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Efficacy and safety of recently approved drugs for sickle cell disease: a review of clinical trials

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Sickle cell disease is prevalent in several parts of the world. Most hospitalizations of these patients are related to pain crisis episodes. Moreover, levels of hemoglobin are lower in sickle cell disease patients as compared with the general population. Complications related to sickle cell disease are managed with blood transfusions, hydroxyurea, and opioids. Despite these therapies, patients with sickle cell disease experience multiple pain crisis episodes leading to hospitalizations and end-organ damage. The US Food and Drug Administration has approved three new drugs—L-glutamine, voxelotor, and crizanlizumab—for the prophylaxis and treatment of complications related to sickle cell disease. This review was aimed at assessing the efficacy and safety of recently approved drugs for the treatment of sickle cell disease. A comprehensive search was made on PubMed and clinicaltrials.gov to look for clinical trials reporting the efficacy and safety of recently approved drugs for sickle cell disease. Based on the results of clinical trials, L-glutamine, voxelotor, and crizanlizumab were well tolerated by sickle cell disease patients. L-Glutamine and crizanlizumab reduced the number of sickle cell crisis episodes, while voxelotor improved the level of hemoglobin in sickle cell disease patients. These drugs were effective alone and in combination with hydroxyurea.

Sickle cell disease (SCD) is caused by mutation of \(b\)-globin gene alleles with the involvement of at least one sickle mutation. The patients may have both sickle mutations (HbSS), one sickle mutation and one hemoglobin C mutation (HbS), one sickle mutation and one thalassemia mutation (HbS), and other similar mutations with one sickle mutation in \(b\)-globin genes. The sickle mutation is a substitution of nucleotide thymine (T) by adenine (A) at the 17th nucleotide (sixth codon) in exon 1 of the \(b\)-globin gene and reflects a replacement of glutamic acid by valine at the sixth amino acid in the \(b\)-globin chain. This mutation decreases the solubility of hemoglobin (Hb), resulting in clinical symptoms [1].

SCD is the most prevalent genetic disease in the United States. Every twelfth African American is a carrier of sickle cell trait. Every year, 300,000 infants are born with SCD. Environmental factors (weather, air quality), fetal Hb levels, infections, and different genetic subtypes play a key role in exhibiting this disease. However, knowledge of the phenotypic expression of SCD is still limited [2,3].

Long-term irreversible complications of SCD, for example, vaso-occlusive crisis (VOC) and hemolysis, are the most common causes of morbidity and death.
Affected red blood cells (RBCs) in SCD have a shorter life span, resulting in chronic hemolytic anemia. Chronic hemolysis leads to compensatory changes such as an increase in RBC formation and adjustment to lower Hb levels. These modifications are beneficial for the survival of SCD patients. VOC occurs because of multiple changes in the adhesion of sickle RBCs to the endothelial cells of vessels and the activation of inflammatory and hemostatic mechanisms. Hydroxyurea, RBC transfusion, and opioids are the treatments commonly used to manage these symptoms [4].

Hydroxyurea increases $\gamma$-globin gene expression, which causes a shift in gene expression away from the $\beta$-globin gene. This shift in gene expression results in a higher level of fetal Hb (HbF: $\alpha_2\gamma_2$), and a reduction in the production of adult Hb (HbA: $\alpha_2\beta_2$). Patients taking hydroxyurea can experience gastrointestinal toxicity, such as nausea and anorexia, but the significant adverse effect is myelosuppression [5,6].

RBC transfusion can be life-saving in VOC, red cell aplasia, or splenic sequestration. But RBC transfusion has its adverse effects as well, for example, excessive iron storage, allo-immunization, infections related to transfusion, and hyperviscosity. Curative treatment options for SCD are hematopoietic stem cell transplantation (HSCT) and gene therapy [7,8].

The U.S. Food and Drug Administration (FDA) has approved three novel drugs for the treatment of sickle cell complications in recent years. L-Glutamine is the oldest of the three drugs. The FDA approved L-glutamine for the treatment of complications of SCD in July 2017. L-Glutamine is an amino acid required in the production of NAD (nicotinamide adenine), which is a cofactor in the reduction—oxidation reactions in the body. Oxidative stress is proven to be a critical factor in the pathophysiology of SCD [9]. It has been reported that supplementation with L-glutamine in patients with SCD increases the intracellular concentration of NAD within the sickle cells [10].

The FDA approved voxelotor and crizanlizumab for the treatment of complications of SCD in November 2019. Voxelotor is a hemoglobin modulator. It binds to the hemoglobin and increases its affinity for oxygen. Increased affinity for oxygen stabilizes the sickle cell hemoglobin and prevents polymerization [11]. The FDA approved voxelotor for SCD patients above 12 years of age. It is considered for patients who are refractory to hydroxyurea therapy or cannot tolerate hydroxyurea therapy or as an additional therapy in patients with worsening anemia [12].

Crizanlizumab is a humanized monoclonal antibody that binds P-selectin. P-Selectin is the primary mediator of the vaso-occlusive crisis in SCD. P-Selectin binds with its ligand P-selectin glycoprotein-1 (PSGL-1), an adhesion molecule. They capture leukocytes, which then activate platelets and form aggregates with sickled erythrocytes. These aggregates block vessels and lead to sickle cell pain crisis. The FDA approved this drug for patients above 16 years of age [13—15].

This review was aimed at assessing the efficacy and safety of new drugs, that is, L-glutamine, voxelotor, and crizanlizumab, for sickle cell disease.

Methods
A comprehensive search was performed on PubMed and ClinicalTrials.gov with the key words “voxelotor” OR “crizanlizumab” OR “glutamine” AND “sickle cell anemia” by June 5, 2020. One article was added through citation analysis—Supplementary Table E1, online only, available at www.exphem.org.

Inclusion and exclusion criteria
All clinical trials providing efficacy (change in hemoglobin, change in reticulocyte count, change in vaso-occlusive crisis episodes, etc.) and safety (treatment-related adverse effects) were included. All preclinical studies, case reports, case series, reviews, meta-analyses, and clinical trials not providing the efficacy and safety of drugs in SCD were excluded.

Data extraction
Information regarding the efficacy (change in hemoglobin, change in reticulocyte count, change in indirect bilirubin, change in vaso-occlusive crisis episodes, etc.) and safety (treatment-related adverse effects) were extracted from the selected clinical trials.

Risk of bias assessment
The Cochrane collaboration tool [16] was used by two researchers (WA and MYA) for the quality of bias assessment in randomized clinical trials. Disagreements were settled by a third researcher (MAA).

Results
One hundred eleven articles were identified through a search on PubMed and clinicaltrials.gov. A total of seven clinical trials (two phase III, three phase II, and one pilot study) with 976 participants were selected based on inclusion criteria.

Risk of bias
The risk of bias was unclear in the 2014 trial by Niihara et al. [17] and high in the 2018 study by Niihara et al. [18] on L-Glutamine. For voxelotor, the risk was high in the trial by Howard et al. [19] and low in the trial by Vichinsky et al. [20]. For crizanlizumab, the risk was high in trials by Ataga et al. [21] and Kutlar et al. [22] (Figure 1).

L-Glutamine
The results of the pilot study were reported in 1998 by Niihara et al. [23]. This study included only seven patients (age 19—60 years) who were administered 30 g of L-glutamine orally each day for 4 weeks. The
primary endpoints of this study were the change in NADH levels and NAD redox potential. The total NADH level increased from 47.5 to 72.1 nmol/mL ($p < 0.01$). The NAD redox potential also increased significantly from 47.2 to 62.1 ($p < 0.01$). The mean hemoglobin level did not significantly change from baseline; the Hb was 8.5 mg/dL at baseline and 8.7 mg/dL at 4 weeks for the study population. In addition to the changes in these levels, the study also included some patient-reported outcomes. All patients reported an increase in energy level and a decrease in chronic pain levels. None of the patients reported any adverse events associated with L-glutamine.

In the phase II trial reported in 2014 [17], outcomes were reported for a total of 62 patients (aged 9–58 years) with SCD who had a history of painful sickle cell crisis. Of these patients, 33 were administered L-glutamine, and 29 were administered a placebo. The patients were followed up for 53 weeks, and the outcomes were reported at 48 weeks. At week 48, the mean number of events for painful sickle cell crisis was 4.5 for the L-glutamine group and 10.8 for the placebo group, with a $p$ value of 0.001 for the difference between the two groups. The study also reported the mean number of events for hospitalization for sickle cell crisis. Of these patients, 33 were administered L-glutamine, and 29 were administered a placebo.

In 2018, a phase III study [18] was conducted to assess the efficacy of L-glutamine in improving SCD. In this randomized controlled trial, a total of 230 patients (aged 5–58 years) were assigned in a 2:1 ratio to L-glutamine ($n=152$) and placebo ($n=78$), with most of the patients receiving concomitant hydroxyurea as well. The patients in the L-glutamine group were administered 0.3 g/kg glutamine powder twice daily. The total treatment duration was 48 weeks, and the overall trial duration was 53 weeks. This trial showed statistically significant results. The mean numbers of pain crises in the L-glutamine and placebo groups were 3.2 and 3.9, respectively, with a $p$ value of 0.005, proving the results to be statistically significant. The mean numbers of hospitalizations for sickle cell-related pain were 2.3 in the L-glutamine group and 3.0 in the placebo group, with a $p$ value of 0.005, proving the difference between the two groups to be statistically significant. The improvement in hemoglobin levels, hematocrit levels, and reticulocyte count between the drug and placebo groups was not significant statistically. TRAEs were higher in the placebo group as compared with the L-glutamine group, indicating that it is safe to administer L-glutamine (Table 1).

Voxelotor

In the phase I/II trial of Howard et al. 2019 [19], different doses of voxelotor were used in 54 SCD patients 18–60 years of age. In the 28-day follow-up ($n=16$), the median change in hemoglobin was 0.4 g/dL with the 1,000-mg dose of voxelotor, 0.7 g/dL with 700 mg of voxelotor, 0 with 500 mg of voxelotor, and −0.1 g/dL with placebo. The difference was statistically significant. For markers of hemolysis, with 1,000 mg of voxelotor, the median percentage changes in the reticulocyte count, unconjugated bilirubin, and LDH were −49.9%, −56.3%, and −12.4%, respectively, versus changes in the placebo group of 9.0%, −3.6%, and −6.6%. The difference in changes in reticulocyte count and unconjugated bilirubin between 1000 mg and placebo was statistically significant. In the case of patients given voxelotor, vaso-occlusive episodes were reported when the patients were off-treatment. No grade 3 adverse effects were reported in this trial.

In 2019, Vichinsky et al. [20] conducted a phase III, placebo-controlled, double-blinded trial on patients aged 12–65 years with SCD treated with different doses of voxelotor, with a follow up of 24 weeks ($N=274$). The least-squares (LS) mean changes in hemoglobin were 1.1, 0.6, and −0.1 g/dL in the 1,500-mg voxelotor ($n=90$), 900-mg voxelotor ($n=92$) and placebo ($n=92$) groups, respectively ($p < 0.001$). Among markers of hemolysis, the LS means of changes in reticulocyte count, indirect bilirubin, and LDH were −19.9%, −29.1%, and −4.5%, respectively, in 1,500-mg voxelotor group, −1.3%, −20.3%, and 1.4%, respectively, in the 900-mg voxelotor group, and 4.5%, −3.2%, and 3.4% in the placebo group, respectively. The differences in mean change in reticulocyte count and indirect bilirubin among were significant in the 1,500-mg voxelotor and placebo groups. The difference
in vaso-occlusive crisis episodes in the three groups was not significant. Treatment-related adverse events were reported in 94%, 93%, and 89% of participants in the 1,500-mg, 700-mg, and placebo groups, respectively (Table 1).

**Crizanlizumab**

A phase II double-blinded, placebo-controlled study was performed by Ataga et al. [21] on the efficacy and safety of crizanlizumab. The total population was 198 and the median age 29 (range: 16–63); and 55% were females. Sixty-two percent of participants had concomitant hydroxyurea use. The total population \((N=198)\) was divided into high-dose crizanlizumab (group 1, \(n=67\)), low-dose crizanlizumab (group 2, \(n=66\)), and placebo (group 3, \(n=65\)). Of 198 participants, 129 completed the trial. Thirty-six percent of participants in group 1, 18% of participants in group 2, and 17% of participants in group 3 had no vaso-occlusive crisis during the treatment phase. The median crisis rate was 1.04 in group 1 versus 2.18 group 3 \((p=0.02)\). The median rate of days hospitalized was 4/year in group 1 versus 6.87/year in group 3 \((p=0.45)\). The median time to first crisis was 4.07 months in group 1 versus 1.38 months in group 3 \((p=0.001)\). In the high-dose crizanlizumab group, the rate of uncomplicated crises per year was 62.9% lower as compared with the placebo group. Serious adverse events occurred in 26%, 33%, and 27% of participants in groups 1, 2, and 3, respectively. The differences in changes in hemoglobin levels and markers of hemolysis between the drug and placebo groups were not statistically significant.

Kutlar et al. [22] conducted a post hoc descriptive analysis of the phase II analysis on the SUSTAIN study on crizanlizumab. The total number of participants was 132, and the age range was 16–65 years. In this post hoc analysis, 35.8% of participants in group 1 versus 16.9% of participants in the hydroxyurea group to 5.68 months versus 2.86 months in the placebo group and that in the hydroxyurea group to 5.68 months versus 2.86 months in the placebo group. No results were conducted on adverse events because the incidence of events was too low to provide subgroup analysis (Table 1).

**Ongoing clinical trials**

There are 11 ongoing clinical trials on these drugs, with 1,288 participants registered on ClinicalTrials.gov

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**Table 1. Efficacy and safety of new drugs of sickle cell disease**

| Trial | Vaso-occlusive crisis | Hemoglobin levels | Markers of hemolysis | Adverse events |
|-------|-----------------------|-------------------|----------------------|----------------|
| Niihara et al. 1998 [23] Pilot study | Decrease in chronic pain levels in all patients | No change in hemoglobin levels | Not assessed | Drug was well tolerated |
| Niihara et al. 2014 [17] Phase II randomized trial NCT01179217 | Mean number of crisis episodes in drug group was half that in placebo group \((p=0.07)\) | Difference not statistically significant between drug and placebo groups | Not assessed | TRAEs were similar in drug and placebo groups |
| Howard et al. 2019 [19] Phase I/II randomized trial NCT02285088 NCT03041909 | No crisis episode during treatment with drug | Improved significantly in drug groups as compared with placebo group | Improved significantly in drug groups as compared with placebo group (except LDH) | TRAEs were similar in drug and placebo groups |
| Vinchinsky et al. 2019 [20] Phase III randomized trial NCT03036813 | No statistically significant difference between drug and placebo groups | Improved significantly in drug groups as compared with placebo group | Improved significantly in drug groups as compared with placebo group (except LDH) | TRAEs were similar in drug and placebo groups |
| Kutlar et al. 2019 [22] Phase II randomized trial NCT01895361 Post hoc analysis | Reduced percentage of crisis episodes in drug group as compared with placebo group | Not assessed | Not assessed | |

**Voxelotor**

**Crizanlizumab**

**Ongoing clinical trials**

There are 11 ongoing clinical trials on these drugs, with 1,288 participants registered on ClinicalTrials.gov
Four of them are phase III clinical trials (Table 2).

**Discussion**

Hematopoietic stem cell transplantation (HSCT) with fully matched donors is the most effective treatment available for SCD, especially for patients refractory to hydroxyurea. However, the complications of stem cell transplantation, unavailability of suitable donors, financial burden, and insufficient stem cell transplant centers in certain parts of the world limit the use of HSCT [35–37]. Therefore, almost all new therapies and further avenues of exploration are directed toward the reduction of adverse events encountered in SCD to improve the quality of life. The main aim is to reduce pain crises and number of hospitalizations as well as improve hemoglobin levels in these patients.

In the past, hydroxyurea was the only drug available for SCD, along with supportive therapy (hydration, opioids) and blood transfusions. Hydroxyurea was approved in 1998. Although it has clinical efficacy and has been to decrease hospitalizations to 47% and pain crises to 43% [38], adherence to hydroxyurea always remained a challenge [39]. Moreover, patients taking hydroxyurea still experience end-organ damage, crisis episodes, and decreased life expectancy [40].

The trials on L-glutamine use in SCD patients paved the way for FDA’s approval of L-glutamine. In preclinical studies, it was found that sickle RBCs transport threefold more glutamine as compared with reticulocyte controls [41]. Similarly, in a trial on the pharmacokinetics (PK)/pharmacodynamics (PD) of oral glutamine supplementation, increased glutamine and arginine levels in RBCs were noted [42].

In the pilot study in 1998, almost all patients reported improvement in quality of life, although the study was not randomized, and the sample size was quite small. The statistically significant improvement in NADH levels in the participants using L-glutamine laid the foundation for further trials investigating the efficacy of L-glutamine. In the phase II clinical trial, the reduction in the mean number of hospitalizations was statistically significant in the L-glutamine drug group as compared with the placebo group at 24 weeks of follow-up. Although there were a decrease in hospital admissions and painful sickle cell crisis events at 48 weeks of follow-up, there was no statistically significant difference between the L-glutamine and the placebo groups, possibly because of the smaller sample size in that study. In the phase III clinical trial, the difference in sickle cell crisis episodes between the L-glutamine and placebo groups was statistically significant. Most of the patients in this trial were administered hydroxyurea concomitantly, as its benefits are well documented and proven [43]. Subgroup analysis with and without hydroxyurea also revealed a statistically significant difference between the L-glutamine and placebo groups regardless of hydroxyurea usage.

As far as the safety profile is concerned, L-glutamine has shown promising safety results in all these trials. There were no serious adverse events reported in any of the trials that could be attributed to L-glutamine use; however, patients with co-morbidities were not included in these clinical trials.

In the phase I/II clinical trial, voxelotor exhibited a substantial, durable, and rapid reduction in hemolysis in the limited number of patients. The affinity of oxygen, hemoglobin levels, and markers of hemolysis showed improvement in a dose-dependent fashion. The reduction in hemolysis was independent of hydroxyurea use. The maximum dose used was 1,000 mg. The adverse events in voxelotor groups were comparable to those in the placebo group without any safety concerns. In the phase III trial, an increased dose of 1,500 mg was used. The increased dosage of voxelotor has produced better outcomes as compared with low doses.
without causing any severe side effects. Anemia was improved irrespective of baseline hemoglobin level or use of hydroxyurea. The improvement in hemolysis was consistent with the impact of voxelotor on HbS polymerization. In the phase I/II trial, vaso-occlusive episodes were seen in patients when they were not taking voxelotor, but the results were inconclusive. However, in the phase III trial, it was clear that the incidence of vaso-occlusive crisis episodes did not increase with voxelotor use. An abandoned SCD drug, senicapoc, was also a hemoglobin polymerization inhibitor. Senicapoc prevented polymerization by inhibiting Gardos channels of sickle cell RBC, which resulted in increased viscosity of blood and an increase in vaso-occlusive pain episodes [44]. In contrast, voxelotor acts by causing allosteric changes in hemoglobin, leading to increased affinity on sickle cell RBCs. This mechanism does not lead to an increase in viscosity or increase in vaso-occlusive episodes.

Ataga et al. [21] conducted the first trial on crizanlizumab in SCD patients in 2017. The annual rate of sickle cell pain crisis was reduced by 45.3% in the crizanlizumab group as compared with the placebo group. In a subgroup of patients treated with hydroxyurea, the annual crisis rate was 32.1% lower in the crizanlizumab group as compared with the placebo group. Similarly, in non-hydroxyurea-treated patients, annual crisis episodes were reduced significantly in the crizanlizumab group as compared with the placebo group. In the post hoc analysis by Kutlar et al. [22] in 2019, the percentage of VOC-free patients taking hydroxyurea was 33.3% in the crizanlizumab group as compared with 17.5% in the placebo group. It is noticeably clear that crizanlizumab significantly reduced VOC and delayed time to first VOC despite therapy with hydroxyurea. Similarly, the annual rate of crises decreased to 32.1% in patients taking crizanlizumab (5 mg/kg) versus placebo, even in patients with continued hydroxyurea therapy [21]. Also, no significant changes were observed in hemolytic variables between the crizanlizumab and placebo groups.

The safety profiles of crizanlizumab and placebo therapy were comparable. The incidence of serious infections was similar in the crizanlizumab and placebo groups in both analyses, but the trial only included patients without any co-morbidity.

VOC episodes lead to multiple acute and chronic complications that are associated with increased mortality. Similarly, the improvement in hemolysis and hemoglobin level is crucial in preventing end-organ damage. Hemolytic anemia is associated with stroke, renal failure, silent infarcts, pulmonary hypertension, and early mortality. Therefore, all three drugs can decrease mortality in SCD [45–47]. However, the completed trials did not assess the effects of these drugs on other complications, such as priapism, gallstones, and nephropathy. In addition, the trials did not assess efficacy and safety in pregnant or comorbid patients.

Trials on other drugs with a similar mechanism, such as prasugrel, sevuparin, rivipansel, and senicapoc, have not revealed any clinically significant improvements in SCD patients in phase II/III clinical trials [48–51].

L-Glutamine, crizanlizumab, and voxelotor did not significantly increase treatment-related adverse events. The targets of action of these drugs also differed from each other, so it is possible to add the three drugs together with hydroxyurea, especially for patients who experience sickle cell complications with a two-drug combination.

SCD drugs have low compliance because of the daily dosing schedule [39]. Crizanlizumab has the benefit of a single dose in 4 weeks, which can increase compliance with this drug. However, the drug can only be given in the form of a 30-min-long infusion. Compliance with crizanlizumab can be increased if a simpler form of administration is developed. In epidemics or pandemics such as COVID-19, crizanlizumab can help reduce the number of pharmaceutical visits.

L-Glutamine, voxelotor, and crizanlizumab are almost 20–50 times more expensive than hydroxyurea, which can be a hurdle in the extensive use of these drugs, especially in the case of crizanlizumab and voxelotor. Although the reduction in hospitalization can compensate for the expense of these drugs, reductions in the cost of crizanlizumab and voxelotor are needed for these drugs to be used as primary treatment options for SCD [52,53].

Matched SCT is the best curative treatment available, but matched donors are found for only a limited number of patients. Other curative treatments under consideration are haplo-identical SCT and gene therapy. Haplo-identical SCT broadens the availability of donors to almost all SCD patients. Still, an increase in mortality caused by complications of SCT, especially graft-versus-host disease, has limited its use in SCD patients. Recent trials have reported improvement in outcomes with refined preparative regimens and radiation therapy [54,55]. There remains a need for more randomized clinical trials to reach any definitive conclusion. Gene therapy is also being tested for SCD patients. Matched donors are not required with gene therapy, and treatment-related complications are limited as compared with SCT. There are six ongoing clinical trials assessing the efficacy and safety of gene therapy in SCD patients, but the results are not yet available [56–61]. The ongoing clinical trials are assessing the efficacy in different types of SCD based on the types of mutations and types of vectors available. Gene therapy is an expensive treatment, and expert skills are
required to conduct this procedure. Collection of a sufficient number of stem cells can be a major factor in determining the outcome.

Haplo-identical HSCT and gene therapy are currently being tested, and a limited number of fully matched donors are available, the best possible treatment is pharmacological management with drug combinations. Gene therapy has the potential to become a major curative option for SCD patients in the future. Still, it will take a certain amount of time to train the professionals with new techniques, obtain long-term outcomes, and make gene therapy cost-effective and widely available.

Conclusions
With gene therapy and haplo-identical HSCT still under experimentation, pharmacological management is the best available treatment for patients for whom matched HSCT donors cannot be found. All three drugs—L-glutamine, voxelotor, and crizanlizumab—are well tolerated without any alarming adverse effects. L-Glutamine was tested in patients ≥5 years old, voxelotor in those ≥12 years old, and crizanlizumab in those ≥16 years old. L-Glutamine and crizanlizumab reduce the number of vaso-occlusive crisis episodes and hospitalizations, regardless of hydroxyurea use. However, these two drugs do not improve hemoglobin levels. On the other hand, voxelotor improves hemoglobin levels and prevents hemolysis in SCD patients regardless of hydroxyurea use. In the trials on voxelotor, the increase in hemoglobin levels was not associated with an increased number of VOC episodes. More multicenter, randomized, double-blind clinical trials are needed to determine the efficacy and safety of these drugs in all age groups and in participants with different health conditions.

Limitations
Only one randomized clinical trial with a low risk of bias was available. In the trials on L-glutamine and crizanlizumab, a significant number of participants left the treatment without reaching the end phase. Moreover, different clinical trials tested the efficacy and safety at different doses in a specific age group. Despite these limitations, our review is able to provide a comprehensive assessment of the efficacy and safety of L-glutamine, voxelotor, and crizanlizumab in sickle cell disease.

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The authors declare no conflicts of interest.

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## Supplementary table 1. Search history.

| Search database     | Search term                                                                 | Results |
|---------------------|-----------------------------------------------------------------------------|---------|
| PubMed              | (sickle cell anemia) AND (((voxelotor) OR (crizanlizumab)) OR (glutamine)) OR (GBT440) OR (Seg101)) | 86      |
| Clinicaltrials.gov | Voxelotor OR GBT440 AND sickle cell anemia = 13                              | 25      |
|                     | Crizanlizumab OR Seg101 AND sickle cell anemia = 7                           |         |
|                     | Glutamine AND sickle cell anemia = 5                                        |         |