partly attributed to treatment duration and baseline patient characteristics. Thus, higher drug doses may be required if more clinically meaningful reductions are to be achieved. This brings us to the main advantage of this drug, a favorable safety profile that may permit trials of higher doses. First, the drug was not associated with any reductions in absolute neutrophil counts or rashes, which are noted with deferiprone and deferasirox therapy, respectively.[4] Second, treatment was associated with a lower incidence of most gastrointestinal side effects compared with that reported with deferasirox therapy in core trials.[6] Although gastrointestinal side effects attributed to deferasirox therapy are often mild and transient, the effect on patient compliance cannot be dismissed. Third, FBS0701 treatment was not associated with dose-dependent changes in serum creatinine. Fluctuations in serum creatinine level with deferasirox therapy have been a subject of concern. Although reports of overt renal impairment fail to provide convincing causal evidence and were mainly observed in elderly patients with several comorbidities,[7] mild, dose-dependent increases in serum creatinine were observed in 38% of patients receiving deferasirox at doses of 20 to 30 mg/kg per day.[5] These increases were sometimes transient, mostly within the normal range, and did not exceed twice the upper limit of normal. Safety data with deferasirox in TM children and adults have now been reported for up to 5 years of treatment and confirm absence of progressive increases in serum creatinine over longer-term treatment,[8] even in heavily iron-loaded patients who require dose escalation to > 30 mg/kg per day.[9] Even so, one cannot disregard the promising opportunity of FBS0701 for absolute renal safety. The other controversial concern with existing oral chelators is the effect on hepatic function and histology. With all fairness, data presented on FBS0701 cannot yet be interpreted, because 3 of 8 patients showing elevations in liver enzymes acquired hepatitis C virus infection through an unknown cause while on the study drug.

What should we expect next from FBS0701? The extensive clinical trial program devised for deferasirox should be a lead example for any iron chelator hoping to establish its efficacy and safety in the management of transfusional iron overload, especially in an era of evidence-based health care. The efficacy and safety of the drug at higher doses should be established and compared with available chelators in different disease and age subgroups. More importantly, the ability to chelate iron from the heart should be promptly investigated and compared with the remarkable success of deferiprone and its combination with DFO,[10] as well as emerging evidence from deferasirox.[11] Lastly, a favorable cost-effectiveness profile needs to be demonstrated before the drug becomes widely used, especially in developing countries where hemoglobinopathies are common yet resources are poor.

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REFERENCES

1. Neufeld EJ, Galanello R, Viprakasit V, et al. A phase 2 study of the safety, tolerability, and pharmacodynamics of FBS0701, a novel oral iron chelator, in transfusional iron overload. *Blood*. 2012;119(14):3263-3268.
2. Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica*. 2004;89(10):1187-1193.
3. Gabutti V, Piga A. Results of long-term iron-chelating therapy. *Acta Haematol*. 1996;95(1):26-36.
4. Musallam KM, Taher AT. Iron chelation therapy for transfusional iron overload: a swift evolution. *Hemoglobin*. 2011;35(5-6):565-573.
5. Cappellini MD, Cohen A, Piga A, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. *Blood*. 2006;107(9):3455-3462.
6. Vichinsky E. Clinical application of deferasirox: practical patient management. *Am J Hematol*. 2008;83(5):398-402.
7. Ponticelli C, Musallam KM, Cianciulli P, Cappellini MD. Renal complications in transfusion-dependent beta thalassaemia. *Blood Rev*. 2010;24(6):239-244.
8. Cappellini MD, Bejaoui M, Agaoglu L, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. *Blood*. 2011;118(4):884-893.
9. Taher A, Cappellini MD, Vichinsky E, et al. Efficacy and safety of deferasirox doses of >30 mg/kg per d in patients with transfusion-dependent anaemia and iron overload. *Br J Haematol*. 2009;147(5):752-759.
10. Galanello R, Agus A, Campus S, Danjou F, Giardina PJ, Grady RW. Combined iron chelation therapy. *Ann N Y Acad Sci*. 2010;1202:79-86.
11. Pennell D, Porter JB, Cappellini MD, et al. Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with beta-thalassemia major [published online ahead of print January 22, 2012]. *Haematologica*. doi:10.3324/haematol.2011.049957.

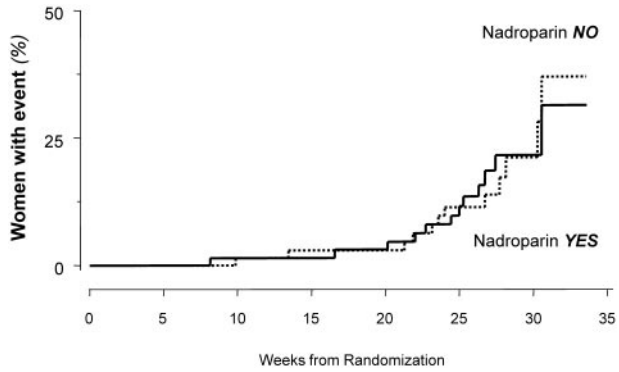
● ● ● CLINICAL TRIALS

Comment on Martinelli et al, page 3269

Evidence over hope for pregnancy complications

Ian A. Greer UNIVERSITY OF LIVERPOOL

Low molecular weight heparins are widely used to try to prevent pregnancy complications. In this issue of *Blood*, Martinelli and colleagues report a critical randomized trial that demonstrates no efficacy from such treatment.[1]



Women with primary composite outcomes during the observation period according to treatment arm. See Figure 2 in the article by Martinelli et al on page 3269 of this issue.[1]

Obstetricians are frustrated by the lack of effective interventions to prevent late complications of pregnancy such as pre-eclampsia, fetal growth restriction (FGR), and abruption. Despite considerable research over many years, no definitive cause has been

identified for these problems, which are likely to be heterogeneous in origin, but manifest through common pathophysiologic processes; specifically, disturbance of the hemostatic system and inadequate placentation. For example, in preeclampsia we have known for almost half a century that there is coagulation activation, thrombin generation, microvascular fibrin deposition, endothelial dysfunction, disturbed trophoblast invasion of the maternal circulation, and placental infarction.[2] Indeed this knowledge led to antiplatelet therapy with low-dose aspirin being introduced in the 1980s with a modest effect (~ 15%) in preventing preeclampsia and FGR.[3] However, these conditions remain major challenges affecting approximately 10% of pregnancies, with major contributions to both maternal and perinatal morbidity and mortality.

In antiphospholipid syndrome similar hemostatic changes and placental infarcts are seen. This is manifest clinically not only by the late pregnancy problems of preeclampsia, FGR, and abruption, but also by recurrent miscarriage. The latter problem is responsive to antithrombotic intervention with low-dose aspirin and heparin.[3] Further, women with acquired or heritable thrombophilia are more likely to develop preeclampsia and FGR, although the risk may be overestimated from retrospective case-control and cohort studies as prospective investigations have not confirmed these findings.[3] Nonetheless, a logical conclusion from these data was that antithrombotic interventions may prevent late pregnancy complications. The increasing awareness of the association between thrombophilia and late pregnancy complications, and the lack of alternative treatment, led obstetricians to use low molecular weight heparins (LMWHs), which are safe in pregnancy,[3,4] for prevention and treatment of these conditions. This practice, driven by the lack of effective therapy, was based on extrapolation, with the hope and anticipation that subsequent supportive evidence would emerge. Trials were therefore urgently required to test the hypothesis that such treatment was actually effective.

Martinelli et al report the first large, well-designed, multicenter, prospective, randomized trial to examine Heparin in pregnant women with Adverse Pregnancy outcome to improve the rate of successful PregnancY (the HAPPY trial).[1] They compared event recurrence in 135 women, after screening 250, considered at increased risk because of previous late pregnancy complications. The women were randomized to treatment with a LMWH (nadroparin) in addition to medical surveillance, or to medical surveillance alone. The difficulty in conducting these trials should not be underestimated given the demand from women for an active intervention, the frustration felt by obstetricians because of the lack of an effective therapy, and the now widespread nonevidenced-based use of LMWH for pregnancy complications. Despite the commendable perseverance of the researchers, after 3 years only 50% of the planned study participants had been recruited and the trial was stopped by reason of futility. Overall, 21% of participants randomized to active treatment developed a combined end point compared with 18% of controls. This is a nonsignificant event risk difference of 2.2 (95% CI: −11.6 to 16.0). The distribution of the single components of the composite end point (preeclampsia, eclampsia, HELLP [Hemolysis Elevated Liver enzymes and Low Platelets] syndrome, FGR, intrauterine fetal death, and abruption) was also similar. There were no serious adverse events associated with LMWH.

These data show that nadroparin has no impact in preventing these conditions (see figure). This is in agreement with other reports including a systematic review of several heterogeneous studies of LMWH for women with late pregnancy complications,[5] and is also consistent with 2 recent large, randomized trials that showed no benefit from LMWH and low-dose aspirin in women with recurrent pregnancy loss.[6,7] The results of these large, methodologically sound trials may differ from smaller, methodologically limited or pilot studies,[3,8] thus emphasizing the critical importance of an adequate evidence base to avoid the premature adoption of potential new interventions into clinical practice. Such interventions might still prove effective in specific subgroups, such as those with thrombophilia, but this cannot be assumed and specific trials are required, some of which are under way.

In the meantime we should learn the lesson of premature acceptance of hypothetically beneficial treatment into routine clinical practice. This is important, not only to reduce cost in already challenged health care services, but also to protect our patients from unnecessary risk, and specifically to protect women suffering such devastating pregnancy complications from iatrogenic false hope.

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REFERENCES

1. Martinelli I, Ruggenenti P, Cetin I, et al. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood*. 2012;119(14):3269-3275.

2. Greer IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet*. 1999;353(9160):1258-1265.

3. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis (9th Ed): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e691S-e736S.

4. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005;106(2):401-407.

5. Dodd JM, McLeod A, Windrim RC, Kingdom J. Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. *Cochrane Database Syst Rev*. 2010;CD006780.DOI: 10.1002/14651858. CD006780.pub2.

6. Clark P, Walzer ID, Langhome P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low dose aspirin in women with recurrent miscarriage. *Blood*. 2010;115(21):4162-4167.

7. Kaandorp SP, Goddijn M, van der Post JAM, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med*. 2010;362(17):1586-1596.

8. Rey E, Garneau P, David M, et al. Dalteparin for the prevention of recurrence of placental mediated complication of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *J Thromb Haemost*. 2009; 7(1):58-64.

● ● ● LYMPHOID NEOPLASIA

Comment on Xi et al, page 3330

BRAF mutation: supporting diversity in HCL

Jan A. Burger MD ANDERSON CANCER CENTER

In this issue of *Blood*, Xi and colleagues report on v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations in hairy cell leukemia (HCL) subsets, demonstrating that BRAF V600E mutations are absent in variant HCL forms and in a subset of classic HCL (HCLc).[1]