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MSBT 10/14

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

GRO-C

MINUTES OF THE MEETING HELD ON 18 NOVEMBER 1996

Chairman : Dr J S Metters

Members present :
Dr A J Cant
Dr D W Gorst
Dr D B L McClelland
Prof P McMaster
Dr P Mortimer
Dr R J Perry
Dr T J Snape
Dr E A Robinson
Dr R E Warren
Professor J D Williams*

Also present:
Professor Thomas (items 1-4 and part of 5)
Dr J Gillon (items 1-3 only)

Observers:
Mrs J Dhell (MDA)
Dr P Doyle (DH)
Mr K J Guinness (DH)
Dr A Keel (SHHD)
Mrs E Lipton (Solicitor to DH)
Dr G Mock (DHSS - N.I.)
Dr I H Nicholas (DH)
Mrs G Silvester (MCA)

Secretariat:
Dr A S M Rejman
Miss A Towner
Mr M Harvey

*Present only for part of the meeting

1. Chairman's introduction and welcome

The Chairman welcomed members, and Mrs Lipton, a Department of Health solicitor who was attending to give advice on the item on HTLV.

2. Apologies for absence

Apologies for absence had been received from Dr Rotblat of MCA, who would be taking over attendance from Dr Purves; Mrs Sylvester was attending in her place. There were also apologies from Dr Toy , Dr Westmoreland (Hepatitis C look-back working group) and Dr Ruth Hall (Welsh Office). Professor Zuckerman had expected to arrive late, but in the event did not get to any of the meeting.

3. Hepatitis C look-back

3.1 The paper provided by Dr Robinson had been circulated as MSBT 10/1. The Chairman drew attention to Page 2, where the update had been amended by the Secretariat in the light of figures supplied by DHSS Northern Ireland and Scottish Home and Health Department.

3.2 Dr McClelland queried whether "relevant donations" in line 2 of page 2 of MSBT 10/1 could be taken to read as "components". Dr Rejman felt that "donation" was a single donation, but in discussion it became apparent that there was some uncertainty over interpretation.

3.3 Professor Thomas commented that the figures on Page 16 of the paper were very much an underestimate. It was agreed that more detailed follow-up was desirable; this might be obtained through the registry.

3.4 There were also concerns over the number of recipients tested who were negative. Was this because the donors had been negative on these earlier occasions or was it that the donors were false-positives who had not been checked with PCR ?

3.5 The Chairman said the Secretariat would write to Dr Robinson for confirmation of the definitions used for lines 2 and 3 of the table on Page 2 of MSBT 10/1.

ACTION: Secretariat to clarify definition of terms used on Page 2 of MSBT 10/1

4. GBV-C/HGV

4. 1. The Chairman advised that MSBT refer to the virus as GBV-C/HGV , as recommended by Professor Zuckerman (Annex 1 to paper MSBT 10/11). It was not yet certain that this was a hepatitis virus.

4. 2 MSBT 10/11 included the note of a meeting in July to discuss research. The Chairman asked whether, in the light of this, the committee thought there was any action the Health Departments should take - or ask MRC to take - to improve knowledge of the virus, beyond what was already being done, eg in the commercial field.

4.3 The consensus view was that this virus was likely to be a common infection and therefore merited study. Professor Thomas suggested that information might be derived from the Hepatitis C look-back - testing donors rather than recipients. About a third seemed likely to be co-infected with GBV-C/HGV, although infection would not necessarily have arisen at the same time. Studies could show if co-infection with GBV-C/HGV caused more problems than Hepatitis C infection alone. It was suggested that studies look at other diseases as well as liver disease, and extend also to those infected only with GBV-C/HGV. Some information might come from transplant cases, but those patients were immuno-suppressed.

4.4 It was not yet clear whether the new virus caused liver disease or any fulminant disease. Spouses and children born to women with GBV-C/HGV might be included tested to investigate whether sexual or vertical transmission occurred. A rate of 20% neo-natal transmission had been suggested, and semen specimens seemed to suggest transmission by that route was possible. Other aspects of natural history would also be important, eg specific acquisition events. Premature babies could offer a worthwhile subject for study, covering the possibility of maternal transmission, and receipt of blood products, and offering the prospect of a long follow-up period.

4.5 It would be helpful to know if there was a correlation between GBV-C/HGV infection and eg the number of transfusions or numbers of doses of FFP given to liver transplant cases. Some transplant patients developed problems for which it was not clear whether treatment or

immunosuppression was causal. Recent papers suggested that in immuno-competent biopsy patients the virus did not cause significant liver damage. But these findings only related to a two year period. Medium/long-term studies seemed desirable.

4.6 While some local studies were in progress, aggregated data from a number of centres would be valuable. Dr Mortimer agreed to provide the committee, in confidence, with a copy of an anonymous study he was involved in.

4. 7 The committee noted that the Hepatitis C look-back registry could provide a valuable data base to establish, within ethical constraints, whether GBV-C/HGV made the natural history of Hepatitis C worse. Patient consent for GBV-C/HGV testing was unlikely to be a significant problem. Most of these patients would be treated at larger liver centres, so consent could be sought through the small number of clinicians involved.

4. 8 Annex 4 of paper MSBT 10/11 outlined the look-back study already under way in Scotland, where costs were being shared between SHHD and the clinicians. However the numbers involved were small and it seemed desirable to extend this work. This would require more resources, to permit more PCR testing and prolonged follow up .

4.9 The Chairman noted that MSBT was not empowered to allocate research grants, but it was in a position to advise the research directorates of the Health Departments about research studies. The Secretariat would ask colleagues responsible for research to explore the possibility of funding for research with donors, parallel to the Scottish work.

4.10 Professor Thomas and Professor McMaster agreed to draw up proposals for co-operative work on transplant cases and in hepatology departments; the latter particularly for cases of fulminant hepatitis.

4. 11 Dr Doyle noted that it might be possible to consider any proposals for studies of GBV-C/HGV in liver transplant patients within the overall centrally purchased liver transplant programme. He would be prepared to discuss this with the Directors of the six English Transplant Units if appropriate studies were suggested.

ACTION

- Dr Mortimer to provide committee with details of current study (para. 4.6)

- Professors Thomas and McMaster to draw up suggestions for work relating to transplant patients and hepatology centres (para. 4.10)

- The Secretariat to ask colleagues responsible for research to explore possibility of funding for extension of research (para. 4.9)

- Those involved in the Scottish study to make preliminary contact with colleagues in England over possible collaboration in extending the transfusion study

5. Minutes of the ninth MSBT meeting - 2 July 1996 - and matters arising

5.1 There were no comments on the minutes (paper MSBT 9/4).

HTLV

5.2 The Chairman explained that, as outlined in paper MSBT 10/13, the issue was being brought back to MSBT principally to allow consideration of the implications of Mr Justice

Morland's High Court judgement in respect of patients treated with HGH who developed CJD, and other legal cases, for the responsibilities of committees and Government Departments. The committee were first advised of general legal principles and consideration of recent court judgements.

5.3 Ms Lipton, from the Department's Solicitor's Branch, explained that a tort of negligence arose where there was a duty to take reasonable care, and a breach of that duty by the defendant, causing damage to the plaintiff. Reasonable care had to be taken to avoid injury (harm) to those the defendant ought reasonably to have foreseen might be affected by the action in question.

5.4 In the case of infection with HTLV through blood, it seemed likely that the Secretary of State (SoS) owed a duty of care to recipients of that blood. While he had delegated responsibility for treatment to HAs, and for blood services to the NBA, that was not thought to sever the link. SoS also directed what screening tests the NBA should carry out.

5.5 The fact that SoS decided whether or not to act on the recommendations of MSBT seemed to break the direct link between MSBT and affected individuals. The purely advisory role of MSBT put it in a different position from the committee in the HGH/CJD case. If MSBT acted negligently, in theory SoS could seek redress against individual members. However, in practice this would not happen. It was not in the public interest and would discourage service on committees. That did not mean that advisory committees were immune from judicial review. For example, if a committee gave advice that no properly constituted and serviced committee could reasonably have given, that advice could be open to challenge by way of judicial review.

5.6 The recent CJD judgement indicated that committees needed to ensure that they had the necessary expert skill and judgment, and material, available to them to enable them to carry out their role effectively. Evidence of what had occurred at meetings might be derived from documents and memories. Absence of records might be taken to indicate that particular matters had not been properly considered. This underlined the importance of proper and full documentation, and of ensuring that the Secretariat provided all relevant documents to the committee.

5.7 Ms Lipton confirmed that resource constraints were one of the considerations SoS could properly take into account in exercising his duty of care; but all risk factors must be considered together to assess the overall risk. Members mentioned the absence of any other expert body comparable to MSBT in the UK, against which its judgement could be compared. Ms Lipton advised that it would be reasonable to take account of decisions made by other countries.

Further discussion of HTLV screening

5.8 Taking all the above points into account, the Chairman asked members to review whether the criteria changed MSBT's July advice to Ministers about HTLV. The Executive Board needed to be assured about this when considering the issue and before referring it to Ministers. There seemed little doubt that the committee had the relevant expertise. But had the case for testing been properly made and documented in July ? Several members confirmed that the position had not changed since July, and none proposed a change in the recommendation, as regards blood.

5.9 Dr Robinson said that the figure for investment for new equipment (third paragraph, first page, main body of paper MSBT 10/13) should read £500,000, not £700,000. The NBA did not envisage that equipment would be bought or HTLV testing carried out at blood centres whose bulk processing and testing work was due to be taken over by other blood centres.

5.10 Pool rather than individual testing could significantly reduce costs and might be worth exploring. However it did not seem a realistic option in the short-term. It would involve

renegotiation of contracts with suppliers and require careful validation. Administrative and IT problems were likely as present systems were geared to individual testing. The Chairman pointed out that the Morland judgement meant that procrastination could be held to be negligent. Awaiting developments on pool testing could not justify further delay in taking a decision. It was agreed to proceed currently on the basis of individual testing.

5.11 While it might be possible to modify the cost estimates somewhat, it seemed clear that costs would remain high. Concerns were expressed by some members that these costs involved were probably higher than for any other test, and if it was accepted in this case then no other test could be refused on grounds of cost. There might also be a case for re-examining the cost-effectiveness of existing screening tests. There was an absence of general guidelines which could be applied to potential tests. Members did not feel competent to recommend whether HTLV testing represented a better use of resources than other medical procedures. The Chairman advised that MSBT could never-the-less make recommendations from a public health point of view, giving estimated costs and benefits of the specific proposal.

5.12 Dr Robinson felt there was a public health risk and that screening of blood donations should be recommended because the infection could cause serious illness; besides TSP and ATLL, other effects were being identified. The virus was not latent, and it was sexually transmitted. Other members took differing views on whether the virus had been shown to be responsible also for other significant diseases.

5.13 Dr Rejman asked if members were convinced about the sensitivity and specificity of HTLV tests. Recent material based on a Portuguese study suggested that antibody tests might be missing a number of cases. Dr Mortimer considered those papers speculative. He had no real concerns about the accuracy of the tests or their ability to remove risks of the two main diseases. There were no documented cases of either which were not sero-positive. He would provide figures for inclusion in the paper to Ministers.

5.14 While content with MSBT's previous recommendation as regards blood, Dr Gorst suggested the implications for the availability of organs for transplants should perhaps be re-examined. Professor McMaster proposed that in striking a balance the Committee should err on the side of safety. He wondered whether clinicians should be advised they could depart from any new requirement on HTLV where the balance of circumstances in a transplant case made it desirable. This was in line with the general principles of the guidance on tissues and organs for transplantation.

5.15 Dr Robinson reiterated her concern if, having identified infected donors who had given blood, we did not undertake a look-back. Others, including the Chairman, considered it appropriate to determine first whether any effective treatment could be given to those infected. It was the licensing of alpha interferon which had prompted MSBT to recommend the hepatitis C look-back.

5.16 The Chairman pointed out that information about other European countries would be needed for the submission to Ministers. Ireland was thought to have begun testing. One member suggested that the UK probably had the highest Afro-Caribbean population in Europe. However when France introduced testing this was initially for overseas territories, and only later for metropolitan France.

5.17 It was noted that in other Ministries a specific sum was acceptable to be spent to prevent the loss of a life. Was this a factor Health Department Ministers should consider ?

5.18 The Chairman referred back to MSBT's position as recorded in paragraph 4 of the minutes of the last meeting. The committee had indicated then that it might take a different view on testing for HTLV were a system in place to compensate anyone affected by a rare infection, for which it had been decided not to test.

5.19 In conclusion, the Chairman said that officials would summarise MSBT's comments on the public health arguments, the costs, the case for reassessment of existing screening arrangements, and its estimates of costs and benefits into a structured report for the Executive Board and for Ministers. This should make clear that MSBT could not make comparative judgements about other possible uses of funds. A draft would be circulated to members for comment before it went to the Executive Board and then to Ministers.

ACTION

- **Dr Mortimer to send Dr Rejman figures on specificity and sensitivity of HTLV tests (para. 5.13)**

- **Officials to draft and circulate paper for Executive Board/Ministers. (para. 5.19)**

6. Fresh frozen plasma

6.1 Dr Robinson advised that all FFP was now from repeat donors. Figures for risks of HBV -paper MSBT 10/2- were not easy to establish. She hoped to have better figures in time for the next meeting. While it was clear that transmission did occur, the risk, while recognised, on the available data seemed small. Dr Robinson considered S-D was a very robust treatment, provided the size of pools was kept small. Once it was licensed, which would probably be soon, could we continue to provide non-inactivated plasma which could transmit infection ? Costs of switching to S-D treated products might be in the order of £6m (£20 per unit), although probably bringing the beneficial side-effect of discouraging inappropriate usage of FFP. Experimental work on inactivating single donations was in progress in Denmark, but was at an early stage. It might be two years before such a system was in general use.

6.2 Dr Snape agreed the S-D process could be assumed to prevent transmission of enveloped viruses. PCR testing might be necessary to deal with non-enveloped viruses. If the Octapharma product was to be licensed, should the UK use it to treat plasma ? This would involve either Octapharma carrying out the process and returning the plasma to the blood service, or the work being carried at BPL under licence - in the event of Octapharma agreeing. The Chairman pointed out that any such treatment would also require a licence from the MCA.

6.3 Mrs Silvester also agreed that S-D treatment was effective with enveloped viruses; but pooling brought increased risks. Other European countries' views ranged from accepting S-D treatment, accepting it but limiting the number of donations in each pool, to wanting to inactivate individual donations. The process involved manufacturing and so fell within the scope of the EU directive 89/381/EEC.

6.4 Besides the question of whether the S-D treated product would be safer if large pools were used, members mentioned the extra costs. The Committee's advice on S-D treatment could set a precedent for dealing with virally inactivated platelets, which might become available soon.

6.5 Some clinicians were not waiting for licensing and were already using Octaplas, on a named-patient basis. It was suggested that in future clinicians might need to spell out for patients the different risk involved with the respective products.

6.6 The Chairman questioned whether any action before S-D treatment was licensed was premature. In the event of licensing, should decisions on treatment be left to clinicians, or should MSBT advise use of S-D treated products rather than of other products ?

6.7 Whilst recognising that no licensed product was available yet, it was agreed that Dr

Rejman should arrange a small sub-group, and summarise the estimated risk and benefits, between S-D treated plasma from commercial sources compared with non S-D treated UK plasma from voluntary non-remunerated donors, along with costs, for consideration at the next meeting,

ACTION

- Dr Rejman to prepare summary note for next meeting (para. 6.7)

7. Parvovirus B 19

7.1 The Chairman reminded members of the two papers concerning Parvovirus B 19 which had been circulated as MSBT 10/3 and 10/7. The former was a set of proposals by Dr Robinson; the latter was a copy of an article from the British Journal for Haematology, circulated for information.

7.2 Dr Robinson spoke briefly about her paper, indicating that Parvovirus was a seasonal virus, which was difficult to inactivate, and that improved technology was needed for pool testing. A special meeting was needed to review the literature and particularly to consider obtaining more information from clinicians (item 4 of the paper). In discussion, Dr Cant said he was only aware of one case of red cell aplasia (in a child). Dr Mortimer explained that immuno-suppressed patients and sickle cell patients were more at risk of contracting aplasia. It was agreed no urgent action was necessary.

8. Red cell transfusion products for neo-nates

8.1 Members commented that much of what was proposed in paper MSBT 10/10 was not new; only the first and fourth items under "proposed action" went beyond existing BCSH guidelines. As such, members did not feel the paper warranted a submission to Ministers.

8.2 Although there were arguments, already discussed at earlier meetings, for extending similar treatment to groups other than neo-nates, eg bone marrow recipients, who had similar immune system problems and multiple use of blood products, it was agreed this advice should relate only to neo-nates. If it was so decided locally, the principles could be adapted for application to other groups. For clarity, the guidance would refer to "neo-nates and infants of less than a year".

8. 3 It was agreed that the best approach to dissemination was as in paragraph 2(i), but not also 2(ii) or (iii), of the paper. The recommendations would be disseminated to local level by the NBA, and territorial equivalents, through discussion between their blood transfusion service consultants and hospital haematologists and paediatricians, underlining that the recommendations had the support of MSBT. The transfusion service would approach the Royal Colleges informally.

8.4 The Chairman noted it would be sensible to let Ministers know what was intended, although this was not seen as a significant new policy.

ACTION

- Blood services to disseminate the guidance (para. 8.3)
- Secretariat to advise Ministers of intention (para. 8.4)

9. CJD: blood and blood products

9.1 The article by Dr Dealler and related papers attached to paper MSBT 10/5 were for information. The Chairman emphasised the confidentiality of the draft for a retrospective study, in paper MSBT 10/4. These proposals had been submitted for funding, but it was not clear how long a decision would take.

9.2 Dr Robinson said transfusion service representatives had had a meeting with SEAC about relevant areas for research, to see if anything would throw any light on implications for blood donations/transfusion. She had just received the framework proposals, which she asked the Secretariat to send on to members.

9.3 The Chairman said that it had been shown that "buffy coat" extracts had transmitted infection experimentally in animals. It was not known whether this could happen in humans. SEAC had not changed its view that there was no evidence of any human transmission by blood transfusion. Dr Robinson suggested that it there were transmission by buffy coat , leucocyte removal should help.

ACTION : Secretariat to circulate paper provided by Dr Robinson

10. Any Other Business

Progress reports

10.1 Paper MSBT 10/8 was discussed; this consisted of progress reports on the anti - hepatitis B core look-back study, European activities relevant to the Committee and arrangements for reporting transfusion events (SHOT). On the Terms of Reference of the Serious Hazards of Transfusion Scheme (SHOT), Dr Robinson commented that there was serious under reporting. A protocol was in preparation regarding what happened between donor and product, this was not yet completed. Dr Warren felt it was important to lay out who was responsible for investigation. Dr Rejman pointed out that the French system had been overwhelmed by a large number of reports, many of which were comparatively trivial.

10.2 The update report on Anti-hepatitis B Core look-back study was noted.

10.3 Mrs Silvester spoke briefly on her paper on EU activities relevant to the Committee and commented that overall outcomes on tests kits were encouraging. The introduction of testing for viral nucleic acid in plasma pools had implications for transfusion of labile components.

10.4 The Chairman asked members if they had found it helpful to have updates on minor matters circulated in a summary paper, as had been done for the first time, and whether they would like this to continue. Members agreed they had found this practice helpful.

Guidance notes on the processing, storage and issue of bone marrow stem cells

10.5 The Chairman asked members to let Dr Rejman have any comments on the guidance notes on the processing, storage and issue of bone marrow stem cells (MSBT 10/6). Members agreed that it would be preferable to exclude the second part of Table 1 which referred to discretionary tests. In response to questions from Territorial observers, Dr Rejman said that a list of those organisations consulted on the guidance would be included in the submission to Ministers, a copy of which would be sent to Territorial colleagues.

UKTSSA Pocket Guide to Medical Contraindications

10.6 Members were content, subject to some minor amendments, with the UKTSSA Pocket Guide to Medical Contraindications (MSBT 10/9).

Collection and storage of bone allografts

10.7 The Chairman explained that he had received a request (MSBT 10/12) from Owandar Medical Limited that MSBT should revise its guidance in respect of bone allografts that had been collected using their Marburg system. Data on the system and its capacity for viral inactivation had also been submitted to the MDA and would be considered by the Microbiological Advisory Committee (MAC). It was agreed that MSBT should not consider the request until the views of MDA/MAC were known.

11. Date of next meeting

The Chairman said the next meeting would probably be held around February, on a date to be arranged.

ACTION - Secretariat to arrange date of next meeting

12. Membership of MSBT

The Chairman thanked Professor Williams for his valued contribution to the work of MSBT.