To the Editor:

The report by de Biasi et al. is an important contribution to the debate regarding the possible role of product purity in modulating immune function in hemophiliacs. However, some aspects of the study bear comment. Patients treated with an intermediate-purity concentrate showed a deterioration in immune function compared with those treated with a high-purity product. The two products, however, did not differ simply in the degree of purity. Indeed, it is curious that the investigators state that "both the concentrates have been previously established to be efficacious and safe in the treatment of hemophilia A patients." Their supporting reference shows that the intermediate purity concentrate, Kryobulin TIM 3, has been implicated in the transmission of hepatitis B. As is remarked in this latter study, this may also have masked transaminase elevations from hepatitis C infection. Recent findings suggest that hepatitis C infection is more closely associated with certain immunologic abnormalities in both human immunodeficiency virus (HIV)-positive and HIV-negative hemophiliacs than the amount or type of concentrate infused. Previously unexposed hemophiliacs treated over 5 years with an intermediate-purity, severely heat-treated concentrate have shown no evidence of infection by HIV, hepatitis B virus, and hepatitis C virus, and immune function was unaffected. Although this patient group was HIV-negative (due to life-long treatment with a severely heated product), as opposed to the patients studied by de Biasi et al., it seems that infection with agents other than HIV may play a role in immune modulation. This may be difficult to distinguish from any effects due to chronic protein infusion unless fully accredited methods, such as severe dry heating or solvent detergent treatment, are used to sterilize the intermediate-purity concentrates being compared with the high-purity products. Until such studies are made in both HIV-positive and HIV-negative hemophiliacs, it is difficult to fully endorse de Biasi et al.'s conclusion that "the results of this study clearly support the use of very high purity concentrates for the replacement therapy of HIV-infected hemophiliacs."

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REFERENCES


RESPONSE

Dr Farrugia raises the possibility that the immunologic differences observed in our study between the two groups of patients randomly assigned to continue the intermediate-purity concentrate or to receive the very high purity products may be due to infection with agents other than human immunodeficiency virus (HIV), especially hepatitis C virus (HCV), which may also play a role in
immunomodulation. It was the purpose of our study to evaluate the hypothesis that “purer” clotting factor concentrates are of benefit to HIV-infected hemophiliacs. This study has focused on 20 patients carefully matched according to age, immunologic status, and hepatitis B antigen (HBsAg)-negative status. Furthermore, when assayed (retrospectively) for their HCV status at entry into the trial, all patients were seropositive, which was expected because these patients had all been previously exposed to concentrate that had not been treated with procedures known to inactivate viruses. Consequently, because both groups of patients were equivalent as to HCV serostatus, it seems unlikely that the observed immunologic differences might be due to or established new infections by the HCV. We believe that the data support the conclusion in favor of the use of very high purity factor VIII concentrates for the replacement therapy of HIV-infected hemophiliacs.

Nevertheless, Dr Farrugia’s letter raises other questions appertaining to the choice of clotting factor concentrates for the replacement therapy of HIV-positive and HIV-negative hemophiliacs. The first issue, specifically applicable to HIV-positive patients, focused on the need to optimize immune function in this threatened group of patients. The question then becomes whether other blood-borne viral infections may play a role (cofactor) in the progression of HIV disease. Even though the role of the hepatitis agents, cytomegalovirus (CMV), and the Epstein-Barr virus (EBV) is still controversial, there is no question as to the negative clinical impact of infection with these viruses on long-term outcomes. There are, however, in vitro data indicating that exposure to other viruses activates latent HIV within monocytes, and coinfection of cells by HIV and DNA viruses such as CMV and hepatitis B virus (HBV) can stimulate the expression of HIV. Furthermore, the HBV may be associated with more rapid progression of both the immune defects and hepatocellular destruction in HIV-HBV-coinfected individuals, and there is an association between CMV and HIV disease progression, with CMV-positive patients moving more quickly towards acquired immunodeficiency syndrome (AIDS) than CMV-negative individuals. Thus, HIV-infected hemophiliacs should be exposed to as little viral load as possible. Hence, those concentrates with effective viral inactivation procedures should be administered to all persons with hemophilia who are HIV-infected. However, the choice of the “best” concentrate is still difficult to make. Despite the documented nontransmission of monitored blood-borne viruses with all the viral inactivation processes currently used for all currently available products both in the United States and in Europe, prospective studies and case reports have documented hepatitis agent transmission with various procedures, including pasteurization. Furthermore, paroviruses, the clinical importance of which has still not been completely elucidated, as well as other nonlipid enveloped viruses, will survive solvent/detergent treatment. Given this scenario, there appears a need to choose the very high purity products that provide a double barrier for both viral inactivation and effective viral exclusion procedures.

One other issue is the relationship between HCV (and HBV) infection and the immune status of HIV-negative hemophiliacs, as well as the potential impact of contaminating proteins such as the IgG, fibrinogen, and fibronectin on the long-term outcomes of HCV infection. Ideally these questions could be answered by a prospective controlled trial that would randomize HCV-infected, HIV-negative hemophilic patients to either intermediate-purity or high-purity concentrates. However, these intermediate-purity products are becoming less available on the market. Furthermore, as some of the intermediate-purity concentrates continue to bear the potential for contamination with blood-borne viruses, ethical and safety issues arise.

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Purity of factor VIII concentrates and immune function in hemophiliacs [letter; comment]

A Farrugia