DRAFT ISSUE SUMMARIES

TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES ADVISORY COMMITTEE MEETING

18-19 JANUARY, 2001

ISSUE 2.

Suitability Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products: CJD and vCJD

ISSUE

Classic CJD has been transmitted through the transplantation of certain tissues, i.e., dura mater and cornea. Based on known and theoretical risks, FDA currently recommends that blood donors and donors of human tissue intended for transplantation should be screened for classic CJD and CJD risk factors. Additionally, blood donors are screened for history of travel or residence in the United Kingdom as a precautionary measure to reduce the theoretical risk for transmission of variant CJD (vCJD) based on possible exposure to the BSE agent. The committee is asked to consider the scientific basis for development of policies to address the risk of transmission of vCJD by donations of human cells, tissues and cellular and tissue-based products other than blood. [Note: While FDA regulates these entities, HRSA and HCFA oversee organ transplantation.]

BACKGROUND AND DISCUSSION

Current FDA guidances contain recommendations to exclude donors of tissue (musculoskeletal, ocular, integumental) who are diagnosed or have risk factors for TSEs, specifically classic CJD, although current FDA regulations for human tissue do not address TSEs (1). In an FDA guidance to industry on screening and testing donors of human tissue intended for transplantation (2), the agency recommends that the donor medical history screening interview should include questions to defer potential donors with a diagnosis of CJD, a known family history (blood relative), or who have received human pituitary growth hormone or dura mater transplants. In another FDA guidance to industry specifically about human dura mater (3), donor evaluation includes all of the above, and in addition recommends exclusion of donors diagnosed with any degenerative or demyelinating disease of the CNS, or who died in a neurological/psychiatric hospital. Other recommendations include gross and histological examination of the brain (full autopsy), archiving samples of brain and dura mater tissue for at least 10 years, performing a validated test for PrP-RES, when available, CJD disinfection by a method validated to reduce CJD infectivity, record keeping and tissue tracking, consistent with medical device requirements, and prohibition of batch processing.

Recently, the Centers for Disease Control and Prevention (CDC), together with the Infectious Disease Society of America and the American Society of Blood and Marrow Transplantation, published guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients (4). They recommend that the medical history of the prospective donor should include history of risk factors for classic CJD, including any blood relative with CJD, receipt of a human pituitary-derived growth hormone or receipt of a corneal or dura mater graft, in addition to vCJD risk factors, including a history of cumulative travel or residence in the UK for 6 months or more during 1980-1996 or receipt of injectable bovine insulin since 1980, unless the product was not manufactured since 1980 from cattle in the UK. The guidelines state that although no classic or vCJD has ever been reported among hematopoietic stem cell transplant recipients, donors with a history of these risk factors should be excluded from allogeneic donation if a choice exists between two otherwise equally suitable donors.

Voluntary industry standards contain recommendations to prevent transmission of prion-associated diseases through transplantation of tissues. The American Association of Tissue Banks (AATB) Standards excludes persons with a history of dementia or degenerative neurologic disorders of viral or unknown etiology. The Eye Bank Association of America (EBAA) Medical Standards consider death with neurologic disease of unestablished diagnosis as a contraindication to corneal donation. However, none of these guidances or standards address donor deferral for risk of vCJD, i.e., residence/travel to BSE countries.

There have been no reports of transmission of vCJD by transplantation of human tissues. Iatrogenic transmission of classic CJD has been reported through dura mater and cornea. The majority of dura mater transmissions occurred from the use of one particular brand of cadaveric dura mater graft, Lyodura, which prior to May 1987 was batch-processed, resulting in cross-contamination (5). Transmissions of CJD by ocular tissue have included one definitive case in the U. S. (1974), one possible case in Japan (1994) and in Germany (1997), and the transplantation, and subsequent explantation of two corneas and sclera from a Scottish woman who was later determined to have CJD (6).

FDA is implementing a new proposed approach to the regulation of cellular and tissue-based products. This tiered, risk-based approach attempts to regulate all cells, tissues, and products containing cells and tissues under one umbrella. These would include musculoskeletal tissue (bone, cartilage, ligament, tendon, fascia, pericardium), ocular tissue (cornea, sclera), skin, somatic cell and gene therapy products, reproductive cells and tissue (semen, oocytes, embryos), hematopoietic stem cells from peripheral blood and from placental/umbilical cord blood, and combination products consisting of tissue and a device-like component. These cells and tissues are obtained from living or cadaveric donors.

The donor suitability regulations being proposed for <u>all</u> of these donors (7) would require screening the donor for risk factors and clinical evidence of relevant communicable diseases, including HIV, HBV, HCV, and TSEs (e.g., CJD). All donors would be tested for relevant communicable disease agents, including HIV-1, HIV-2, HBV, HCV, and

syphilis. In addition, donors of certain types of cells and tissue would be tested for HTLV-I and II, CMV, Chlamydia and Neisseria. The proposed regulation does not mention specific risk factors or clinical evidence—these details would be contained in a guidance document currently under development.

Therefore, at this time, FDA is asking the TSEAC to advise them on whether or not to recommend deferral of cell and tissue donors based upon risk factors for vCJD, i.e., residence in or travel to BSE countries and potential exposure to the BSE agent. Should such deferral occur for donors of all types of cells and tissue, or, based upon differential risks of transmission, should deferral be limited to donors of certain types (e.g., dura mater and cornea, which have historically transmitted classic CJD)? Since the protease-resistant prion protein in vCJD appears to have a predilection for lymphoid tissue, should deferral of donors of leukocyte rich cells and tissues (e.g., hematopoietic stem cells, semen) be considered?

In November 1999, FDA published revised precautionary measures to reduce the possible risk of transmission of vCJD by blood and blood products (8), following the recommendations of the TSEAC, by implementing a policy that would defer persons who have spent six months or more cumulatively in the United Kingdom from 1980-1996 from blood donation. (The guidance also addresses risk factors for classic CJD.) This deferral policy for blood donors was a conservative approach, since blood and blood products have never been reported to transmit vCJD in humans. With this in mind, and knowing that certain tissues have indeed transmitted classic CJD to human recipients, we ask for your recommendations concerning cell and tissue donors and their exclusion based upon travel/residence history.

To FDA's knowledge, states that license tissue banks (NY, FL, CA) have not adopted any policy concerning vCJD. Although foreign governments have taken a position regarding blood donation, they have not made similar decisions regarding tissue donation. The one known exception is Canada. The preamble to its proposed donor screening questionnaire for tissue donors, developed by an Expert Working Group, discusses the rationale, based upon risk management, for not applying a UK residence exclusion to organ and tissue donation. Part of this decision was the possibility of making up for the loss of blood donors by increased recruitment methods. Such a strategy would not be feasible for organs and tissues where there is a limited supply. It was noted that the risks and benefits of all transplants were significantly different from blood and blood products.

There is very little data on the effect of a UK deferral on the supply of particular cells and tissues. A survey, similar to the one conducted of blood donors, may provide additional information, if it were to be conducted. The Eye Bank Association of America (EBAA) commissioned a committee to provide an independent report on the occurrence and transmissibility of CJD as it relates to cornea transplantation and the impact of screening on donor supply (9).

It is unlikely that travel/residence history, or some information about risk factors for classic CJD, for that matter, could be obtained from a review of medical records. This type of information is more likely to be obtained by direct questioning of the living donor, or for the cadaveric donor, a person knowledgeable about the donor, such as the next of kin, a relative, a household member, another individual with an affinity relationship, or the primary treating physician. Certain states (FL, TX, MD) have active legislative consent laws, which permit cornea retrieval without the consent of the next of kin. In these states, approximately 50% of all corneas recovered are procured in this manner, whereas nationwide, the number is 5-10% of all corneas recovered. These states might experience local shortages of corneal grafts if FDA were to require a donor medical history interview in order to obtain information about risk factors for CJD and vCJD. According to the 1999 EBAA Statistical Report, the total number of corneal grafts has increased by 1% and the number of grafts exported internationally has increased by 31% since 1998.

REFERENCES

1. Human Tissue Intended for Transplantation. FDA Final rule. 62 Federal Register 40429, July 29, 1997. txt

2. FDA Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation. July 1997 txt

3. FDA Guidance for Industry and/or for FDA Reviewers/Staff and/or Compliance: Guidance for the Preparation of a Premarket Notification Application for Processed Human Dura Mater. July 31, 1999.

4. MMWR 2000; 49(No. RR-10): 1-128. Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients.

5. MMWR 1997; 46(No. 45): 1066-1069. Creutzfeldt-Jakob Disease Associated with Cadaveric Dura Mater Grafts—Japan, January 1979-May 1996.

6. Hogan NR, Brown P, Heck E, Cavanaugh HD. Risk of Prion Disease Transmission from Ocular Donor Tissue Transplantation. Cornea. 1999. 18(1): 2-11.

7. Suitability Determination for Donors of Human Cellular and Tissue-Based Products. FDA Proposed rule. 65 Federal Register 52696. Sept. 30, 1999. txt

8. FDA Guidance for Industry: Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Creutzfeldt-Jakob Disease (nvCJD) by Blood and Blood Products. November 1999.

9. Kennedy RH, et al. Summary Report by Committee on Prion Disease, commissioned by EBAA, January 27, 2000.

CHARGE

FDA asks the TSEAC to evaluate the risk of transmission of vCJD through the transplantation, implantation, infusion, or transfer of human cells, tissues, and cellular and tissue-based products, and compare this risk to that of the transfusion of blood and blood products, for which precautionary measures have already been adopted. Based upon this evaluation, and considering the potential effect on supply, the committee is asked to recommend whether FDA should defer donors of these cells and tissues who have possibly been exposed to the BSE agent through residence in or travel to BSE countries.

In addition, the TSEAC is asked to consider how information about residence/travel history can best be obtained. This is particularly relevant to the situation, in which corneas are procured under legislative consent. This term relates to state laws that allow the medical examiner or coroner to procure corneal tissue in the absence of consent of the donor's next of kin, and hence, in the absence of a donor medical history interview with the next of kin.

QUESTIONS

1. Compared to the risk of transmission of variant CJD by blood transfusion, is there a significant risk of transmission of vCJD from human cells, tissues, and cellular and tissue-based products that are transplanted, implanted, infused, or transferred?

    --What are the relative risks for different cells and tissues?

2. The committee has previously assessed the risk of transmission of vCJD by blood, and has made recommendations accordingly. Based upon the committee's assessment of the risk of transmission of vCJD by human cells and tissue, and considering the potential impact on supply, should FDA recommend donor deferral criteria for possible exposure to the BSE agent?

    A. If no, are there additional data that should be gathered that might alter this decision?
    B. If yes, what deferral criteria should FDA recommend:

        i. Exclusion only for certain types of cells and tissues (which ones?)
        ii. UK only? UK and France? Other BSE countries (which ones?)
        iii. Time period of exposure—limit to 1980-1996
        iv. Duration of exposure—limit to 6 months cumulative exposure?

3. If a deferral policy were to be put into place, how can information about the donor's risk factors for CJD and vCJD be obtained—is a donor medical history interview required?

   --Currently, several states permit the recovery of corneas under legislative consent, whereby an interview with the next of kin may not take place. Should FDA require an interview for all cornea donors?