Inquiry: variant Creutzfeldt-Jakob Disease (vCJD)

Submission by Dr Matthew Helbert on behalf of the UK Primary Immunodeficiency Network

1 Executive summary

Immunoglobulin is a type of plasma product. About 5000 PID patients in the UK rely on life long immunoglobulin infusions. In 1997 use of British plasma to manufacture immunoglobulin was stopped as a precautionary measure. PID patients subsequently received immunoglobulin manufactured from non UK sourced plasma. However by 1997, some PID patients had already been exposed to immunoglobulin manufactured from blood donated by people who went on to develop vCJD.

In 2004, an individual risk assessment was carried out, using tracking of which batches of immunoglobulin had been infused into which patients. The risk assessment suggested a low risk of exposure for any given PID patient. No special precautions were subsequently required for PID patients, who have thus not experienced stigmatisation or anxiety. Since 2006, ongoing surveillance, relying on tissue sampling, has shown no evidence of prion infection in PID patients.

In the future, it would be difficult to recommend that patients choose immunoglobulin manufactured from UK sourced plasma, unless each donor had been screened for prion infection with a well evaluated blood or urine test. The safe reintroduction of UK sourced immunoglobulin would be further enhanced by electronic batch tracking, to facilitate individual risk assessment and product recall in the event of further prion infection (or other pathogen) outbreaks.

2 UKPIN

UKPIN (http://ukpin.org.uk)is the professional body for doctors, nurses and scientists involved in the care of patients with primary immunodeficiency disorders (PID). In 2006, UKPIN initiated a study on surveillance of prion infection in these patients, lead by Dr M Helbert.

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3 Background to immunoglobulin and prions

Approximately 5000 primary immunodeficiency patients in the UK require lifelong injections with immunoglobulin. Immunoglobulin is manufactured from donated plasma, along with Factor VIII (for haemophilia). Manufacture of these plasma products (or 'blood products') requires pooling several thousand plasma donations. As a result, plasma products have transmitted blood borne pathogens and, in the past, immunoglobulin and has caused outbreaks of hepatitis C. Factor VIII is manufactured slightly differently has been contaminated with HIV and hepatitis C virus. As a precautionary response to the BSE and vCJD epidemics, processing of UK sourced plasma ceased in 1997. Since then, PID patients have only received immunoglobulin manufactured from plasma imported from overseas. There has been no evidence of prion transmission via immunoglobulin, although there is some evidence that a haemophiliac patient was infected via Factor VIII.

4 2004 prion infection risk assessment

Once it became clear that some blood donors went on to develop vCJD, The CJD Incidents Panel initiated risk assessment programmes for patients who had received UK sourced plasma products, as part of the strategy to reduce the risk of secondary infection. UKPIN and patient representatives decided that an individual risk assessment approach was best for PID patients: Data were collected on how much of any given implicated batch of immunoglobulin each patient had received. A noteworthy observation is that it was often very difficult to track down which batches of immunoglobulin had been dispensed by pharmacies and infused into patients. To do this, paper records had to be searched by hand for evidence of batch tracking. However, the result of the individual risk assessments was that no PID patient was assessed at being at more than 1% risk of exposure to abnormal prions. Thus PID patients did not require special measures, such as quarantining of endoscopes after procedures. On the other hand, the haemophilia community chose to undergo a collective risk assessment, and when this established that some patients could be at risk, several thousand haemophiliacs faced difficulties arranging surgical and endoscopic procedures, along with stigmatisation and anxiety.

5 Immunoglobulin manufacture since 1997

In the UK, plasma is currently discarded (at a value of about £65 per donation – G Grazzini, Blood Transfusion, 2013). Immunoglobulin continues to be manufactured in the UK and abroad, using pooled plasma sourced overseas. Unlike any other blood borne infection, no

laboratory screening test is available to rule out prion infection in donors. Donor screening questions are used to eliminate those perceived as being at high risk of prion infection, although given uncertainties of the biology of prion infection, the utility of these is very unclear. The manufacturing process includes steps to reduce the infectivity of plasma, should a donor have undiagnosed prion infection. Immunoglobulin products used in the EU contain statements about blood borne pathogens in their Summaries of Product Characteristics.

6 The impact of the vCJD epidemic on PID patients - 2004 onwards

British PID patients now only receive immunoglobulin manufactured from non UK plasma. This has placed PID patients at the mercy of a finite global immunoglobulin market, with occasional supply problems and increases in prices. The DH now operates a demand management scheme for immunoglobulins. Even though currently available immunoglobulins are perceived as safe from the point of view of prion infection, good practice is to inform patients of this theoretical risk as part of obtaining informed consent to start, or stay on, immunoglobulin. PID patients are not be able to be blood donors because they have received plasma product infusions, but also because of their underlying illness. Following the 2004 risk assessment, PID patients have not required other measures to reduce secondary infection. Despite these ongoing concerns, these is no evidence that prion infection has been a significant source of anxiety for British PID patients, including the subset exposed to UK sourced immunoglobulin prior to 1997. I am not aware of any prion – specific life insurance problems in this group.

7 PID Prion surveillance project 2006 onwards

In 2006, the DH funded a surveillance programme for PID patients exposed to UK sourced immunoglobulin. To date, 60 patients have given consent to participate and tissue samples are available on just over half of these. These samples were collected during routine surgical procedures or post mortem a median of 8 years after potential exposure to prion infection. No tissue samples show evidence of prion infection. The major limitations on these data are the long incubation period of prion infection after expsoure, the inevitable poor access to tissue samples and absence of a blood or urine test. Thus, these data can not yet reassure that no PID patients were infected with prions in the 1990s or, by inference, that it would be safe to re commence processing of British plasma.

8 Should UK sourced plasma be used to manufacture immunoglobulin?

There are no data on the opinions of PID patients or their clinicians on this question. However, any patient embarking on life long immunoglobulin treatment could receive either a product manufactured from plasma sourced overseas, from a country with no history of BSE or vCJD, or UK sourced plasma. In the UK there is thought to be a measurable rate of background asymptomatic prion infection, but no blood or urine test to screen individual donors. Even though prion transmission has not been shown to take place via immunoglobulin, it would be illogical for a patient to choose immunoglobulin manufactured from UK sourced plasma, until a sensitive prion screening blood or urine test is in routine use.

9 Lessons Learnt

9.1 If plasma processing is resumed in the UK, robust means of **batch tracking** are required for on going risk assessment. The process must enable rapid identification of which batches of product have been infused into which patients and also enable rapid product recall in the event of any future pathogen outbreaks.

9.2 **Individual risk assessment** was negative in all PID patients. No PID patients required expensive quarantining of equipment and there has been no lasting anxiety or stigmatisation. In the event of future outbreaks or donor infection, we recommend this approach over 'umbrella' risk assessment.

9.3 A **blood or urine test for asymptomatic prion infection** is a pre requisite for the re establishment of processing of UK sourced plasma. There is a reasonable chance that such a test would be adopted for screening plasma donors from outside the UK. A blood or urine test would be an invaluable research tool, for example to validate our prion surveillance study.

10 Response to TOR

Are UK policies governing who can donate blood and blood products, tissues and organs sufficiently evidence-based? Is NHS Blood and Transplant overly restrictive about who can donate, or should greater precautions be taken to further reduce risk?

Current policies are sufficiently evidence based given current technical and scientific constraints. A well evaluated prion blood or urine test would further mitigate risk.

Is the Government and its scientific advisory structure sufficiently responsive to the threat posed by emerging diseases being transmitted through blood and blood products, tissues and organs?

Up until about 2011 there were clear lines of accountability and management. For example, had our study detected a PID patient with prion infection, I would have known who to contact the CJD Incidents Panel – and this was enshrined I the ethics application for our project. However, this is no longer the case and I do not know who to contact or how they would respond.

Has the threat of ongoing transmission of vCJD through the blood and blood product supply been adequately mitigated?

Blood supply – the risk would be better mitigated with a well evaluated prion blood or urine test.
Blood products (plasma products) - currently, well mitigated, although with an expensive solution, ie using products manufactured from non UK plasma.

What are the strengths and weaknesses of NHS Blood and Transplant's strategy, "Taking Organ Transplantation to 2020"? What further changes could be made to safely increase the supply of blood and blood products, tissues and organs?

No specific response.

What lessons could be learnt from the screening and donation practices of other countries?

No specific response.