-effective screening programs in the countries where this program is currently being implemented. This metric will be used to convince public health policy experts in all countries with large populations of patients with SCD to implement such programs more widely. Importantly, the success of this program will be judged not only based on the identification of the children who are affected but also based on the development of effective strategies for the early implementation of vaccinations and treatment with hydroxyurea.

The metrics of success of the newly developed SCD Clinical Trials Network will be based on how effective it will be in facilitating and hastening the evaluation of potential new therapeutics and combination therapies for the treatment of this disease. A critical feature that needs to be constantly evaluated is whether the Clinical Trials Network is providing the appropriate infrastructure to promote collaborations between clinical investigators and sites and between sponsors of trials and the community with SCD.

Making a difference

The combination of SCD-focused initiatives, the ASH Research Collaborative, CONSA, the Sickle Cell Clinical Trials Network, and others has enormous potential to dramatically alter the course of SCD care worldwide. CONSA will establish models that can ensure that patients receive a diagnosis and obtain preventive care. The Clinical Trials Network contains built-in features that will facilitate the efficient completion of clinical trials. Although the Clinical Trials Network is limited to the US and will not directly involve CONSA sites, the pharmaceutical industry should be recognized for its efforts to include the global SCD community in therapeutic trials. As pharmaceutical industry partners join each of these efforts, a focus must remain on discovering new therapeutics for this long-overlooked disease. In addition, the benefits of these new therapies must be shared equitably. The climate is ripe to embark on these critical and worthwhile initiatives that will dramatically change lives.

Authorship

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Footnote

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