CJD Incidents Panel

Technical Subgroup to discuss plasma product issues, 21st April 2004
Royal Society of Medicine, London

Present

CJD Incidents Panel
Dr Gerry Bryant
Dr Pat Hewitt
Professor James Ironside
Professor Don Jeffries (Chair)
Dr Mike Painter
Dr Hester Ward
Haemophilia Society
Mr John Morris
Mr Bill Payne
Haemophilia Centre Directors' Organisation
Professor Frank Hill
Professor Christopher Ludlam
Primary Immunodeficiency Association
Mr David Watters
St Mary's Hospital, Manchester
Dr Matthew Helbert
Bio Products Laboratory
Dr Steve Jenkins
Scottish National Blood Transfusion Service
Dr Peter Foster
Dr Marc Turner
Health Protection Agency
Dr Angie Bone
Dr Nicky Connor
Professor Noel Gill
Ms Helen Janecek
Ms Anna Molesworth
Ms Katie Oakley
Observers
Dr Peter Christie
Dr Gladys Tinker
Apologies
Dr Roland Salmon

Objectives of the meeting

The objectives of the meeting were to discuss the notification of patients exposed to implicated blood products in the light of the work undertaken to date by the HPA and to make recommendations about the approach to be taken for the full Panel meeting on 10th May.

Technical update

Dr Bone summarised the current information on the risk of the various plasma products. So far, 23 plasma donations had been identified from eight donors who subsequently developed vCJD. Implicated SNBTS products had been supplied to centres in Scotland and N Ireland; implicated BPL products had been sold in the UK and worldwide. Product data from the fractionators concerning each batch of products manufactured using implicated plasma had been entered into the risk calculator developed by the Department of Health from the DNV risk assessment to give:

- an estimate of infectivity per unit for each product batch
- the dose of each product batch required in order to reach the risk threshold of 1%.

A pre-meeting on 10th March had enabled issues to be resolved concerning:

- The method of calculation to be used
- The calculation of infectivity in the absence of some data.

Completion of the calculations on the products notified so far had enabled the products to be stratified by levels of risk:

- High risk: one dose alone required to cross 1% risk threshold (Factor VIII where intermediate implicated, Factor IX, antithrombin)
- Medium risk: repeated doses required to pass the 1% risk threshold; recipients may receive threshold dose (intravenous immunoglobulin, albumin?)
- Low risk: products usually given infrequently in lifetime; very large numbers of doses required to cross risk threshold; recipients highly unlikely to receive such doses (intramuscular immunoglobulin, anti-D).

The issue of whether to use the annual or cumulative dose in the risk calculation for individuals was less serious than previously supposed because:

- Only one dose was required to cross the threshold for high risk products
- The combined shelf-life of implicated intravenous immunoglobulin was only three years (excluding the earliest batch used in the clinical trial).

However, it might need to be resolved in order to complete satisfactory risk assessments for the recipients of albumin, where, currently, the degree of risk remained unclear. Although some information was still outstanding, albumin could not be dismissed altogether. As an example, doses of albumin used in the SAFE (Saline versus Albumin Fluid Evaluation) study carried out in Australia and New Zealand might have been sufficient to cross the risk threshold had some of the implicated products been used.

The proportion of the total yearly output of products by the fractionators which was implicated was relatively low: 23% or lower, except in the case of albumin where the proportion was 55% or lower.

Previous notifications

The development of vCJD in three donors (six donations) had been reported to BPL in 1997. In accordance with guidance at the time, consignees were not notified of products made from these donations if they had expired. Implicated products that were still within shelf-life were withdrawn. Some recipients (particularly of Factor VIII and Factor IX) were traced and informed by their clinicians.

In 1999, SNBTS were advised of a donor with possible vCJD who had provided two donations. The products were traced and all had expired several years previously. Consignees were not formally notified. Information on clotting factor batches was passed to haemophilia centres at their request. Patients were offered the choice of whether to be informed of their possible exposure.

In 2000, BPL was informed of a further donor who had developed vCJD. The two donations were traced and the products identified. Guidance at the time required consignees to be notified of all products, regardless of whether they were still within shelf-life. Some recipients (particularly patients who had received Factor VIII and antithrombin) were traced and informed by their clinicians.

In some cases, patients had already been notified where the risk was now known to be low ie recipients would be unlikely to have reached the risk threshold.

Discussion of technical update

It was **agreed** that:

- a recommendation be made to the Panel that recipients of products in the 'low risk' category should not be notified
- SEAC should be asked at their meeting on 29th April to review the issue of the annual vs cumulative dose
- All stages of the notification should explicitly reflect the following five components on which its rationale was based:
  - The DNV risk assessment of infectivity endorsed by SEAC and ACDP
  - The determination by the Panel of a risk threshold exceeding 1%
  - The relative likelihood of a possibly infective dose
  - The fact that to date there was no evidence of transmission to recipients of plasma products
  - The notification strategy concerning a threshold of additional risk reflected a context whereby the majority of the British population were already at some risk of vCJD from eating beef (this was not so in the case of recipients outside the UK).

Other issues raised included:

- Albumin and antithrombin had been used as excipient in some products which would be expected to give rise to a lower risk, but the implicated batches had not yet been traced. It was **agreed** that this would be made

explicit in the notification exercise and that, until a risk calculation was available, a statement would be made to the effect that products where albumin had been used as an excipient were 'probably' low risk.

- One area where more information was required was how the products were used in clinical practice at the time they were available. It was **agreed** that an approach would be made to the appropriate specialist committee of the Royal College of Physicians to obtain a specialist opinion on clinical practice at the time.
- An allied issue was that of use of the plasma products for purposes which were not licensed, for example the use of immunoglobulins off-licence.
- Also raised was the use of prothrombin complex concentrates for the emergency reversal of Warfarin in accordance with BCSH guidelines, including before cardiac surgery. This was considered to be an issue for individual clinicians but one which needed to be mentioned in the information for NHS Trusts.
- It was likely that some recipients of intravenous immunoglobulin G, , would reach the risk threshold, but only where albumin had been used as an intermediate, not where it had been used as an excipient. (The dose was 0.2-0.4g/kg 3-4 weekly for primary and secondary immuodeficiencies; 1-2 gm / kilo as a single dose, sometimes repeated, for autoimmune disorders.)
- Albumin 20% was used only in a small number of patients, but albumin 4.5% was widely used, usually as a plasma expander. The volume received might be limited by the need for blood components to avoid haemodilution in a medical situation of this kind.
- Plasma exchange patients might fall into the contactable group.
- There is a National Registry of Kawasaki patients, another group treated with intravenous immunoglobulin.
- The documentation of batches received by individual patients before 1990 was reported to be very variable. The tracing of batches to individual patients in paper records was likely to be a time-consuming process and, even then, some patients might be deceased or hard to locate. Concern was expressed about local teams being required to do a lot of work only to find that there was no need to notify any patients. A feasibility study in one or more trusts was proposed. It was **agreed** that, whilst the notification to consignees was required to be complete, it should be possible for the Panel to list the exact product batches where local investigations needed to be undertaken, working with the Committee for Proprietary Medicinal Products and keeping the Medicines and Healthcare Products Regulatory Agency informed.

Estimate of the proportion of each sub-group actually exposed to implicated batches

Professor Gill stated that the core issue concerning notification was to see whether different patient subgroups merited different notification strategies. For example, in a group where the majority of individuals were likely to have reached the threshold of risk, it might be appropriate to use a blanket

approach, informing them all that public health measures needed to be undertaken. By contrast, where only a small minority of a particular patient population might be at increased risk of developing vCJD, it might be appropriate to relieve the anxiety of the many by tracing the individual recipients of implicated batches and conducting an individual risk assessment for each one. If this was an acceptable approach, what proportion of individuals likely to be at increased risk, as determined by the Panel, would be used to determine the policy for notification?

It was **agreed** that transparency was an important principle and care needed to be taken regarding the fact that notifications were likely to be ongoing, with some individuals possibly crossing the risk threshold not at the initial stage, but later. It was also **agreed** that a new dataset needed to be compiled of notifications of implicated donations by year to help estimate the likely rate of future notifications.

People with haemophilia

Professor Hill presented data from the Haemophilia Centre Directors' Organisation showing the proportion of the haemophiliac population who had received plasma products. The use of Factor VIII units was rising by approximately 10% a year, whilst the use of Factor IX was rising but at a lower rate. This was thought due to changes in treatment practices, rather than a change in the incidence of the disease. The proportion of Factor VIII manufactured by BPL during the relevant period ranged from 32% to 78%: the number of recipients of implicated plasma products was likely to be high, although some people with haemophilia could be excluded from the notification, for example, some children who had received only recombinant products and patients who had received only products manufactured from foreign plasma. In effect, the recipients of implicated products fell into three groups: low risk, high risk and 'open-ended' where the threshold of risk might be crossed at some future date. Professor Hill emphasised the importance of transparency in the notification exercise so as to re-build and maintain the trust of patients and clinicians.

It was **agreed** that an 'umbrella' approach should be recommended to the Panel for haemophiliacs who had received British plasma products since 1980 (the earliest date at which the British population was exposed to BSE), informing them that public health measures would be taken for the whole group and giving them the choice of discovering whether they had received an implicated batch if they wished. Whether or not they chose to know, the need for special public health measures would be recorded in their medical notes. This was especially important to protect haemophiliac children not at background risk undergoing surgical procedures in specialised units.

It was **agreed** that a separate piece of work be undertaken to clarify guidance in relation to the use of endoscopes, since gastro-intestinal bleeds occur more frequently in haemophiliacs.

At a later stage individual risk assessments may be carried out for the purposes of long term follow up, with the information being recorded on the haemophilia database. Further ethical approval is likely to be necessary (in addition to the existing approval) to record exposure to implicated batches and for a flagging exercise to determine whether any recipients of implicated products subsequently develop vCJD. The NCJDSU already examine all death certificates where CJD is the cause of death.

People with Primary Immunodeficiency Disease

Dr Helbert reported that intravenous immunoglobulin G was issued by pharmacies and much usage for particular conditions was not officially recommended. Only a minority of people with PID had been exposed to VIGAM (about 200) or the SNBTS product (about 50). The average annual dose was 350g so some recipients may have crossed the risk threshold if they have received implicated batches. It was therefore proposed that an individualised approach to the notification of this group of fewer than 300 patients be taken, particularly as the implicated batches may have been confined to certain regions. It was proposed that individual clinicians would submit information on the volume of implicated plasma products received by their patients to CDSC for the risk calculation to be undertaken. Patients shown to have crossed the risk threshold would then receive this information from their clinician. It was considered that the exercise could be synchronised within a period of two weeks, with sufficient planning. Dr Helbert recommended a fully individualised risk assessment, including batches where the intermediate and excipient were implicated, and considering the cumulative rather than annual doses. There would be complementary information on the PIA website. Endoscopy was regarded as a high risk procedure for PID patients because of lymphoid hyperplasia and it was therefore more likely for abnormal prion protein to contaminate instruments.

It was pointed out that patients with PID were not being given the choice of finding out whether or not they were at increased risk of developing vCJD, unlike the patients with haemophilia. Dr Helbert was therefore asked to consider whether there was a subgroup of the PID population who might be subject to special public health measures, but who could choose not to receive an individualised risk assessment. It was **agreed** that this would be discussed with PIN/PIA representatives.

[In Scotland, PFC products are released through regional transfusion centres, hospital blood banks and haemophilia centres. Commercial products are mainly issued through hospital pharmacies.]

Patients with other conditions

This was a diverse group. It was **agreed** that subgroup members would send information about other conditions requiring treatment with plasma products to the HPA CJD team. A CMO decision may be necessary to determine the extent to which patients in this group should be traced, given the anticipated difficulties in finding records and tracing patients in this potentially large and

heterogenous group who are unlikely to have existing professional support networks.

Management of exposed patients

It was **agreed** that letters would be sent to all centres about the notification exercise, not just to those which were known to have received implicated plasma products, so that everyone was aware of the process. Dr Jenkins offered to explore developing a restricted BPL internet site where a list of implicated batch numbers could be located.

It was **agreed** that the letter to Medical Directors needed to contain detailed information about the stratification of risk, the apparent risk for each implicated product batch and the dosage required of each product batch to cross the threshold of risk and a request to pass this information to individual clinicians so that they might appraise their caseload. It was considered acceptable for this process of notification to take longer than in the case of patients with haemophilia and PID, because of the anticipated difficulties in tracing records

It was **agreed** that the HPA CJD team would draw up a detailed plan for the dissemination of information and the notification of the three different groups of patients. The first priority was to disseminate information about the implicated product batches to consignees. All the information provided needed to be clear, simple and honest.