We might never know the answer to these specific questions, but we should continue to document real-world findings, particularly regarding the risks and benefits of voxelotor to end-organ function. Building on preclinical models,[7] preliminary studies showing preserved or lowered cerebral blood flow,[8] together with the results of this study[1] and ongoing studies, such as HOPE Kids 2 (NCT04218084), which is investigating the effect of voxelotor on transcranial doppler velocity, are already looking to address cerebrovascular outcomes. Longitudinal studies assessing end-organ damage are surely also needed.

Reduced haemoglobin concentrations is a risk factor for sickle cell disease-related morbidity and mortality.[9] Howard and colleagues[1] show the reliable increase in haemoglobin concentrations, decrease in haemolysis markers, and a lower annualised incidence of acute anaemic episodes in patients with sickle cell disease taking voxelotor compared with those taking placebo. These results suggest that acute anaemic crises could be potentially managed in patients with alloimmunisation or hyperhaemolytic syndrome. The absence of improvement in the incidence of vaso-occlusive crises and patient-reported quality of life with voxelotor versus placebo, however, shows that there is still much to learn and optimise with regards to modulators that increase the affinity of haemoglobin for oxygen.

BPDI reports personal fees from Novartis, Cyclerion, and AstraZeneca, outside the area of work commented on here; and educational support from Novartis, Cyclerion, Global Therapeutics, Pfizer, AstraZeneca, and Celgene outside the area of work commented on here. MC reports advisory board and speaker honoraria from Novartis outside the area of work commented on here. AC reports consultancy fees and research grants from Global Blood Therapeutics and Bluebird Bio outside the area of work commented on here. NA reports grants from Global Blood Therapeutics and the National Institute of Diabetes and Digestive Kidney Diseases outside the area of work commented on here.

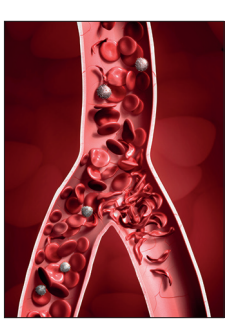
*Baba Psalm Duniya Inusa, Maddalena Casale, Andrew Campbell, Natasha Archer
**baba.inusa@gstt.nhs.uk**

Paediatric Haemotology, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK (BPDI); Università degli Studi della Campania Luigi Vanvitelli, Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica Napoli, Naples, Italy (MC); Department of Hematology, Children's National Hospital, Washington, DC, USA (AC); Children's National Hospital, George Washington University School of Medicine, Fredericksburg, VA, USA (AC); Department of Pediatric Hematology and Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, MA, USA (NA)

1 Howard J, Ataga KI, Brown RC, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol* 2021; published online April 7. https://doi.org/10.1016/S2352-3026(21)00059-4.
2 Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med* 2019; **381:** 509–19.
3 Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia a molecular disease. *Science* 1949; **110:** 543–48.
4 Ingram VM. A specific chemical difference between the globins of normal human and sickle-cell anaemia haemoglobin. *Nature* 1956; **178:** 792–94.
5 Platt OS. Hydroxyurea for the treatment of sickle cell anemia. *N Engl J Med* 2008; **358:** 1362–69.
6 Hebbel RP, Hedlund BE. Sickle hemoglobin oxygen affinity-shifting strategies have unequal cerebrovascular risks. *Am J Hematol* 2018; **93:** 321–25.
7 Dufu K, Lucas A, Rodrigues Muller C, et al. Pharmacological increase of Hb-$O_2$ affinity with a voxelotor analog does not decrease brain tissue $pO_2$ or limit $O_2$ extraction in brain tissues of sickle cell mice. *Blood* 2019; **134** (suppl 1)**:** 3564 (abstr).
8 Estepp JH, Wang W, Hwang S, Hillenbrand C, Ogg R. Cerebral blood flow in adolescents with sickle cell anemia receiving voxelotor. *Hemasphere* 2019; **3:** 324 (abstr).
9 Ataga KI, Gordeuk VR, Agodoa I, Colby JA, Gittings K, Allen IE. Low hemoglobin increases risk for cerebrovascular disease, kidney disease, pulmonary vasculopathy, and mortality in sickle cell disease: a systematic literature review and meta-analysis. *PLoS One* 2020; **15:** e0229959.

# Sevuparin trial for acute pain in sickle cell disease: the dog that did not bark

Sickle cell disease affects millions of people worldwide and is due to the abnormal polymerisation of sickle haemoglobin within the red blood cell. Resultant abnormal cell–cell interactions between red blood cells, white blood cells, and vascular endothelial cells mediate painful vaso-occlusive crises and chronic organ damage in sickle cell disease.[1] Several mechanisms have been implicated in vaso-occlusive crises, including endothelial cell activation and expression of adhesion molecules, such as selectins, integrins, and von-Willebrand factor, thereby initiating abnormal blood cellular adhesion and activating coagulation.[2] Clinically effective inhibition of these abnormal cellular interactions was shown through chronic administration of the anti-P-selectin antibody, crizanlizumab.[3] This pivotal study[3] set a precedent for symptom management through modifying adhesion, and stimulated interest in the development of additional therapies targeting these interactions. Further, in light of the complexity, expense, and


Tim Vernon/Science Photo Library

See **Articles** page e334

safety concerns for curative-intent therapy for sickle cell disease, approaches that successfully target adhesion are attractive and timely adjuncts to current management, and patients need options while they wait for a cure.

Despite being a global disease with high morbidity and mortality, sickle cell disease has relatively few available treatments. There are four treatments approved by the US Food and Drug Administration, and two approved by the European Medicines Agency;[4] three gaining approval in the last few years. In sub-Saharan Africa, hydroxyurea is only beginning to be successfully and broadly used. In *The Lancet Haematology*, Bart J Biemond and colleagues[5] report negative results from a randomised placebo-controlled trial of sevuparin, a heparinoid with retained anti-adhesion (anti P-selectin) properties and attenuated anticoagulation, as a treatment for acute vaso-occlusive crises in sickle cell disease (there was no difference in the primary endpoint—median time to vaso-occlusive crisis resolution—between the sevuparin and placebo groups [100·4 h (95% CI 85·5–116·8)] *vs* 86·4 h (70·6–95·1); hazard ratio 0·89 (0·6–1·3); p=0·55]).

Like Sherlock Holmes, what can we learn from what did not 'bark' in this study?

First, are anticoagulant properties a missing piece of the whole? Data have shown, for example, that tissue factor inhibition can prevent pulmonary cellular aggregates in mouse models of sickle cell disease,[6] a process upstream from cellular adhesion to the endothelium and thus a potentially critical target in vaso-occlusive crises. Coagulation itself appears to play a role in ongoing adhesion, vaso-occlusive crisis, and end-organ damage in sickle cell disease.[7] Perhaps the anticoagulant properties of heparins are important in terminating a vaso-occlusive crisis, once started, although previous results from studies using anticoagulants alone have been mixed.[8]

Second, is there a subset of patients who might benefit from heparinoids acutely or chronically? Adhesion of blood cells to endothelium, although a prominent feature of white cells and sickled red blood cells, appears to be dominant in only a subset of patients.[9] Other studies of anti-adhesive therapies have suggested that timing (within 24 h of pain initiation) might be crucial to success of the treatment.[10] Future trials with novel anti-adhesive drugs might benefit from in-vitro screening and novel or chronic administration schedules to better target those individuals most likely to benefit.

Finally, a ubiquitous critique of many clinical trials, and especially in sickle cell disease, is whether the defined clinical endpoints are providing a full picture. Because of the evidence for thromboinflammation contributing to the phenotype of sickle cell disease,[7] pain is clearly an imperfect surrogate for disease severity. Opioid use and hospitalisation duration are important, measurable, and patient-centred endpoints, but additional exploratory biomarkers could highlight potential health benefits from treatments. The authors of this study have considered this point and are evaluating the effect of therapy on several biomarkers (data in the appendix of the article).[5] These forthcoming data will be of great interest.

The authors conclude that sevuparin did not prevent complications secondary to vaso-occlusive crisis when compared with placebo. The sickle cell disease community will learn from efforts, such as those described by the authors,[5] how to better manage the protean pathophysiological manifestations of and distressing symptoms from sickle cell disease in patients living in the present as the future unfolds, and while curative therapies overcome evolving barriers to development. Adhesion is a complex interaction, comprising both initiation and maintenance, and as such, future trials will need to match that complexity with creativity and a willingness to fail. Just as physicians and scientists advise trainees (and themselves) not to overgeneralise positive findings, clinicians, scientists, and industry should not lose interest by over-generalising negative or null findings. As noted by the authors,[5] anti-adhesive strategies in combination with drugs targeting other mechanisms might be efficacious and should continue to be studied. Accompanied by appropriate biomarkers and more robust patient-reported outcomes, a multimodal approach to therapy, a familiar modus operandi in oncology, is not only inevitable, but is also desirable. As has been eloquently addressed by others,[4] well-designed and executed negative studies are important to the research community's efforts to iteratively refine goals and practices in pursuit of a truly effective comprehensive approach to therapy for people with sickle cell disease.

We declare no competing interests.

*Patrick Ellsworth, Jane A Little
**patrick_ellsworth@med.unc.edu**

UNC Blood Research Center, Chapel Hill, NC 27599, USA

1 Novelli EM, Gladwin MT. Crises in sickle cell disease. *Chest* 2016; **149:** 1082–93.
2 Rai P, Ataga KI. Drug therapies for the management of sickle cell disease. *F1000Res* 2020; published online June 11, 2020. https://doi.org/10.12688/f1000research.22433.1.
3 Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med* 2017; **376:** 429–39.
4 Telen MJ, Malik P, Vercellotti GM. Therapeutic strategies for sickle cell disease: towards a multi-agent approach. *Nat Rev Drug Discov* 2019; **18:** 139–58.
5 Biemond BJ, Tombak A, Kilinc Y, et al. Sevuparin for the treatment of acute pain crisis in sickle cell disease: a multicentre, randomised, double-blind, placebocontrolled phase 2 trial. *Lancet Haematol* 2021; **8:** e334–43
6 Sparkenbaugh EM, Chen C, Brzoska T, et al. Thrombin activation of PAR-1 contributes to microvascular stasis in mouse models of sickle cell disease. *Blood* 2020; **135:** 1783–87.
7 Conran N, De Paula EV. Thromboinflammatory mechanisms in sickle cell disease-challenging the hemostatic balance. *Haematologica* 2020; **105:** 2380–90.
8 Seaman CD, Novelli E, De Castro L, Ragni MV. Unfractionated heparin in acute chest syndrome: a pilot feasibility randomized controlled trial of unfractionated heparin vs. standard of care in acute chest syndrome. *Pilot Feasibility Stud* 2020; **6:** 174.
9 Man Y, Goreke U, Kucukal E, et al. Leukocyte adhesion to P-selectin and the inhibitory role of Crizanlizumab in sickle cell disease: a standardized microfluidic assessment. *Blood Cells Mol Dis* 2020; **83:** 102424.
10 Dampier CD, Telen MJ, Wun T, et al. Early initiation of treatment with rivipansel for acute vaso-occlusive crisis in sickle cell disease (SCD) achieves earlier discontinuation of IV opioids and shorter hospital stay: reset clinical trial analysis. *Blood* 2020; **136** (suppl 1)**:** 18–19 (abstr).

# Factor B inhibition for paroxysmal nocturnal haemoglobinuria

Published **Online**
March 22, 2021
https://doi.org/10.1016/S2352-3026(21)00061-2

See **Articles** page e344

Paroxysmal nocturnal haemoglobinuria is a complement-mediated haemolytic anaemia that presents with intravascular haemolysis, thrombosis, and bone marrow failure.[1] Paroxysmal nocturnal haemoglobinuria blood cells are deficient in glycosylphosphatidylinositol-anchored proteins (GPI-AP) because of a somatic mutation in *PIGA*. Intravascular haemolysis in paroxysmal nocturnal haemoglobinuria results from the absence of CD55 and CD59, both cell surface GPI-APs that regulate autologous complement. CD55 accelerates the decay of C3 and C5 convertases, and CD59 blocks formation of the terminal membrane attack complex. The alternative pathway of complement is continuously active at low levels through a process known as tick over, which continuously challenges cell surfaces. Paroxysmal nocturnal haemoglobinuria erythrocytes are particularly susceptible since a single membrane attack complex can lead to intravascular haemolysis. This explains why patients with this disease have chronic haemolysis and why complement amplifying conditions (eg, inflammation, infections, surgery, pregnancy) lead to paroxysms. Before approval of eculizumab in 2007, thrombosis was the leading cause of death related to paroxysmal nocturnal haemoglobinuria and median survival was 15–20 years.

Eculizumab, a monoclonal antibody that prevents terminal complement activation by targeting C5, was the first drug approved to treat paroxysmal nocturnal haemoglobinuria. Eculizumab blocks intravascular haemolysis, prevents thrombosis, eliminates the need for blood transfusions in more than 80% of patients, and improves quality of life.[2] Ravulizumab, an analogue of eculizumab with a relatively long half-life, is the current standard of care, and is administered intravenously, every 8 weeks to patients with paroxysmal nocturnal haemoglobinuria. Thus, terminal complement inhibition at C5 is highly effective and has changed the natural history of paroxysmal nocturnal haemoglobinuria; however, 15–20% of patients continue to require transfusions

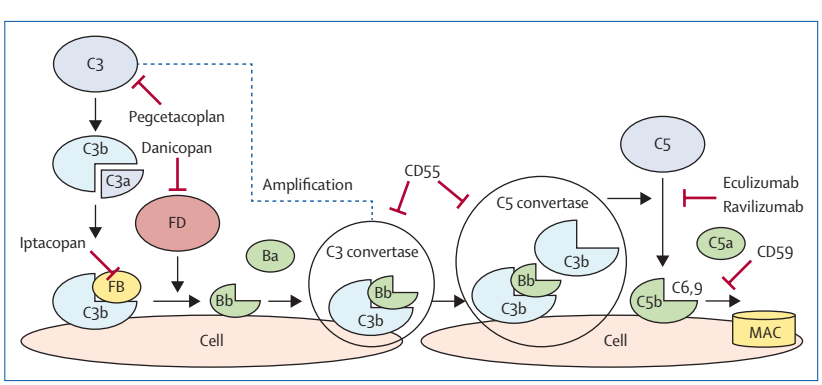



***Figure*: The alternative pathway of complement**
The alternative pathway is triggered by the hydrolysis of C3 which forms C3a and C3b (not shown). C3b becomes bound to the cell surface and is then able to interact with factor B, which is cleaved by factor D, creating the Bb fragment that binds to other surface-bound C3b molecules to form C3bBc; the C3 convertase pathway triggers an amplification loop, with further hydrolysis of C3. Ultimately, there is further production of C3b which joins with C3 convertase to form C5 convertase which cleaves C5 to C5a and C5b, and this leads to formation of a membrane attack complex. CD55 accelerates decay of the C3 and C5 convertases and CD59 prevents formation of the MAC. Iptacopan, danicopan, and pegcetacoplan block complement upstream of CD55 and CD59. MAC=membrane attack complex.