ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF BLOOD AND TISSUES FOR TRANSPLANTATION

EXTRAORDINARY MEETING FRIDAY 18 FEBRUARY 2000

140B SKIPTON HOUSE

Present: Dr Pat Troop (Chair)
Dr P Doyle
Dr DW Gorst
Dr A Keel
Dr B McClelland
Dr M McGovern
Dr H Nicholas
Dr F Rotblat
Dr Bill Smith
Dr TJ Snape
Dr J Stephenson
Dr RE Warren
Dr A Wight
Dr L Williamson (representing Dr Robinson)

Secretariat: Gwen Skinner, Ann Willins

Introduction

1. Dr Troop thanked members for attending at very short notice to discuss the implications of new research from the Institute of Animal Health (IAH) on the transmission of BSE through plasma in mice. The exact date of publication was not known as yet, but was expected to appear in the Lancet in the coming weeks. SEAC had discussed the research at their meeting on 15 February and would issue a public summary. It was important to have MSBT's view before the issue of the SEAC public summary.

Research

2. Dr Wight advised members that the research carried out by the IAH was part of research into whether processing made blood products safer, as an alternative to spiking studies. About 55 mice had been innoculated intracerebrally with BSE. When symptoms appeared, the mice were exsanguinated and the blood was pooled and separated into fractions: plasma, buffy coat and red cells. The plasma fraction was innoculated, again intracerebrally, into 48 mice and 4 developed BSE.

3. Dr Wight reviewed earlier research by Paul Brown, published in December 1999, on blood infectivity in an experimental model of TSE in which mice were innoculated intravenously with a mouse adapted strain of familial TSE. The research had set out conclusions as to why blood components do not transmit

familial CJD. The BSE strain used in the IAH research was more relevant to variant CJD and showed transmission of BSE through blood in previously asymptomatic mice for the first time.

SEAC discussion

4. MSBT members were advised that for their meeting SEAC had received an extract from the November/December edition of "Transfusion", on the research led by Paul Brown. SEAC had not discussed the research previously, but it was considered useful background to the IAH research. In their discussion of the IAH research, SEAC had not made any specific points about blood, taking the view was that there were no significant new implications. They had expressed a wish to see more research using blood from animals in the pre-clinical phase of spongiform encephalopathy.

MSBT discussion

Methodology

5. MSBT sought more information about the methodology of the research in order to assess its significance for clinical practice and the blood services. Key questions were whether the pooled plasma used in the research was platelet contaminated, indicating whether the infectivity was in the plasma or the platelets; whether the plasma had been separated and processed in the same way as human plasma is to make FFP and as used for blood products, eg leucodepleted, centrifuged, filtered; whether fractionators had advised the research team, whether the titre levels and their relevance had been considered; whether the remaining mice had been sacrificed and if so, whether there were any peripheral markers.

Other factors

6. MSBT also discussed the difference, between mice and humans, in the distribution of prion proteins, and the relative differences between the normal and abnormal proteins, in relation to clinical implications.

7. Members explored the effects of pooling on infectivity, in particular the possibility that the vCJD infectious agent could be diluted if the pool was large as suggested by the DNV risk assessment. For virally inactivated plasma, the pools were small, from 500 to 1,500 donations, and likely to be associated with increased risk.

Interim Conclusions

8. It was agreed that information on the methodology was critical. A fundamental question was the extent of any platelet contamination. The researchers would be asked about the protocol for the fractionation of the plasma, whether there was a check for platelets before innoculation, and for the protocol for all stages from the collection of the blood onward. They would also be asked about the behaviour of the

strain of BSE used, and whether prion protein was, to their knowledge, distributed anywhere outside the brain.

9. It was also crucial to gather research information on the pre-clinical phase and information on the remaining 44 mice might be helpful here.

10. The committee concluded that if the plasma was contaminated with platelets, the research did not add to existing information about vCJD transmissibility through blood. MSBT, and especially members from the fractionation centres, extended an offer to work with the researchers on design and methodology of further studies.

11. As immediate contact could not be established with the researchers, it was agreed that information would be obtained as soon as possible and sent to members. There would be further discussion at the MSBT meeting on 13 March. The SEAC press briefing would be on 16 March.

Possible implications for Fresh Frozen Plasma and Cryoprecipitate

12. The committee considered that there might be implications for the use of UK sourced Fresh Frozen Plasma and Cryoprecipitate and that these would need to be considered in the light of the methodology.

13. Members reviewed the precautionary measures which had been introduced in the light of the theoretical risk of variant CJD. The Committee on Safety of Medicines had advised that manufactured blood products should not be sourced from UK plasma for the present time. This advice did not include Clinical Fresh Frozen Plasma or Cryoprecipitate, which were not licensed blood products. At the time, there was also no capacity to obtain non-UK supplies. However, the position had now changed and it was likely to be possible to obtain non-UK supplies, mainly from the US and from paid donors.

14. Publication of the IAH research and the SEAC public summary would focus attention on the measures in place, reassuring the public that all sensible action was being taken. There was a risk that public concern about red cells and platelets might again be raised in the event of a decision to outsource FFP.

15. Members agreed that there were two basic issues to consider, the theoretical risk of vCJD in UK plasma and the known risk of viral infection from FFP sourced from outside the UK. The National Blood Service had prepared a paper listing broad options, which was tabled. The broad options were:

Non virally inactivated, single donor UK plasma – TSE risk, low viral risk
Non virally inactivated, single donor non-UK plasma – higher viral risk

Enhanced non virally inactivated single donor UK plasma – TSE risk, very low viral risk
Enhanced non virally inactivated single donor non-UK plasma – higher viral risk

Methylene Blue treated single donor unlicensed UK plasma – TSE risk
Methylene Blue treated single donor unlicensed non-UK plasma – acceptable viral risk, acceptable toxicity risk if MB removed

Solvent detergent treated, pooled, licensed UK plasma – TSE risk and probably consequently unlicensable

Solvent detergent treated, pooled, licensed non-UK plasma – acceptable viral risk (known viruses) if B19 genome testing undertaken, theoretical risk from unknown non-enveloped viruses.

16. The NBS paper advised that, balancing the risks of pooled FFP and single donor FFP, there was a risk of TRALI (Transfusion Related Acute Lung Injury) with single donor units, up to 15 cases a year being reported to SHOT. Pooling was helpful in reducing TRALI, because the antibodies were diluted from a high titre.

17. The committee agreed that as well as considering the non-UK sourcing of FFP, the unnecessary use of FFP in the UK should be reduced in line with 1992 guidelines. It was widely recognised that FFP was overused in the UK in clinical practice.

18. Members advised that the cost of importing FFP was likely to be high, anything from £60 to £100 per unit compared with £20 a unit for UK sourced FFP. If UK FFP was no longer to be used, the cost implications for the NHS would be significant.

19. Dr McClelland advised that fibrinogen (which could be made from non-UK plasma) could replace FFP and Cryoprecipitate in the future. It could soon be made available on a named patient basis as it was not licensed, and clinical trials were being set up.

20. It was agreed that there would be further discussion of FFP at the 13 March meeting.

Publication of research and SEAC summary

21. Members recognised that there could be alarm when the Lancet article and SEAC public summary were issued. People who received blood and blood products in the 1980s and 1990s would seek information out. It was important to be clear about the detail of the precautionary measures already in place.

22. Dr Williamson advised that the level of effectiveness of FFP leucodepletion in the UK was very good. The leucocyte and platelet counts were below the level of detection of normal laboratory analysers.

23. All newly issued FFP and Cryoprecipitate was leucodepleted. A planned recall of any remaining unfiltered units was now under way and would be complete by 31 March.

24. Dr Snape and Dr Perry confirmed that all blood products were being made from non-UK plasma. The rabies immunoglobulin had been delayed because of the lack of suitable hyperimmune plasma but it was now being made by BPL on a UK wide basis using US-sourced immunoglobulin. It might also still be possible to access the UK- sourced product. Dr Troop advised that it was important to ensure that adequate supplies were available, despite the minute risk, because of the imminent piloting of the pet travel scheme.

Date of next meeting

25. The meeting would be on 13 March.