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DEBATE

Treatment of hemophilia: recombinant factors only? Yes

P. L. F. GIANGRANDE

Oxford Haemophilia Centre and Thrombosis Unit, Churchill Hospital, Oxford, UK

Dear Sir,

Safety with regard to transmission of pathogens is of prime concern in the selection of products for the treatment of hemophilia. The introduction of heat-treatment and solvent/detergent treatment in the mid 1980s effectively eliminated the risk of transmission of HIV and HCV (hepatitis C) through the use of plasma-derived products. However, outbreaks of hepatitis A in several countries in the early 1990s served to remind us that such virucidal methods cannot be relied on to protect patients against all viruses [1]. Similarly, an outbreak of hepatitis B in 1994 amongst patients treated with a heat-treated prothrombin complex concentrate to reverse the effect of anticoagulation emphasized the importance of vaccination of patients with bleeding disorders against this heat-stable virus [2]. Parvovirus B19 may still be transmitted by administration of modern plasma-derived concentrates subjected to heat treatment at 100 °C or even a combination of heat and solvent/detergent treatment [3]. Even though infection with parvovirus is of little significance in normal subjects, this again demonstrates that no current viral inactivation process will entirely eliminate the risk of transmission of conventional viruses. It must be conceded that there have been reports of the isolation of parvovirus and TTV (transfusion-transmitted virus) from some batches of first-generation recombinant factor (F)VIII products using PCR technology [4,5], but there has never been any evidence that this represents anything other than degraded and non-infectious viral particles incapable of transmitting infection. Such concentrates contained human plasma-derived albumin added to the final vial as a stabilizer, but this excipient has been eliminated in more modern preparations. Furthermore, the same phenomenon has also been demonstrated with hepatitis C virus with plasma-derived concentrate subjected to heat treatment [6].

More recently, experimental evidence from transfusion studies in sheep has suggested that there is a real potential for transmission of prions through blood [7]. The perception that this is a potential problem confined to the UK or even Europe is misplaced, in the light of evidence that potentially infected meat and bone meal was exported from the UK as cattle feed to many countries around the world during the critical period of 1979–90 [8]. No cases of either the classical or variant form of CJD (Creutzfeldt–Jakob disease) have been reported in a person with hemophilia anywhere in the world, although the disease has a prolonged incubation period and no serological test exists to detect infected individuals. Reassurance from experts that 'the risk of vCJD from the [plasma-derived] products used to treat patients with hemophilia appears remote' [9] is welcome but no-one has yet dared to venture that there is absolutely no risk. Whatever the eventual outcome, it cannot be disputed that the issue of bovine spongiform encephalitis (BSE) and vCJD has, once again, raised anxieties in the hemophilia community around the world. In the UK, we have had to counsel many patients who were notified in early 2001 that they had been treated with batches of FVIII and FIX concentrates issued in 1996/1997 to which a donor had subsequently died of vCJD had contributed plasma [10]. These patients would have been spared this ordeal if recombinant products had been widely adopted for the treatment of hemophilia as soon as they were licensed in 1994.

Initial concerns about a potential increase in the incidence of inhibitors amongst people with hemophilia receiving recombinant products have proved unfounded. Although randomized trials comparing the incidence in previously untreated patients (PUPs) receiving recombinant with those receiving plasma-derived products have never been conducted, it would be fair to say that the current consensus is that the incidence of inhibitor development is very similar for both types of product [11–13]. There was certainly no evidence of an increased incidence of inhibitors following the whole-scale switch to recombinant products in Canada in 1994 [14]. It is now appreciated that the single most important risk factor for inhibitor development is the underlying molecular defect [15]. There has never been any suggestion that the incidence of inhibitors is increased in patients with hemophilia B receiving recombinant factor IX [16].

The recent experience of an acute and world-wide shortage of recombinant factor VIII has certainly served to focus minds on the fact that the number of manufacturing plants is very limited, particularly so in the cases of recombinant factor IX and recombinant factor VIIa. However, the situation has improved considerably in the last year, with two companies opening new plants for the manufacture of recombinant factor VIII and others facilities are being planned by other companies. Now that supplies of recombinant products have now been restored, the tables have been turned and it is the supply of plasma-derived products which is looking increasingly vulnerable. This is largely, but not solely, due to measures taken in response to the perceived threat of BSE and vCJD, which have included deferral of donors who have spent variable periods in the UK

Correspondence: Dr Paul Giangrande, Oxford Haemophilia Centre and Thrombosis Unit, Churchill Hospital, Oxford OX3 7LJ, UK.
E-mail: paul.giangrande@ GRO-C

and other European countries. The demand for plasma from the USA (a country hitherto unaffected by BSE and/or vCJD) has soared, resulting in price rises for plasma-derived products and for immunoglobulin preparations in particular as there is no recombinant equivalent. This undue reliance on the plasma from one country also entails risks: what will happen if BSE and/or vCJD appear in North America? Another step which will reduce the plasma supply even further is the deferral of any potential donor who has himself (or herself) received a blood transfusion. This measure, already adopted in France and being considered in other countries, will have a big impact on plasma supply as recipients of blood donations are often the most motivated of all donors. Looking to the future, it is anticipated that there will be a further decline in blood donor numbers when a screening test for vCJD eventually becomes available, as many potential donors will be understandably concerned about being tested for a disease which has a very long incubation period and for which there is no effective treatment. A further aggravating problem at this critical period has been a recent proposal from the European Parliament to restrict blood collection to unpaid volunteer donors only. Even though such proposals have now been effectively rejected, at least for the time being, the philosophy of using volunteer donors exclusively is likely to gain increasing ground in the future although any such move will have a serious impact on the availability of coagulation factor concentrates.

Finally, by switching to recombinant products we are helping to secure effective and safe treatment for people in developing countries. The World Federation of Haemophilia estimates that two-thirds of the people with hemophilia in the world receive no treatment for their condition. For example, the inhabitants of India, Bangladesh, China and Indonesia account for 45% of the world's population and 10% of the diagnosed persons with hemophilia, but yet consume just 2% of the products available for treatment [17]. As patients in such fortunate parts of the world as North America, Europe and Australia and Japan convert inexorably to recombinant products, manufacturers of plasma-derived products there will be forced to seek new markets in the developing world and these will also have to be competitively priced.

The reality is that it is simply the increased cost of recombinant concentrates compared to conventional plasma products, rather than rational scientific arguments, which is the principal obstacle to their wider use. In view of all the problems associated with viral infections in people with hemophilia over the last two decades, it is clear that there is indeed much wisdom in Aldous Huxley's aphorism that the lesson of history is that the lessons of history are never learnt [18].

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