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THE SAFETY OF PLASMA-DERIVED VERSUS RECOMBINANT CONCENTRATES

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P.M. Mannucci

Introduction

During the Global Forum on the Safety and Supply of Hemophilia Treatment Products organized in 2003 by the World Federation of Hemophilia in Budapest [1], the participants were asked to vote on the following question: what is the most critical issue facing the hemophilia community? Affordability of treatment products was chosen by 48% of the participants, supply by 26%, and safety by 26%. The result of this vote was impressive but not surprising, considering that in the world four-fifths of the estimated 400,000 people with hemophilia receive no treatment at all. The proportion of those voting for safety would probably be higher if voting was restricted to participants from those countries where products are affordable and supplied in sufficient amounts.

By pointing this out, I am not saying that safety is a disposable luxury. The drama and the agony of AIDS and hepatitis are still too overwhelming in my memory and mind to be understated [2]! Safety of treatment for persons with hemophilia mainly relates to two aspects: infections and inhibitors. Other adverse effects of treatment such as allergic reactions are fortunately too rare to be a compelling problem, even though we still do not understand the mechanism of the anaphylactic reactions that occur, albeit very rarely, in patients with hemophilia B treated with plasma-derived or recombinant factor IX. Inhibitors are still a huge problem, even though a lot of progress in the management of bleeding episodes have taken place since I started to treat persons with hemophilia in the late 1960s/early 1970s.

Significant breakthroughs in understanding the mechanism of inhibitor onset, leading to the availability of weapons for primary prevention, are necessary to help eradicate this complication of hemophilia treatment, hopefully in a not too distant future.

With this as background, I shall limit myself to discuss herewith my perspectives on safety from infections, first for recombinant products and then for plasma-derived products, that I suspect will continue to be the only realistic option for patients from developing countries for many years to come.

Safety of Recombinant Products

What is the evidence for safety of recombinant products? I cannot help but state that, in more than 15 years of clinical experience, no infectious complication has ever been reported in scientific literature to agencies involved in drug surveillance nor, to my knowledge, by word of mouth within the community of persons with hemophilia and their caregivers. This is biologically plausible. Materials of human and animal origin are being progressively eliminated not only from the formulation of these products but also from the manufacturing process. The current prototype of this improvement in perceived safety of factor VIII products (actual safety was impeccable even with the earlier products) is epitomized by the recent licensing, in the USA as well as in Europe, of a so-called third generation preparation of factor VIII characterized by the absence of any contact with human or animal proteins during the purification process [3], except for hamster proteins in the cell culture and mouse monoclonal immunoglobulins. A factor VIII recombinant product now undergoing clinical trials, but not yet licensed, is going to be even further improved since the use of mouse immunoglobulins is avoided. These very features already apply to recombinant factor IX, available and licensed for patient use [4].

Have we attained absolute safety? Rationally I would say yes if I was not baffled in the past by the unexpected emergence of such events as AIDS or the less tragic hepatitis outbreaks. Is there any residual risk? Strictly speaking, any

theoretical risk (until we have truly synthetic factors which is unrealistic but not impossible) is related to the possibility that pathogenic viruses may be harbored or may grow in the hamster cell cultures that are still being used to produce recombinant factors. However, it must be borne in mind that in the majority of second and third generation recombinant products an additional safety net is represented by the adoption of those virucidal methods that proved to be so efficacious in making safe plasma-derived factors (see below).

Safety of Plasma-Derived Products

The era of hepatitis and AIDS is a quarter of a century behind us. Yet, the real and perceived consequences are still alive in the hemophilia community, even though the last decade of the second millennium has witnessed the production of safer plasma concentrate of coagulation factors.

The current safety of these products is based upon the adoption of measures meant to decrease viral load in source plasma and to inactivate and/or eliminate infectious agents that may have escaped plasma screening. These measures were progressively adopted in 1984–5 (moderate 'dry' heating that minimized the risk of HIV infection, but not that of hepatitis C virus [HCV] infection), 1986–7 (stronger 'dry' and 'wet' heating or solvent-detergent that minimized the risk of HCV transmission), 1996–7 (adoption of more than one virucidal method to inactivate non-enveloped viruses such as the hepatitis A virus) and 1999–2000 (adoption of PCR testing and quarantine of source plasma). As a consequence of these measures, the safety of plasma-derived factors has dramatically improved so that no significant transmission of the aforementioned blood-borne viruses has been unequivocally documented since the progressive adoption of these measures, as it stems from recent surveys [5, 6]. However, the highly thermoresistant B19 parvovirus is still being transmitted by plasma concentrates [7]. Even though B19 infection is normally of little consequence in people with hemophilia, a few clinically significant events have been reported [8]. B19 infection must also be seen as evidence that particularly resistant blood-borne viruses other than the hepatitis viruses and HIV may still be transmitted. Another perceived threat is new variant Creutzfeldt-Jakob disease, with the fear that the abnormal prion protein might be contained in, and transmitted by, plasma coagulation factors. Even though several studies, carried out also in multitransfused patients, have definitely shown that sporadic Creutzfeldt-Jakob disease is not transmitted by blood or its derivatives, these data cannot be necessarily extrapolated to variant disease. The latter has a different incubation period and, at least in the United Kingdom, the number of blood donors potentially incubating the transmissible agent may be very high. An objective cause for concern is the recent demonstration of the possible transmission of the abnormal prion by whole blood transfusion and the related occurrence of the fatal disease in man [9, 10]. On the other hand, the fractionation process used to purify plasma proteins, including coagulation factors, contributes significantly to clear abnormal prions (more than six infectivity logs), making it unlikely that these agents even if present in plasma would be carried into the factor concentrates at concentrations capable of causing clinical disease [11, 12].

Are other 'new' infectious agents a possible threat? The dramatic experience with HIV tells us that this possibility should not be overlooked. For instance, the recently documented transmission through blood transfusion and organ transplantation of the West Nile virus prompts specific surveillance, even though this enveloped flavivirus is likely to be inactivated by the currently used virucidal methods. It is also unlikely that the coronavirus causing Severe Acquired Respiratory Syndrome (SARS) or the agent of avian influenza might be transmitted through transfusion or concentrates.

Concluding Remarks

To answer the question implicit in the title of this essay, i.e., whether or not recombinant antihemophilic products are safer than plasma-derived products, my views are that there is no evidence that recombinant factors are safer simply because both forms of hemophilia treatment are very safe. It is understandable that, even if evidence-based medicine allows us to make the aforementioned statement,

recombinant products are inevitably perceived as safer in our community. However, one should make a point of reassuring the large number of persons with hemophilia that are using, and will continue to use, plasma-derived factors since they are the only foreseeable option for 4/5 of the persons with hemophilia worldwide who at the moment have no access or limited access to any replacement material. The risks of blood-borne infections transmitted by plasma factors are more theoretical than real, and patients and policy makers should be educated to distinguish real from perceived risks. One would expect increased availability and decreasing prices for these products but this is not occurring, perhaps because the very demanding precautionary measures currently enforced by regulatory authorities make source plasma increasingly scarce and expensive. Progress is warranted in the quality of plasma fractionation technologies. The yield of factor VIII from source plasma is still only 5-10%, a loss that is difficult to accept in an era of high technology!

Finally, it should be reiterated that desmopressin (DDAVP) is the treatment of choice in patients with mild hemophilia A (and von Willebrand disease). Its early adoption in Italy in the late 1970s and early 1980s, at the time of the onset of the HIV epidemic, minimized the proportion of patients with mild hemophilia A who became infected; the latter group was much smaller than that of a comparison group of Italian patients with mild hemophilia B who, being unresponsive to desmopressin, could only be treated with unheated plasma-derived factor IX [13].

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