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. Second, treatment was associated with a lower incidence of most gastrointestinal side effects compared with that reported with deferasirox therapy in core trials. 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, 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. 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, even in heavily iron-loaded patients who require dose escalation to >30 mg/kg per day. 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, as well as emerging evidence from deferasirox. 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
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. 3 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 abortion, 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 anti-thrombotic therapy 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**


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**BRAF mutation: supporting diversity in HCL**

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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

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**Comment on Xi et al, page 3330**
Evidence over hope for pregnancy complications

Ian A. Greer