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inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

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MAGiC: VOC remains but kids with SCA appear

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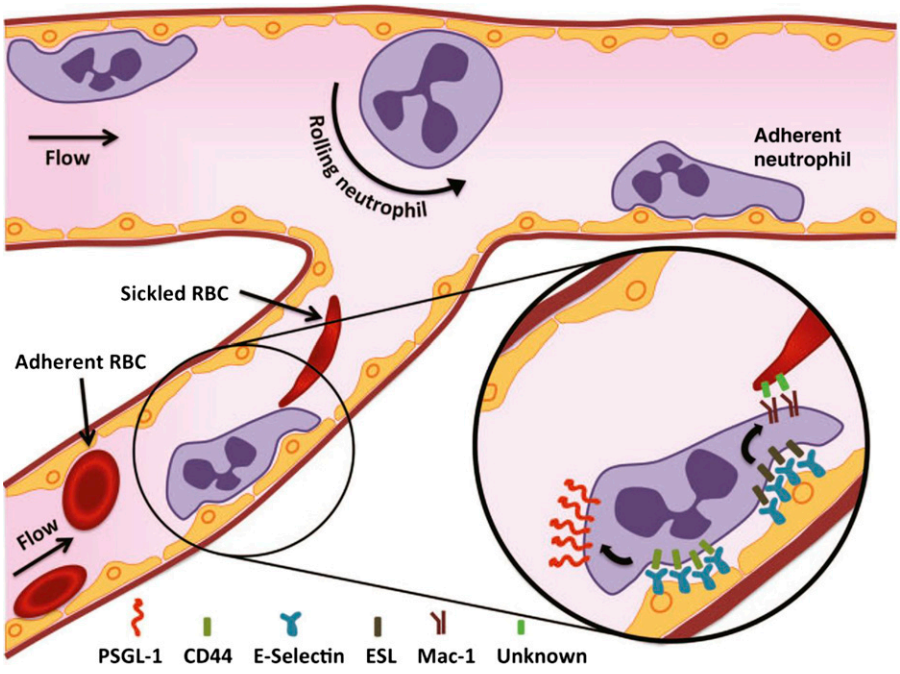
In this issue of *Blood*, Brousseau et al report results from the Magnesium for Children in Crisis (MAGiC; #NCT01197417) trial.[1] This multicenter, double-blind, placebo-controlled trial compared the effects of intravenous magnesium to saline in children with sickle cell anemia (SCA) admitted to the hospital for acute vaso-occlusive pain (VOC). Although magnesium was found to be ineffective, MAGiC illustrates an effective strategy for rapid and efficient patient accrual in pediatric SCA studies.

Sickle cell disease affects nearly 100 000 Americans and is characterized by recurrent vaso-occlusive complications, most commonly episodes of severe pain. Each year, children with SCA (HbSS or HbSβ^0thalassemia) require an average of 1 to 2 emergency room visits and/or hospitalizations to manage painful episodes.[2] Most experts recommend regular prophylactic hydroxyurea administration,[3] which alleviates SCA-related problems but is not fully effective in preventing organ damage or pain.[4]



Pathophysiology of vaso-occlusive crises in SCA. Sickled red blood cells and other inflammatory mediators induce the activation of vascular endothelium. The damaged and stimulated endothelium is poised to recruit leukocytes. E-selectin on the vascular endothelium generates a secondary wave of activating signals, which produces expression of Mac-1 at the leading edge of the crawling neutrophil, facilitating the capture of circulating discoid and sickled red blood cells. Reprinted from Manwani and Frenette[5] with permission.

Erythrocyte sickling triggers a complex pathophysiology that includes neutrophil activation and release of inflammatory mediators and activation of vascular endothelium (see figure). (See a recent review in *Blood* for the pathophysiology of vaso-occlusion in sickle cell disease and discussion of novel therapeutic agents.[5]) Magnesium has long been proposed as a potential therapy for vaso-occlusion. It is reported to have anti-inflammatory and vasodilatory effects, and magnesium is an important regulator of erythrocyte cation transporters with chronic magnesium replacement, potentially improving intracellular hydration of sickle cells and providing a clinical benefit.[6,7] Hence, the MAGiC investigators hypothesized intravenous magnesium would augment standard therapy for acute management of severe VOC pain episodes. The MAGiC trial was a double-blind, randomized, multicenter study, with the primary outcome measure being length of hospitalization from the time of first drug infusion until 12 hours after the last intravenous opioid dose or time of discharge, whichever occurred first. Secondary outcome measures included opioid use, health-related quality of life, and biomarkers of inflammation, hemolysis, and endothelial activation.

The study showed that the median length of hospitalization was similar for magnesium (56.0 hours [range, 27.0-109 hours]) and placebo (47.0 hours [range, 24.0-99.0 hours]) groups ($P = .24$). In post hoc analyses of length of hospitalization, magnesium was not beneficial for children presenting early in the

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course of the pain crisis (1 or no days of pain prior to evaluation), nor was it beneficial for children who were stratified by the number of hospitalizations in the previous 3 years. The secondary end points of opioid use, health-related quality of life and biomarkers, were also similar between the 2 groups. The authors concluded that magnesium is not effective for VOC in children with SCA.

At first glance, MAGiC may be interpreted as a "negative" trial because magnesium infusions did not improve VOC. Although these results are disappointing, an important result and accomplishment of the MAGiC trial is less readily apparent. In particular, the MAGiC team produced a potential solution for a problem that SCD investigators have struggled with for years—MAGiC made participants appear. Since 2008, >15 multi-institutional clinical trials for SCA were closed prematurely due to low enrollment.[8] Failure to enroll an adequate number of subjects in a clinical trial is costly and may expose participants to risks of toxicity without providing the potential benefits of a successful study. With these challenges in mind, the MAGiC team created a unique partnership between Pediatric Hematologists and Emergency Department Physicians in the Pediatric Emergency Care Applied Research Network. Impressively, in 8 medical centers from December 2010 to December 2013, 807 children were screened for eligibility. Of those eligible, 76% (n = 410) were approached, and 39% (n = 214) of children enrolled. On average, the MAGiC team enrolled 1 patient per site per month and completed their enrollment goals in 2 years, a rate of patient accrual that surpasses most other clinical trials for SCA.

Recent insights into the pathophysiology of SCA[5] and mechanisms of globin gene expression promise innovative new therapies,[9,10] which must be vetted efficiently and rapidly in a patient population that has historically been difficult to enroll in clinical trials. The legacy of the MAGiC trial may be its development of an improved model for participant identification, screening, and enrollment based on multidisciplinary collaborative interactions between pediatric health care providers. Adoption of this paradigm for future trials should ultimately benefit individuals with sickle cell disease by magically accelerating the identification of effective new therapies.

Conflict-of-interest disclosure: J.H.E. receives funding support from Daiichi Sankyo and Eli Lilly and Co. ■

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● ● ● LYMPHOID NEOPLASIA

Comment on Bernard et al, page 1695

Is the open mouth mightier than the needle?

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In this issue of *Blood*, Bernard et al provide evidence that ibrutinib, the orally administered inhibitor of Bruton tyrosine kinase (BTK), crosses the blood-brain barrier and has activity against mantle cell lymphoma (MCL) in the central nervous system (CNS).[1]

Over the last decade, several groups have evaluated the incidence and risk factors for CNS involvement by MCL.[2-5] Like diffuse large B-cell lymphoma (DLBCL), roughly 5% of patients with MCL will develop CNS disease. Like DLBCL, patients with the most aggressive MCL biology (eg, blastoid histology, high lactate dehydrogenase, and high Ki67) are most likely to experience CNS relapse, as many as 25% in some reports. Like DLBCL, there is limited evidence in MCL that the choice of primary therapy impacts the incidence of CNS relapse. The use of agents with potential activity against CNS lymphoma, including rituximab, high-dose cytarabine, methotrexate, and autologous stem cell transplantation, was not associated with a reduced risk of CNS involvement in 3 retrospective series, although the dosing of methotrexate may have been suboptimal for CNS penetration, and the use of prophylactic intrathecal therapy was not reported.[2,4,5] Finally, like DLBCL, the survival of people that experience CNS progression of MCL is typically poor despite subsequent administration of CNS-directed intravenous or intrathecal therapies (see figure). However, MCL and DLBCL are biologically distinct entities, and there are important differences with respect to CNS involvement. Unlike DLBCL, which tends to relapse in the brain parenchyma within the first 6 months of diagnosis, the average time to progression of MCL in the CNS, often with leptomeningeal disease, is typically >1 year from diagnosis and frequently occurs after multiple prior lines of therapy. Unlike DLBCL, regardless of location, MCL is not curable.

Recent reports of oral agents with newly discovered activity against CNS lymphomas

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