Review Article

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Precision Medicine and Sickle Cell Disease

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ABSTRACT

Sickle cell disease (SCD) is characterized by variable clinical outcomes, with some patients suffering life-threatening complications during childhood, and others living relatively symptom-free into old age. Because of this variability, there is an important potential role for precision medicine, in which particular different treatments are selected for different groups of patients. However, the application of precision medicine in SCD is limited by difficulties in identifying different prognostic groups and the small number of available treatments. The main genetic determinant of outcomes in SCD is the underlying β-globin genotype, with sickle cell anemia (HbSS) and hemoglobin SC disease (HbSC) forming the 2 major forms of the disease in most populations of African origin. Although there are clear differences in clinical outcomes between these conditions, treatments approaches are very similar, with little evidence on how to treat HbSC in particular. Other genomic information, such as the co-inheritance of α-thalassemia, or high fetal hemoglobin (HbF) levels, is of some prognostic value but insufficient to determine treatments. Precision medicine is further limited by the fact that the 2 main drugs used in SCD, penicillin and hydroxyurea, are currently recommended for all patients. Newer treatments, such as crizanlizumab and voxelotor, raise the possibility that groups will emerge who respond best to particular drugs or combinations. Perhaps the best current example of precision medicine in SCD is the selective use of blood transfusions as primary stroke prevention in children with evidence of cerebral vasculopathy. More precise treatments may emerge as we understand more about the pathology of SCD, including problems with erythropoiesis.

INTRODUCTION

Precision medicine is an increasingly popular term, which has emerged over the last decade, gradually evolving from a theoretical concept to actual medical practice.[1] Paradoxically, precision medicine is not very precisely defined and overlaps with terms such as personalized medicine, deep phenotyping, targeted therapy, and stratified medicine.[2] It refers to the possibility that medical management can be chosen based on the specific features of a group of patients with the same disease, rather than all cases of the disease being approached in the same way. The most extreme form of precision medicine is personalized medicine, in which different treatments are chosen for each individual patient, particularly based on genomic analysis. The move towards precision medicine has really been driven by the possibility of performing whole genome sequencing on every patient, together with bioinformatic resources and computational power to allow these data to be interpreted. Ideally, precision medicine also incorporates other causes of variability, including environmental factors, blood and imaging biomarkers, and personal preferences, although genomics remains at its core.

The 2 key things necessary for the practice of precision medicine are being able to reliably classify different subgroups of patients with a particular diagnosis and then having a range of treatment options available, which have different outcomes for the different subgroups. Both of these are problematical in sickle cell disease (SCD).

SCD is one of the commonest severe inherited diseases in the world; it is thought to affect 3–6 million people, although the precise number of affected individuals is unknown.[3] More than 70% patients with SCD live in Africa, with limited access to health care.[4] Although every person with SCD has at least 1 copy of the same variant in the β-globin gene (*HBB*; c.20A>T, p.Glu7Val), it is a remarkably variable condition, with a wide range of clinical manifestations and the potential for every organ to be damaged both acutely and chronically.[5] Typical complications include acute and chronic pain, hyposplenism, increased infections, cerebrovascular disease, cardiopulmonary dysfunction, renal impairment, hepatopathy, retinopathy, priapism, and leg ulcers. Life expectancy is shortened by at least 20 years even with the best medical care,[6] and the majority of patients with SCD die in childhood in many low-income countries, where more than 70% patients live.[7] The majority of this variability, apart from that associated with socioeconomic factors, is unexplained by known genetic factors, creating a problem for any attempts to apply precision medicine to SCD.

Treatment options are fairly limited for patients with SCD at the moment, which makes the application of precision medicine more difficult. All children are offered penicillin prophylaxis because of hyposplenism.[8] There is increasing evidence that nearly all patients with sickle cell anemia (SCA) (HbSS and HbS/β[0] thalassemia) benefit from taking hydroxyurea

at the maximum tolerated dose,[9] with a definite reduction in acute complications and a probable improvement in long-term outcomes.[10] Other available treatments include intravenous fluids, oxygen, analgesia, and blood transfusions for acute complications; blood transfusions, analgesia, physiotherapy, and hematopoietic stem cell transplantation (HSCT) for chronic complications.[11]

More treatment options are starting to emerge, with L-glutamine, crizanlizumab, and voxelotor being available in some high-income countries, and further drugs in later stage clinical trials.[12] In parallel, gene therapy in various forms is developing rapidly, with new possibilities emerging every month, and it seems likely that this will eventually become the treatment of choice, although technical and economic issues mean that we are a very long way from this at the moment.[13]

However, there are currently many barriers to the use of precision medicine in SCD, including difficulties in predicting outcomes and a very limited number of treatments. Even if it were theoretically possible to apply precision medicine to SCD, the cost of the genomic, proteomic, and other -omic analyses would be prohibitive in the majority of countries where SCD is prevalent.

In this review, we will consider how precision medicine is currently applied for patients with SCD and consider how emerging and new investigations might change this in the future, including consideration of abnormalities in red cell adhesion and erythropoiesis.

CAN WE IDENTIFY PROGNOSTIC GROUPS IN SICKLE CELL DISEASE?

Different types of sickle cell disease

There are more than 15 different genotypes that can cause SCD, although most of these are very rare.[14] There are clear differences in outcomes associated with these different genotypes. Most notable is the distinction between patients with sickle cell anemia (HbSS) and those with hemoglobin SC disease (HbSC), with the latter being associated with less severe and less frequent acute and chronic complications, although some problems, such as retinopathy, are more common in HbSC.[15,16] Despite this representing a clear opportunity to practice precision medicine, there are really no evidence-based specific treatments targeted at the different genotypes, with the treatment for HbSC largely inferred from the management of HbSS. Perhaps the only example is the emerging use of venesection for some patients with HbSC and high hemoglobin levels, although there is as yet no high-quality evidence to support its use.[17]

The other major genotype of SCD is HbS/β-thalassemia, which is again relatively poorly characterized, despite being very common in the Middle East, India, and Southern Europe. In particular, HbS/β[+] thalassemia is often described, and even managed as a mild form of SCD, ignoring the reality that the severity varies widely from mild to severe, depending on the nature of the β[+] thalassemia variant.[14] Many studies have shown that splenomegaly is much more common in HbS/β-thalassemia,[18] with up to 30% patients undergoing splenectomy, suggesting that a different approach to managing splenomegaly might be appropriate in these patients.

There are probably distinctive features associated with each of the different genotypes; for example, HbS-Oman is associated with a particular pattern of cation loss and red cell dehydration.[19] However, these are all fairly rare conditions, which are relatively poorly described, and precise management strategies have not yet been developed.

Variation in hemoglobin F levels

There is a lot of evidence that higher hemoglobin F (HbF) levels are associated with better acute and chronic outcomes in SCA,[20] and possibly other types of SCD, stemming from Janet Watson's observation[21] more than 70 years ago that newborn babies with SCA have high HbF levels and few clinical complications. HbF falls quite rapidly over the first 2 years of life and most evidence on prognosis refers to these "adult" levels. However, there is evidence that HbF measured even in the first year of life is also of prognostic value.[22]

The genetic basis of variability in HbF has been extensively studied, potentially offering prognostic information prenatally and neonatally. Initially, this centered on the study of β-globin haplotypes based on restriction enzyme analysis,[23] which seem to act almost entirely by influencing HbF levels.[24] As the genetic basis of HbF variability has become better understood, traditional haplotypes have become largely redundant. Three genetic loci account for up to 50% of the variability in HbF levels in SCD: *Xmn1-HBF2*,[25] *BCL11A*,[26] and *HBS1L-MYB*.[27] However, studies to date do not show that analysis of these loci offers useful prognostic information for clinical outcomes beyond actually measuring the HbF percentage.

Co-inheritance of α-thalassemia

In most populations with SCD, at least 40% people also have some form of α-thalassemia. The commonest variant causing α-thalassemia is caused by a 3.7 kb deletion ($-\alpha^{3.7}$), and about 35% patients are heterozygous for this, with 5% homozygous.[28,29] Co-inheritance of α-thalassemia is associated with a very wide range of effects in SCD, most of which are beneficial; these include increased hemoglobin,[28] reduced renal impairment,[30] and fewer cerebrovascular complications.[31] α-thalassemia has a more complicated relationship to episodes of acute pain, with many studies suggesting that it is associated with more frequent painful episodes, possibly due to the higher hemoglobin and impaired blood flow in some blood vessels.[32] Overall, the number of functional α-globin genes has a distinct effect on the phenotype of SCA and is an important determinant of severity.

Other genetic factors

Some genetic factors have been shown to contribute to specific complications of SCD. The best examples of this are probably the increased incidence of gall stones associated with variation in the number of thymine-adenine (TA) repeats in the promoter of the uridine diphosphate-glucuronosyltransferase 1A (*UDGT1A*) gene,[33] and the increased risk of nephropathy associated with the G1 and G2 variants of *APOL1*.[30,34] Of note, both of these associations were identified in the general population, and the association subsequently confirmed in SCD. Patients with SCD are not currently routinely genotyped for these factors, and they are not used to direct management.

A large number of other studies have been performed to try and identify genetic associations with particular complications of SCD. In general, none of these have identified significant results that have been validated in independent studies. Perhaps most effort has gone in to identifying genetic risk factors for cerebrovascular disease; promising candidate genes for large-vessel disease include *APOE*,[31] *TNF-α*,[35,36] *GOLGB1*,[37] and *PON1*.[37] Even less is known about the genetics of the more common silent cerebral infarcts, with α-thalassemia being the only factor which possibly offers some protection.[38] None of these factors have reached the stage where they are clinically useful and can be used to influence the choice of treatment.

Blood tests and biomarkers

Most blood tests are abnormal in SCD, and many studies have correlated these with clinical outcomes, attempting to identify prognostic groups that may allow more precise use of available treatments.[39] In summary, very few of these have been validated prospectively, and none beyond routinely performed tests are currently in clinical use. Overall, hemoglobin concentration is probably the most informative biomarker, with

increased anemia associated with several adverse outcomes, including increased risks of cerebrovascular disease,[40] kidney disease, pulmonary hypertension, and earlier death.[41] Lactate dehydrogenase has also been extensively studies, and its correlation with various outcomes defined, including cerebrovascular disease,[42] pulmonary hypertension, priapism, leg ulcers, and earlier death.[43] Similarly, various adverse outcomes have been correlated with increasing reticulocyte and white cell counts.[39] Although these correlations are all fairly robust and have been duplicated in multiple studies, in general, all these biomarkers also correlate fairly closely with each other, and it is very difficult to know whether there are any causal relationships, or whether these are just associations, which all correlate with the causative event, such as the rate of HbS polymerization.

There is increasing interest in developing other assays, which might reflect more fundamental aspects of SCD pathophysiology, such as abnormal red cell adhesion (discussed later) or the rate of HbS polymerization. HbS polymerization cannot currently be measured directly. There has been some interest in the use of oxygen-gradient ektacytometry as a biomarker potentially able to predict clinical complications. Although studies show that the various ektacytometry parameters correlate with many factors in SCD, such as total hemoglobin and HbF percentage, there is nothing to suggest that this approach offers any additional or independent prognostic information.[44]

Imaging and precision medicine

Modern imaging techniques offer the possibility of precise diagnoses, although their use has mostly not been evaluated in SCD. Although widely used, it is not clear exactly when even simple tests such as chest and limb x-rays should be requested in SCD, although there is some evidence that they are probably used inappropriately.[45]

Perhaps the best example of precision medicine in SCD is the use of transcranial Doppler (TCD) ultrasound assessment of the circle of Willis, to identify children at increased risk of stroke, as developed by Dr Robert Adams.[46] The use of blood transfusions,[47] hydroxyurea,[48] and HSCT[49] in children with abnormal TCDs has seen a fall in the incidence of stroke in SCD in high-income countries of more than 90%, which will hopefully be translated into similar benefits in sub-Saharan Africa.

Other factors associated with prognosis

Understanding and interpreting genetic variability is the cornerstone of precision medicine, but as discussed above, this is difficult in SCD, as the majority of differences in patient outcomes are not explained by genomics. This is perhaps best illustrated by differences in survival of patients with SCA: in northern, high-income countries, such as the United Kingdom, more than 95% children with SCA survive to adulthood,[50] whereas recent estimates suggest that at least 40% children with SCA die before the age of 10 in sub-Saharan Africa.[7] These populations are genetically very similar, and the differences are almost certainly explained by nongenetic factors, including socioeconomics, infections, and access to medical care. Similarly, variation in day-to-day symptoms, such as the frequency of acute painful episodes, is not easily explained by genomics, and is likely to be associated with environmental factors, such as weather, air quality, stress, and infection.[51]

THE SELECTION OF DIFFERENT TREATMENTS IN SICKLE CELL DISEASE

Although more treatments are emerging, there are still relatively few options available in SCD, limiting the application of precision medicine to a large extent. Penicillin is the most established treatment, offered to all children with SCD from the age of a few months, although there is uncertainty about when it should be stopped, and lack of evidence on how it should

be offered to the less severe types of SCD, including HbSC disease.[52] There is good evidence on the use of blood transfusion and primary stroke prevention[47] but not much precision in the use of blood transfusions in other circumstances.[53] Similarly, although there is increasing evidence of the benefits of HSCT in SCD,[49] there are no randomized controlled trials in this area, and therefore it is difficult to know when the different types of transplant should be offered.[54] There is almost complete imprecision when it come to the management of acute complications in SCD, with no evidence on the use of even the most basic treatments, such as oxygen[55] and intravenous fluids,[56] and no specific drugs that are known to change outcomes.

However, new treatments are being developed in SCD, and it seems likely that over the next 10 years more precise management of this condition will emerge (Table 1).

Drugs promoting HbF synthesis

Hydroxyurea is established as the most effective treatment currently available to treat SCA, and its main mode of action is to promote HbF production. Most guidelines in high-income countries recommend that every patient with SCA is started on hydroxyurea from early childhood,[57] which limits the possibilities around selecting patients most likely to benefit. Nevertheless, many studies have attempted to identify who responds best to hydroxyurea, particularly in terms of HbF increases. Most studies find that those with higher HbF levels before starting hydroxyurea are more responsive to the drug, and unsurprisingly this corresponds to the presence of particular variants in or near the *BCL11A*, *HMIP*, and *HBG2* genes.[58] A study of the changes in the plasma proteome associated with hydroxyurea use suggested that the HbF increase was greatest in those with the least inflammation,[59] suggesting the potential for synergistic actions between hydroxyurea and drugs reducing inflammation, such as canakinumab.[60]

Perhaps the best approach to a more precise use of hydroxyurea in SCA involves using pharmacokinetic measurements to individualize the dose of hydroxyurea and rapidly achieve the maximum tolerated dose,[61] which has been shown to offer the most clinical benefit.[9] Traditionally, patients have been started on moderate dose of hydroxyurea and the dose gradually increased over months and years until there is clinical benefit or evidence of myelosuppression, as suggested by some degree of neutropenia. This approach is fairly slow, with many patients never reaching optimal doses. Quinn et al,[61] showed that high HbF levels could be rapidly achieved by starting children on the maximum tolerated dose from the onset, as predicted by pharmacokinetic methods. This approach has not been widely adopted yet, partly because of limited availability of hydroxyurea pharmacokinetic measurements, although there is a trend toward starting children on higher doses rather than gradually building up. It is also less clear how well this approach will work in adults, who seem to be more sensitive to hydroxyurea, possibly because of progressive damage to the bone marrow (BM) niche.

Increasing hemoglobin levels

Voxelotor has been licensed for use in SCD in some countries, including the United States. It binds covalently to the α-globin chain, to stabilize hemoglobin in the oxygenated form, which then does not form polymers but also does not release oxygen. Clinically voxelotor increases hemoglobin by at least 1 g/dL in 75% of patients, with a 20% fall in reticulocyte percentage. Disappointingly, in the randomized controlled trial, there were no detectable clinical benefits at 72 weeks, including no change in the frequency of acute pain or evidence of an improved quality of life.[62] It may be that the clinical benefits of voxelotor emerge with time, although it seems possible that the benefits of reduced anemia are offset by a proportionate reduction in oxygen delivery.[63] As mentioned earlier, lower hemoglobin levels are

Table 1.

Current Routinely Used Nonacute Treatments Used in the Management of Sickle Cell Disease in the Context of Precision Medicine

Treatment	Patient Groups Most Likely to Benefit	Uncertainties	Precision
Penicillin V	All	When to stop Use in HbSC	Low
Hydroxyurea	Sickle cell anemia	Use in HbSC	Low
Regular blood transfusions	Sickle cell anemia with abnormal TCDs	Use for other complications	High
Crizanlizumab	Vaso-occlusive complications	Limited information on HbSC	Moderate
Voxelotor	Possibly those with more anemia	Clinical indications and benefits	Low
L-glutamine	Frequent episodes of acute pain	Limited evidence of efficacy	Moderate
ACE inhibitors	Significant proteinuria	Limited evidence of efficacy	Moderate
Overnight oxygen	Low oxygen saturations	Limited evidence of efficacy	Moderate
HSCT from HLA-identical sibling	Possibly all young patients with SCA	No RCTs, limited long-term data	Moderate
HSCT from alternative donors	Life-threatening complications despite optimal care	No RCTs, limited data	Low

ACE = angiotensin-converting-enzyme; HbSC = hemoglobin SC disease; HSCT = hematopoietic stem cell transplantation; RCT = randomized controlled trial; SCA = sickle cell anemia; TCD = transcranial Doppler.

associated with various adverse outcomes in SCA,[41] and drugs such as voxelotor may be of particular benefit when used in patients with lower hemoglobin levels. Other drugs are starting to emerge that also reduce anemia, including pyruvate kinase activators such as mitapivat,[64] and this may become an important therapeutic approach in SCA.

Blocking abnormal red cell adhesion

Acute vaso-occlusion is the hallmark of SCA. It is believed to be initiated by abnormal adhesion of blood cells to the vascular endothelium, followed by obstruction of fine capillaries by the rigid nondeformable red blood cells (RBCs).[65] There are several factors that underly abnormal adhesion of sickle RBCs. One important problem resides in the fact that SCD patients have high reticulocyte counts. Reticulocytes are immature RBCs that exit the BM and undergo the final step of maturation in the circulation. During this last step, they are subject to important changes such as membrane remodeling and removal of organelle remnants and a subset of proteins, including adhesion proteins, by autophagy.[66,67] In SCD, circulating reticulocytes exhibit an abnormal repertoire of surface proteins, with high levels of adhesion molecules such as Lutheran blood group/basal cell adhesion molecule (Lu/BCAM), intercellular adhesion molecule 4 (ICAM4), and lymphocyte function associated antigen 3 (LFA-3).[68–70] This is believed to be the consequence of stress erythropoiesis and the premature exit of reticulocytes from the BM, at an earlier stage than in healthy individuals, because of severe anemia. Consequently, SCD patients have high numbers of circulating adhesive red cells of the magnitude of 10^{12} (5%–10% of the RBC count), which is a tremendous number of cells harboring the adhesive potential to initiate vaso-occlusion. For this adhesion to occur, several studies have shown the importance of signaling events in activating adhesion molecules through phosphorylation of their cytoplasmic domain by protein kinases such as protein kinase A (PKA).[71] These signaling cascades are probably overrepresented in RBCs containing sickle hemoglobin because of the high numbers of circulating reticulocytes and of the altered maturation of stress reticulocytes in SCD patients.

Anti-adhesive strategies have been developed to target RBC abnormal adhesion either by blocking adhesive interactions, using small molecules or antibodies,[72,73] or by inhibiting signaling pathways using soluble inhibitors.[74] Such strategies, limited to experiments performed in vitro or in animal models, had rather limited success because of the complexity and the multifactorial aspect of vaso-occlusion, and targeting a single erythroid adhesion molecule does not seem sufficient to completely block RBC adhesion to endothelium under inflammatory conditions.

A breakthrough in the understanding of vaso-occlusion occurred in the early 2000s with a study showing that this was a multicellular phenomenon that involves adherent leukocytes.[75] Leukocytes were shown to play a primary role in initiating vaso-occlusion by adhering to inflamed venules followed by recruitment of RBCs to the vessel wall. This adhesion involves endothelial P-selectin and E-selectin, whose expression is upregulated by inflammatory cytokines. With the development of sophisticated in vivo imaging techniques and ex vivo settings mimicking the blood circulation, abnormal adhesion and aggregation of polymorphonuclear neutrophils with RBCs and platelets were further documented using SCD mouse models[76] and blood samples from SCD patients.[77,78] Importantly, mice lacking P- and E-selectins were shown to be protected from vaso-occlusion following the defective recruitment of leukocytes to the vessel wall,[75] paving the way for therapeutic strategies targeting selectins in SCD. The synthetic pan-selectin inhibitor rivipansel (GMI-1070) was found to predominantly inhibit E-selectin–mediated neutrophil adhesion and RBC-leukocyte interactions in a humanized SCD mouse model, improving the blood flow in the microcirculation as well as animal survival.[79] An anti-P-selectin aptamer was also tested in an SCD mouse model and proved efficient at inhibiting the adhesion of both RBCs and leukocytes to endothelial cells.[80] These preclinical studies formed the scientific basis of the 2 main clinical trials in the field that used the E-selectin inhibitor GMI-1070 (rivipansel)[81,82] and the anti-P-selectin humanized monoclonal antibody crizanlizumab.[83] The clinical trial using crizanlizumab showed significant reduction in the rate of SCD-related pain episodes compared with placebo. In this study, for a total of 198 patients, the median rate of episodes of acute pain per year dropped from 2.98 to 1.63 with high-dose crizanlizumab; the median time to the first and to the second episode was also longer than with placebo. Although crizanlizumab did not affect hematological parameters or quality of life, it has been approved by the US Food and Drug Administration as it precisely targets a complication of SCD and might also be of interest in combination therapy to achieve additive effects. As such, it is currently licensed for patients with SCD aged 16 years and older, as an add-on therapy to hydroxycarbamide or as monotherapy in patients for whom hydroxyurea therapy fails or is inadequate. Trials are ongoing in the pediatric population and early results suggest a similar benefit to that seen in adults. The phase 3 trial of rivipansel has not been formally published yet, but Pfizer, who make the drug, have announced that it did not meet its primary or key secondary endpoints.[12]

It is not currently possible to identify which patients benefit most from crizanlizumab, although it seems likely that in the future patients expressing a particular pattern or level of adhesion molecules might be most responsive, and the availability of this new drug certainly opens up the possibility of precision medicine in SCD.

Drugs targeting abnormal erythropoiesis and the bone marrow niche

Ineffective erythropoiesis (IE) is an important factor in many types of anemia, including β-thalassemia.[84] Although IE in

SCD is still not widely recognized as important, observations more than 30 years ago showed that the BM of SCD patients possessed an architecture that is very different from the BM of healthy individuals, with irregular and patchy cellularity.[85] Recent studies have shown that the hematopoietic stem progenitor cells extracted from BM samples of SCD patients are characterized by increased inflammation, aggregation, and activation, which further hints that the BM niche is abnormal in patients with SCD, which contributes to the pathophysiology of the condition.[86] The SCD BM vascular niche was further studied using the humanized Townes SCD mice. Using in vivo imaging, it was shown that the SCD mice have abnormal and disorganized BM vasculature, with increased levels of proangiogenic growth factors and soluble vascular adhesion molecule-1, markers of vascular dysfunction. Interestingly, this study also showed that erythroblasts from BM of SCD mice had increased reactive oxygen species production and increased level of apoptosis, both of which are characteristics of IE.[87]

More recently, using both in vivo human-derived erythroblasts and in vitro differentiated erythroblasts from SCD patients, the extent of IE in SCD was evaluated. By mimicking the hypoxic environment of the BM niche, it was shown that hypoxia-induced high levels of apoptosis during the late differentiation stages, specifically starting from the polychromatic erythroblasts. These high levels of apoptosis, therefore, coincide with the hemoglobin accumulation stage of differentiation, and the presence of higher levels of HbF decreased apoptosis levels and decreased IE, suggesting that HbS polymerization is the main contributor to these defects.[88]

As IE has proven to be an important feature of SCD, quantitation of IE in SCD patients is important to facilitate studies on response to treatment. Using 2 biological markers, soluble transferrin receptor and absolute reticulocyte count, Brewin et al[89] were able to develop an index, named index of ineffective erythropoiesis (IoIE) to quantitate IE in SCD patients. This study showed that IE is a feature of SCD and more prominent in patients with HbSS rather than HbSC. Regular blood transfusions were shown to decrease IE, whereas paradoxically hydroxyurea seemed to cause an increase.[89] Increased

understanding of erythropoiesis in SCD, combined with quantitative information from the IoIE, offers the potential for precision medicine, in which patients with high levels of IE might benefit from regular blood transfusions or treatments aimed at reducing inflammation or oxidative stress. In particular, it is important to recognize that HbS has significant effects on erythropoiesis and the BM niche, which may be need to be precisely targeted to optimize the health of patients with SCD (Figure 1).

CONCLUSIONS

Precision medicine potentially offers very important benefits for patients with SCD, particularly because it is such a variable condition, with multisystem manifestations. It seems very likely that different patients need different treatments: for example, some patients may benefit most from treatments to prevent renal impairment, whereas others need protection against pulmonary vascular disease. Unfortunately, the current availability of precision medicine in SCD is very limited, both because of difficulties separating patients into prognostic groups, and the limited availability of different treatments, and the only good example in clinical practice is of primary stroke prevention using TCD and selective blood transfusion, hydroxyurea, and HSCT.[47–49]

Genomics and emerging treatments offer hope for more applications of precision medicine in SCD, including more focused use of crizanlizumab and better understanding of IE. Developments in many other fields including proteomics, lipidomics, radiomics, metabolomics, transcriptomics, and microbiomics, offers the prospect of a more complete understanding of the pathophysiology of SCD, and the identification of novel, validated biomarkers. All these technologies generate huge amounts of data, and the increasing sophistication of statistical analysis, using artificial intelligence and machine learning may allow the development of predictive models able to quantify the risks of hugely complex events, such as acute vaso-occlusive episodes. This approach is epitomized by the Trans-Omics for Precision Medicine program, sponsored by the National Institutes of Health, which is supporting several studies on SCD, including studies of heart, lung, and kidney disease
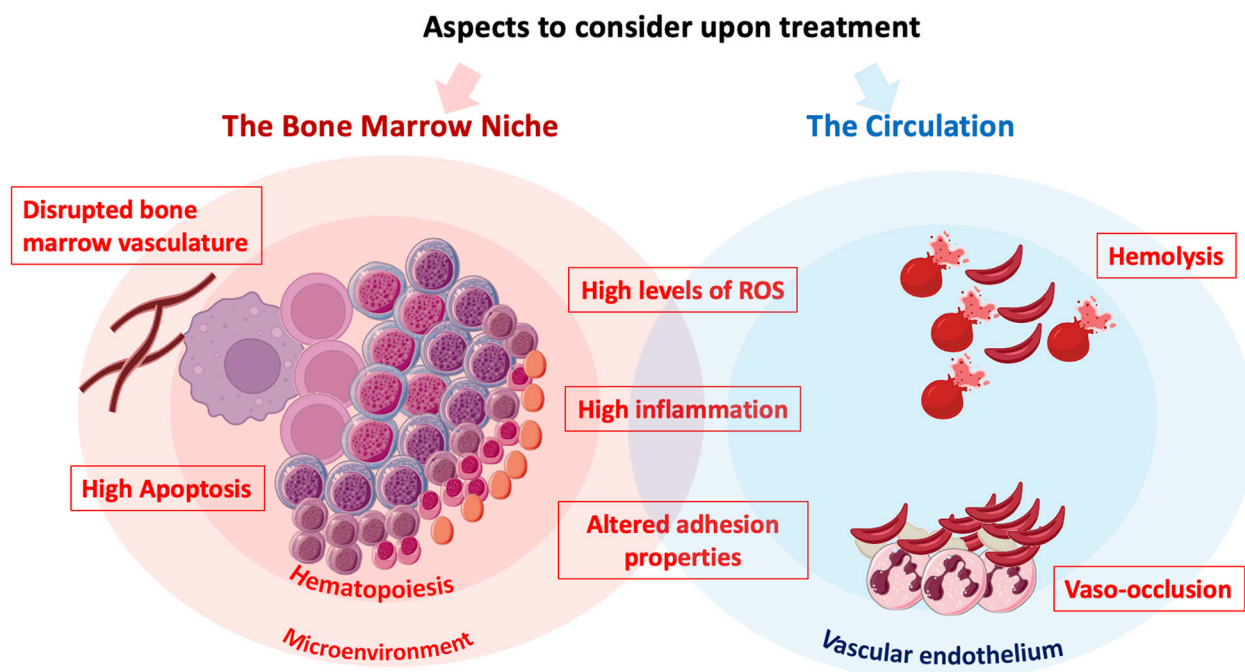

Figure 1. The interaction between the bone marrow and circulation. ROS = reactive oxygen species.

(https://topmed.nhlbi.nih.gov). In the future, precision medicine may become less relevant as all patients benefit curative treatments,[90] such as gene therapy, although the widespread use of this approach is still decades away, and precision medicine in SCD is likely to be beneficial for the foreseeable future.

AUTHOR CONTRIBUTIONS

All authors contributed to planning, writing, and revising the article.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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