Time to rethink haemoglobin threshold guidelines in sickle cell disease

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Summary

Alleviating anaemia in patients with sickle cell disease (SCD) is crucial in managing acute complications, mitigating end-organ damage and preventing early mortality. Some disease-modifying and curative therapies have increased haemoglobin (Hb) levels to exceed 100 g/l, a threshold above which complications from red blood cell (RBC) transfusions have occurred, raising concern about whole-blood viscosity-related complications with these therapies. Here we discuss the rationale behind this limit, the effect of viscosity on blood flow and the applicability of this Hb threshold to therapies for SCD beyond RBC transfusions.

Keywords: sickle cell disease, hyperviscosity, blood transfusion, hydroxycarbamide, voxelotor.

The potential benefits of raising haemoglobin (Hb) in patients with haemolytic anaemia have been well established for sickle cell disease (SCD).[1–3] Low Hb levels and increased intravascular haemolysis in patients with SCD are associated with increased risk of end-organ damage, including cerebral vascular disease, kidney disease, pulmonary vasculopathy and early mortality.[4,5] For the past several decades, red blood cell (RBC) transfusion, hydroxycarbamide and haematopoietic stem cell transplantation (HSCT) were used to increase Hb levels and treat other SCD-related complications. Voxelotor, a recently approved treatment for patients with SCD, has been also shown to raise Hb in patients and improve markers of haemolysis. However, treatment with these therapies may cause some patients' Hb levels to exceed 100 g/l, raising concern about whole-blood viscosity-related complications. Anecdotal case reports have reported complications in patients with Hb exceeding 100 g/l when receiving transfusions for acute complications. As a result, treatment guidelines recommend avoiding increasing Hb beyond 100 g/l in patients receiving a RBC transfusion.[1,3,6] However, the 100 g/l Hb threshold alone may not accurately reflect the risk of viscosity-related complications with disease-modifying therapies. The mechanisms whereby these therapies improve Hb levels differ substantially from that of RBC transfusion. Therefore, there is a need to revisit Hb treatment goals with disease-modifying therapies.

The rationale behind the haemoglobin 100 g/l limit with red blood cell transfusion

Case reports of patients with sickle cell anaemia (SCA; HbSS and HbSβ^0 genotypes) who developed complications after RBC transfusions have contributed to recommendations for avoiding Hb increases beyond 100 g/l. Patients in these reports developed adverse neurological outcomes, ranging from headaches to seizures and fatal cerebral bleeds, within days of receiving RBC transfusions.[7–11] As such, the rate of Hb increase, in addition to the final Hb value, may be an important factor that engenders complications, e.g. an increase in Hb concentration over hours to days *versus* over weeks to months. Moreover, excessive increases in viscosity have raised concerns about impaired oxygen delivery to

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tissues due to reduced blood flow. While hyperviscosity has also been considered a risk factor for increased vaso-occlusive crises (VOCs) in some patients with SCA, those with haemoglobin SC disease (HbSC) generally have higher Hb and viscosity levels but lower rates of VOCs.[12,13] Given the lack of clinical and observational studies evaluating adverse events associated with increasing Hb beyond 100 g/l, the true incidence of viscosity-related complications in SCD is difficult to assess. As such, SCD transfusion guidelines recommend to not increase Hb beyond 100 g/l in patients with acute complications related to SCD.[1–3] However, with long-term transfusions, where the rise in Hb occurs more slowly and is accompanied by a parallel decline in sickle Hb (HbS), patients who are able to maintain a lower percentage of HbS (<30%) can have their Hb increased safely to about 120–130 g/l, implying that Hb concentration alone may not account for viscosity-related complications.[3,6]

The effect of viscosity on blood flow in sickle cell disease

In addition to Hb concentration, haematocrit and RBC rheological properties have a substantial effect on blood viscosity. The underlying cause of SCD, polymerisation of HbS, drives a multitude of effects that increase whole-blood viscosity and alter blood rheology. Patients with SCD have more viscous blood than those without SCD, leading to a more dramatic rise in viscosity when haematocrit exceeds 30%.[14,15] RBC sickling caused by intracellular HbS polymerisation and extracellular tonicity can impair RBC deformability, thereby increasing RBC resistance to flow.[15,16] Recurrent HbS polymerisation and cellular dehydration can result in the formation of irreversibly sickled cells that create a further rise in blood viscosity.[15] While RBCs tend to aggregate at low shear rates in conditions with low or stagnant flow, sickle RBC aggregates are substantially more robust than healthy RBC aggregates, despite being less likely to form, causing additional increases to blood viscosity.[15]

Sickle cell disease further alters blood rheology by impairing vascular function. Circulating free haem, resulting from chronic haemolysis, reduces nitric oxide bioavailability and restricts vasodilation.[14,15] An acute rise in blood pressure has been noted in case reports of patients who received several RBC transfusions before developing neurological complications.[7–11] Given the underlying vascular dysfunction, the microvasculature may be unable to compensate for this rapid change in blood volume and Hb level. Therefore, the rate of Hb increase associated with RBC transfusions, rather than absolute Hb, may affect the risk of viscosity-related complications.

Therapies that improve other parameters of blood viscosity and RBC rheology may allow Hb to be safely increased without the risk of complications associated with hyperviscosity. Thus, the mechanism and onset of action of a treatment may be important considerations when determining the extent to which Hb can be safely increased in patients with SCD. Pancellular therapies that improve viscosity and RBC rheological properties, including RBC deformability, aggregation and adhesion, may allow higher Hb limits. As emerging therapies have drastically different mechanisms of action than mainstay therapies for SCD, the threshold for a patient's Hb should be evaluated on a per-treatment basis.

Sickle cell disease therapies and haemoglobin elevation

Hydroxycarbamide

In several clinical studies, treatment with hydroxycarbamide has resulted in Hb increases in patients with SCA at 10 weeks of treatment (mean Hb concentration increased from 84 to 91 g/l) and in those with HbSC at six months of treatment (mean Hb concentration increased from 108 to 110 g/l).[17–19] Improvements in Hb were accompanied by increased percentages of foetal Hb (HbF) and reduced rates of SCD-related complications, including VOCs and acute chest syndrome (ACS).[18,19] The safety profile of hydroxycarbamide is well understood; short-term haematological toxicities are used to determine the maximum tolerated dose of hydroxycarbamide.[1,20] About 20% of clinical trial participants developed mild, reversible cytopenia (neutrophil count <1 500/μl), which led to a temporary hold or dose reduction of hydroxycarbamide.[1]

There are no data to support the notion that hydroxycarbamide-associated improvements in Hb predispose patients to viscosity-related complications. Additionally, the risks of ACS, leg ulcers and osteonecrosis were not increased with hydroxycarbamide in a randomized, double-blinded clinical trial.[18] Patients with HbSC receiving hydroxycarbamide generally experienced fewer VOCs despite having their Hb levels exceed 100 g/l.[19] Anecdotally, phlebotomy was beneficial in patients with HbSC who did not respond to hydroxycarbamide.[21] Hydroxycarbamide, a ribonucleotide reductase inhibitor, induces the production of HbF that inhibits intracellular HbS polymerisation and reduces RBC sickling.[22] Treatment with hydroxycarbamide has also been associated with increased RBC size (mean corpuscular volume), improved deformability and reduced vascular adhesion.[18,22] In patients with HbSC, treatment with hydroxycarbamide was associated with stable Hb levels, mildly increased HbF percentages and increased RBC size, with corresponding decreases in VOC events.[19] Achieving and maintaining HbF percentages of ≥20% has been associated with reduced clinical events, independent from improvements in Hb.[20] The increased viscosity associated with Hb increases may be counterbalanced by HbF-associated pancellular improvements in RBC health that reduce RBC sickling and its associated alterations to blood viscosity.

Voxelotor

In the phase 3, placebo-controlled HOPE study, voxelotor 1 500 mg was associated with an adjusted mean increase in Hb of 11 g/l, and 41% of patients had their Hb reach at least

100 g/l by week 24.[23] Voxelotor 1 500 mg was also associated with significant improvements in markers of haemolysis, including indirect bilirubin and reticulocyte percentage, indicative of reduced haemolysis. Patients who achieved the highest Hb levels with voxelotor experienced the lowest VOC rates compared with patients receiving placebo.[24] Treatment with voxelotor was well tolerated, and the most common adverse events with an incidence of at least 20% were headache and diarrhoea.[23] Most adverse events were grade 1 or 2, and no notable differences in the rates of SCD-related adverse events, which included SCA with crisis, ACS, pneumonia, priapism and osteonecrosis, were observed between voxelotor treatment and placebo.[23] No hyperviscosity-related complications were detected during the trial.[24]

Thus far, there are no data to support an Hb limit at which voxelotor would be considered unsafe due to hyperviscosity. Voxelotor, a HbS polymerisation inhibitor, binds reversibly to Hb and stabilises it in its oxygenated state to reduce RBC sickling, resulting in a pancellular distribution of modified Hb.[23,25] In the HOPE study, improvements in Hb occurred within two weeks of initiating voxelotor, and no adverse events of stroke or transient ischaemic attack were observed in the voxelotor 1 500 mg group.[23] The mechanism whereby voxelotor reduces haemolysis and improves anaemia has allowed the Hb concentration to safely exceed 100 g/l without hyperviscosity-related complications. Voxelotor has been shown to reduce RBC sickling and viscosity, improve RBC deformability and prolong the half-life of RBCs.[26,27] The upper Hb limit with voxelotor may need to be evaluated on a per-patient basis, with considerations for markers of haemolysis and RBC health.

Caution should be taken when abruptly discontinuing voxelotor in a patient whose Hb concentration has risen above 100 g/l. The reversible binding of the agent may be associated with a theoretical risk of developing VOCs in this setting; however, recent data in mice have shown that cessation of HbS polymerisation inhibition with a voxelotor analogue did not increase viscosity compared with that in control mice 48 hours after discontinuing treatment.[28] Additional data are needed to better understand these theoretical risks in patients.

Cellular therapies

Haematopoietic stem cell transplantation and gene therapy studies have reported patient Hb levels >100 g/l, with varying percentages of HbS.[29–34] Most patients in HSCT and gene therapy studies had their Hb increase beyond 100 g/l within six to 12 months after transplant. Patients also experienced reduction or an absence of VOCs or ACS following transplant in studies that evaluated SCD-related clinical outcomes.[32,34] Most patients who were receiving chronic transfusion therapy before treatment were able to stop or reduce the frequency of their RBC transfusions within two to three months after gene therapy.[31,32,34] Adverse events reported in HSCT and gene therapy trials were primarily associated with myeloablative conditioning and stem cell source, which were not SCD-related. For HSCT, post-transplant complications included sirolimus-associated complications (pneumonitis, arthralgias), abdominal pain, primary graft failure and graft rejection.[29,33] In gene therapy studies, adverse events were generally associated with the transplantation.[31,32,34] The most common grade ≥3 adverse events included nausea and haematologic alterations associated with myeloablative conditioning.[31,32]

While assessment of viscosity and rheological markers are limited in these patients, there have been no appreciable viscosity concerns that have emerged over time in HSCT and gene therapy studies. Patient Hb levels have reached >120 g/l without viscosity-related issues.[29–33] In HSCT, the recipient's bone marrow and RBC production are replaced by the donor's system, thus altering production of RBCs and HbS. At ≥1 year after HSCT, patient HbS percentages were reduced to 35% from 60% to 70% before transplantation.[30,33] Low HbS levels may persist in transplant patients due to sibling donors with the sickle trait or remnant native haematopoietic stem cells. In gene therapy, bone marrow cells are transduced to express modified Hb genes that inhibit HbS polymerisation. In a phase 1/2 study of LentiGlobin, the rates of VOC and ACS events were considerably reduced or eliminated after infusion of modified cells, despite patients having a median total Hb of 115 g/l and HbS of up to 60% at ≥6 months of follow-up.[32] Patient HbS levels persist due to intact native genes expressing the sickle beta-globin gene. Because HSCT and gene therapy reduce overall HbS levels and the genetic modification results in less HbS polymerisation, the impact of HbS on blood viscosity is substantially reduced.

Discussion and conclusion

Although clinical practice guidelines have suggested a maximum safe Hb concentration of 100 g/l in patients with SCD receiving intermittent RBC transfusions, the evidence does not support extrapolating this threshold for other SCD therapies when making treatment decisions. Hb concentration alone is not an adequate indicator of blood viscosity-related safety issues with older (hydroxycarbamide) or newer (voxelotor) disease-modifying therapies that promote Hb rise. As patients are achieving near-normal Hb levels, additional parameters such as RBC deformability, aggregation and adhesion need to be considered as predictors of viscosity-related complications in SCD. Changes in the intracellular Hb composition following treatment with curative therapies may also mitigate risk otherwise associated with increased total Hb. By reducing the contribution of HbS to viscosity, Hb levels >100 g/l have been safely reached in patients via chronic transfusions, hydroxycarbamide, voxelotor, HSCT and gene therapy. While phlebotomy has been performed in

some patients with HbSC to reduce iron levels, there is no need to preventively phlebotomise patients solely based on higher Hb levels during use of disease-modifying therapies. Patients with HbSC who have higher steady-state Hb levels can also tolerate hydroxycarbamide-promoted Hb rises without an increase in the rate of VOCs or other SCD-related complications but should be closely monitored. Overall, patients with a favourable safety profile, based on their steady-state Hb, SCD genotype, HbS percentage and RBC rheological parameters, have reduced risk of hyperviscosity-related complications. As such, higher Hb levels that may occur with SCD therapies, other than RBC transfusions, may not be a cause for concern provided they are within the normal range for a patient's age and sex. However, it is essential to further understand the implications of Hb changes with these disease-modifying therapies. Providers may consider prospectively measuring their patients' blood viscosity to determine the relationships of treatment dose, time of use and RBC parameters with viscosity. There continues to be a need to redefine target Hb levels for disease-modifying therapies in SCD that promote an increase in Hb.

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