consequently in many plasma pools.[2] More refined products (eg, albumin) were, however, consistently TTV-negative.[2,3] These findings confirm longstanding experience, derived from numerous viral validation studies, of the Cohn HSA manufacturing process as one with a high capacity for removing viruses. The explanation for the recent unexpected findings[1] thus remains enigmatic. Using the same 2 TTV primer sets and a third independent in-house primer system, we confirmed earlier reports[2,3] from research groups at regulatory bodies who unanimously found HSA to be TTV-negative.

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Response:

First-generation recombinant factor VIII concentrates are free from viral contaminations?

Kreil et al (from Baxter BioScience) failed to detect TT virus (TTV) DNA in 11 lots of a Baxter first-generation recombinant factor VIII concentrate (rFVIII) (Recombinate) as well as in 13 lots of human serum albumin (HSA), a difference from our previously reported results.[1] As regards the rFVIII, the results of Kreil et al are not significantly different from ours (3 out of 13 were positive for TTV DNA). However, with regard to the contamination by TTV in HSA lots, the difference between the results obtained by the 2 groups is more evident. Kreil et al cite, as we too have done, the paper of Pisani et al,[2] who failed to detect TTV DNA in HSA, in order to strengthen their own conclusions. As we already stressed, Pisani et al used only the N22 polymerase chain reaction (PCR), which is unable to detect a high number of TTV variants.[3] In this case the difference in the methods used may well justify the different results. In addition, it is well known that, even using the same methods, the results obtained from different laboratories are not fully comparable if international standards are not available and used, as in the case of TTV so far. Furthermore, when the size of the study is so small, a negative result can be affected by a type II statistical error. According to the "rule of 3," the one-sided 95% confidence intervals of the Kreil et al study are 0 and 27.3.[4]

Similar viral safety problems emerged concerning the possible contamination of several blood products by parvovirus B19. As regards the possibility of B19 contamination, we failed to detect B19 DNA in either rFVII or HSA, even using very sensitive nested PCR, whereas other groups reported different results.[5,6]

It is likely that the residual amount of virus (or better, of viral genome) (TTV or B19 virus or perhaps other viruses) in such products after the manufacturing process is very low, near to the limit of sensitivity of the analytical methods available at present. Such a condition, in addition to the lack of standardization of methods, makes a comparison of results obtained in different laboratories very hazardous.

We would like to emphasize again the need for continuous drug-surveillance with prospective protocols of informative hemophiliacs, treated for the first time even with rDNA-derived clotting factor concentrates. In addition, there is also the need to implement the standardization of the molecular methods for the detection of viral contaminations by the development and use of calibrated reference samples.

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To the editor:

Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy

Thalidomide has emerged as an active agent for the management of advanced multiple myeloma (MM) and is currently under investigation also in patients with newly diagnosed disease.[1] It is relatively well tolerated; more common side effects include constipation, sedation, skin rash, fatigue, and peripheral neuropathy.[2,3] Recently, an increase in the frequency of deep-vein thrombosis (DVT) from 1% with thalidomide alone[2] to the range of 21% to 28% with thalidomide plus chemotherapy was reported by several groups,[4-6]

more frequently in association with doxorubicin-contaning regimens.[7] We report here on an unexpectedly high incidence of DVT in patients with newly diagnosed, symptomatic MM who received first-line therapy with thalidomide-dexamethasone. By study design, both drugs were administered for 4 months in an attempt to reduce tumor cell mass before collection of peripheral blood stem cells to support 2 subsequent autotransplants. The starting dose of thalidomide was 100 mg/d, with a subsequent increase to 200 mg/d after 14 days; the monthly dose of dexamethasone was 40 mg/d for 4 days, with cycles repeated on days 9 to 12 and 17 to 20 on the first and the third month of therapy. At the present time, 19 patients entered this phase II trial and received at least 2 months of therapy. Of these 19 patients, 5 (26%) had symptomatic DVT, of whom 1 had associated nonfatal pulmonary embolism. DVT was documented by doppler ultrasonography and developed in the lower extremities (popliteal vein: 3 patients; calf veins: 2 patients). Thrombosis occurred during the first month of therapy in 2 patients, the second month in 1 patient, the third month in 1 patient, and at the end of the fourth month of therapy in the last patient. Baseline laboratory evaluation for inherited risk factors for thrombosis—including antithrombin III deficiency, protein C and protein S deficiencies, resistance to activated protein C, lupus anticoagulant and antiphospholipid antibodies, and prothrombin gene abnormalities (G20210A)—was performed in all patients and excluded primary hypercoagulable states. Additional risk factors for thrombosis included hormonal therapy in a single patient. Anticoagulation therapy consisting of low-molecular-weight heparin with or without warfarin was promptly started after the diagnosis of DVT. There were 3 patients who safely continued thalidomide-dexamethasone without evidence of progression of DVT; thalidomide was stopped in the other patients, 1 with associated pulmonary embolism and 1 by study design before priming therapy with high-dose cyclophosphamide. In addition to recent reports on the use of thalidomide administered in combination with multiagent chemotherapy and dexamethasone,[4-6] present data show an increased risk of DVT also for patients with MM receiving first-line thalidomide-dexamethasone. This observation was not reported in previous studies with the same regimen, but different thalidomide and dexamethasone dose intensities, as salvage therapy for patients with advanced and refractory MM.[7,8] Efforts aimed at elucidating biologic mechanisms associated with thrombosis and thalidomide-based therapy should continue. In the interim, careful monitoring for DVT should be recommended for patients enrolled in investigational clinical trials including thalidomide as part of therapy for MM. In these patients prophylactic low-dose warfarin should be considered in an attempt to reduce the risk for DVT.

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To the editor:

Involvement of the *MLL* gene in T-lineage acute lymphoblastic leukemia

Translocations involving 11q23 are considered synonymous with rearrangements of the *MLL* gene. They are usually associated with B-lineage acute lymphoblastic leukemia (ALL) and acute myeloid leukemia but have also been reported in T-lineage ALL.[1-6] Although most can be identified by routine cytogenetic analysis, their prognostic importance means that molecular methods are frequently employed to ensure detection.

Recently, Hayette et al[7] reported the results of screening 81 patients with T-ALL for the involvement of the *MLL* gene using Southern blotting, reverse transcriptase–polymerase chain reaction (RT-PCR), and fluorescence in situ hybridization (FISH). They reported that 4 of 47 (8%) adults and 0 of 34 children had a rearrangement of the *MLL* gene. Using molecular methods, 3 cases with a del(11)(q23) by cytogenetics were found to have a t(6;11)(q27;q23), while the other case had a cryptic t(10;11)(p12;q23) with no cytogenetically visible 11q23 abnormality. These observations led Hayette et al to recommend the routine screening of all adults with T-ALL for *MLL* abnormalities.

The EU Concerted Action Workshop on 11q23 reported 9 patients with T-ALL and an established 11q23 translocation, with molecular techniques confirming the involvement of the *MLL* gene in 4 cases. The series comprised 3 cases of t(11;19)(q23;p13.3);[1] 2 of t(10;11);[2] and one each of t(4;11)(q21;q23),[3] t(6;11),[4] t(9;11)(p21∼22;q23),[5] and t(11;17)(q23;q21).[6] The age of these patients spanned from 3 months to 49 years and consisted of 2 infants (younger than 1 year), 3 children (15 years or younger), and 4 adults.

Since 1998 the Leukaemia Research Fund (LRF) UK Cancer Cytogenetics Group (UKCCG) Karyotype Database in ALL[8] has been screening patients entered into the Medical Research Council (MRC) ALL treatment trials for abnormalities of the *MLL* gene by interphase FISH. Currently, a total of 210 patients with T-ALL have been screened using commercially available probes: the LSI MLL probe (Vysis, United Kingdom) or the MLL DNA probe (Appligene Oncor, United Kingdom). Overall, rearrangements of the *MLL* gene were found in 10 (5%) cases. The incidence among children and adults was very similar—7 of 159 (4%) and 3 of 51 (6%), respectively. Six cases had a t(11;19), of which 5 were also