

diagnosis one major cytogenetic defect, mostly del(13q), del(20q), or partial trisomy 1q.³ IM, however, is not characterized by any "unique" chromosomal abnormality. As such, the chromosomal abnormalities found to be associated with IM are considered secondary genetic events in the multistep progression of a disease whose primary genetic cause, the IM locus, is still to be identified.

The genes that are currently under investigation as candidates for the IM locus are represented by classic tumor suppressor genes, such as the retinoblastoma (*RBI*)⁴ and the *p53* genes or the *p16* gene and the *RAS* family of proto-oncogenes.^{5,6} Alternatively, genes that are involved in the control of proliferation of early hematopoietic cells, such as stem cell factor (*SCF*) and its receptor *c-kit*, and elements of the b-fibroblast growth factor (*b-FGF*) pathway⁷ are also being considered. Among those, *SCF/c-kit* are slightly favored because of the observation that the progenitor cells circulating in myeloproliferative disorders present both elevated expression⁸ and point mutation^{9,10} of *c-kit*. However, none of the many mouse mutants in the *SCF* and *c-kit* locus available has been described up to now to develop myelofibrosis. Furthermore it is not clear how any of these genes would specifically induce the abnormalities in the E and Mk pathway, which are the landmarks of the disease.

Hypothesis-driven research has suggested genes in the thrombopoietin (TPO) pathway, the growth factor which specifically regulates Mk production in vivo,¹¹ as possible candidates for the IM locus. This hypothesis gained considerable favor when it was demonstrated that IM can be experimentally induced in mice by in vivo manipulation of the levels of TPO.¹²⁻¹⁴ However, a later study failed to find autocrine TPO production or mutations in the TPO receptor (*Mpl*) gene in 14 cases of human IM,¹⁵ leaving the relationship between possible presence of alterations in the TPO/*Mpl* pathway and the increased numbers of Mk observed in these patients still to be ascertained.

GATA-1 is a gene specifically involved in the regulation of the number of both E and Mk in vivo.¹⁶ Our paper,¹⁷ showing that *GATA-1*^{low} (*GATA-1*^{Im2Sho}) mutant mice develop a frank myelofibrotic syndrome with age, opens the possibility that genes involved in *GATA-1* function might be directly responsible for the development of the disease. The letter by Martyré et al, showing that CD34⁺ cells circulating in the patients express lower levels of *FOG-1* (one of the *GATA-1* obligatory partners), further encourages research in this direction. Both reports are far away from having identified the IM locus. In fact, since the mouse develops IM very late in life, it is possible that in this case the *GATA-1*^{low} mutation has a permissive role by inducing the hyper-proliferation of the progenitor cells that allows them to accumulate secondary mutations. On the other hand, since the letter by Dr Martyré et al does not provide any evidence for genetic abnormalities in the *FOG-1* locus, it is possible that the alterations it describes are pleiotropic to an underlying genetic defect.

It must be said that many excellent experimental papers on the pathophysiology of IM have been recently published. Among those, especially worthy of mention is the report that forced expression of *TPO* transforms normal, but not transforming growth factor- β ^{null} (*TGF- β ^{null}*), stem cells into IM-inducing clones.¹⁸ All

the data that are being accumulated, plus the existence of national and international registries of the disease, which have been carefully established in the mean time, raise great hope that by unifying the experimental efforts we might be finally very close to grasp the etiology of human IM.

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To the editor:

Deferiprone and hepatic fibrosis

We write to request that Wanless and colleagues correct the record on the efficacy and safety of deferiprone for treatment of transfusional iron overload by providing the data on hepatic iron omitted

from their publication in *Blood*.¹ This rectification would document the failure of deferiprone therapy to prevent iron accumulation in thalassemia major and make evident the inherent bias against

detecting deferiprone-induced progression of hepatic fibrosis in their retrospective, nonrandomized, and uncontrolled study.

In a poster presentation at the 42nd annual meeting of the American Society of Hematology but not in the published abstract,² these authors reported assessment of hepatocellular and macrophage iron using an unspecified modification of the method of Deugnier et al.³ Over a mean duration of deferiprone therapy of 3 years or more, mean hepatocellular and hepatic macrophage iron scores rose significantly and substantially in all patients, either with or without antibodies to hepatitis C virus. The greatest increase was the 85% elevation in hepatocellular iron score in patients without antibodies to hepatitis C (from 3.2 ± 1.6 to 5.9 ± 1.09 , $P < .0002$, on a scale from 0 to 8); other increases ranged from 32% to 43%. These results, not included in the published paper,¹ add to the evidence that deferiprone does not adequately control the body iron burden in many patients with thalassemia major.⁴

More importantly, the failure of Wanless et al¹ to include the hepatic iron data obscures the marginal power of their study to detect deferiprone-induced progression of hepatic fibrosis. The original report by Olivieri et al⁴ of the potential risk of exacerbation of hepatic fibrosis emphasized that deferiprone had stabilized or decreased the hepatic iron in all patients with a worsening of fibrosis; no patient with an increase in hepatic iron had progression of fibrosis. If we consider only those patients with biopsies judged as adequate by at least 2 of the 3 pathologists in Wanless et al,⁴ informative data were available from only 34 (or 18%) of the 187 patients originally entered into the study. Because the hepatic iron must have risen significantly in many or most of these patients, few would have had liver iron stabilized or diminished with deferiprone and been at apparent risk for acceleration of hepatic fibrosis. The cruel dilemma posed by deferiprone seems to be that the drug is either ineffective in controlling iron accumulation or, if active in stabilizing or decreasing the body iron, may carry a risk of promoting hepatic fibrosis. These divergent effects may relate to rates of inactivation of deferiprone by hepatic glucuronidation in different patients.

Response:

Deferiprone and the treatment of iron overload

We are delighted to respond to each of the points raised by Brittenham et al in regard to our paper reporting the lack of an association between deferiprone and hepatic fibrosis in patients with thalassemia major. Although Brittenham et al ask us to “correct the record,” we believe the record needs no such correction and that our findings will help many physicians who seek alternative forms of chelation therapy for patients who have failed to control their iron stores adequately with deferoxamine.

First, our study of hepatic fibrosis was designed to address a safety concern originally reported in a small, retrospective, nonrandomized, and uncontrolled study¹ and repeated by Dr Olivieri in scientific meetings, in letters to regulatory agencies, and in the press. Our study was not designed to assess the effectiveness of deferiprone; several recent studies have shed important new light on this subject.^{2,3} The hepatic iron data included in the poster at the annual meeting of the American Society of Hematology⁴ were based on Perl staining of biopsies, a method that Brittenham et al would surely agree is inappropriate for the formal assessment of iron stores, especially when the tissues were stained several years

Finally, the claim by Wanless et al that there is “no reason to believe that there was bias in selection of patients who were biopsied”¹ is disingenuous. Entry into the study required either serum ferritin level higher than 2000 $\mu\text{g/L}$ or liver iron level higher than 4 mg/g dry weight. Most of the patients who initially underwent hepatic biopsy were from the site in Turin, where all study patients were biopsied and most had been previously well-chelated with deferoxamine. In the 2 other Italian sites, biopsies were performed, with 2 exceptions, only in patients with serum ferritin level lower than 2000 $\mu\text{g/L}$; no patients in the United States underwent biopsy. Thus, far from being representative, the 18% of patients with a liver biopsy yielding a specimen adequate for evaluation almost certainly consists disproportionately of patients previously well-chelated with deferoxamine. We do not know how such selection of patients with an initially lower iron burden may influence the risk of deferiprone-induced acceleration of hepatic fibrosis.

Unfortunately, almost 5 years after the original report of the potential risk, “before deferiprone can be considered for clinical use, even in patients who are unwilling or unable to use deferoxamine in standard regimens, prospective clinical trials are mandatory to evaluate the possibility of irreversible hepatic damage.”⁴

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apart. Indeed, Brittenham has previously described histologic assessment of liver iron stores as “semiquantitative at best.”⁵ He added, “Comparison of histologic with chemical determination of iron in bone marrow or liver shows a substantial amount of overlap in iron concentrations between the histological grades...The amount of iron in those assigned to the highest grade may vary by a factor of 10 or more.”

Second, Brittenham et al propose the unorthodox concept that deferiprone causes hepatic fibrosis in patients in whom the chelator stabilizes or reduces iron stores but not in patients with increasing iron stores. They derive this concept from the finding in the previous study by Olivieri et al in which 5 patients with worsening fibrosis had stable or decreasing hepatic iron concentrations, while “no patient with an increase in hepatic iron had progression of fibrosis.”¹ However, a close look at Table 3 and Figure 1 of that paper may explain why the authors could not find fibrosis among patients with increasing iron stores. Of the 14 patients included in the evaluation of hepatic histology, 13 appear to have had stable or decreasing iron stores; only one patient had increasing iron stores.

This distribution precludes any conclusions about the relationship between changes in iron stores and potential toxicity of deferiprone. In proposing a “cruel dilemma” that has no scientific underpinning, Brittenham et al miss the truly cruel dilemma for patients with thalassemia: In the absence of chelation therapy, iron that comes from lifesaving transfusion therapy causes life-threatening damage to the liver and other organs.

Third, we agree that it is impossible to demonstrate with absolute certainty the absence of a selection bias in our study or, for that matter, in the much smaller study by Olivieri et al in which biopsies were analyzed in only 14 of 21 patients treated with deferiprone and 12 of 20 patients treated with deferoxamine.¹ Brittenham et al suggest that the patients in our study who underwent biopsy may have had less severe iron overload than the remainder of the group, and, by implication, may have been less susceptible to potentially toxic effects of deferiprone. Having previously invoked the duration of follow-up and the theory of protection of increasing iron stores as reasons to disregard the absence of an association between deferiprone and liver fibrosis in our study, Brittenham et al now put forth a third unsubstantiated explanation, that is, less severe iron overload. We continue to believe that the most likely explanation for our findings is that deferiprone does not cause liver fibrosis.

Finally, Brittenham et al believe that deferiprone should not be given to patients with thalassemia, even if they are “unable or unwilling to use deferoxamine.” Given the absence of an alternative chelator at present, this approach means no chelation and virtually certain iron-related morbidity and mortality for patients who are not using deferoxamine effectively. We respectfully disagree with this approach, and we believe that physicians in most major thalassemia centers would disagree as well. Most impor-

tantly, we strongly believe that the best way to address the issues surrounding deferiprone and to be fair to the patients, who are, after all, the major stakeholders in this debate, is to focus on the science and to encourage the unfettered and dispassionate exchange of scientific views.

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To the editor:

Donor serostatus and CMV infection and disease among recipients of prophylactic granulocyte transfusions

We read with interest the recent report by Vij and colleagues,¹ in which they suggested that the cytomegalovirus (CMV) serostatus of the donor has no impact on CMV viremia or disease when 2 prophylactic granulocyte transfusions are given to allogeneic stem cell transplant recipients (on day +3 and +6 or +5 and +7). Patients in this study were allocated to receive granulocyte transfusions (or not) according to “biologic” randomization, namely, the availability of an ABO-compatible, HLA-matched sibling donor. Thus, the granulocyte donor for these patients was the same HLA-matched sibling who served as the allogeneic peripheral blood stem cell (PBMC) donor. In the subgroup of primary interest (CMV-seronegative recipients of stem cells from seropositive donors [D+/R-], patients who are at risk for primary infection from this approach), those who received granulocyte transfusions had similar rates of CMV viremia (5 of 15; 33%) when compared to those who did not receive granulocytes (8 of 26; 30.8%). Rates of CMV disease appeared to be higher in the granulocyte arm (2 of 15; 13.3%) than in the standard arm (1 of 26; 3.8%), though not significantly so. The authors conclude that the approach is therefore safe.

Closer inspection of their findings, however, may be needed. It is particularly important to note the limited setting to which these conclusions may apply, namely, the use of 2 prophylactic granulo-

cyte transfusions from the same matched sibling donor who provided the PBSC product. The study does raise the possibility that there simply are blood donors who transmit CMV (via the stem cell allograft, granulocyte, or other blood product) and those who do not, a hypothesis that is supported by the near-identical primary infection rate in the 2 groups. One possible explanation would be that a critical viral load in the stem cell and/or granulocyte product is required for CMV transmission, and this variable is relatively stable in the same donor for 1-2 weeks (the time period between stem cell donation and the 2 prophylactic granulocyte donations). While this may be true, one also must consider that external triggers may make immunocompetent donors transiently viremic,² which could theoretically place the CMV-seronegative recipient at risk even when the same donor is used for both the stem cell product and the granulocyte products. Unfortunately, the application of current technology (such as highly sensitive polymerase chain reaction for CMV DNA) has not permitted identification of those donors (or those products) who are more likely to transmit.³

The conclusions drawn in this study are thus not generalizable to the population suitable for therapeutic granulocyte transfusions, whose numbers are potentially much larger and who increasingly rely on unrelated granulocyte donors.⁴ This is because the frequency of granulocyte transfusions and the number of different donors used in the