at the last injection. However, according to Dasgupta et al, VWF protects FVIII from endocytosis by human dendritic cells and subsequent presentation to FVIII-specific T cells.[4] If VWF provides protection during the initiation of treatment, this analysis option underestimates the rFVIII/pdFVIII RR and, by the same mechanism, could hinder study of the effect of VWF concentration. Chalmers et al took into account the appearance of inhibitors within the first 50 CEDs and studied the effects of the initial FVIII treatment.[3] If patients changed product before 50 CEDs (which is probable), the difference between the treatments could also have been underestimated. Using a nonexperimental approach, we think that the best strategy is to consider product type as a fixed cofactor and to not take into account follow-up after the first switch. Secondly, in the CANAL study, the patients received 23 different pdFVIIIs, including 1201 CEDs to Beriate,[1] which represents 38% of the CEDs to pdFVIII "containing considerable quantities of VWF."[1] However, this product has very low VWF concentration (0.09 IU/IU FVIII),[5] and it appears that the immunoprotective effect of VWF is concentration dependent.[4] Furthermore, in FVIII knockout mice, this product was as immunogenic as 2 first-generation rFVIII products.[5] Thus, this pdFVIII could be associated with a particular immunogenicity, and it would be interesting to perform a sensitivity analysis excluding patients having received it in the rFVIII/pdFVIII comparison and to include testing of the classification of Beriate with pdFVIII products with low VWF content to study the effect of VWF concentration. The possibility that certain pdFVIII products could be less immunogenic and, most importantly, identification of the physiopathological mechanisms of these possible differences remain major issues for the development of new FVIIIs.

Thierry Calvez, Yves Laurian, and Jenny Goudemand

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Jenny Goudemand, Hematology Institute, Cardiology Hospital, Boulevard du Professeur Leclercq, 59037 Lille Cedex, France; e-mail: j-goudemand@chru-lille.fr.

References

1. Gouw SC, van der Bom JG, Auerswald G, et al. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study. Blood. 2007;109:4693-4697.
2. Goudemand J, Rothschild C, Demiguel V, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. Blood. 2006;107:46-51.
3. Chalmers EA, Brown SA, Keeling D, et al. Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. Haemophilia. 2007;13:149-155.
4. Dasgupta S, Repesse Y, Bayry J, et al. VWF protects FVIII from endocytosis by dendritic cells and subsequent presentation to immune effectors. Blood. 2007; 109:610-612.
5. Behrmann M, Pasi J, Saint-Remy JM, et al. Von Willebrand factor modulates factor VIII immunogenicity: comparative study of different factor VIII concentrates in a haemophilia A mouse model. Thromb Haemost. 2002;88:221-229.

Response:

Plasma-derived or recombinant factor VIII products and inhibitors in previously untreated patients with severe hemophilia

We appreciate the letter by Calvez et al and we agree that analytic decisions affect the findings from studies. Calvez et al propose 2 explanations for the observed differences between the findings of the study by Goudemand et al,[1] the study by Chalmers et al,[2] and our analyses of the Concerted Action on Neutralizing Antibodies in severe hemophilia A (CANAL) study.[3] It was suggested that we found a smaller effect from recombinant products as opposed to plasma-derived products because we misclassified the exposure days of patients who received Beriate. Calvez et al proposed that Beriate should not have been included in the high–von Willebrand factor group. To examine this possibility, we repeated our analyses after excluding all 32 patients who had been treated with Beriate. In accordance with our previous findings, we found that patients on recombinant factor VIII products have the same risk as the patients on plasma-derived products with high–von Willebrand factor content (Table 1). Thus, Beriate did not explain the difference between our findings and the ones from Goudemand et al.[1]

Table 1. Relative rate of developing inhibitory antibodies against factor VIII in severe hemophilia A patients receiving recombinant factor VIII products as compared to plasma-derived factor VIII products

	RR (95% CI)
All patients*	N=322
Crude relative rate	1.0 (0.5-1.7)
Adjusted relative rate	1.2 (0.7-2.1)
Exposure days on Beriate excluded	
Crude relative rate	0.9 (0.5-1.6)
Adjusted relative rate	1.1 (0.6-2.0)
Exposure days after switch of product excluded	
Crude relative rate	1.3 (0.7-2.4)
Adjusted relative rate	1.5 (0.8-3.0)
Beriate and postswitch exposure days excluded	
Crude relative rate	1.3 (0.6-2.7)
Adjusted relative rate	1.4 (0.6-2.9)

*For recombinant F VIII compared with plasma-derived products with high VWF content.

High von Willebrand factor concentration was defined as more than 0.01 IU VWF antigen per IU factor VIII antigen.

RR indicates relative rate; CI, confidence interval; and VWF, von Willebrand factor.

The other explanation concerned the fact that we had considered the factor VIII product as a time-varying variable, implying that the patients on plasma-derived products who switched to recombinant products during follow-up contribute their early exposure days to the plasma-derived group, and, immediately after the switch, they contribute exposure days to the recombinant product group. To evaluate this possibility, we excluded all postswitch exposure days and again repeated our analyses. The findings confirmed that the risk of inhibitors is not clearly increased in patients who received recombinant products as opposed to plasma-derived products with high–von Willebrand factor content (Table 1). In the table, we also present the findings of the CANAL study in the subgroup of patients who did not receive Beriate and whose exposure days are censored after switching from one product to another.

We have shown that the proposed explanations for differences between our study and the study by Goudemand et al[1] do not hold. Two other explanations could be the subject of future research:

(i) other risk factors for inhibitors, such as intensity of treatment,[4] may have confounded the study by Goudemand et al[1]; (ii) some plasma-derived products indeed confer a lower risk of inhibitors. Yet, it seems unlikely that von Willebrand factor is a major player in this.

Johanna G. van der Bom, Samantha C. Gouw, and H. Marijke van den Berg

Correspondence: Johanna G. van der Bom, Department of Clinical Epidemiology, Leiden University Medical Center and van Creveldkliniek/Department of Hematology, University Medical Center Utrecht, The Netherlands; e-mail: j.g.vanderbom@lumc.nl.

References

1. Goudemand J, Rothschild C, Demiguel V, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. Blood. 2006;107:46-51.
2. Chalmers EA, Brown SA, Keeling D, et al. Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. Haemophilia. 2007;13:149-155.
3. Gouw SC, van der Bom JG, Auerswald G, Escuriola EC, Tedgard U, van den Berg HM. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study. Blood. 2007;109:4693-4697.
4. Gouw SC, van der Bom JG, van den Berg HM. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. Blood. 2007;109:4648-4654.

To the editor:

Lenalidomide therapy in a patient with POEMS syndrome

The immune modulatory drugs (IMiDs) are powerful drugs against malignant plasma cells.[1,2] They also reduce the production of proinflammatory and proangiogenic cytokines. The POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome is a paraneoplastic syndrome that is driven by such cytokines,[3] most notably vascular endothelial growth factor (VEGF).[4] There are anecdotal reports of benefit of thalidomide for patients with POEMS.[5] Enthusiasm for its use in a condition in which the dominant complaint is sensorimotor peripheral neuropathy is tempered by the high incidence of thalidomide-induced peripheral neuropathy with long-term use.[6]

A 40-year-old African-American man presented to the Mayo Clinic with a 4-year course of progressive peripheral neuropathy, weight-loss, fatigue, anasarca, hypertrichosis, hyperpigmentation, gynecomastia, and erectile dysfunction. One year into his symptoms, he was diagnosed with chronic inflammatory demyelinating neuropathy (CIDP). For this diagnosis, he was treated with corticosteroids, plasmapheresis, and finally azathioprine without significant benefit. He continued to deteriorate, and a

Table 1. Patient findings before and after lenalidomide therapy

Patient's parameters	Activities of daily living	
	Before lenalidomide†	After 9 cycles‡
Karnofsky score	40	70
Hypertrichosis	Present	Improved
Hyperpigmentation	Present	Improved
Edema	++++	Trace
Gynecomastia	Present	Improved
Neuropathy impairment score*	121	113
C-reactive protein, mg/dL	0.4	<0.3
Gamma globulin, g/L	31	20
IgG, g/L	31.6	17.8
Kappa, mg/L	145	42.6
Lambda, mg/L	177	82.4
K/L ratio	0.82	0.52
Monoclonal protein	IgG lambda by immunofixation	IgG lambda by immunofixation
Bone marrow plasma cells, %	5% (monoclonal lambda)	10% (polyclonal)
Cytogenetics	t(9;17)(q22;q25)	No abn by FISH or metaphase
VEGF, pg/mL	948	303
IL-6, pg/mL	140.1	6.6
Testosterone, total, ng/dL	276	424
Testosterone, bioavailable, ng/dL	17	36
Urine total protein, mg/24 h	427	158
Pulmonary function		
FVC, % predicted	75	81
FEV-1, % predicted	70	79
PImax, % predicted	47	75
PEmax, % predicted	25	49

Normal values: VEGF < 83 pg/mL; IL-6 < 5 pg/mL; total testosterone, 240–950 ng/dL; bioavailable testosterone, 61–213 ng/dL.

FISH indicates fluorescent in situ hybridization; AFO, ankle foot orthotic; FVC, forced vital capacity; FEV-1, forced expiratory volume of 1 second; PEmax, maximal exploratory pressure; PImax, maximum inspiratory pressure; and ++++, high level of edema.

*The lower the number, the better the function.

†Barely able to roll over in bed; unable to bathe, dress, or transfer himself; transportation restricted to wheelchair.

‡Capable of all ADLs except pulling on support hose; walks with AFOs and walker with ease.