Response:

The role of γδ T cells in graft-versus-host disease

Anderson et al are right to remind us of the important limitations of mouse models in the dissection of complex graft-versus-host disease (GVHD) biology, particularly when results from different models conflict. Although our conclusions that host γδ T cells regulated intestinal acute GVHD are also supported by another group, we agree with Anderson and colleagues’ elegant summary of potential causes for discrepancies between the models. We were unaware of their work prior to the submission of our manuscript, and we did not examine the role of host γδ T cells in minor histocompatibility antigen–mismatched strain combinations. Since GVHD of the skin dominates their model, their data might be reconciled with ours if host γδ T cells contribute to the inflammation of intestinal acute GVHD but not to fibrotic skin changes characteristic of chronic GVHD. In any event, we wholeheartedly concur that all insights from animal models must be extrapolated to human patients with caution, and that the efficacy of any approach must be verified in well-designed, carefully controlled clinical trials.

To the editor:

Assessing the risk of inhibitor formation with different factor VIII products

The article by Goudemand et al dealing with the influence of different types of factor VIII (FVIII) concentrates on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A is interesting and timely. The authors retrospectively analyzed 2 previously reported cohorts that had been treated with plasma-derived (pd) FVIII or recombinant (r) FVIII, updating the cohorts with a few additional patients not included in the previous publications. The perusal of this article leaves me with some questions that warrant comments from the authors.

The main question deals with the validity of comparing inhibitor incidence in very different cohorts. Although the authors state that the interval of inhibitor testing was similar for the 2 cohorts, 13 (23%) of 56 patients from the cohort treated with pdFVIII were actually tested only once per year, whereas patients from the rFVIII cohort were tested every 3 months (84%) or every 6 months (16%). This difference in frequency of inhibitor testing is critical, because more frequent testing is more likely to detect transient or low-titer inhibitors that may be of little clinical relevance but impinge upon inhibitor incidence. Indeed, previously untreated patients included in studies carried out to license FVIII products (and thus frequently assessed for inhibitors) demonstrate a more than 3-fold higher incidence of inhibitors than patients treated in the frame of postlicensure studies. Nevertheless, the Kaplan-Meier analysis carried out by Goudemand et al considers patients tested only annually as not having developed an inhibitor up to the first year. Another questionable point is that in 10 patients of the pdFVIII cohort treated before 1991, the quantitative Bethesda inhibitor assay was used only to confirm inhibitors suspected on the basis of a semiquantitative test based upon the partial thromboplastin time, whereas all the rFVIII-treated patients were evaluated from the onset using the Bethesda assay. Considering these differences, the adjusted relative risk of inhibitor formation calculated by the authors may be substantially biased in favor of pdFVIII treatment.

Despite these limitations, the study of Goudemand et al and other smaller retrospective studies hint that there may be a difference between different types and source of FVIII in determining the occurrence of inhibitors in previously untreated patients with hemophilia A. However, only prospective controlled studies can truly address this issue. Such studies are certainly warranted, and regulatory authorities such as the Food and Drug Administration (FDA) in the United States and the European Agency for the Evaluation of Medicinal Products (EMEA) should prompt FVIII manufacturers to tackle this issue.

References


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In his letter, Dr Mannucci refers to 2 historical French cohorts of previously untreated patients (PUPs) with severe hemophilia A: one treated with a French plasma-derived FVIII concentrate (FVIII-LFB) between 1988 and 1993 (first pdFVIII), the other with one brand of recombinant FVIII (rFVIII) between 1991 and mid-1997. These 2 cohorts were updated in 2002 according to criteria defined in our study, including the intron 22 inversion test (not required in the first pdFVIII cohort) and inhibitor detection based only on the Bethesda method. This resulted in the exclusion of several patients from the original cohorts, especially from the first pdFVIII cohort. Also, other patients treated for the first time with FVIII-LFB after 1993 or rFVIII after mid-1997 were added. Thus, the current 2 cohorts of patients reported in our paper are partly different from the previous ones published in 1995 and 1998.

Mannucci refers to the possibility of a differential misclassification bias related to less-frequent detection of inhibitor in the group of patients receiving pdFVIII. The frequencies of inhibitor testing reported in our study are not those of the historical studies quoted by Mannucci. As shown in Table 1, the frequency of inhibitor testing in the FVIII-LFB cohort increased compared with the study published in 1995 (probably due to the gradually increasing attention paid by the clinicians to these aspects of 1992-1993) and decreased in the rFVIII cohort compared with the study published in 1998. This reduced the difference between the pdFVIII and the rFVIII cohorts in particular, if one considers the mean interval per patient between 2 inhibitor tests expressed in cumulative exposure days (CEDs): a median of 5.4 (25th-75th percentile, 4.0-7.4) in the FVIII-LFB cohort versus a median of 5.2 (25th-75th percentile, 3.5-7.4) in the rFVIII cohort, median values that are almost identical. The difference persists for the mean interval of time per patient between 2 tests: a median of 4.4 months (25th-75th percentile, 3.3-6.3 months) in the FVIII-LFB cohort versus a median of 3.2 months (25th-75th percentile, 2.4-4.5 months) in the rFVIII cohort. However, the periodicity of inhibitor detection based on the number of CEDs appears more relevant and has been adopted in the course of the most recent prospective clinical trials. The information bias pointed out by Mannucci is thus possible, but its intensity is undoubtedly less than the figures quoted in his letter would imply, as they do not apply to the current cohorts. The convergence of the analysis of the 3 endpoints (“all inhibitors,” “high inhibitors,” and “high inhibitor and/or ITI”) allows us to conclude that in this study the frequency of inhibitors was approximately 2.5 times higher in the group of patients treated with rFVIII than in those treated with a pdFVIII (FVIII-LFB).

We agree that randomized studies between (some) pdFVIII and rFVIII would be a more convincing design, but such studies may be long and difficult to set up. In addition, no epidemiologic study alone would be able to demonstrate the causality of association between inhibitor incidence and the type of cohorts. Thus, it would be more suitable and efficient to investigate by experimental in vitro studies or animal models on the endpoints (“all inhibitors,” “high inhibitors,” and “high inhibitor and/or ITI”) allows us to conclude that in this study the frequency of inhibitors was approximately 2.5 times higher in the group of patients treated with rFVIII than in those treated with a pdFVIII (FVIII-LFB).

We agree that randomized studies between (some) pdFVIII and rFVIII would be a more convincing design, but such studies may be long and difficult to set up. In addition, no epidemiologic study alone would be able to demonstrate the causality of association between inhibitor incidence and the type of cohorts. Thus, it would be more suitable and efficient to investigate by experimental in vitro studies or animal models on the main explanations for this difference; possibilities include differences in von Willebrand factor, transforming growth factor β (TGFB), or some unknown factor. Such investigations may help to consider the development of new recombinant concentrates whose level of risk would be equivalent to that of plasma-derived concentrates.

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References

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