The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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EMEA EXPERT MEETING ON HUMAN TSEs AND MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD AND PLASMA
1 December 2000

SUMMARY REPORT

1. Introduction

An EMEA Expert Workshop was held in May 2000 to provide an update on the latest information on human transmissible spongiform encephalopathies (TSEs) in relation to plasma-derived medicinal products[1]. A further EMEA Expert Meeting was held on 1 December 2000 to consider:

- The new information that had become available since the May expert Workshop and, in particular, the preliminary report of transmission of the BSE agent to a sheep by transfusion of blood from an experimentally infected sheep[2].
- Whether the new information affects the conclusions or the May Expert Workshop.
- Whether or not country-based exclusion of donors (e.g. time spent in UK) should be considered as a precautionary measure.

2. New information

Transmission of BSE by blood transfusion in a sheep

C. Bostock clarified aspects of the study that make it very likely that the reported transmission is a true transmission, most probably of BSE. Strain typing in mice will be used to confirm the result but this will take some time (1-2 years). No further transmissions had been seen. However, it was too early to reach conclusions since the incubation period in sheep challenged with BSE by the intravenous route is not known.

It is expected that further experiments will be set up to look at how infectivity partitions and the effect of leucodepletion. The design of such experiments was being considered including whether sheep blood will behave similarly to human blood on leucodepletion filters.

Update from R. Will

At the time of the meeting, there were 87 definite and probable cases of vCJD in the UK (45 male, 42 female), with a mean age of 29 (mean age at onset 28), and an age range of 14-74 years. The youngest case was aged 12 at onset. All cases genotyped so far are methionine homozygotes.

The case in a 74 year old is the first case found in this older age group. There is some concern that vCJD in the elderly may not be recognised. However in this case, the geriatrician recognised that the symptoms were very atypical with respect to other forms of dementia in this age group and deterioration was rapid.

Outside the UK, there are 3 cases in France and 1 case in Ireland. (The Irish case had spent time in the UK.)

There is still an upward trend in the number of UK cases.

There is no evidence of transmission of vCJD by blood or blood components or plasma-derived medicinal products. However, as it is an emerging disease, it is still too early to conclude on the absence of risk.

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3. Does the new information affect the conclusions of the May Expert Workshop?

The European Commission's Scientific Steering Committee had concluded that the preliminary information from the sheep transfusion experiment reported in the Houston *et al* paper "does not change the basis of risk assessment" but "it does reinforce the substance of previous opinions by the scientific committees"[3]. In line with this opinion, the EMEA Expert Meeting considered that the conclusions of the May Expert Workshop were still valid and discussed further precautionary measures that might be considered.

It was suggested that further donor exclusion measures might be considered such as neurosurgery and permanent (rather than temporary) exclusion of donors who previously received transfusions. The percentage of donors lost by exclusion of donors who have received transfusions may be significant (approx. 5% loss in France when this measure was introduced). This suggestion would be drawn to the attention of the European Commission (Health and Consumer Protection Directorate-General) for its consideration.

The CPMP recommendation[4] to avoid using, as an excipient, albumin derived from plasma collected within countries where a number of cases of vCJD have occurred was endorsed. It was again clarified that this was an issue of supply rather than safety. A country that has had cases of vCJD has the potential to have further cases and this could involve a blood donor. A single batch of albumin may be used to produce a number of batches of a medicinal product because of the small amounts that are typically used. A recall could affect complete stocks of a product and create severe shortages.
Since this is a supply issue, care is needed that supply problems are not created when it becomes advisable to make a transition to an alternative source of albumin for use as an excipient (e.g. in the case of albumin derived from plasma collected in France).

The lymphoreticular involvement seen with vCJD and the finding that TSE infectivity, when present in blood of experimentally infected animals, has been found mainly in the buffy coat, leads to the consideration of leucodepletion as a precautionary measure. There is currently insufficient information to establish whether leucodepletion will be effective and further research is needed[1,5]. In the meantime, leucoreduction steps (filtration/centrifugation) as soon as possible after collection of blood/plasma could be considered as a precautionary measure to reduce the white blood cells contaminating the starting plasma.

4. Country-based donor exclusions

The meeting considered the following questions:

Whether or not exclusion of donors who have spent some time in the UK should be considered as a precautionary measure?

Information from donor surveys within Member States and written contributions from associations involved in blood collection and plasma fractionation were taken into account in the discussion.

Residence in the UK is a recognised risk factor for vCJD and has led to the UK deciding no longer to fractionate from UK plasma.

Germany and Italy have decided to follow the exclusion criterion used by the US and Canada (i.e. exclusion of donors who have stayed for a cumulative period of 6 months or more in the UK between 1980 and the end of 1996). Germany chose the 6 month period as it was considered impractical to set different criteria. This exclusion criterion can be implemented in Germany and Italy without too great a loss of donors. There will be some countries where this measure could not be sustained because of the loss of donors.

Member States considering such a measure need to make a benefit/risk analysis. The evaluation done in France on this issue indicates the factors that need to be taken into account[6]. These include the pattern of

travel to the UK and the endogenous risk from BSE within the Member State and from meat imports. The viral risks introduced when moving to first-time donors also needs to be considered.
The benefit of such an exclusion measure is difficult to evaluate. Available information indicates that the pattern of travel to the UK is different in the EU compared to the USA. Also the risk of donors having been exposed to BSE risk in their country of origin has to be recognised.
The benefit of such a measure should be balanced against the risk of shortage in blood supply (transfusion as well as plasma-derived medicinal products).

It was noted that different decisions in different Member States have the potential to create difficulties with the movement of plasma-derived medicinal products between Member States.

Whether or not blood/plasma that is collected in countries that have cases of vCJD should continue to be used in the manufacture of medicinal products derived from human blood and plasma?

France indicated that a detailed evaluation is underway and the result would be presented to ministers very soon (see postscript to this report).

It was agreed that a similar evaluation should be undertaken in any country where cases of vCJD are found. (In this respect, it should be noted that CJD cases will be reported according to the country of residence at the time of disease onset.)

It has to be recognised that any precautionary measure based on population exclusion can be expected to have a large impact on the overall supply of plasma-derived medicinal products. Such measures could become progressively impracticable should the epidemiology of vCJD change.

Whether or not exclusion of donors who have spent some time in France should be considered as a precautionary measure?

The group decided that it should await the decision of France on whether it would continue fractionating from French plasma.

Whether or not blood/plasma that is collected in countries that have the potential for vCJD development should continue to be used in the manufacture of medicinal products derived from human blood and plasma?

The group considered that there was a difference between a potential risk and confirmation of that risk with the occurrence of cases.

Postscript

The latest recommendations from France on the analysis of risk of transmission of vCJD by blood and its derivatives was published in December[7]. France has decided that plasma collected in France can continue to be used for fractionation. Leucodepletion is recommended as a precautionary measure. Donors who have spent more than a cumulative period of 12 months in the UK between 1980 and end of 1996 will be excluded from donation.

References

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2. Houston F, Foster JD, Chong A, Hunter N, Bostock CJ. Transmission of BSE by blood transfusion in sheep. Lancet 2000; 356:999-1000.

3. Scientific Steering Committee Opinion on "The implications of the Houston *et al* paper in The Lancet of 16 September 2000 on the Transmission of BSE by blood transfusion in sheep. (The Lancet, vol. 356, pp 999-1000; 955-956; 1013), adopted 26-27 October 2000. http://europa.eu.int/comm/food/fs/sc/ssc/out143_en.pdf

4. CPMP Position Statement on "New variant CJD and plasma-derived medicinal products", February 1998, CPMP/201/98. http://www.emea.eu.int/pdfs/human/press/pos/020198en.pdf

5. "Update of the Opinion given by the Scientific Committee on Medicinal Products and Medical Devices on the Risk Quantification for CJD transmission via substances of human origin, 16 February 2000.http://europa.eu.int/comm/food/fs/sc/scmp/out28_en.pdf

6. "Revision of measures to minimise the risk of TSE transmission via blood products", Report of expert group convened under the aegis of the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) and the Etablissement Français du Sang (EFS), February 2000. http://afssaps.sante.fr

7. "Analysis of the risk of transmission of new variant Creutzfeldt-Jakob disease by blood and its derivatives", Recommendations of expert group convened at the initiative of AFSSaPS, 11 December 2000. http://afssaps.sante.fr

Meeting of TSE Expert Group on Human TSEs and Medicinal Products derived from Human Blood and Plasma

Friday 1 December 2000

Participants

Rapporteur	**Prof. J-H Trouvin** Agence Française de Sécurité Sanitaire des Produits de Santé,France	
TSE Expert Group	**Prof. D. Dormont** Laboratoire de Neuropathologie Experimentale et Neurologique, France	
	Prof. J. Löwer Paul-Ehrlich-Institut, Germany	
	Prof. M. Pocchiari Istituto Superiore di Sanità Laboratorio di Virologia, Italy	Via Audio Conferencing
	Dr. L. Tsang Medicines Control Agency, UK	
Invited TSE Experts	**Prof. C. Bostock** Institute for Animal Health, UK	
	Prof. R. Will National Creutzfeldt-Jakob Disease Surveillance Unit Western General Hospital, UK	
CPMP Chairman	**Prof. J-M Alexandre** Agence Française de Sécurité Sanitaire des Produits de Santé, France	Afternoon only
CPMP/BWP/BPWG Members and Experts	**Dr. G. Duff** Medicines Control Agency, UK	
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