New variant CJD and blood transfusion Services - where is it all leading?

Introduction

At the time of the initial report of a new variant of Creutzfeldt-Jacob disease (nvCJD) in February 1996 few would have predicted that two years later universal leucodepletion of all blood components and a major shift away from UK volunteer donor plasma might be required to combat theoretical concerns relating to possible transmission of this new disease by transfusion. This short article aims to review the background to current events and to provide an assessment of the impact that this might have on the pattern of transfusion provision within the UK during the next few years.

nvCJD and BSE

25 cases of nvCJD have now been confirmed world-wide , 24 within the UK and one case in France. There is increasing evidence supporting the view that nvCJD represents the human form of Bovine Spongiform Encephalopathy (BSE), infection having been acquired through consumption of beef products infected with offal prior to the implementation of the Specified bovine offal ban in 1989. Data produced by Moira Bruce and colleagues from the Institute of Animal Health in Edinburgh demonstrating that nvCJD and BSE share a common "fingerprint" in experimental models appears to confirm the link.

Although there is currently no evidence of any increase in the rate of diagnosis of new cases it is too early to predict the likely scale of any epidemic of nvCJD within the UK.

Can CJD be transmitted by transfusion?

In March 1997 the World Health Organisation held a consultation on the topic of Transmissible Spongiform Encephalopathies (TSEs) and medicinal products. The potential risk that these disorders, including CJD, posed in relation to transfusion was considered during the meeting. The meeting concluded that "**There is no proven or even probable instance of transmission of Creutzfeldt-Jacob disease by blood, blood components or plasma derivatives.**" The possibility that the nvCJD would behave differently to the classical form of the disease was however acknowledged and a requirement for careful surveillance and specific research in this area was identified. The absence of evidence that CJD has been transmitted by transfusion is not evidence of an absence of risk and a number of recent observations have raised concern that the infective agent of nvCJD, the prion, might be present in blood and thus that transfusion might be capable of transmitting the disease. Two sets of observations are of particular concern. A report from the CJD Surveillance Unit that prion protein can be demonstrated in tonsillar biopsies taken from nvCJD cases, a finding not seen in classical cases of the disease. This suggests increased lymphoreticular involvement in nvCJD raising the likelihood that the agent might be present in blood. Experimental studies undertaken within the National Institutes of Health in the US by Brown and co-workers have apparently demonstrated infectivity in blood , plasma and crude plasma fractions. Currently unpublished, this data is undoubtedly fuelling current concerns. These studies were undertaken in experimental mouse models using a laboratory strain of CJD. Mice were inoculated intracerebrally and blood was then drawn late in the course of disease. Blood was pooled from several mice , separated

into components and these were then injected into further mice, utilising both intacerebral and intravenous routes. Infectivity was apparently demonstrated in red cells, buffy coat and plasma (including various fractions) following intracerebral inoculation, and in one instance following intravenous injection. Further work to confirm these findings is underway. Brown has indicated that caution should be undertaken in interpreting this data, particularly so in extrapolating to the human situation.

In summary, there is currently no direct evidence that nvCJD is present in blood of individuals incubating the disease. Research is currently being planned to address these concerns but it will be some years before results are available. Inevitably however concerns have been raised and these must be considered in the context of the uncertainty over the likely number of cases that will arise in future years within the UK.

Announcement of "precautionary measures"

In October of last year the Secretary of State for Health announced that following advice from SEAC (The Spongiform Encephalopathy Advisory Committee) he planned to commission an independent risk assessment of the possibility that leucodepletion of blood components might reduce any risk of transmission of nvCJD by transfusion. At the same time UK Blood Services were instructed to develop plans for implementation of leucodepletion. The outcome of the risk assessment is awaited.

UK transfusion specialists have long promoted the importance of reliance on blood and plasma derived from non-remunerated volunteer donors. The possibility that the CSM review will lead to importation of plasma form paid US donors has raised concerns that action taken in respect of theoretical risks might increase the risk from known transfusion transmissible agents, in particular viruses. Prospective plasma suppliers will be subject to inspection by UK fractionators and the situation will be closely monitored by Regulatory Authorities, in particular the MCA - will this be enough? The safety of fractionated plasma products has improved considerably in recent years. The application of specific viral inactivation steps as part of the manufacturing process has been a major factor contributing to the excellent safety record of these products. The viral load present in the start pool must also be considered. Source plasma collectors within the US have responded to concerns in this area notably through programmes developed by the American Blood Resources Association (ABRA). A number of approaches have been developed which together should significantly reduce viral loads of start pools. This includes a move to community based collection sites, meticulous donor selection procedures, donor accreditation and careful inventory management. These combined with the use of PCR testing have significantly improved the quality of plasma entering start pools. Preliminary data suggests that significant reduction in viral load can be achieved, with figures similar to that seen in the not for profit sector. Such claims should be viewed with caution, but it must also be remembered that products manufactured in the commercial sector already have a significant market share within the United Kingdom. It must also be emphasised that these approaches will not be apply in the

context of labile blood component production where the benefit of continued reliance on components derived from UK based non remunerated volunteer donors will significantly outweigh theoretical concerns in relation to nvCJD.

The data reported by Brown and colleagues indicating that, in experimental conditions, CJD infectivity can be demonstrated in plasma fractions is inconsistent with the clinical observation that haemophiliacs and other closely observed patient groups have not been seen to be at increased risk of acquiring CJD. A number of explanations for this apparent discrepancy can be identified. One intriguing possibility is that current manufacturing approaches result in partitioning of the infectious agent. Research in this area will be important. This possibility considered in the context of reports from Zurich of specific monoclonal antibodies against the prion protein offer hope that any switch away from UK plasma will be temporary. Appropriate funding will be necessary to properly pursue these, and other relevant, opportunities.

Where is it all leading?

It would be wrong to anticipate the outcome of the various initiatives commissioned by the Department of Health. It seems however increasingly clear that precautionary measures taken in relation to a theoretical risk will significantly impact on the work of all involved in transfusion. These considerations must be viewed in the context of a government and general public sensitised to inappropriate reassurances on the risk that BSE posed to man - and in the context of TSE experts genuinely concerned that transfusion might provide a vehicle for onward transmission of a fatal disease.

In recent years divergent approaches have emerged within Europe and the United States in respect of the requirement for action to be taken following "late notifications" of donors being diagnosed as suffering from CJD. This refers to the situation when a donor is diagnosed with CJD, and a review of previous donations identified that plasma had entered a fractionation pool. Within the US manufacturers are required to quarantine implicated pools and to recall product. In 1995 European Regulatory Authorities concluded that in the absence of evidence of any risk associated with plasma products that such action was unnecessary and would be likely to lead to shortage of essential products. In November 1997 UK authorities recommended in view of the emerging concerns identified above that action should be taken in respect of "late notifications" involving confirmed cases of nvCJD. This lead to recall of several batches of fractionated products, and also of products where albumin had been used as an excipient (or diluent).

UK Haemophilia Directors convened to consider the evidence. They recommended that funding for recombinant factor eight should be provided, and that when this was not possible consideration should be given to the use of factor eight derived from plasma sourced from countries where BSE had not been identified.

In January 1998 the European Committee for Proprietary Medicinal Products (CPMP) initiated a formal review of the position developed in 1995. In February new recommendations emerged (CPMP/201/98). These identified that :

-Given the lack of specific information on nvCJD , as a precautionary measure, it would be prudent to withdraw batches of plasma-derived medicinal

products from the market if a donor to a plasma pool is subsequently strongly suspected, by a recognised reference centre, of having nvCJD.

- Since a recall involving albumin used as an excipient has the potential to cause major supply difficulties for essential products, manufacturers should avoid using, as an excipient, albumin derived from countries where a number of nvCJD cases have occurred.

Within the UK the Committee for the Safety of Medicines (CSM) , whilst stressing that the theoretical nature of the risk endorsed the recommendations of CPMP. At the same time it advised the Secretary of State that , in consultation with its Expert Group on nvCJD, a risk assessment should be undertaken for medicinal products containing components derived from pooled human plasma. Accepting this advice the Secretary of State announced that recombinant factor eight would be made available for treatment of all new haemophiliacs and for those under the age of 16 years. He also identified that the CSM review will be undertaken on a product by product basis taking into account the therapeutic benefit of the product, details of the manufacturing process, the theoretical risk of transmission and the supply situation. At the same time, anticipating the outcome of the review, he announced that UK Fractionation authorities would be permitted to import plasma for onward manufacture. The media widely, but wrongly so, interpreted this announcement as a "ban on the use of British plasma products". The outcome of the CSM review is not yet known although it seems likely that this will result in a major shift to non-UK plasma.

Risk reduction or risk substitution?

If the risk posed by this new disease is uncertain so must be the effect of the proposed interventions. Current events provide a real opportunity to reassess and reinforce the principles of good transfusion practice. Concerns relating to nvCJD might facilitate the introduction of policies that minimise exposure to allogeneic blood. Clinical audit of transfusion practice, promotion of autologous transfusion and alternatives to transfusion will need to be pursued. Potential recipients will require reassurance, as will prospective donors - care will need to be taken that patients who genuinely require transfusion continue to have access to effective and safe blood components and plasma derivatives.

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