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Policy, Position, & Research Subcommittee

Review of HTLV-1 & HTLV-2 Serologic Testing

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This document provides information to assist the Medical Advisory Board of the Eye Bank Association of American (EBAA) in re-evaluating the clinical utility of serologic testing for human T-lymphotropic viruses type I and type II (HTLV-I and HTLV-II) and to assist in the determination of whether or not HTLV testing is applicable and indicated for selection of donors of ocular tissue.

INTRODUCTION

The EBAA Medical Standards contain extensive requirements for donor screening and donor testing to ensure patient and Eye Bank staff safety and to avoid disease transmission. Current knowledge about HTLV infection, disease, and pathogenesis is vast compared with what was known just a decade ago. Current evidence-based,

scientific data suggest that routine cornea (eye) donor screening for HTLV disease and testing cornea (eye) donors for HTLV antibodies are unnecessary steps for donors of ocular tissue. Additionally, a donor who tests positive or repeat reactive for anti-HTLV-I or anti-HTLV-II is deemed not to be a risk for transmitting HTLV disease to a recipient of their ocular tissue.

SUPPORTIVE STUDIES & SCIENTIFIC RATIONALE

HTLV is a retrovirus that primarily affects T lymphocytes (through integration of its genome with that of the host T lymphocyte. More specifically, HTLV-1 has an affinity predominantly for CD4 lymphocytes, while HTLV-2 predominantly affects CD8 lymphocytes.[1] Viable leukocytes are the host cells with which the HTLV viral particles integrate, and these cells enable the virus to proliferate. Thus, if transplantable ocular tissues do not contain viable lymphocytes, then HTLV-associated disease becomes an irrelevant issue since the virus is unlikely to be present or activated.

Studies of HTLV virus transmission following blood transfusion have found that a sufficient number of viable leukocytes must be present in the blood to successfully transmit the disease.[7] The number is in the range of 10 to the 8th power.[3] This is where the term, "*rich in viable leukocytes*," is derived, which is used by the Food and Drug Administration (FDA) to describe a tissue type that would be relevant for HTLV transmission risk (e.g. whole blood, semen, pancreatic islet cells). Ocular human tissues (corneas, sclera) distributed for transplantation do not contain sufficient blood or viable leukocytes and are not designated by FDA as a cell or tissue type that is relevant for HTLV disease.

This rationale is supported by experience with human plasma. Studies have demonstrated that plasma has not transmitted the infection, even though donor red cells derived simultaneously from the same donors (via whole blood donation) have transmitted HTLV-I infection.[4] Human plasma for transfusion does not contain viable

leukocytes and has not been shown to transmit HTLV. HTLV transmission does not occur from transfusion of non-cellular components of blood.[5] Results of a retrospective investigation showed that in transfusion recipients of units of blood and/or platelets (*donor products considered rich in viable leukocytes*) from donors who subsequently tested positive for HTLV Ab, only 30% became infected with HTLV.[6] The infectivity rate for HTLV disease transmission is low.

Clinical expression of infectivity and the pathogenicity of HTLV infection are rare when immunocompetent individuals have received blood products contaminated with HTLV.[7] Allograft recipients do not require systemic immunosuppression after receipt of most ocular grafts. Candidates are considered healthy to undergo reparative eye surgery for tissue that has been affected by a disease process or due to trauma. Although it is not tracked, recipients of allograft tissue are not typically immuno-incompetent.

In the United States, the prevalence of HTLV infection is low, and the country is not considered an endemic area.[8] While there is an increased incidence in certain subgroups (e.g. IV drug users, sex workers), these individuals/groups are not eligible for ocular tissue donation by current EBAA screening regulations.[8]

REGULATIONS: HTLV SCREENING & TESTNG OF OCULAR DONORS

Regulations promulgated by the FDA for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) do not require ocular donors be tested or screened for HTLV disease.[9,10] HTLV testing is also not required by Health Canada[11,12,13] or by the Official Compilation of Codes, Rules and Regulations of the State of New York.[14]
The FDA regulations additionally do not determine an ocular donor to be ineligible if the result for HTLV-I/II antibody testing is positive or repeat reactive, or if a history for HTLV disease risk is identified.

TEST KIT HISTORY

Routine testing for anti-HTLV-I was introduced for blood, organ, and tissue donors in the late 1980's and early 1990's. Testing for anti-HTLV-II was added about a decade later and combination test kits (anti-HTLV-I/II) became available and were commonly used. Currently, three test kits are licensed by the Food and Drug Administration (FDA), but only one remains in production.

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm#approved

The table of licensed assays for Human T-Lymphotrophic Virus Types I & II lists three test kits with these trade names (and testing formats):

- Abbott HTLV-I/HTLV-II EIA (EIA);
- Abbott PRISM HTLV-I/HTLV-II Assay (ChLIA); and
- Vionostika* HTLV-I/II Microelisa System (EIA).

**EIA/ELISA Ezyme Immunoassay / enzyme-linked immunosorbent assay*
**ChLIA chemiluminescent immunoassay*

Today, the Vionostika HTLV Ab kit is no longer commercially available. Additionally, per a notice supplied by Abbott in February 2009, the last ship date of the Abbott HTLV-I/HTLV-II EIA kit was December 31, 2009. The expiration date of this kit was April 18, 2010. Only one test kit is now available to screen donors for HTLV I/II antibodies. Moreover, that test kit, the Abbott PRISM HTLV-I/HTLV-II Assay (ChLIA), is licensed for testing only blood samples from "living" donors (see the FDA website link cited above.) This test kit has not been approved for testing blood specimens from cadaveric donors and recent communications with testing laboratories have revealed testing errors in over 2/3 of the cadaveric specimens evaluated. Moreover, these errors were not resolved on repeat testing.

SUMMARY

- In the United States, the prevalence of HTLV infection is relatively low, and the country is not considered endemic for the virus.
- For HTLV transmission to occur via transplantation, implantation, injection or ransfusion, there must be sufficient viable, infected lymphocytes present in the product.

- In the United States, preserved ocular tissue does not contain leukocytes or viable leukocytes in high numbers

- There is only one test kit available for HTLV testing; that test kit is not licensed for testing cadaveric blood specimens

- Screening and testing ocular donors for risks associated with HTLV is not relevant or warranted and would not increase safety for recipients

CONCLUSION

This comprehensive evaluation of all key data on the epidemiology and virology of HTLV infection and disease, relevant clinical issues and pathogenesis, and HTLV testing, with references to peer-reviewed literature, infers that screening or testing ocular tissue donors for HTLV infection is not necessary and is not pertinent to the enhancement of safety among persons who receive ocular tissue. Viable leukocytes, which are required for HTLV transmission to occur, are effectively not present, or are present in insufficient numbers, in ocular tissue released for transplantation. Routine HTLV screening and testing would decrease the supply of donor ocular tissue, serve only to increase labor time and costs and and would not improve patient safety . If an ocular donor tests positive for anti-HTLV-I or anti-HTLV-II, the result is not clinically relevant and the donor may still be considered eligible.

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[9] Final Rule, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, dated May 25, 2004 (effective May 25, 2005). See Sections 1271.3©(1)(ii), 1271.75(b), and 1271.85(b).

[10] Final Guidance for Industry, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), dated August 2007

(effective August 28, 2007). See III. THE DONOR-ELIGIBILITY DETERMINATION (§ 1271.50) at C. What are "relevant communicable disease agents or diseases (RCDADs)"?, 1.b.; and at IV. DONOR SCREENING (§ 1271.75) at A. For what diseases or conditions must I screen cell and tissue donors?; at F. What clinical evidence do I look for when screening a donor? 7.; and at VI. DONOR TESTING: SPECIFIC REQUIREMENTS (§ 1271.85) at B. For what additional diseases must I test donors of viable, leukocyte-rich cells or tissue and what tests should I use? 1.a. and 2.

[11] Health Canada, Safety of Human Cells, Tissues and Organs for Transplantation Regulations, June 27, 2008, Canada Gazette, Part II; see 18.b. and 20.

[12] Guidance Document: Safety of Human Cells, Tissues and Organs for Transplantation, April 6, 2009, http://www.hc-sc.gc.ca/dhp-mps/brgtherap/reg-init/cell/cto_gd_ld-eng.php

[13] Canadian Standards Association, General Standard CAN/CSA Z900 series, Cells, Tissues, and Organs for Transplantation and Assisted Reproduction, 2003 with update 2007. General Requirements; see Sections 13.1.2 ©, 13.2.2 (d), 13.1.3 (e), 14.2.6 (a), 14.2.6.3 (d), 17.2.2 (d)

[14] Title 10 (Health) of the Official Compilation of Codes, Rules and Regulations of the State of New York, Subpart 52-7, Eye Banks

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