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An update review of new therapies in Sickle Cell Disease: the prospects for drug combinations

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Abstract

Introduction: Sickle cell disease (SCD) is an inherited disorder characterised by polymerisation of deoxygenated haemoglobin and microvascular obstruction. Generalised, it affects millions of people over 85% from low-and-middle-income countries. The cardinal feature is generalised pain referred to as vaso-occlusive crises (VOC), multi-organ damage and premature death.). SCD is the most prevalent inherited reduced life-threatening disorders in the world and over 85% of world's 400,000 annual births occur low-and-middle-income countries. In the UK with about 250 annual births (1:200 livebirths, and over 14,00 living with the disorder. For decades span. Since 1998 Hydroxyurea remained the only disease modifying therapy until the FDA approved L-glutamine (2017), Crizanlizumab and Voxelotor (2019) and gene therapies (Exa-cel and Lovo-cel, 2023).

Areas covered: A literature review, we discuss established and new treatment. We provide an in-depth review of key clinical trials from 2013-2023. However, for pragmatic purposes we have approached this review in line with the different mechanisms of action, considering the possible options for search was performed in Pubmed Central using the search terms [sickle cell disease] or [sickle cell anaemia] and the known treatments, i.e. Hydroxycarbamide/Hydroxyurea, L-Glutamine, Voxelotor, Crizanlizumab, Mitapivat, Etopivat, gene therapy, haematopoietic stem cell transplantation, and combination therapy. Clinical trials performed in the last 10 years (November 2013 – November 2023) were selected.

Expert opinion: In our opinion section, we recommend the consideration for combination therapies for specific complications such as VOCs, pain and renal impairment as well as personalised medicine based on disease phenotype and patient patience characteristics. Following the wake of recent approval of gene therapy for SCD, more curative option is now a reality, the challenge is addressing how to address the issues such as for access, affordability and shared decision- making with families.

Keywords: Sickle cell disease treatment, Hydroxyurea, L-Glutamine, Voxelotor, Crizanlizumab, Mitapivat, Etavopivat, Vaso-occlusive crises, anaemia, foetal haemoglobin, Gene therapy, Haematopoietic stem cell transplantation, Combination therapy in sickle cell disease.

Article highlights

- Sickle cell disease (SCD) is a multi-organ disease with a reduced life expectancy.
- Treatments for SCD are not globally available for patients due to costs and health care structure differences.
- Hydroxyurea is effective and safe in adults and children with sickle cell disease
- Recently FDA approved Novel treatments include Crizanlizumab, Voxelotor and L-glutamine and the prospects for drug combination therapies are required.
- Various agents in the pipeline of development include phase 2/3 trials of second-generation anti-sickling agents, pyruvate kinase activators and compliment inhibitors
- December 2023 the FDA landmark approval of Gene therapies is welcome development for SCD.
- Our expert opinion is that it is now time to undertake clinical trials for combination of approved and pipeline therapies based on mechanisms of actions and effectiveness for optimal patient benefits.

1. Introduction

Sickle cell disease (SCD) is an autosomal recessive inherited disorder caused by a single-nucleotide mutation due to substitution of glutamic acid by valine in position 6 of β-globin gene referred to as Haemoglobin S (HbS). SCD includes sickle cell anaemia (HbSS) and double heterozygous states (HbSC, HbSbeta Thalassaemia and HbSO-Arab) [1]. In the deoxygenated state affected HbS polymerises to rigid polymer fibres and changes the red blood cells (RBCs) shape into sickle forms. The sickle shaped RBCs cause blockage of the circulation, tissue infarction, haemolysis and endothelial damage and multi-organ pathology [1]. The cardinal feature is generalised pain due to acute vaso-occlusive crises (VOC) in addition to acute splenic sequestration crisis, acute chest syndrome, multi-organ damage and stroke [1]. These complications are associated with poor health related quality of life [1,2] and reduced life span [3]. The role of blood transfusions in acute and chronic complications of SCD are well-established and will therefore not be further discussed [4].

The development of new drug therapies in SCD has been historically slow and Hydroxyurea (Hydroxycarbamide) had remained for decades the only approved therapy until the United States Food and Drug Administration (FDA) approved L-glutamine in 2017, and Crizanlizumab and Voxelotor in 2019. In 2023, two gene therapies for SCD were approved, i.e. Exa-cel and Lovo-cel. Despite recent developments in new drug trials, there are still

limited breakthroughs in novel therapies [5]. In addition, the limited effective therapies are dependent on affordability for access.

In this review, we provide a scoping literature review of clinical trials of pharmacological agents, including Hydroxyurea, as well as recently approved new therapies and ongoing studies for future novel therapies.

2. Methods

A literature search was performed in Pubmed Central using the search terms [sickle cell disease] or [sickle cell anaemia] and the known treatments, i.e. Hydroxycarbamide/Hydroxyurea, L-glutamine, Voxelotor, Crizanlizumab, Mitapivat, Etavopivat, gene therapy, haematopoietic stem cell transplantation, and combination therapy. Clinical trials performed in the last 10 years (November 2013 – November 2023) and reported in English language were selected. In parallel, we searched on the clinicaltrial.gov website for clinical trials that were 'open', 'planning to open', 'ongoing' or 'recently completed' in the same timeline. The novel treatments included in these clinical trials; Vorinostat, Panobinostat, Crovalimab, Tetrahydrouridine-Decitabine, Poloxamer 188 and HQK-1001 were included in our literature review. All abstracts were pre-screened by one expert author and validated by another expert author. The final selection of publications was based on importance, outcome and change in practise ranked by our panel of five experts using votes for the trials. A summary of the clinical trials selected are shown in Table 1. The trial outcomes involving haematopoietic stem cell transplantation is outlined in Table 2.

3. Haemoglobin F inducers

3.1. Hydroxyurea (HU)

Hydroxyurea (HU) is the standard of care for prevention of VOCs in adults and children with SCD. The dose related bone marrow suppression is believed to induce fetal haemoglobin (HbF), which results in a reduction in red blood cell sickling. This ribonucleotide reductase inhibitor was first used in myeloproliferative diseases as an anti-neoplastic agent and was approved for clinical use in SCD patients in 1998 by the FDA and in 2007 by the European Medicines Agency's (EMA) [6,7]. Numerous clinical trials have been conducted through the years, to study the safety and benefits of the use of HU in SCD patients.

In sub-Saharan Africa, the REACH trial (NCT01966731), a phase 1/2, open-label trial, investigated the effects of Hydroxyurea in SCD children from Angola, Democratic Republic of Congo, Kenya and Uganda. The purpose was to evaluate the feasibility, safety, and benefits of the treatment with HU. A total of 606 children started treatment (1-10 years age), 600 completed 3 months of treatment, 415 completed 24 months, 235 completed 36 months, and 5 reached 48 months. The initial dose of HU was 17.5±1.8 mg/kg/day, and after 6 months dose escalation began to a 22.5±4.9 mg/kg/day for 515 children. After one-year, significant increases in total haemoglobin (1.0g/dL, mean value 8.3±1.4) and in HbF (12.5%, mean value 23.4±9.1) were registered. Rates of painful events, infection, malaria, transfusions, and death were reduced. Daily HU treatment in children was considered by the authors, safe and feasible for SCD children in Sub-Saharan Africa [8].

The NOHARM Trial (NCT01976416) was to study the safety and efficacy of HU in a malaria-endemic region, Uganda as HU, by inducing HbF, could also be beneficial in cases of malaria infections. This randomized, double-blinded, placebo-controlled trial conducted with SCD children in Uganda. A total of 207 children (1-4 years old) were enrolled in this study, 104 took HU 20 ± 2.5 mg/kg/day, and 103 a placebo for 12 months. All were given monthly oral malaria prophylaxis, so the incidence of malaria infections was low. Malaria incidence and severity, clinical sepsis or bacteraemia, did not differ between the groups. In

HU treated children, the number of SCD related events (including VOCs, dactylitis, and hospitalizations) was significantly lower. After 12 months of treatment values of HbF (22.9±8.6 vs 10.4±4.8) and total haemoglobin (8.7±1.3 vs 7.4±1.0) were significantly higher in the treatment group [9]. This trial was followed by the NOHARM MTD Trial (NCT03128515) a randomized, double-blind trial. This included the children previously enrolled in the NOHARM trial, who started HU in a 20 mg/kg/day dose. After a few months 187 children were reassigned to two groups, one maintaining a fixed dose (n=94), and the other one escalating to a maximum tolerated dose (MTD) (n=93). The MTD group had fewer clinical adverse events, VOCs, acute chest syndrome or pneumonia, transfusions and hospitalizations. After 24 months 86% of patients in the MTD group and 37% of the fixed-dose group achieved HbF levels ≥20% or total haemoglobin ≥9.0g/dL [10].

Clinical trials of HU, also focused on its effects in stroke prevention and transcranial doppler (TCD) velocities. Standard therapy in SCD for prevention of secondary strokes included regular and indefinite blood transfusions, which may lead to iron overload. In the SWITCH trial (NCT00122980), HU (20 mg/kg/day) was proposed as an alternative therapy. This phase 3 randomized clinical trial included 133 children (5.2–19.0 years) with previous stroke, and more than 18 months of transfusions with documented iron overload, followed in 26 United States (US) based centers. After randomisation, 66 patients started treatment with transfusions and chelation, and 67 with HU and phlebotomy. The trial was closed after the first interim analysis, as one of the primary outcomes would not be achieved i.e., the reduction in the liver iron content was not higher in the HU group. The number of SCD related adverse events was similar in both groups, but the number of serious adverse events was higher in the HU group. Therefore, the standard therapy with regular blood transfusions continued to be the treatment of choice in children with previous stroke, for preventing secondary stroke and iron overload [11–13].

TCD with Transfusions Changing to Hydroxyurea (TWITCH) Trial (NCT01425307), a multicentre, phase 3, randomized, open-label, trial comparing the effects of regular blood transfusions and HU treatment in primary stroke prevention was reported in 2016. Children between 4-16 years of age, with SCD and abnormal TCD (n=121), were assigned to two groups of treatment: Standard Group (patients received monthly transfusions to keep HbS ≤ 30%, n=61) and Alternative group (patients treated with HU, at their MTD, n=60), and followed for 24 months (+ extra visit 6 months after the end of the treatment). Final values of HbF in the Alternative group were 24.4 ± 7.9 %, reflecting a significant increase of 15.5 ± 7.1%. Baseline values of TCD were similar, but after 24 months, were slightly lower on the alternative group. Hydroxyurea was considered a good substitute in children that have no severe vasculopathy, to maintain TCD velocities and prevent primary stroke [14].

In Nigeria, to evaluate the effects of HU as a viable option for primary stroke prevention, a single arm feasibility trial (SPIN trial - NCT01801423) was conducted, with children with SCD and TCD time-averaged maximum mean velocity readings superior to 200 cm/s in the middle cerebral artery. Twenty-five children with abnormal TCD were recruited to receive fixed-dose HU therapy (treatment group) and 210 children with TCD measurements inferior to 200 cm/s integrated the comparison group and were followed prospectively (4 of these children crossed over at some point to the treatment group after abnormal TCD velocities were registered during the follow up). After 24 months of follow up, HbF levels increased from 8.8% to 14.3%. TCD velocities decreased significantly after 3 months of treatment and remained lower during the 24 months of follow up (mean TCD at baseline 208.0, after 3 months 183.0, and after 2 years 163.0). The stroke incidence rate between the groups was not significantly different. There were no significant differences in death rate between the groups, although there were significantly lower episodes of uncomplicated VOC events with hospitalization in the treatment group [15,16].

In summary, the treatment with HU is considered safe, feasible and beneficial for the treatment of adults and children with SCD [17–21]. HbF induction by HU depends in part on a proliferating erythroid bone marrow, this is most evident in childhood. However, with time, intramedullary sickling and marrow infarction reduces the erythroid capacity of the marrow leading to HbF decline with increasing age. HU may therefore not always be effective in HbF response or the reduction in clinical symptoms. The safety of hydroxyurea has been proven even in high malaria endemic countries despite concerns observed when earlier mice studies reported possible immune suppression. Nevertheless common side effects such as nausea and gastro-intestinal symptoms have been reported. Furthermore potential toxic effects, such as bone marrow suppression underlies the need for regular monitoring The recommended dosage for HU is 15-35mg/Kg and this is variable depending on individual patients response and the effect of cytopenias particularly relating to total neutrophil, reticulocyte and platelet count.

3.2. DNMT1 inhibition

The induction of HbF is also possible by inhibiting the DNA methyltransferase 1 (DNMT1), a chromatin modifying enzyme that mediates HbF silencing. Results from a single-blind, dose-escalating, phase 1 trial (NCT01685515), using decitabine combined with Tetrahydrouridine (THU), in 25 SCD patients (HbSS or HbSβ0-thalassemia), in different doses. THU-decitabine was considered safe and was well-tolerated by these patients. Clinically significant increases in HbF were achieved with the highest dose administered (0.16 mg/kg). Laboratory biomarkers of haemolysis, coagulation, and inflammation also improved [22]. Another clinical trial with THU-decitabine, ASCENT1, is still in progress. ASCENT1 is a randomized, placebo-controlled phase 2 trial, with a larger cohort, that aims

to provide proof of concept and determine optimal dose so it can be applied in future clinical trials [23].

3. HDACs

In vitro studies have shown that histone deacetylase (HDAC) inhibitors are able to induce HbF in human erythroid progenitor cells [24,25], which makes them promising therapeutic alternatives to treat sickle cell disease. Studies with SCD patients in the 90's showed that the use of a fatty acid analogue valproic acid and butyrate, could stimulate HbF synthesis [26,27]. However, recent clinical trials with HDACs did not show the same level of efficacy. In a placebo-controlled phase 2 study, the pharmacodynamics, efficacy and safety of 2,2-dimethylbutyrate (HQK-1001) was evaluated. Sixty patients with HbSS and 16 with HbSβ0-thalassemia were enrolled in the study, that was expected to last 48 weeks. After 24 weeks it was terminated as there were no significant increases in HbF, and patients on HQK-1001 presented a higher rate of pain crisis and acute chest syndrome [28]. Another HDAC inhibitor tested in a phase 1/2 trial (NCT01000155), to assess the safety, tolerability and efficacy was Vorinostat (suberoylanilidine hydroxamic acid) and was performed in 5 SCD adult patients. Although Vorinostat was considered safe and tolerable, the efficacy was not demonstrated, as only 1 patient registered a considerable increase of HbF [29].

For Panobinostat (LBH589) there is currently a phase 2 trial ongoing and results are expected in 2026 [30].

3.4. IMR-687

Tovinontrine (IMR-687) is a highly selective and potent small molecule inhibitor of phosphodiesterase-9 (PDE9). PDE9 selectively degrades cyclic guanosine monophosphate, increasing HbF and reducing hemolysis markers [31]. The phase 2a study in adult patients

with sickle cell disease showed that IMR-687 increased F cells and improved trends of hemolysis and VOC rate [32]. The subsequent phase 2b clinical trial failed to meet the primary end point, i.e. no statistical difference in VOC rate or increased HbF percentages in the high dose treatment group compared to the placebo group (NCT04474314). Tovinontrine is not approved anywhere.

4. Anti-sickling agents

Under low oxygen saturation, sickle haemoglobin (HbS) assumes the tense (T-state) deoxygenated conformation that forms polymers, leading to rigid erythrocytes with impaired blood vessel transit, compounded or initiated by adhesion of erythrocytes to endothelium, neutrophils and platelets. This leads to vessel occlusion and ischaemia, with consequent clinical symptoms such as acute pain and chronic organ damage. Anti-sickling agents stabilize the higher oxygen affinity relaxed state (R-state) and/or destabilize the lower oxygen affinity T-state of haemoglobin have the potential to delay the sickling of erythrocytes by slowing polymerization kinetics [33].

4.1. Voxelotor

Voxelotor binds covalently to the N-terminal valine of the α-globin chain to stabilize the oxygenated HbS that leads to increase in haemoglobin oxygen affinity. The oxygenated HbS prevents deoxygenation and haemoglobin polymerization, which prevents erythrocytes from sickling. Voxelotor is a once daily oral tablet, which is well tolerated in adults and children [34]. The phase 3 HOPE trial showed an absolute haemoglobin increase of at least 1.0 g/dL in 51% of the patients in the Voxelotor group versus 7% in the placebo group [35]. In addition, long term follow-up revealed that the increase in haemoglobin was sustainable at 72 weeks

[36]. EMA has added Voxelotor to their priority medicines program in 2018. FDA approval was granted in November 2019 for SCD patients 12 years and older.

In children older than 4 years the HOPE –KIDS 1 trial showed that at week 24, 35% and 21% of patients had a >1.5 g/dl increase and a >2.0 g/dl increase from baseline in Hb concentration, respectively. Voxelotor was well tolerated in this young cohort, with no newly emerging safety concerns [37]. Further clinical trial results are expected soon.

4.2. GBT021601

GBT021601, a next generation HbS polymerisation inhibitor, with an increased oxygen affinity compared to Voxelotor, which leads to a higher haemoglobin occupancy. GBT021601 is currently being investigated in a phase 2/3 clinical trial for adult and paediatric sickle cell disease patients (NCT05431088). Preliminary results showed a mean (standard deviation) increase in Hb from baseline was 2.67 (1.52) g/dL for the 100-mg group (n=12) and 3.17 (1.82) g/dL for the 150-mg group (n=11) after 12 weeks of treatment. A favourable trend towards reduction from baseline was observed in markers of haemolysis. For 27 patients with ≥1 VOC at baseline, the baseline annualized VOC rate was 2.30 (95% confidence interval (CI) 1.81-2.92), and the on-study annualized VOC rate was 1.16 (95% CI 0.55-2.43) with a median (range) on-study duration of 0.4 (0.03-0.41) years [38]. Further clinical trial results are expected soon.

5. Anti-adhesion molecules

5.1. Crizanlizumab

Crizanlizumab, a humanized antibody against the adhesion molecule P-selectin, was the first drug reducing VOCs in SCD in decades being granted FDA approval in 2019. In the SUSTAIN trial, a double-blind, randomized, placebo-controlled, phase 2 trial, SCD patients

receive an intravenous low-dose Crizanlizumab (2.5 mg/kg body weight), high-dose Crizanlizumab (5.0 mg/kg body weight), or placebo, 14 times over a period of 52 weeks. The primary end point was the rate of VOCs, days hospitalized, uncomplicated VOCs and the acute chest syndrome. A total of 198 patients underwent randomization at 60 sites. A 45.3% lower rate of crises per year with high dose Crizanlizumab, compared to placebo (P = 0.01) was observed. The time to the first crisis was significantly longer with high dose Crizanlizumab than with placebo (4.07 vs. 1.38 months, P = 0.001), as was the median time to the second crisis (10.32 vs. 5.09 months, P = 0.02). A 62.9% lower rate of uncomplicated crises per year with high dose Crizanlizumab, compared to placebo (P = 0.02) was also observed. Adverse events occurred in a high proportion of patients and included arthralgia, diarrhoea, pruritus, vomiting, and chest pain [39].

After completion of SUSTAIN, the patient on Crizanlizumab 5mg experienced sustainable effect up to 52 weeks in median time to first VOC and annual VOC rate [40]. A post hoc analysis of SUSTAIN [41] showed that in patients with a high number of prior VOCs, on concomitant hydroxyurea and/or with the HbSS genotype, Crizanlizumab treatment increases the likelihood of patients being VOC event-free and delays time-to-first VOC.

Subsequently, the STAND trial (NCT03814746), which is a phase 3, multi-centre, randomized, double-blind study to assess efficacy and safety of two doses of Crizanlizumab versus placebo, with or without hydroxyurea therapy, in adolescent and adult SCD patients with frequent VOCs, showed no statistically significant difference between Crizanlizumab 5mg/kg or Crizanlizumab 7.5mg/kg and placebo in annualized rates of VOCs (pain crises) leading to a healthcare visit over the first-year post randomization. These findings were inconsistent with previous trial results from SUSTAIN. STAND trial results did not suggest new safety concerns with Crizanlizumab.

EMA withdrew Crizanlizumab from use in the European Union in 2023. However, it remains approved for use by the FDA for the reduction in frequency of vaso-occlusive crises in adults and paediatric patients aged 16 years or older with sickle cell disease.

5.2. Rivipansel

Rivipansel (GMI-1070), is an intravenous administered E-selectin antagonist, that targets selectin pathways and the pathophysiology of vaso-occlusion. Rivipansel acts as a pan-selectin antagonist, disrupting E-selectin mediated leukocyte adhesion to vascular endothelium. A phase 2 randomized, placebo controlled, double-blind study with 76 SCD patients with VOCs enrolled were given Rivipansel or placebo every 12 hours for up to 15 doses. Rivipansel led to statistically insignificant but large reductions in mean and median time to resolution of VOC (41 and 63 hours, 28% and 48%) in the active treatment group vs placebo. As a secondary end point, Rivipansel appeared safe and a significant reduction in opioid use was observed with Rivipansel compared to placebo (83% reduction (P=.010)) [42].

The RESET study, a phase 3, randomized, controlled trial for VOC requiring hospitalization, evaluated the efficacy and safety of Rivipansel. A total of 162 patients were treated with Rivipansel and 158 with placebo, with an intravenous (IV) loading dose, followed by up to 14 additional 12-hourly maintenance doses of Rivipansel or placebo, in addition to standard care. Rivipansel was similarly administered during subsequent VOCs. There were no differences between Rivipansel and placebo in the primary, nor in secondary end points, namely the median time to readiness for discharge, or time to discharge, time to discontinuation of IV opioids, and cumulative IV opioid use [43]. A post hoc analysis showed that the early use of Rivipansel appeared to shorten length of hospital stay and duration of IV opioid use. To date, Rivipansel is not authorised anywhere globally.

5.3. Sevuparin

Sevuparin is a non-anticoagulant low molecular weight heparinoid, with anti-adhesive properties. A multi-centre, phase 2, randomized, double-blind, placebo-controlled trial to investigate efficacy and safety of Sevuparin infusion for the management of acute VOC in SCD patients was performed. The primary end points were time to VOC resolution, the effect on pain intensity, duration of pain, and cumulative dose of parental opioids. A total of 144 patients were randomly assigned to receive Sevuparin (18 mg/kg per day) (N=69) or placebo (N=75) intravenously for 2–7 days until VOC resolution. The primary endpoint showed no significant difference in median time to VOC resolution between the Sevuparin and placebo groups. The trial showed that anti-adhesive therapy aimed primarily at P-selectin is not able to change the duration or the severity of pain in patients with sickle cell disease [44]. Sevuparin is not authorised anywhere in the EU or USA for treatment in sickle cell disease.

5.4. Poloxamer 188

Poloxamer 188 is a non-ionic block linear copolymer that reduces blood viscosity and confers anti-inflammatory and cytoprotective effects [45]. Previous clinical trials with purified Poloxamer 188 (Vepoloxamer) showed shortened duration of painful VOCs in SCD patients [46,47]. Poloxamer 188 has limited side effects [47].

A phase 3, randomized, double-blind, placebo-controlled, multicenter, international trial was carried out between 2013 to 2016 to reassess the efficacy of Poloxamer 188 for VOCs [48]. A total of 388 individuals aged 4 to 65 years with acute moderate to severe pain typical of painful vaso-occlusive episodes requiring hospitalization were included. The main outcomes of the trial were the time in hours from start to the last dose of parenteral opioids. Poloxamer

188 did not significantly shorten time to last dose of parenteral opioids during vaso-occlusive episodes either in children or adults.

6. Antioxidants

6.1. L-Glutamine

Oxidative stress contributes to the complex pathophysiology of sickle cell disease. Oral therapy with pharmaceutical-grade L-glutamine has shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which is believed to reduce oxidative stress. Oral L-glutamine was FDA approved in 2017 with the indication to reduce acute complications of sickle cell disease in patients aged 5 years and older. Niihara et al., reported in their randomised double-blind placebo-controlled phase 3 trial that the median VOC rate and time to first VOC reduced significantly. Side effect included gastrointestinal symptoms [49]. The L-glutamine phase 3 trial reanalysis using annual rates of VOC resulted in a median difference between treatment and placebo of 1.93 crises [50]. However, the EMA rejected the approval of L-glutamine in 2019 due to not sufficiently proven efficacy.

7. Vaso-dilatation

7.1. Arginine

Nitric oxide (NO), enzymatically produced from L-arginine, is a potent vasodilator. Arginine exerts multiple effects on vascular and blood cells, including the inhibition of platelet aggregation, down-regulation of adhesion molecules, and modulation of ischemia-reperfusion injury. All pathways are adversely affected during a VOCvaso-occlusive crises in SCD.

Morris et al. reported the first randomized placebo-controlled study that demonstrated benefits of arginine therapy in children with SCD hospitalized for severe pain [51–53]. Total

opioid use decreased by 54% and pain scores were significantly lower at discharge in the group treated with arginine compared to the group given placebo. A subsequent randomized controlled trial in children in Nigeria confirmed the findings from Morris et al., and in addition showed a significant reduction in the total length of hospital stay and time-to-crisis-resolution [54].

Currently, the STArT (Sickle Cell Disease Treatment With Arginine Therapy) a double-blind, placebo controlled, randomized, phase 3, multi-center trial of IV arginine therapy in children with a VOC in SCD is open. Further knowledge on efficacy and safety of the therapy of IV arginine will follow after the trial completion in 2027 (NCT04839354). Arginine is currently not approved anywhere.

8. Complement inhibitors

8.1. Eculizumab

The pathophysiology in SCD has been attributed to various interactions between sickle cells and neutrophils, platelets or endothelial cells in blood vessels leading to haemolysis. The role of complement activation has been increasingly investigated. Importantly, complement inhibition with eculizumab, a monoclonal antibody against C5, has shown beneficial effects in delayed haemolytic transfusion reaction in SCD [55]. It is approved for this indication in the US, UK and Europe. However, the biggest barrier in complement inhibition seems to be the increased risk of infections [56].

Eculizumab has been used in SCD patients suffering with a VOC. These patients considerably benefited from the reduction of heme-induced thrombo-inflammation through C5 inhibition [57]. In a case report, eculizumab was found to be effective in one case of bone marrow necrosis of a young adult SCD patient, where other lines of treatment failed [58].

In addition, Crovalimab is another anti-C5 recycling monoclonal antibody. The CROSS-WALK, randomized double-blind phase 2a trial evaluates the efficacy, safety, pharmacokinetics, and pharmacodynamics of Crovalimab as adjunct treatment in VOC prevention in SCD patients aged 12-65 years is recruiting and aiming to close in July 2024 (NCT05075824) [59]. There are currently no clinical trials open for other anti-C5 compliment inhibitors i.e. Ravulizumab and Pozelimab in SCD.

9. Pyruvate Kinase activators

In red blood cells (RBCs), pyruvate kinase activators reduce the build-up of the glycolytic intermediate 2,3-diphosphoglycerate (2,3-DPG) thus increasing production of adenosine triphosphate (ATP). The reduction of 2,3-DPG levels is associated with an increase in oxygen affinity and consequently the reduction in HbS polymerisation (sickling). The increased ATP may improve RBC membrane integrity and RBC hydration and various metabolic processes. There are currently two PK activators in clinical development: Mitapivat (AG-348) and Etopivat (FT-4202).

9.1. Mitapivat

Mitapivat (AG-348) is a novel, first-in-class oral small molecule allosteric activator of the pyruvate kinase enzyme. Mitapivat has been shown to significantly upregulate both wild-type and numerous mutant forms of erythrocyte pyruvate kinase (PK), increasing adenosine triphosphate (ATP) production and reducing levels of 2,3-diphosphoglycerate. Mitapivat has been an FDA approved treatment for PK deficiency since 2022 and is well tolerated in this patient group.

A phase 1 proof of concept study showed a mean haemoglobin increase of 1.2 g/dL at the 50 mg BID dose level, with 9 of 16 (56.3%) patients achieving a haemoglobin response of a ≥1 g/dL increase compared with baseline in patients with SCD [60].

The ESTIMATE study was a phase 2, investigator-initiated, open-label, single center study that evaluated the safety plus efficacy and provided proof of concept for Mitapivat treatment in SCD patients. Van Dijk et. al showed that treatment with Mitapivat, improves anaemia, Hb-oxygen affinity, and sickling parameters, and reduces hemolysis in patients with SCD in the 8-week dose-finding period. An increase in Hb level of ≥1 g/dL from baseline was achieved in 75% (6/8) of participants. Mitapivat was well tolerated [61].

RISE UP (NCT05031780) is a phase 2/3 study that aims to determine the recommended dose of Mitapivat and evaluate its efficacy and safety in sickle cell disease patients. The study is expected to complete in 2025 [62]. Mitapivat has been granted orphan drug designation by the FDA in the USA.

A second-generation molecule AG-946 has completed a phase 1 trial (NCT04536792). Further plans to conduct a phase 2/3 trial are awaited.

9.2. Etavopivat

Etavopivat (FT-4202) is another selective activator of PKR which increases PKR activity and resulting in decreased 2,3-DPG and increased ATP. Data from the Phase 1 study showed that Etavopivat 400 mg once daily was generally well tolerated [63]. A subsequent phase 2/3 trial (HIBISCUS, NCT04624659) will identify dose, confirm efficacy and safety in sickle cell disease patients [64]. The study completion date is the end of 2026. Etavopivat is currently not approved.

10. Haematopoietic Stem Cell Transplantation

Haematopoietic stem cell transplantation (HSCT) is a curative treatment for sickle cell disease [65]. Many studies have shown that overall survival is between 92% to 100% in both children and adults when using a matched related donor (MRD) as shown in Table 2 [66–72].

The indications for HSCT can be classified into clinical, laboratory and radiological markers of disease severity plus end organ damage [73].

Earlier HSCT research in SCD focused on demonstrating if transplant could cure SCD, defining the source of stem cells and minimum donor chimerism required to achieve cure [71,74,75]. It has been demonstrated that use of myeloablative conditioning regimens and stem cells from matched bone marrow or cord blood resulted in the best disease-free survival (DFS) but also resulted in significant toxicity [76]. Matched unrelated stem cells from bone marrow and cord blood had lower DFS and were associated with more complications including graft failure [71,77,78]. SCD patients can receive stem cell donations from both sickle cell trait and non-trait matched related donors resulting in similar success rates. In addition, mixed chimerism resulted in SCD cure, therefore, the focus of HSCT research in the current decade from 2013 had shifted to reducing toxicity by developing reduced intensity non-myeloablative conditioning (RIC) regimens [70,76] and initial work to reduce graft versus host disease (GVHD) especially in adult patients [73]. The RIC have resulted in increased use of HSCT in older individuals with co-morbidities. Advances in conditioning regimens for haplo-identical transplantation, GVHD prophylaxis such as depletion of T-cells, enrichment of CD34 cells and improvement in supportive care have improved outcomes [79–82]. In addition, stem cell options are increased i.e., haplo-identical transplantation, matched unrelated donor, cord blood stem cells, for SCD patients without a matched related donor [77,83,84]. Future research should continue focusing on reducing conditioning regimens toxicity and side effects including GVHD (acute and chronic) and fertility preservation in both adults and paediatric SCD patients [85].

Finally, the availability of HSCT is limited for a variety of reasons including infrastructure e.g. While the US has about 215 centres delivering transplants, in all of Africa there are only about 6 centres with different capacities. There are efforts to improve global availability of

HSCT in the near future [86]. Other limitations include the cost of treatment, acceptability and the availability of suitable donors.

11. Gene therapy

Gene therapy includes a transplantation of genetically modified autologous haematopoietic stem cells. Stem cells get mobilised from the SCD patient, i.e. the recipient, from peripheral blood. The stem cells get altered genetically, where after the recipient undergoes conditioning chemotherapy followed by infusion of the modified stem cells.

There are different technologies used to genetically modify genes; 1) gene addition, 2) gene silencing, 3) gene editing and 4) gene correction. Examples include, 1) Lentiglobin BB305, 2) Suppression of BCL11A, 3) Gene therapy targeting BCL11A, 4) Introducing non-sickling haemoglobin, respectively.

We kindly refer to two excellent in depth reviews discussing gene therapy in SCD which have been published recently [87,88]. We have selected two gene therapy products which recently have been approved.

Exagamglogene autostemcel (Exa-cel) was the first gene therapy for SCD approved by the MHRA in England in November 2023 and FDA approved in December 2023. Exa-cel uses a CRIPR/cas9 to disrupt the BCL11A erythroid enhancer to increase HbF. A mean proportion of HbF > 20%, Hb level > 11 g/L were found 3-months post-infusion. The majority of patients (n=29/30, 96.7%) in the primary efficacy group did not experience a VOC for 12 months after the Exa-cel infusion. All patients remained free from hospitalisation at 12 months. Mean VOC-free duration was 22.4 months (range: 14.8 to 45.5 months). The study reported rapid, robust, and durable increases in HbF levels [89].

Lovotibeglogene autostemcel (lentiglobin bb1111, lovo-cel) adds functional copies of a modified beta-globin gene (B T87Q) in stem cells. It showed a high and sustained level of

HbA expression, with a reduction in HbS resulting in resolution of VOCs and haemolysis markers [90,91]. There was one acute myeloid leukaemia case reported, which was not related to the gene therapy itself, but due to a combination of causes including the genetically predisposition abnormal bone marrow niche in SCD [92](Chapman et al.) and the conditioning chemotherapy [93]. FDA approval was granted for Lovo-cel in December 2023. In conclusion, gene therapies hold promise as a cure for sickle cell disease, but long-term information on safety and efficacy are needed. Currently, this treatment is not yet accessible for SCD patients.

12. Conclusion

SCD is a multi-organ disease with significant morbidity and mortality, a reduction in health related quality of life and premature mortality. The life-expectancy is reported to be in the range of 30 years shorter compared to the general population. Hydroxyurea the first approved disease modifying agent has been extensively studies over the last 10 years affirming the safety in malaria endemic regions and significant effects in primary and secondary stroke prevention. The FDA in 2017 approved L-glutamine for SCD from aged 5 years, and 2019 both Crizanlizumab (from aged 16) and Voxelotor (from aged 4) were approved for aged 16 and 4 years respectively. However, due to no statistical difference in Crizanlizumab primary outcome in the STAND trial which did not show beneficial effect over placebo, it was withdrawn from the European market. Voxelotor is a first in class oral polymerisation inhibitor that increased haemoglobin levels in SCD patients even though yet to demonstrate beneficial patient related outcome. There are many other molecules in pipeline development we have grouped them according to their mechanism of actions. However, many trials have not met their primary endpoints and are considered ‘negative’ trials.

Haematopoietic stem cell transplantation is a curative treatment option for patients with a matched sibling donor, haplo-identical and matched unrelated donor. Beside the type of donor, the conditioning and GVHD play a large role in the outcome and complications of this treatment. The recent ground-breaking approvals of gene therapy Exa-cel and Lovo-cel by the FDA in December 2023 and are available for patients older than 12 years. The approved therapies are not available everywhere, but even areas where it can be afforded there is need for a robust treatment guideline in sickle cell disease.

13. Expert Opinion

SCD is a multi-organ disease that if left untreated has an inferior outcome with a global life expectancy of 54 years [94]. Given the complex pathophysiology of SCD and inter-patient variability, novel drug treatments will likely be managed with a patient-tailored approach which could include a combination of different drugs according to the individual characteristics or sequencing of agents.

There are currently no clinical trials planned that are looking at combining therapies, however this is a route that need to be explored. The overall reduction of complications in SCD patients could be achieved if patients get offered hydroxyurea from childhood. Combining different modalities of therapy might be the way forward to tackle HbS polymerisation. In patients with frequent VOCs; L-glutamine and/or Crizanlizumab with HU could be used. For patients with mainly anaemia; Voxelotor, or GBT 601, and/or a PK agonist should be offered. For patients with renal involvement and anaemia – a combination of HU with GBT 601 may be considered. More real-word-evidence generation of data is needed to determine efficacy of the treatment combinations. This requires comparing each combination to the single treatment in a phase 2/3 trial.

In the era of gene therapy and HSCT, this type of treatment will be used mostly in younger SCD patients (below the age of 35 years), which leaves the elderly group available for other treatment options. The long-term outcomes of these treatments remain to be characterised and therefore shared decision making with patients, families and the multidisciplinary team is key. This exciting novel therapy is also associated with ethical controversies as it is not a therapy one can withdraw for life and receiving one form of gene therapy product will exclude a patient from receiving future improved gene therapy products. Currently, gene therapy is approved for SCD patients aged 12 till 35 years, meaning younger children with severe disease who may benefit the most in preventing organ damage are excluded. However, it represents the most innovative novel therapy for SCD to date.

Lastly, the perennial issue of access, affordability especially for the majority of patients in low- and middle-income countries can only be addressed by a coordinated and concerted efforts by multinational bodies e.g. World Health Organisation, United Nations, African Union, and European Union.

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Table and Figure legends

Table 1. Overview of pivotal clinical trials investigating novel drugs in sickle cell disease opened between 2013 and 2023. As discussed in the Methods a selection of pivotal clinical trials is provided in this table. Per trial the trial title/name, trial phase, number of randomised

subjects, primary and secondary outcomes are listed. Thereafter, the fore last column includes if the trial was completed (C), terminated (T) or ongoing (O).

Figure 1. Overview of treatment options for patients with sickle cell disease. Different treatment options for patients with sickle cell disease divided in drug class and/or mechanism of action. The trials of therapies of which results are pending in a phase 2 or phase 3 clinical trials are marked (*). The inferior clinical trials are depicted as (-). The gene-therapy and haematopoietic stem cell transplant sections are separated as these therapies are limited to a subgroup of children and young adults with sickle cell disease.

Ref.	Trial name/Title Study	Phase of trial	Randomized Number of subjects	Primary Outcome measures	Secondary outcomes		Comments
[8]	REACH - Realizing Effectiveness across Continents with Hydroxyurea	1 and 2	606	Δ HbF.	Other haematological parameters, growth, number of vaso-occlusive pain crises, acute chest syndrome, infections, transfusions, and hospitalizations.	O	Reach was not a formally efficacy trial. Hematologic dose-limiting toxic effects in the first 3 months of hydroxyurea treatment in the first 133 children enrolled at each clinical trial site were assessed as a primary safety end point.
[9]	NOHARM - Novel Use Of Hydroxyurea in an	3	208	Incidence of clinical malaria.	(1) a composite of 1 or more SCD-related adverse events (pain,	C	

	African Region With Malaria				dactylitis, acute chest syndrome, splenic sequestration, or transfusion); (2) clinical AEs; and (3) dose-limiting toxicities.		
[10]	NOHARM MTD - Optimizing Hydroxyurea Therapy in Children With SCA In Malaria Endemic Areas	3	187	Total Hgb≥9.0 g/dL or HbF≥20% after 24 months.	incidences of malaria, vaso-occlusive crises, and serious adverse events.	C	
[11,12]	SWITCH - Stroke With Transfusions Changing to Hydroxyurea	3	134	Secondary Stroke and Δ liver iron level.	non-stroke neurological events, non-neurological sickle cell events, Quality of Life Assessment , functional evaluation, neurocognitive evaluation, growth and development; transfusion related	T	Closed after the first interim analysis.

					complications, chelation-related complications, hydroxyurea-related complications, phlebotomy-related complications; liver biopsy-related complications, and adverse events and serious adverse events.		
[14]	TWITCH - Transcranial Doppler (TCD) With Transfusions Changing to Hydroxyurea	3	121	Time-averaged mean velocity on the index side.	TCD velocity on the non-index side, new stroke or non-stroke neurological events, new brain MRI/MRA lesions, hepatic iron overload, sickle-related events, neuropsychological status, quality of life, growth, and treatment-related complications.	C	

[15]	SPIN - Stroke prevention in Nigeria	NA	235* screened, 25 recruited for high TCD	Trial feasibility was measured: recruitment, retention, and adherence rates to hydroxyurea therapy.		C	* not randomised
[95]	SACRED - Stroke Avoidance for Children in República Dominicana	2	283* recruited, 77 eligible, 74 started HU	Δ TCD velocities.	hydroxyurea-related toxicities and clinical and laboratory correlates of TCD velocities.	C	* not randomised
[17]	SPRING - Primary Prevention of Stroke in Children With SCD in Sub-Saharan Africa II	3	220	Initial stroke or transient ischaemic attack, centrally adjudicated.	All-cause hospitalisation.	C	

[18]	SPHERE - Stroke Prevention with Hydroxyurea Enabled through Research and Education	2	202	Δ TCD velocities.	SCD-related clinical events; changes in splenic volume and function; change in renal function; incidence of infection, especially malaria; hydroxyurea pharmacokinetics; and genetic modifiers of disease including pharmacogenomics.	O	
[21]	EXTEND - EXpanding Treatment for Existing Neurological Disease	2	43	Change in maximum TAMV obtained in the main intracranial arteries, typically the middle cerebral artery or distal internal carotid artery, in both hemispheres after 18-months of	serial TCD velocity changes, incidence of non-neurological and neurological events as determined by history, clinical findings of parenchymal changes demonstrable at magnetic resonance imaging and presence, absence or severity of	O	

				hydroxycarbamide treatment compared to the pre-treatment velocity.	vasculopathy, demonstrable at magnetic resonance angiography, hydroxycarbamide-related toxicities and treatment responses.		
[19]	SCATE - Sparing Conversion to Abnormal TCD (Transcranial Doppler) Elevation	2	38	Cumulative incidence of conversion to abnormal maximum TAMV velocities.	(1) changes in serial TCD velocities; (2) cumulative incidence of neurological and non-neurological acute events including stroke; and (3) health-related quality of life.	T	This study was terminated early due to slow patient accrual and a low likelihood of reaching the primary study endpoint.
[39]	A SUSTAIN study - Crizanlizumab for the Prevention of Pain Crises	2	198	Annual rate of sickle cell–related pain crises.	Annual rate of days hospitalized, the times to first and second crises, the annual rate of	T	

	in Sickle Cell Disease				uncomplicated crises, the annual rate of the acute chest syndrome, and the Brief Pain Inventory questionnaire.		
[96]	STAND trial Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients	3	252	Annualized rate VOC events leading to healthcare visit.	Annualized rate of all VOCs leading to healthcare visit and treated at home.	T	
[42]	Study of GMI-1070 for the Treatment of Sickle Cell Pain Crisis	2	76	Time to resolution of VOC.	Length of stay, cumulative opioid use (morphine equivalent units/kg), safety, and pharmacokinetics.	T	

[43]	RESET - Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease	3	320	Time from initiation of study drug to the time at which all readiness for discharge criteria were met.	Time to discharge.	T	
[44]	Sevuparin for the treatment of acute pain crisis in patients with sickle cell disease	2	144	Time to vaso-occlusive crisis resolution defined as freedom from parenteral opioid use and readiness for discharge as judged by the patient or physician.	Change in pain intensity from baseline recorded every 4h during the awake time until vaso-occlusive resolution and mean daily dose of parenteral opioids per day until vaso-occlusive crisis resolution or readiness for discharge; time to discontinuation of intravenous or parental opioids.	T	

[48]	EPIC-Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease	3	188	Hours from randomization until the last administration of parenteral opioid analgesic for painful vaso-occlusive episodes prior to hospital discharge.	Hospitalization for recurrence of painful VOCs within 14 days of initial hospital discharge and occurrence of acute chest syndrome within 120 hours of randomization.	T	
[35]	HOPE trial - A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease	3	274	Hb response > 1 g/dL.	change Hb level from baseline to week 24, hemolysis markers and the annualized incidence rate of VOC.	C	
[37]	HOPE KIDS 1 - Safety and efficacy of voxelotor in pediatric patients with sickle cell disease aged 4 to 11 years	2	45	Hb response > 1 g/dL.	change Hb level from baseline to week 24, hemolysis markers and the annualized incidence rate of VOC.		

[38]	GBT021601 - Next-Generation HbS Polymerization Inhibitor GBT021601 for the Treatment of Patients with Sickle Cell Disease	2/3	35	Hb change from baseline to Week 12.	Hb response (increase from baseline >1 g/dL) and change from baseline in hemolysis markers at Week 12, PK, PD, and safety.	O O	
[97]	Ardent - A Study of IMR-687 in Adult Participants With Sickle Cell Anemia (Homozygous HbSS or Sickle-β0 Thalassemia)	2b	112	Annualized VOC rates.	Time to first VOC, the proportion of patients with an increase (of at least 3%) in HbF in the high-dose group versus the placebo group.	T	
[49]	A Phase 3 Trial of l-Glutamine in Sickle Cell Disease	3	230	Number of VOCs (48 wk.).	Number of hospitalisations, number of ED visits, effect of l-Glutamine on haematological parameters and vital signs,	C	

[53]	Phase 2 Randomized Control Trial of Arginine Therapy for Pediatric Sickle Cell Disease Pain	2	36	Total parenteral opioid use.	time to VOC resolution, total opioid use, VOC frequency.	C	
[54]	Randomized control trial of oral arginine therapy for children with sickle cell anemia hospitalized for pain in Nigeria	2	70	analgesic usage, quantified by difference in the mean Analgesic Medication Quantification Scale (MQS).	Daily pain scores, time-to-crisis-resolution and length-of-hospital-stay.	C	
[59]	A Study Evaluating the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Crovalimab as Adjunct Treatment in Prevention of Vaso-Occlusive	2	90	Annualized rate of medical facility VOEs (AVR).	Annualized rate VOC, Annualized rate of ACS, Annualized rate of days hospitalized for VOC, annualized rate of days hospitalized for treatment of non-VOC complications of SCD, laboratory characteristics.	O O	

	Episodes (VOE) in Sickle Cell Disease (CROSSWALK-c)						

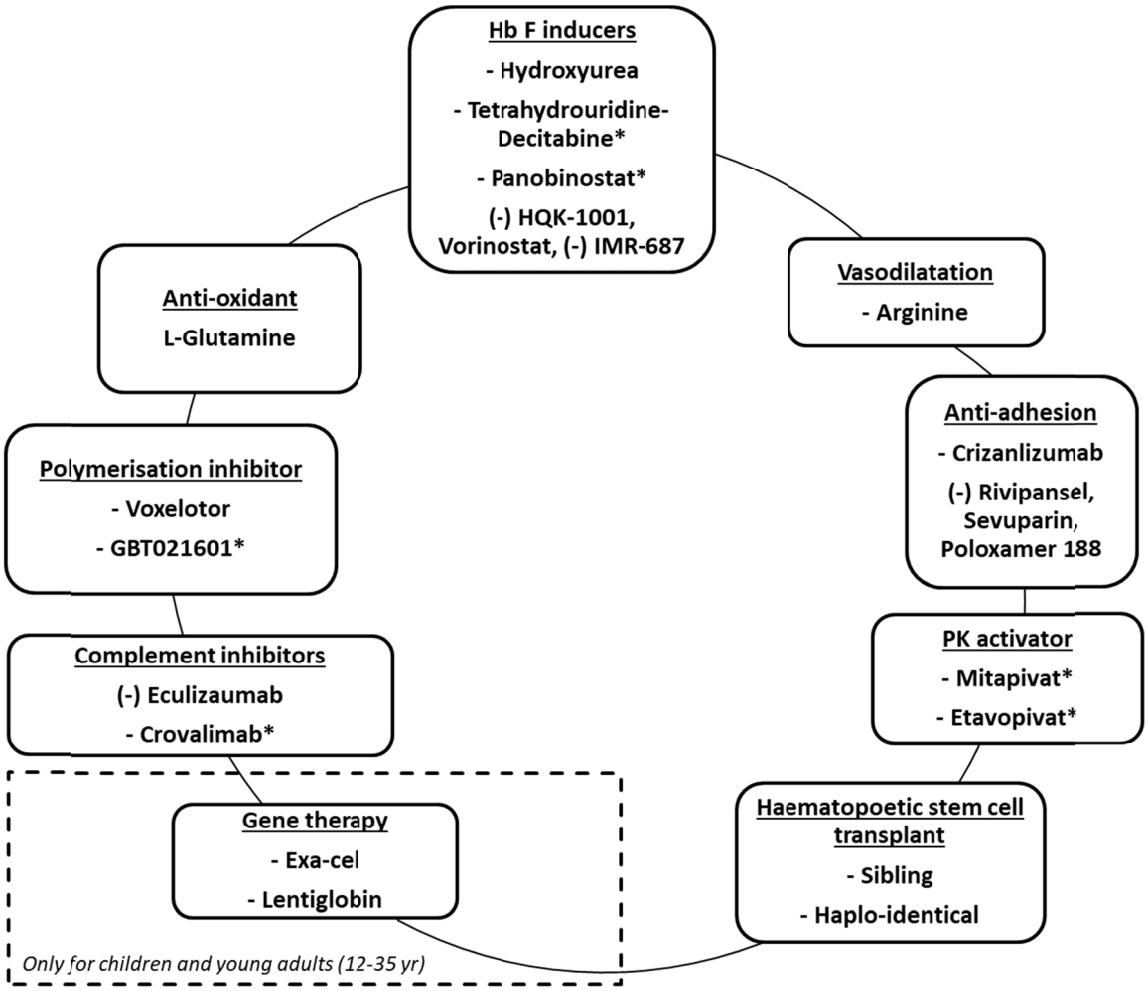
Abbreviations: Δ; difference in, VOC; vasoocclusive crisis, HbF; fetal haemoglobin, ED; emergency department, PK; pharmacokinetics, PD; pharmacodynamics, ACS; acute chest syndrome, SCD; sickle-cell disease, TCD; transcranial doppler.

Table 2. Clinical trials using haematopoietic stem cell transplantation in sickle cell disease listed by difference in conditioning. Per clinical trial the number of patients recruited (N), the median age of patients in years (Age (y)), the conditioning used, their overall survival (OS), percentage of graft rejection, disease free survival (DFS), percentage of chronic graft versus host disease (cGVHD) and treatment relation mortality (TRM) is listed.

Reference	Number of subjects	Age (y)	Conditioning	OS	Graft Rejection	DFS	cGVHD	TRM
Myeloablative conditioning HCT								
[71]	160	–	Bu-Cy ± Thiotepa	–	<2%	90% @ 6 years	–	13%
[67]	50	8.3	Bu-Cy-ATG	94%	8%	86% @ 8 years	20%	<5%
[98]	40	12	Bu-Cy-ATG ± Flu	91%	–	91% @ 9 years	<5%	7.5%
[76]	18	8.9	Bu-Flu-Alemtuzumab	100 %	0%	100% @ 2 years	11%	0%
Reduced Intensity Conditioning HCT								
[99]	52	29	TBI (300	94%	11.5%	88.5%	0%	0%

			cGy)-Alemtuzumab					
[70]	43	13	Flu-Mel-Alemtuzumab	93%	<2%	91% @ 3 years	13%	7%
[72]	13	30	TBI (300 cGy)-Alemtuzumab	100 %	8%	92%	0%	0%
[100,101]	20	33	Flu - Bu - Cy - ATG - TBI (200 cGy)	100 %	0%	100%	0%	0%

Abbreviations: TBI; total body irradiation, Bu; Busulfan, Cy; Cyclophosphamide, Mel; Melphalan, ATG; anti-thymocyte globulin.



List of abbreviations

DFS: disease free survival

DNMT1: DNA methyltransferase 1

EMA: European Medicine Association

FDA: Food and Drug Administration

GVHD: graft versus host disease

HbF: Haemoglobin F

HbS: Haemoglobin S

HDAC: histone deacetylase

HSCT: haemopoeitic stem cell transplantation

HU: Hydroxyurea

IV: intravenous

MRD: matched related donor

MTD: maximum tolerated dose

OS: overall survival

PDE9: phosphodiesterase-9

RBC: red blood cell

RIC: reduced intensity non-myeloablative conditioning

SCD: sickle cell disease

TCD: transcranial Doppler

THU: Tetrahydrouridine

TRM: treatment related mortality

UK: United Kingdom

USA: United States of America

VOC: vaso-occlusive crises