IN STRICT CONFIDENCE

DRAFT DISCUSSION DOCUMENT: 18 June 2004

DEFERRAL OF PLASMA PRODUCT RECIPIENTS FROM BLOOD AND TISSUE DONATION

The UK Forum have asked JPAC to give consideration to what additional donor deferral criteria may be required consequent upon an announcement by the CJD Incidents Panel that some groups of plasma product recipients are to be notified of their exposure to plasma products manufactured from batches to which donors contributed who have subsequently gone on to develop variant CJD.

CJD Incidents Panel Technical Committee

A subcommittee of the CJD Incidents Panel has met on four occasions to discuss the identification and management of patients who have received plasma products manufactured from batches of plasma to which donors contributed who have subsequently gone on to develop variant CJD. Nine UK plasma donors fall into this category – they contributed 23 plasma donations that were made into 174 product batches in total. It should be noted that there are currently 146 probable or definite cases of variant CJD. If the most recent projections are correct, we should expect that there will be a significant further number of implicated plasma products batches identified in the future and potentially also a number of "implicated" plasma product batches which will not be identified as such if the donor is infected but does not develop variant CJD.

An initial meeting of the subcommittee on Thursday 10th April 2003 focussed on the issues of which DNV method of estimating infectivity in blood and blood products was most appropriate to use and the level of risk at which it would be appropriate to take precautions. It was decided that a model based on the work of Professor Paul Brown on endogenous infectivity in the blood of rodents infected with the Fukuoka-1 strain of GSS disease should be used rather than a model based on plasma spiked with brain homogenates from infected rodents. There were two reasons for this. First because a lower degree of prion removal was measured (due to only a limited number of steps being assessed), this approach was viewed as being more precautionary. Second, because infectivity in this model is expected to be in a similar physico-chemical state to that of the variant CJD agent in humans infected naturally, whereas brain derived infectivity may not necessarily be in the same state. It was also agreed that a 1% risk of exposure to an infectious dose (0.02 ID50s by intracerebral inoculation extrapolated from studies on experimentally infected rodents) cumulative over a period of 12 months would be used as a threshold beyond which an individual would be regarded as being at sufficient additional risk of infection (i.e. over and above the risk of infection associated with residence in the UK) to warrant taking specific infection-control measures a propos medical and surgical instrumentation and blood, plasma and tissue donation.

The Department of Health subsequently evaluated data from BPL and PFC regarding the precise nature of their fractionation processes and batch sizes. This has resulted in the calculation of threshold values for each product batch, presented as the number of vials or bottles of product a patient would need to have received before they will be considered to be in the contactable group.

The third meeting of the sub-committee on 21st April discussed the outcomes of these calculations in terms of the nature of the implicated plasma products, the groups of recipients likely to fall above the infection-control threshold and the mechanism by which these patients should be traced and informed.

The implicated products have been categorised into high, medium and low likelihood that the infection-control threshold will be surpassed according to the following definitions:

High likelihood - one dose alone required to surpass the infection-control threshold: includes Factor VIII, Factor IX products and anti-thrombin

Medium likelihood – repeated doses required to pass the infection control threshold; includes intravenous immunoglobulin and albumin.

Low likelihood – very large numbers of doses required to cross the infection control threshold and products usually given infrequently, therefore it is unlikely that a patient would receive an infectious dose. Includes intramuscular immunoglobulin, anti-D and plasma and medicinal products in which albumin from an affected batch has been used as an excipient.

Fibrinogen, thrombin and fibrin sealant have not been evaluated at this stage.

It should be noted that the uncertainties around the assumptions on the level of infectivity in human plasma and the impact of the plasma fractionation process on that infectivity level are so great, that the threshold could not be seen at present as a reliable guide for advising individual patients about their additional risk of developing variant CJD as a result of exposure to an implicated plasma product batch (in addition to the background risk from dietary exposure to the BSE agent). The principal purpose of the infection-control threshold is to assist with practical implementation of public health precautionary measures to limit the likelihood of human-human transmission of variant CJD and so hasten the elimination of the agent from the UK population.

At the 4th meeting of the subcommittee on 9th June management and notification of three broad groups of patients was further discussed.

- Patients with Haemophilia will almost certainly be in the notifiable group if they have received a single unit of an implicated batch. It has been agreed that these patients will be offered the opportunity to know whether or not they personally have been exposed to an affected product and this information would be recorded in their medical notes whether or not they choose to be aware of this information.

- Patients with primary immunodeficiencies are to be informed on a case by case basis following a calculation of their individual level of exposure to an implicated batch on the grounds that a minority of them have been exposed to UK plasma products.

- An attempt will be made to trace other groups of patients including those who have received prothrombin complex concentrates for warfarin reversal, intravenous immunoglobulin for management of secondary immunodeficiencies and autoimmune disorders and recipients of 20% and 4.5% albumin. Again, these patients will be informed following a calculation of their individual level of exposure to an implicated batch.

- All patients who have been exposed to more than 1% likelihood of exposure to an infectious dose will be subject to infection-control measures.

Implications for deferral of plasma product recipients from blood and tissue donation.

There are 3 possible approaches to constructing a donor deferral policy consequent upon this announcement.

1. *Defer all recipients of plasma products.* This is likely to be an over-reaction given that recipients of i.m. immunoglobulin and low doses of albumin are considered to be at low additional risk from a public health perspective, that many people will be genuinely uncertain as to whether they have received the above products and that the impact on the blood donor base is likely to be substantial.

2. *Defer only those recipients identified by the CJD Incidents Panel as being above the 1% infection-control threshold.* Clearly this group of recipients must be deferred, however it should be borne in mind that a significant proportion of such recipients may not be traceable, may not choose to know whether or not they have been exposed to an implicated product batch and may not be on a central register (if one is constructed). Moreover this deferral criterion would be reactive in the sense of deferring only those currently identified as having been exposed to affected plasma product batches, and would take no account of those who have been exposed to an implicated batch but are currently unidentifiable because the donor has not yet, or may never develop clinical variant CJD. These people will be impossible to identify in the absence of a blood-donor screening assay.

3. *Defer donors who have been exposed to UK plasma products in the high or medium risk groups since 1980.* Recipients in this group would include:

   - patients who have received coagulation factors including prothrombin complex concentrate for reversal of over-anticoagulation
   - patients with primary or secondary immunodeficiencies who have received intravenous immunoglobulin
   - patients with autoimmune conditions who have received intravenous immunoglobulin
   - patients who have undergone plasma exchange or received large volumes of albumin for other reasons.

   This selection criterion could have a number of advantages:

   - like other donor selection criteria it relies on self reporting/exclusion rather than checking medical notes or reference to a confidential register.
   - it is consistent with a policy of deferring all blood component recipients
   - it does not rely on whether the recipient has been traced and/or whether he/she has chosen to know whether they have been exposed to an implicated product batch
   - it is proactive in the sense of deferring those who have been exposed to an implicated product but do not yet know it because the donor has not yet developed clinical variant CJD.

- it is proactive also in the sense of deferring those who have been exposed to an implicated product but who will never know it because though the donor may be infected he/she may never develop clinical disease.

- it avoids treating the individual patient or donor as being 'at risk' of disease and puts the emphasis on precautionary measures taken for public health purposes. Experience with blood-component recipient deferral suggests that this approach is manageable in public relations terms.

- the impact on the donor base is likely to be small because many recipients would already be excluded on the basis of their medical history.

Recommendations

The following recommendations are made.

- strategy 3 might provide the most straightforward approach to deferring donors who may be at slightly higher risk of incubating variant CJD due to exposure to implicated plasma products, would be proactive in deferring those recipients who are untraceable, choose not to know about their exposure status, who are likely to be deferred in the future as new implicated plasma products batches are identified, or who will never know about their exposure if the donor does not develop variant CJD. This would also be consistent with the donor deferral strategy for blood component recipients.

- any such decision needs to await the final decisions of the CJD Incidents Panel around notification of patients in these groups and take cognisance of the other public health measures applied. The current date for such announcement is around the first or second week in July.

- the UK Blood Services should urgently investigate the likely impact of the proposed donor deferral criterion, particularly the cross-impact on other recently implemented and proposed donor deferral criteria.

This paper has been developed in consultation with the variant CJD Working Group of SACTTI, SACTTI itself and SAC CSD.

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15th June, 2004.

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