Dr Metters

From: Mike McGovern

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Copies
Sue Shepherd PS/CMO
David Hewlett
David Jefferys
Frances Rotblat
Ailsa Wight
Nich Wingfield
Charles Lister
Mike Skinner
Glyn Austin
Gwen Skinner

Briefing for Dr Metters for the FDA TSEAC Meeting -18 December
You asked for briefing notes on the FDA papers in preparation for your visit 18 December. This note covers i) the issues for discussion paper at attachment 1 ii) the FDA Questions to TSEAC which are the main purpose of this meeting and iii) comments on attachments 9, 10 and 11 forwarded under separate cover. As you requested I enclose the UK equivalent to the US document at attachment 7 -apologies for the quality of the photocopy.

i) Issues for discussion paper
Should FDA recommend the deferral from blood donation of persons with possible exposure to Bovine Spongiform Encephalopathy (BSE) as a precautionary measure to reduce the risk of blood transmission of new variant Creutzfeldt Jakob Disease (nvCJD).

<u>The risk of transmission of nvCJD through blood or blood products</u>
Unmeasurable at present in the absence of any cases. The Det Norske Veritas risk assessment will be discussed by SEAC on 11 January. They are then likely to advise Ministers about the contents. The intention is for DNV to publish the report, once Ministers agree.

<u>The potential risk</u>
The nvCJD agent behaves differently to classical CJD. There appears to be a significant reticuloendothelial phase. Involvement of the follicular dendritic cells/antigen presenting cells and/or B lymphocytes in the disease process. You will need to be aware that a new paper in Nature is said to cast doubt on the role of the lymphocyte. I will get this for you as soon as the Library opens.

The appearance of nvCJD is associated in time with the BSE epidemic and the agents are indistinguishable. Therefore there is a strong but not proven causal link between the human condition and eating beef from infected cattle. Human to human transmission through blood and blood products cannot be ruled out especially because of the significant RE phase of disease.

<u>The relative risks</u>

Assuming that the cause of nvCJD is in fact BSE, then the risks to the general UK population from eating beef will be greater than those of other countries as many more people will have been exposed. The DNV risk assessment suggests that up to 5% of the donor population might be at risk depending on infectivity, the amount of beef eaten, contamination with nerve tissue as the main reservoir of the transmissible agent, the length of exposure and genetic susceptibility.

In addition, residents in the UK, visitors to the country and all those who have eaten UK beef between 1980 and the present are potentially at risk. This is likely to be less than that of the resident population again relative to the exposure and susceptibility. The risk of their transmitting nvCJD through blood and blood products, if there is such a risk, is therefore likely to exist albeit at a lower level than that of the UK population.
The risk is likely to be less in other BSE countries relative to prevalence of cases but it would be impossible to determine this and a blanket ban might need to be considered.

Where to stop

Our position in the UK is that any possible human to human transmission should be avoided. That is the basis for our importing plasma to make blood products and leucodepleting the blood supply. We are on record as saying that if there were an accessible market for labile blood products we would import these also. This implies that if we were running a blood service in another country we would screen out those at risk which would include UK residents between 1980 and the present time.

However just as in the UK we would have to balance the maintenance of the blood supply against the theoretical and unquantifiable risk of nvCJD transmission. If the exclusion compromised supply as would possibly be the case in Canada then we would have to consider how to make up any shortfall through importing blood or increasing greatly those non UK donors. In the US this is unlikely to be the case where links with the UK are not so intimate and there is a huge indigenous population.However if the situation were to be extended to US tourists to the UK and those who have eaten UK beef in the 1980 to the present day period then this might have a significant effect on supply.

From the US point of view, having banned all beef imports from Europe, the deferral is likely to be extended to all Europeans with increasingly significant implications for supply. If this were to be the case it might deflect attention from falling specifically on UK donors. This is strengthened by the fact that one on the people who died from nvCJD was French.

Current scientific knowledge

The main papers are presented in Attachment 2 of the papers. These will no doubt be summarised by several participants. You have a full grasp of the issues and the main findings. As above I will look up the latest Nature article on the role of the B lymphocyte. The evolving science is of course an issue for SEAC and this could be put to them in January.

The data to support the similarity of the BSE and nvCJD agents

Again Bob Will is the expert here. The animal research comes from his group Moira Bruce and from Andrew Hill working with John Collinge at St Mary's. Both articles were published in Nature in October 1997, and are copied in the FDA papers.

Processes which inactivate agents responsible for BSE or nvCJD
I am not aware of any that can be applied to biological treatments. You are aware of the viability of the agents in relation to most physical treatments -20,000 ppm of chlorine or full sterilisation reduce but do not completely eliminate prion infectivity.

Relative risks with different products
Processing of plasma and the and the manufacture blood products is likely to reduce survival of the agent. Spiking studies have indicated decreasing transmission rates the more intensively processed the blood product is. BPL have made an extensive assessment of risk reduction associated with the various processing steps, but this is based on probabilities and knowledge of the specific processes is not an exact science. The issues are covered in the DNV and EOR risk assessments.

Classical compared with nvCJD human, animal and laboratory data
Different clinical diseases, different transmission patterns, different handling by body. There is no epidemiological evidence that classical CJD is transmitted through blood transfusion or treatment with blood products. FDA have agreed with this and repealed their withdrawal policy for classical CJD implicated blood components and blood products. See attachment 4 of the FDA papers. The limited animal and human data available on nvCJD indicates that the possibility of a greater transmission risk cannot be ignored.

Laboratory tests for nvCJD
None available as yet. Hopeful of diagnostic/screening test within two years. The immunocytochemistry to be used in the proposed tissue studies is based on finding of PrP in CD 21 cells follicular dendritic cells. This is described in the papers in attachment 2. The development of monoclonal antibodies to the abnormal protein protease resistant PrP characteristic of nvCJD and TSE is currently the most likely candidate for a screening or diagnostic test.

Genetic predisposition to nvCJD
Of the 32 nvCJD cases so far all those examined have been homozygous for methionine at codon 129 PrP. The frequency of classical CJD is similar in codon 129 genotypes. It may be that methionine/other genotypes are less susceptible to abnormal prion infection , require longer incubation and could form the later vanguard of any epidemic. Careful examination of the cases over the coming years will be needed to determine the exact relationship.

How well characterised is food borne exposure/dietary history
The link is not well characterised. The ubiquity of beef eating in the UK is likely to preclude early definition of any epidemiological link using dietary history as has been the case in general CJD surveillance. It may in the future be possible to link population levels of infection to the size of the BSE epidemic in the various European countries and the decline of the disease in cattle as well as to the various regulatory beef controls put in place.

Donor deferral criteria
How wide ? The UK and Europe? All BSE countries in effect Europe as is the case for the US ban on beef imports.

Impact on US blood supply
The greater the scope of deferral the more likely it is to impact on supply in the US. I presume the FDA/TSEAC group will have scoped the impact of the possible deferral criteria on supply and if not they should, using immigration data etc.

ii) Questions for FDA meeting to address
The Transmissible Spongiform Encephalopathy Committee (TSEAC) will consider the following questions:

> should FDA recommend the deferral from blood donation of persons with possible exposure to Bovine Spongiform Encephalopathy (BSE) as a precautionary measure to reduce the risk of blood transmission of new variant Creutzfeldt Jakob Disease (nvCJD).
>
> how should FDA plan to refer possible nvCJD cases to CDC for investigation and considering FDA's precautionary withdrawal policy for nvCJD.

The Issues
The specific issues for consideration are

> exclusion of donors who have resided in the UK or other BSE Country
>
> distinguishing between donors who were resident in BSE countries between periods of higher and/or lower risk of exposure to the BSE agent.
>
> excluding donors who had less intense exposure to beef products based on limited travel to a BSE country? When did they travel, how long were they there, what did they eat?
>
> recommendations on the withdrawal criteria for blood components and plasma products based on these donor deferral criteria
>
> the precautionary withdrawal of plasma derivatives to which a possible nvCJD donor contributed pending histological/immunocytochrmical/other confirmation of the clinical diagnosis.
>
> diagnostic criteria for withdrawal or reinstatement of products to which a donor with a possible diagnosis of nvCJD contributed.

Possible outcomes
Deferral of UK residents: It is likely that the FDA will give serious thought to deferring donors who were resident in the UK from the late 70s/early 80s to the present be they US or UK citizens or indeed from any other country. This would be logical given the scale and demography of the BSE epidemic, the proposed link between BSE and nvCJD, and the fact that such a move is most unlikely to effect the US blood supply significantly. In reality the move would mirror the precautionary risk reducing measures taken by the UK, importing plasma from countries which have no BSE/nvCJD and leucodepleting the blood supply. By deferring UK residents the US would effectively be putting in place the same

precautions we have for blood products made from plasma and of course the deferral would allow them not to proceed to expensive leucodepletion. Of course a further consequence of this would be that the plasma we are importing from them would at relatively lower risk of nvCJD.

Deferral of residents of BSE countries: In the US this would in effect include all European residents, under their current restrictions on the import of beef and beef products. The same residency time frame is likely to apply. This would have a proportionately greater effect on supply and be more difficult to implement. In addition there might a more vocal reaction from this larger group especially those from countries where there is very little evidence of BSE and even more remote theoretical risk of human to human transmission of nvCJD through blood and blood products. However it would be a logical approach given the FDA food remit and would diffuse focus from the UK and UK blood/blood products and beef.

Deferral based on degree of exposure to beef: This refers to basing donor deferral on the degree of exposure to BSE contaminated beef. An empirical system would need to be devised combining, country visited, date of visit, time spent there, the prevalence of BSE, the restrictions on importing British beef and no doubt a range of other parameters. This would be very difficult to devise and implement. It would include as well as residents all tourists to either the UK and/or all BSE countries between the late 70s/early 80s and the present as well as those travelling out of the US until such time as all BSE is irradiated. While it is stated that only 5% of the US population travels abroad this measure would be likely to have a significant and protracted effect on the US blood supply.

Withdrawal criteria for blood components and plasma products based on these donor deferral criteria: The three scenarios at 5, 6 and 7 above would be increasingly complicated to introduce and would in turn have a proportionately greater impact on the US blood supply and perhaps the blood plasma/product industry. The withdrawal of blood components or blood products based on these criteria would again present serious operational and logistical problems for the transfusion services. The fact that a significant proportion of the plasma industry in the US is now from specially selected stable paid donors might mitigate the residency/tourist effect.

Withdrawal of plasma derivatives to which a possible nvCJD donor contributed: This is likely to reflect current Uk National Blood Service and UK/European regulatory mechanisms. The internationally recognised and accepted diagnostic criteria developed by the CJD Surveillance Unit are likely to apply. These were successfully employed late in 1997 since when there has not been a further case.

Diagnostic criteria for withdrawal or reinstatement of nvCJD implicated blood products: Again the developing range of tests are likely to be employed. These are at a very early stage as yet and difficult/time consuming. In time more routinely usable sensitive and specific tests are likely to be developed and used.

iii) Attachments 9 to 11

Attachment 9 is a set of tables figures and graphs summarising the BSE epidemic in

Europe particularly in the UK. Data are presented fora a range of countries dating back to the early 1980s. The data plot the rise and fall of the BSE epidemic and there is no new information. The information is straight from the MAFF website.

Attachment 10 contains e-mails from five US citizens to the FDA's TSEAC all urging a ban on or withdrawal of blood or plasma donations from people with classical or nvCJD. In particular they refer to the banning of UK and EU donors. The arguments are not scientific and refer variously to cases of children treated with implicated products (albumin from a batch containing a classical CJD donor) and to iatrogenic CJD from dura mater.

Attachment 11 contains four sets of minutes from the FDA's Blood Products Advisory Committee and TSEAC.

> *Minutes of BPAC 15/16 December 1994* charts the case of the withdrawal of blood components/products where a long term voluntary donor was diagnosed as having CJD and considered donor deferral in relation to CJD risk history.
>
> *Minutes of the Special Advisory Committee on CJD 29 June 1995* outlines the development of the US policy on the withdrawal of blood and blood products where a donor was subsequently found to have developed classical CJD. It also considered in detail donor deferral in cases where there was a history or family history of CJD.
>
> *Minutes of TSEAC 2 July 1996* further defines withdrawal policy in relation to blood and blood products in relation to critical supply as well as donor deferral criteria.
>
> *TSEAC minutes of 7 October 1997* considered the use as excipients of plasma products from classical CJD implicated plasma pools. It advised withdrawal of such products with the exception of those using implicated albumin -however where albumin was used in vaccines these should be with drawn. The withdrawals should be considered on a case by cases basis.

General line to take

The risk of transmission of nvCJD is theoretical and unquantifiable. The US regulatory authorities are considering what further precautionary measures they might take to reduce any possible risk of transmission of nvCJD through blood and blood products. One of these precautions is the possibility of deferring US donors who were resident in countries where cases of BSE have been reported including the UK. This is in line with the action already taken by the government in this country. There is no new or further information on the risk of transmission of new variant through blood and blood products and any action by the US is purely precautionary. Blood and blood products are essential and increasingly so for saving the lives of NHS patients. We are dependent on our UK blood donors to continue to give blood and indeed appeal for more people to come forward and donate.

Dr Mike McGovern
Health Services Directorate