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REVIEW

Emerging drugs in randomized controlled trials for sickle cell disease: are we on the brink of a new era in research and treatment?

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ABSTRACT

Introduction: Sickle cell disease (SCD) is caused by a mutation in the HBB gene which is key for making a component of hemoglobin. The mutation leads to the formation of an abnormal hemoglobin molecule called sickle hemoglobin (HbS). SCD is a chronic, complex disease with a multiplicity of pathophysiological targets; it has high morbidity and mortality.

Hydroxyurea has for many years been the only approved drug for SCD; hence, the development of new therapeutics is critical.

Areas covered: This article offers an overview of the key studies of new therapeutic options for SCD. We searched the PubMed database and Cochrane Database of Systemic Reviews for agents in early phase clinic trials and preclinical development.

Expert opinion: Although knowledge of SCD has progressed, patient survival and quality of life must be improved. Phase II and phase III clinical trials investigating pathophysiology-based novel agents show promising results in the clinical management of SCD acute events. The design of long-term clinical studies is necessary to fully understand the clinical impact of these new therapeutics on the natural history of the disease. Furthermore, the building of global collaborations will enhance the clinical management of SCD and the design of primary outcomes of future clinical trials.

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Sickle cell disease; inflammatory vasculopathy; new treatment; hemoglobinopathies

1. Introduction

Sickle cell disease (SCD) is an hemoglobinopathy which affects approximately 100,000 individuals in the United States and almost 20,000–25,000 subjects in Europe, mainly immigrants from endemic areas such as sub-Saharan Africa to European countries [1–4]. Estimates of the number of affected newborns in 2010 are of approximately 312,302 subjects with 75.5% being born in Africa [5]. The invalidating impact of SCD on patient survival, quality of life and cost for health systems [2], requires the development of new therapeutic options to treat sickle cell-related acute and chronic complications. SCD is caused by a point mutation in the β-globin gene resulting in the synthesis of pathological hemoglobin S (HbS). HbS displays peculiar biochemical characteristics, polymerizing when deoxygenated with an associated reduction in cell ion and water content (cell dehydration), increased red cell density and further acceleration of HbS polymerization [6–8]. Pathophysiological studies have shown that dense, dehydrated red cells play a central role in acute and chronic clinical manifestations of SCD, in which intravascular sickling in capillaries and small vessels leads to vaso-occlusion and impaired blood flow with ischemic/reperfusion injury [6,9–12]. In microcirculation, vaso-occlusive crisis (VOC) result from a complex and still partially known scenario, involving the interactions between different cell types, including dense red cells, reticulocytes, abnormally activated endothelial cells, leukocytes, platelets, and plasma factors (Figure 1) [6,10,11,13–15]. Acute VOCs have been associated with increased expression of pro-adhesion molecules such as vascular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1) or selectins [6,10,13,14,16,17]. These molecules are important in recruitment and adhesion of both neutrophils and sickle red cells to the abnormally activated vascular endothelial surface [13,18].

Recently, in SCD mice exposed to hypoxia/reoxygenation (H/R) to mimic VOC, we highlighted the novel contribution of altered pro-resolving events in organ damage due to ischemic/reperfusion stress (Figure 1, inset) [19]. Indeed, in humanized SCD mice, the failure of acute inflammatory resolution sustains the amplified inflammatory response to H/R, making SCD mice more vulnerable to inflammatory vasculopathy (Figure 1) [19]. Thus, targeting pro-resolving mechanisms may represent an interesting new therapeutic strategy to be tested in appropriate human trials in SCD.

This review provides an overview on the more relevant studies on new therapeutic options for SCD. We did a systematic review using specific search strategy, carried out the review of PubMed database, Cochrane Database of Systemic Reviews on early-phase clinic trials, and molecules in pre-clinical development for SCD diagnosis.

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Article Highlights

- SCD is a hereditary red blood cell disorder with high mortality and morbidity.
- Phase II and phase III clinical trials investigating pathophysiology-based agents show promising results in clinical management of acute events in SCD.
- Therapeutic targeting of neutrophils and red cell crosstalk with vascular endothelium is a promising approach to sickle cell related vasculopathy.
- The lack of pharmacogenomic studies may delay the development of algorithm(s) useful for precision medicine.
- Gene therapy is a new curative option for SCD; however, there are issues related to mutagenesis, conditioning regimen, or high costs.
- The design of long-term clinical studies is necessary to fully understand the clinical impact of the new therapeutics on the natural history of SCD.

This box summarizes key points contained in the article.

2. Novel therapeutic strategies to treat sickle cell disease

In the last two decades, the availability of mouse models for SCD has allowed both characterization of the pathogenesis of sickle cell-related organ damage(s) and identification of pathophysiology-based new therapeutic options in addition to hydroxyurea (HU) [6,8,13,14,20–22]. This is in agreement with the reported strong link between scientific publications on rare disease and orphan drug designation [23]. In addition, FDA and EU community has incentivized the development of drugs with orphan designation status to increase therapeutic options for rare diseases such as SCD.

As shown in Table 1, pathophysiology-related novel therapeutic strategies for SCD can be divided into:

- Agents which reduce/prevent sickle red cell dehydration or red cell sickling or HbF inducers to delay;
- Agents targeting SCD vasculopathy and sickle cell-endothelial adhesive events;
- Anti-oxidant agents.

Among the agents preventing red cell sickling, the oral direct anti-sickling agent GBT440 has been shown to be beneficial in SCD (Figure 2). GBT440 (or voxelotor) blocks HbS intermolecular contacts, preventing the generation of HbS fibers and red cell sickling [24–28]. GBT440 has been shown (i) to ameliorate *in vitro* SCD red cell features such as red cell deformability or viscosity and (ii) to improve sickle red cell survival with decrease reticulocyte count [24–28]. Preliminary data on phase I/II double-blind placebo study with GBT440 (voxelotor) in healthy volunteers and few SCD patients show safety and tolerability associated with an amelioration of hemolytic indices and a reduction in reticulocyte count (#NCT02285088) [29–32]. A phase III clinical trial is ongoing to evaluate whether the preliminary evidence of beneficial clinical effects might be transferable in patients with severe, symptomatic SCD (NCT03036813). In addition, FDA has recently defined voxelotor as breakthrough therapy for SCD [33]. Noteworthy, new anti-sickling molecules related to voxelotor such as GBT1118 are under functional characterization to expand the choice on anti-sickling agents [34–37].

In addition to HU, fetal hemoglobin (HbF) inducers such as decitabine or pomalidomide have been recently reported to reduce HbS polymerization and increase red cell survival [38–46]. Decitabine (Dec) is an analogue of 5-azacitidine acting as HbF inducers through the inhibition of DNA methyltransferase (DNMT). The major limitation of this molecule is related to its bioavailability and concentration. A recent report on phase I/II clinical trial with Dec combined with tetrahydrouridine (THU), an

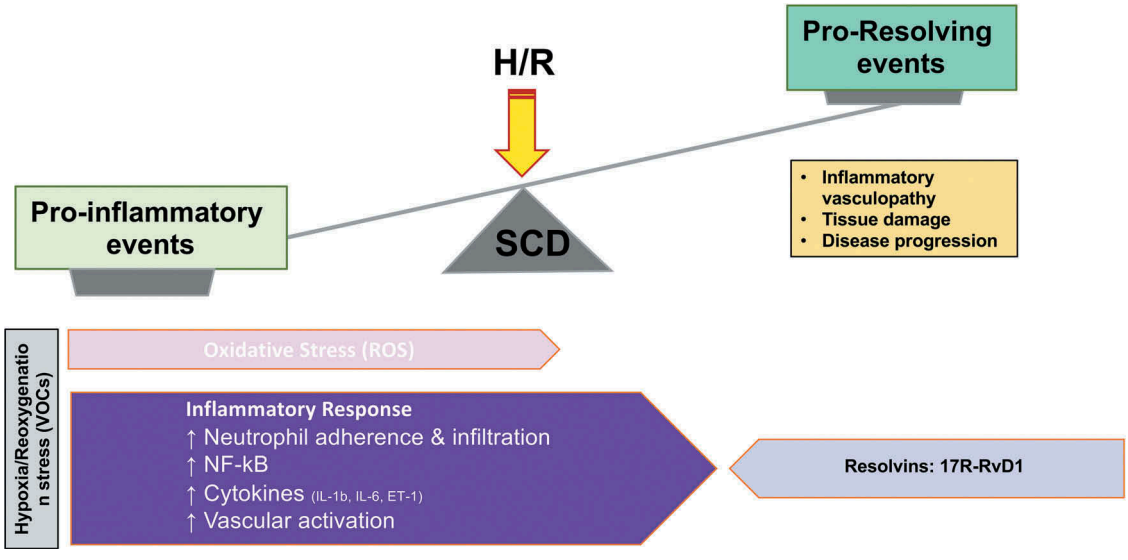

Figure 1. Schematic model of sickle cell-related acute vaso-occlusive crisis (VOCs), which induces hypoxia/reoxygenation (H/R) damage. This induces an inflammatory response, that requires a pro-resolving phase to control and reduce the H/R cellular and tissue injury. In sickle cell disease (SCD), the amplified inflammatory response and the lack in pro-resolving events result in vascular vulnerability and dysfunction. In SCD, altered resolution leads to vasculopathy, tissue damage, and disease progression. 17*R*-RvD1 has multi-pronged effects that revert the hyper-inflammatory phenotype, promote resolution, and prevent damage to organs affected in SCD. In experimental SCD, 17*R*-RvD1 reduces neutrophil-endothelial cell interactions, blunts leukocyte infiltration in lungs and kidney following H/R, thus limiting collateral injuries, and modifies molecular mechanisms underlying inflammation such as NF-κB, endothelin 1 values; vascular activation markers, and microRNAs miR-126 and let7c. **Inset**. Schematic representation of the unbalance in the inflammatory response to H/R stress in SCD. Pro-inflammatory events are preponderant on pro-resolving process, allowing tissue damage and disease progression. Modified from [19].

Matte A, Recchiuti A, Federti E, et al. Resolution of sickle cell disease-associated inflammation and tissue damage with 17R-resolvin D1. Blood. 2019;133 [3]:252–265.

Table 1. Early and late phase clinical trial in sickle cell disease (SCD).

Targets	Phase of development	Key results	Ref.
Red cell sickling and HbF inducers	Phase I/II	Decitabine combined with tetrahydrouridine, an inhibitor of cytidine deaminase, has shown promising pharmacokinetic data for future exploitation in trial with SCD patients.	[40–42, 46]
	Phase III clinical trial on-going	GBT440 is an oral direct anti-sickling agent, to be beneficial in SCD. GBT440 (or voxelotor) blocks HbS intermolecular contacts, preventing the generation of HbS fibers and red cell sickling (#NCT02285088). on-going phase III clinical trial on voxelotor in a larger population of SCD patients (HOPE; #NCT03036813).	[24–32, 34–37]
Agents targeting SCD vasculopathy and sickle cell-endothelial adhesive events	Phase III clinical trial-on going	Humanized anti-P-Selectin antibody (SelG1, crizanlizumab; SUSTAIN, #NCT0185361).	[17, 58, 59]
	Phase I/II clinical trial	SCA411: DHA ester in combination with HU in children with SCD (n = 67 individuals) 20–36 mg/kg/day for 8 weeks L-arginine supplementation in combination with HU in SCD patients L-Citrulline supplementation in SCD patient under steady state condition (*n* = 8 individuals) IMR-687: phosphodiesterase-9 inhibitor safety and tolerability in SCD (enrolling) Olinciguat: oral sGC stimulators safety and tolerability in SCD (enrolling)	[47, 82–90, 97, 100]
	Pre-clinical studies	• Resolvin: 17*R*-RvD1-humanized mouse model for SCD • IMR-687: phosphodiesterase-9 inhibitor-*in vitro, ex vivo* and *in vivo* studies in humanized SCD mice. • Factor H and 19–20 FH fragment- *ex vivo* model	[19, 47, 62]
Oxidative stress	Phase III clinical trial	• L-Glutamine. Glutamine is involved in GSH metabolism. A multicenter, randomize, placebo-controlled double-blind phase III clinical trial with L-glutamine (0.3 g/kg twice a day) supplementation reduced the mean number and length of hospitalization, associated with increased median time to the first crisis.	[106–109]
	Phase I/II clinical trial	• NAC, an exogenous thiol donor. A clinical trial with high dose of NAC during acute VOCs related to SCD is ongoing (#NCT 01800526). • GA exudates mechanically extracted from *Acacia senegal* (#NCT 02467257).	[103–105, 110]

HU: hydroxyurea, SCD: sickle cell disease; HbS: hemoglobin S; DHA: docosahexaenoic acid; RvD: resolving-D; VOCs: vaso-occlusive crisis; sGC soluble guanylcyclase; GSH: glutathione; NAC: N-acetyl-cysteine; GA: gum arabic.

inhibitor of cytidine deaminase, has shown promising pharmacokinetic data for future exploitation in trial with SCD patients [40,41,45,46]. Pomalidomide is a potent HbF inducer through the acetylation of key region in γ-globin gene. Some synergistic effects of pomalidomide and HU have been described [38].

Recently, IMR-687, selective inhibitor of phosphodiesterase-9 (PDE-9), has been tested in vitro and in vivo in humanized model for SCD [47]. IMR-687 is an oral PDE-9 inhibitor. In SCD mice, IMR-687 acts as a multimodal molecule: increasing HbF synthesis with reduction of sickling modulating inflammatory response, being protective against hypoxia-reoxygenation damage that occurs in acute VOCs [47]. The authors propose IMR-687 to be tested alone or in combination to lower dosage of HU in SCD subjects non-responder to HU. On-going randomized multicentric, placebo-controlled study-phase 2 (#NCT03401112) designed to evaluate the safety and tolerability of IMR-687 in SCD patients.

2.1. Agents targeting SCD vasculopathy and sickle cell-endothelial adhesive events

In SCD, anti-adherence therapeutic strategies might represent an interesting, novel therapeutic strategy to prevent the generation of acute VOCs and to lessen SCD related organ damage (Figure 2). The anti-adherence therapeutic options might be divided into three groups based on their mechanism of action:

a. Molecules interfering with the physical properties of the red cell-endothelial adhesion process;
b. Molecules specifically interfering with sickle cell-endothelial adhesive mechanisms;
c. Molecules modulating inflammatory pathways involved in sickle cell endothelial adhesion;
d. Molecules affecting platelet function.

Among these molecules, growing attention has been devoted to inhibitors of Selectin as either pan-selectin inhibitor (Rivipansel) or P-selectin inhibitor (Crizanlizumab). Selectins are a family of molecules mediating adhesion of blood cells with activated vascular endothelial cells, and play a key role in leukocyte recruitment as well as in sickle red cell adhesion to inflammatory-activated vascular endothelium. In addition, studies have shown that P-selectin are increased in plasma of SCD patients [48–53]. Different therapeutic strategies have been developed, to block selectins: (i) pan-Selectin antagonist (GMI-1070, rivipansel); (ii) humanized anti-P-Selectin antibody (SelG1, crizanlizumab); (iii) P-selectin-aptamer; and (iv) sevuparin [13,14,17,22,50,52,54–59].

Rivipansel is a glycomimetic pan-selectin antagonist, which was tested in phase I and phase II studies in SCD. Rivipansel showed a safe profile, reducing the levels of E-Selectin in SCD patients during acute VOCs [54,60]. In phase II study, rivipansel beneficially affected the number of pain crisis in a small number of SCD subjects (#NCT01119833). However, these data were obtained including some SC patients, which generates some difficulties in their interpretation. When this review was under editing, preliminary data of the phase 3 trial with Rivipansel (RESET) were released. Rivipansel treatment did not modify the time of patient discharge for acute VOCs (primary endpoint) and changes in opioid treatment (https://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_phase_3_top_line_results_for_rivipansel_in_patients_with_sickle_cell_disease_experiencing_a_vaso_occlusive_crisis).

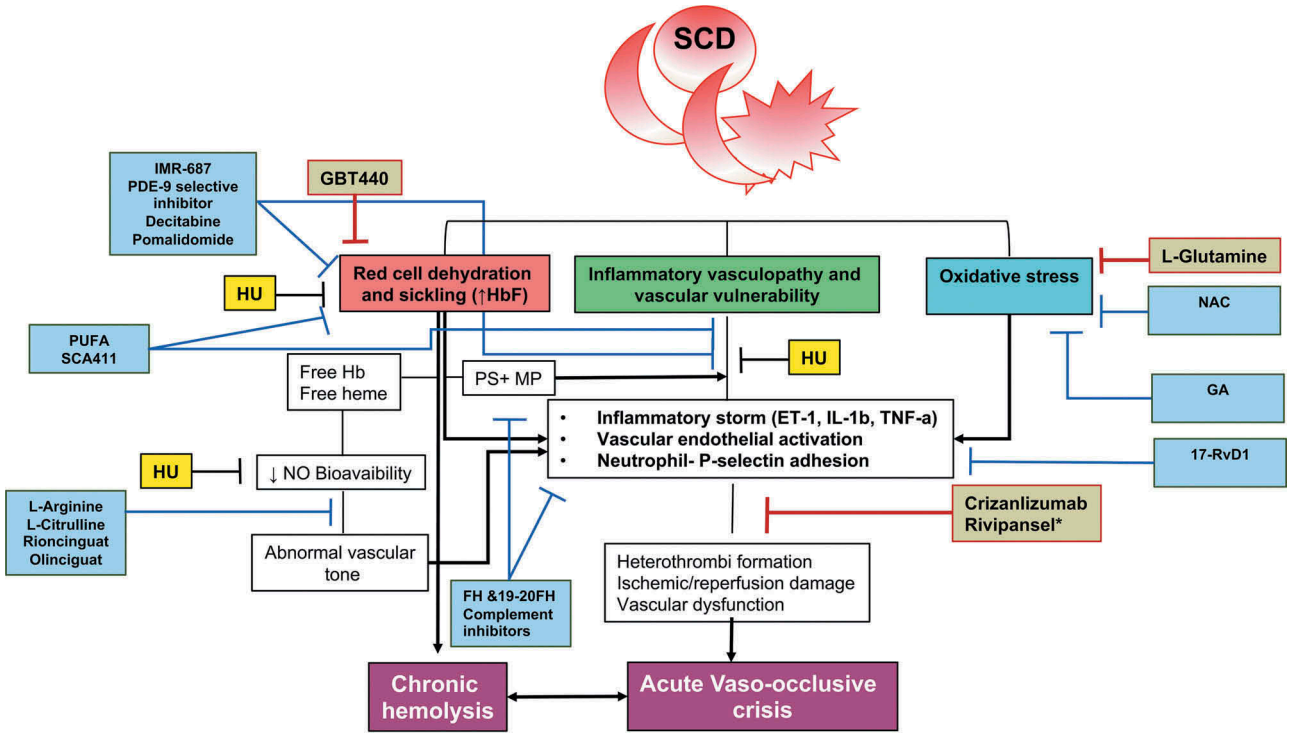

Figure 2. Schematic diagram of the mechanisms of action of pathophysiology-based new therapeutic options for treatment of sickle cell disease and sickle cell vasculopathy as well as for hydroxyurea (HU, in yellow). In brown, we show the agents in late-stage clinical development. In blue, we present molecules in early stage clinical trial or in pre-clinical development. FH: factor H; HbF: fetal hemoglobin; NAC: N-acetyl-cysteine; GA: gum arabic; PUFA: polyunsaturated fatty acid; PDE-9: phosphodiesterase-9; PS: phosphatidyl-serine; MP: microparticles; ET-1: endothelin-1, IL-1b: interleukin-1, TNF-α: tumor necrosis factor-alpha; NO: nitric oxide. (*) When this review was under editing, preliminary data of the phase 3 trial with Rivipansel (RESET) were released from Pfizer. Rivipansel treatment did not modify the time of patient discharge for acute VOCs (primary endpoint) and changes in opioid treatment.

Crizanlizumab is a humanized P-Selectin antibody, which has been tested in a multinational double-blind placebo-controlled trial (SUSTAIN, #NCT0185361) [17,58]. SCD subjects (SS, SC, $S\beta^+$, and $S\beta^0$ genotype) were treated with Crizanlizumab either 2.5 or 5 mg/kg every 4 weeks. Crizanlizumab at the dosage of 5 mg/kg every 4 weeks reduced the number of pain crisis and increased the time between VOCs in SCD independently from possible preceding HU treatment [17,58,59].

An additional strategy targeting P-Selectins is represented by the use of low-molecular weight heparins, such as Tinzaparin, which has been shown to block the P-Selectin system and to reduce the duration and the severity of VOCs in few cases of SCD patients [14,22]. Sevuparin is a derivative of low-molecular weight heparin, lacking anticoagulant activity and it has been evaluated in SCD [56,61]. Sevuparin acts on multiple targets: (i) P- and L-selectins; (ii) thrombospondin-Fibronectin-Von Willebrand factor; and (iii) sickle-leukocyte-endothelial cells interaction. Although Sevuparin is an attractive molecule with multimodal profile in SCD, the phase II multicenter international trial failed to show benefit in SCD patients during acute VOCs (https://www.modustx.com/modus-therapeutics-announces-the-results-of-its-global-randomized-placebo-controlled-phase-2-clinical-trial/).

Another possible strategy to interfere with sickle cell-related pro-adhesion is to modulate/block the activation of complement, which has been linked to chronic inflammation [62,63]. Previous studies revealed (i) an activation of the alternative complement pathway (AP) of complement activation in SCD patients; (ii) a reduction in the activating proteases factor B and D, modulating complement activation; (iii) a decrease in the plasma levels of FH, the major soluble regulator of AP activation; and (iv) increased deposition of the complement opsonin C3b on RBC exposing phosphatidylserine (PS) [64–71]. Preliminary data from a mouse model for SCD suggest a possible role for complement activation in the generation of VOCs, as an additional disease mechanism contributing to the severity of acute clinical manifestations related to SCD [63,72,73]. We recently reported that FH acts by preventing the adhesion of sickle red cells to P-selectin and/or the receptor Mac-1 receptor (CD11b/CD18), supporting the activation of the alternative pathway of complement as an additional mechanism in the pathogenesis of acute sickle cell-related VOCs. Our findings suggest that targeting complement opsonization and/or opsonin-mediated cell adhesion could provide an alternative strategy. Whereas the use of exogenous full-length FH as a therapeutic tool is associated with some challenges for being used as a therapeutic, several smaller variants of the regulator have shown promise in preclinical trials for complement-mediated diseases such as PNH. Owing to the importance of FH domains 19–20 for interfering with RBC adhesion, mini-FH constructs containing this domain pair may be considered, since they may affect both AP activity and the adhesive function of existing opsonins [74,75]. Alternatively, blocking opsonization itself at the level of C3 activation is also expected to impair complement-mediated adhesion. Thus, our data provide a rationale for further investigation of the potential contribution of factor-H and other modulators of the alternative complement pathway with potential implications to the treatment of sickle cell disease [62].

An attempt to target inflammatory vasculopathy and to modulate inflammatory response has been made based on the evidences in other diseases such as in cardiovascular disease looking to dietary manipulation with omega-3 fatty acids (ω-3 PUFAs). Supplementation with omega-3 fatty acids has been reported to (i) beneficially affect red cell membrane lipid composition; (ii) modulate soluble and cellular inflammatory response and coagulation cascade; and (iii) to favor NO production [76–79]. In SCD, the fatty acid profile of sickle erythrocytes is altered compared to healthy controls, with a relative increase in the ratio of ω-6 to ω-3 PUFAs, in agreement with sustained chronic inflammation [80,81]. In humanized mouse model for SCD, PUFA supplementation protects against acute sickle cell-related lung and liver damages during hypoxia/reoxygenation-induced VOCs [16]. A phase II multicenter randomized double-blind placebo-controlled study in SCD patients reported that SCA411, a novel docosahexaenoic acid (DHA) formulation with increased bioavailability, reduced pro-inflammatory markers, and ameliorates home management of pain with a positive trend in decreasing pain episode in SCD subjects without reaching statistical significant differences when compared to placebo group (SCOT, #NCT02973360) [82–85]. Noteworthy, SCA411 (20–36 mg/Kg/day for 8 weeks) administrated in combination with HU in children with SCD showed a safe profile with a good tolerability. Further studies are required to definitively confirm the positive effect of SCA411 supplementation in SCD patient refractory/or still symptomatic under HU treatment [83].

Novel therapeutic options focusing on physiological process promoting resolution of inflammation are of interest for treating acute events and for prevention of SCD-related vasculopathy. The resolution process is actively controlled by the temporal and local production of specialized proresolving lipid mediators (SPM). These include lipoxins (LX), resolvins (Rv), protectins, and maresins from polyunsaturated fatty acids [19]. In humanized mouse model for SCD, Matte et al. demonstrate novel protective actions of 17*R*-RvD1 (7*S*,8*R*,17*R*-trihydroxy-4*Z*,9*E*,11*E*,13*Z*,15*E*,19*Z*-docosahexaenoic acid), a member of endogenous lipid mediators, which play a key role in the resolution of inflammation-related pathologies [19]. The administration of 17*R*-RvD1 reduces *ex vivo* human SCD blood leukocyte recruitment by microvascular endothelial cells and *in vivo* neutrophil adhesion and transmigration.

The mechanism of action of 17*R*-RvD1 is based on a blunting of the activation of NF-κB and reduction of pro-inflammatory cytokines with the modulation of vascular endothelial activation. Based on data in humanized mouse model for SCD, Matte et al. suggest that SCD subjects may be more vulnerable to inflammatory vasculopathy due to altered pro-resolving processes (Figure 1) [19].

The combination of HU with L-arginine has been evaluated in a phase II clinical trial and in a couple of national double-blind randomized trials [86–90]. Low-arginine bioavailability characterizes SCD. NO is generated from L-arginine and L-citrulline by endothelial cells *via* constitutive (eNOS) and inflammatory inducible nitric oxide synthases (iNOS). In SCD, chronic hemolysis leading to increase in the plasma levels of hemoglobin that is an efficient NO buffer, contributes to reducing NO levels in SCD. Thus, the supplementation with either L-arginine or L-citrulline has been evaluated as possible additional strategy against SCD-related inflammatory vasculopathy [8,91–96]. Nitric oxide (NO) is a potent vasodilator and inhibitor of vascular remodeling and affects the multi-step cascade of events involved in leukocyte, platelet, and endothelial activation. In SCD, supplementation with L-arginine in combination with HU has been shown to beneficially impact sickle cell-related pain, leg ulcers, and pulmonary hypertension [86–90]. Thus, L-arginine might be considered as an interesting adjuvant in combination with HU in the clinical management of patients with SCD. Recently, Majumdar et al. have reported a single-center open-label trial to evaluate the safety and tolerability of L-citrulline infusion (50 mg/mL) in patients with SCD under steady state conditions [97]. L-Citrulline was well tolerated without major events except for drowsiness that was recorded in 6 out of 8 L-citrulline treated SCD patients.

An additional strategy to potentiate cellular effects of NO is represented by agents targeting soluble guanylcyclase (sGC), the only known NO receptor. These molecules might be divided into stimulators or activators of sGC, ending in increased intracellular cGMP content that modulates vascular tone and inflammatory response [98,99]. Among the sGC stimulators, Riocinguat (BAY63-2521) and Olinciguat (IW-1701) have been studied in patients with SCD. Riocinguat is an oral sGC activator with very short half-life, showing some beneficial effects in a case series of SCD patients with chronic thromboembolic pulmonary embolism [100]. Olinciguat is a once-a day oral sGC stimulators, which received an FDA orphan drug designation for SCD. A phase II double-blind placebo-controlled trial (NCT#03285178) is now enrolling SCD patients to evaluate the safety and tolerability profile of this drug. Combination therapy of sGC with HU might be considered to potentiate the beneficial effects of HU on NO metabolism. Up to now, sGC activators have been only tested in animal models for SCD [98].

2.2. Antioxidant agents and sickle cell disease

SCD is also characterized by a highly pro-oxidant environment due to the elevated production of reactive oxygen species (ROS) generated by increased levels of pathological free heme and iron and a reduction in antioxidant systems such as GSH (Figure 2) [6,8,14,101,102]. N-Acetyl-cysteine (NAC), an exogenous thiol donor, has been studied both *in vitro* and *in vivo* in SCD patients. NAC supplementation (1200–2400 mg/day) was shown to reduce the formation of dense red cells and the rate of hemolysis and to increase GSH levels in SCD subjects. However, Sins et al. recently reported a randomized, placebo-, double-blind trial (#NCT01849016) on NAC in SCD. Although the study shows a failure of NAC in affecting acute clinical manifestations of SCD, a low adherence of SCD patients to NAC treatment was observed and this might be responsible for the reduced biological effect of NAC in SCD. A clinical trial with high dose of NAC during acute VOCs related to SCD is ongoing (#NCT 01800526) [103–105].

L-Glutamine is a likely antioxidant agent in SCD. Glutamine is involved in GSH metabolism since it preserves NADPH levels required for GSH recycling, and it is the precursor for nicotinamide adenine dinucleotide (NAD) and arginine [106–108]. Recently, a multicenter, randomize, placebo-controlled double-

blind phase III clinical trial with L-glutamine (0.3 g/kg twice a day) involving 230 SS and Sbeta^0 patients with ≥2 pain crisis showed that L-glutamine supplementation reduced the mean number and length of hospitalization, associated with increased median time to the first crisis [106]. Both studies have several limitations such as (i) the high rate of patient drop-out; (ii) the presence of fatal events due to multiorgan failure in L-glutamine arm; (iii) the lack of effects on hematologic parameters and hemolytic indices; and (iv) the absence of clear data on L-glutamine mechanism of action [106,109].

Another antioxidant molecule recently investigated in phase II clinical trial in SCD is gum arabic (GA) exudates mechanically extracted from *Acacia senegal* [110]; 47 SCD patients (aged 5–42 years) were treated with GA at the dosage of 30 g/day for 3 months [110]. The authors observed an improvement of serum total antioxidant capacity and malondialdehyde (MDA) levels in SCD patients treated with GA. Although the data are interesting particularly in respect to the site where the study was carried out, limited information are available on the effect of GA on hematologic parameters and the quality of GA as chemical profile and purity.

3. Conclusion

We are now in a new era for SCD which is characterized by the emergence of novel treatments and the enhancement of patient survival and where a holistic approach should offer an improvement of patient quality of life. This might redirect clinicians and scientists to consider the new field of combinatorial therapy with or without HU [111]. Moreover, long-term studies should be designed to evaluate the real impact of new and emerging agents on natural history of SCD. Soon, we hope that more clinical studies will be reported by African researchers who can contribute to building a global collaboration for the enrichment of SCD management and treatment.

4. Expert opinion

Studies have shown that hemoglobinopathies such as sickle cell disease are in the top 10 causes of anemia and are associated with an increase in years lived with disability [2,112]. Thus, hemoglobinopathies heavily impact patient survival, quality of life, and global health costs. The available therapeutic tools for clinical management of SCD are HU, different transfusion regimes, and hematopoietic stem cell transplantation with the latter as curative approach to SCD. Although progress has been made on SCD clinical management, mortality, and morbidity of patients with SCD is still high relative to healthy subjects [113,114]. The key question is what do we need for patients with SCD? We believe that we should seek intensive treatment to impact SCD natural history and reduce the severity/recurrence of acute VOCs. We know from HU that multimodal therapy could be the key to prevent SCD progression. Thus, therapeutic targets such as neutrophils and inflammatory vasculopathy should be considered as significant contributors to the biocomplexity of sickle cell-related clinical manifestations. This is very important for patients eligible for curative approaches such as bone marrow stem cell treatment (BMSCT) or gene therapy [115]. Recently, lentiviral (LV) gene therapy based on the addition of an anti-sickling globin gene has been reported to be safe and positively impact the hematologic phenotype in a child with SCD [116]. Clinical trials using LV-gene therapy are ongoing in SCD [115,117–119]. Another possible gene therapy strategy targets the up-regulation of endogenous HbF expression by suppression/modulation of Bcl11A in erythroid cells progenitors [120,121]. Preliminary data in an SCD patient indicate a significant increase in HbF expression which successfully reached 23% of total Hb [120]. Finally, the development of CRISPR/Cas9 genome editing (GE) strategy represents another new potential therapeutic tool for the genetic correction of SCD [122]. This might be less expensive than LV-based gene therapy [123–125]. Gene therapy appears to be very attractive as a cure; however, this may be met with caution by researchers and clinicians because of limiting factors such as mutagenesis, conditioning regimen, or high costs.

Pharmacogenomic studies are potentially beneficial for the identification of key genomic variants for inflammatory vasculopathy, inflammasome or pain in SCD. However, these studies are limited and have only recently involved sub-Saharan countries where most SCD patients live [126–130]. Hence, new pharmacogenomic studies should be designed to involve multiple sites in different settings to progress the development of algorithm(s) that might assist in the development of personalized medicine [126]. At least a decade is required to evaluate the real impact of the new therapeutic options on SCD. For now, our efforts should be devoted to offering the best clinical management and accessibility to standard goal treatment, especially in less developed countries.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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