Role of the Hemostatic System on Sickle Cell Disease Pathophysiology and Potential Therapeutics

Zahra Pakbaz, MD[a], Ted Wun, MD[a,b,*]

KEYWORDS

• Sickle cell • Thromboembolism • Hypercoagulable • Anti-platelets • Anticoagulants

KEY POINTS

- Although the pathogenesis of sickle cell disease (SCD) lies in disordered hemoglobin structure and function, downstream effects of sickle hemoglobin include changes in the hemostatic system that overall result in a prothrombotic phenotype.
- These changes include thrombin activation, decreased levels of anticoagulants, impaired fibrinolysis, and platelet activation.
- Limited studies to date suggest that biomarkers of activation can be affected by currently available antithrombotic drugs, and provocative data from pilot studies indicate there may be improvement in clinically important outcomes.
- Therefore, clinical trials with antithrombotic therapies are justified with both SCD-related complications (vaso-occlusive crisis, pain) and thrombotic complications as outcome events of interest.

INTRODUCTION

Sickle cell disease (SCD) is the result of homozygous or compound heterozygous inheritance of mutation in the β-globin gene. The resulting substitution of the hydrophilic amino acid glutamic acid at the sixth position by the hydrophobic amino acid valine, leads to the production of hemoglobin S (HbS). HbS polymerizes when deoxygenated and this polymerization is associated with cell dehydration and increased red cell density.[1–3] The dense, rigid, and sickling red cells lead to vaso-occlusion and impaired blood flow,[2,4] and is thought to underlie acute (painful episodes, acute chest

Z. Pakbaz has no conflict of interest. T. Wun receives grant funding from Glycomimetics, Inc.

[a] Division of Hematology Oncology, Davis School of Medicine, 4501 X Street, Suite 3016, Sacramento, CA 95817, USA; [b] UC Davis Clinical and Translational Sciences Center, VA Northern California Health Care System, Sacramento, CA, USA

* Corresponding author. Division of Hematology Oncology, UC Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016, Sacramento, CA 95817.

E-mail address: ted.wun@ucdmc.ucdavis.edu

Hematol Oncol Clin N Am 28 (2014) 355–374

http://dx.doi.org/10.1016/j.hoc.2013.11.011 **hemonc.theclinics.com**

0889-8588/14/$ – see front matter Published by Elsevier Inc.

syndrome) and chronic (avascular necrosis, renal insufficiency) complications of the disease. Also, intracellular polymerization ultimately damages the red cell membrane and leads to chronic and episodic extravascular and intravascular hemolytic anemia, hemolysis-linked nitric oxide (NO) dysregulation, and endothelial dysfunction,[5] resulting in leg ulcer, pulmonary arterial hypertension (PAH), priapism, and stroke.[6]

Several investigators have reported increased thromboembolic events and alteration in hemostatic system in SCD both under steady state and during acute events. This suggests that perturbation in the hemostatic system may contribute to SCD pathophysiology. Changes that have been described include increased expression of tissue factor (TF) on blood monocytes[7–9] and endothelial cells,[10,11] abnormal exposure of phosphatidylserine on the red cell surface,[12,13] and increased microparticles, which both promote activation of the coagulation cascade,[14–16] and high incidence of antiphospholipid antibodies.[17,18] In fact, SCD meets the requirements of the Virchow triad (slow flow, activated procoagulant proteins, and vascular injury); therefore, it should not be surprising that sickle disease is accompanied by thrombosis. Clinical manifestations of the prothrombotic state of patients with SCD include venous thromboembolism (VTE), in situ thrombosis, and stroke.[2,19–22]

In this section, we highlight the existing evidence for contribution of hemostatic system perturbation to SCD pathophysiology. We will also review the data showing increased risk of thromboembolic events, particularly newer information on the incidence of VTE. Finally, the potential role of platelet inhibitors and anticoagulants in SCD will be briefly reviewed.

EVIDENCE FOR INCREASED THROMBOEMBOLIC EVENTS IN SCD

Stroke has an overall prevalence of 3.75% in patients with SCD and 11% in patients younger than 20 years with sickle cell anemia (HbSS), and is most often caused by large vessel arterial obstruction with superimposed thrombosis.[20,23] New and old thrombi in the pulmonary vasculature are prevalent in autopsy series.[21,24,25] The analysis of a large discharge database in Pennsylvania from 2001 to 2006 found that the incidence of pulmonary embolism was 50-fold to 100-fold higher in the SCD population (0.22%–0.52%) than in the general Pennsylvania population (0.0039%–0.0058%).[26] A retrospective study of reported discharge diagnoses showed that patients with SCD younger than 40 years were more likely to be diagnosed with pulmonary embolism compared with African Americans without SCD (0.44% vs 0.12%); however, the prevalence of deep vein thrombosis was similar between the 2 groups.[19] In contrast, in a retrospective study of 404 patients with SCD cared for at the Sickle Cell Center for Adults at Johns Hopkins between August 2008 and January 2012, 25% of the patients had a history of VTE (18.8% non–catheter related), with a median age at diagnosis of 30 years. Sickle cell variant genotypes, such as HbSC or HbSβ^+ thalassemia, were associated with increased risk of non–catheter-related VTE compared with HbSS. A history of non–catheter-related VTE was an independent risk factor for death in adults with SCD.[27]

SCD also appears to be a significant risk factor for pregnancy-related VTE, with an odds ratio of 6.7.[28,29] A retrospective study showed that patients with SCD had more antenatal complications than those with sickle cell trait, without affecting the fetal outcome.[30] Sickle cell trait is generally benign, but one study suggested that sickle cell trait increases the risk of VTE in pregnancy compared with race-matched controls, with an odds ratio of about 2.5. Although in another study of pregnancy, sickle cell trait was associated with pulmonary embolism (PE) rather than deep vein thrombosis.[31] In a recent larger study, investigators could not detect a statistically significant difference