

Follow-up on Serious Adverse Event in OBA Protocol 705

A Phase I/II Study of Repeat Intra-Articular Administration of tgAAC94, a Recombinant Adeno-Associated Vector Containing the TNFR:Fc Fusion Gene, in Inflammatory Arthritis with and without Concurrent TNF- α Antagonist



NIH Office of Biotechnology Activities
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Final Version



RAC Final Assessment

- **It is the Committee's opinion that this patient's unfortunate death was primarily a result of an opportunistic infection, disseminated histoplasmosis, as well as bleeding complications and multi-organ failure. Her apparent risk factor for histoplasmosis was her systemic RA therapy, chiefly the TNF-antagonist adalimumab. The contribution of an immune response to the AAV vector could not be evaluated.**

Specific Findings with Respect to Role of Gene Transfer

- **There was no evidence of contamination of the product.**
- **The evidence does not support the theory that a helper virus led to widespread dissemination of replication competent AAV.**
 - **The majority of the vector remained in the knee at the injection site with only extremely low levels of the vector present outside the knee.**
 - **AAV2rep gene, which may indicate replication competent AAV, was found in the R. knee as expected. It was also found in very low levels in heart and trachea. Given the lack of vector in those sites the detection of AAV2rep likely represents a natural infection.**

Specific Findings with Respect to the Role of Gene Transfer

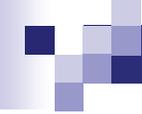
- **Transgene product production does not appear to have played a role in the clinical course**
 - **There were declining blood levels of TNF antagonist in the serum after the subject stopped systemic therapy.**
 - **Levels of TNF antagonist in the blood never exceed the expected steady state.**

Specific Findings with Respect to the Role of Gene Transfer

- While steady-state blood levels were not above that predicted for a systemically administered TNF antagonist, the degree of functional TNF inhibition due to the transgene product cannot be determined.
- The fact that systemic levels of the transgene product do not appear to have been a factor in this case does not diminish the importance of having an assay to specifically detect and quantify levels of the transgene product.

Specific Findings with Respect to the Role of Gene Transfer

- **A possible role of an immunologic response to the AAV vector in the clinical course cannot definitively be ruled out due to a lack of data.**
 - **Blood samples drawn before and after administration of the product were not available for CD8+ capsid specific T-cell assays.**
 - **The absence of significant vector content in the liver and the elevated anti-AAV titer (1:128) are not sufficient data to exclude a cellular immune response.**



Specific Findings with Respect to the Role of Gene Transfer

None of the available laboratory evidence supports the conclusion that the intra-articular injection of the gene transfer vector contributed to the subject's clinical course or her death.

RAC Recommendations on Trial Design

- **The RAC recommends that AAV trials monitor for anti-capsid T cells before and at multiple points after each gene transfer. This may help both in interpretation of adverse events and shed light on the safety of AAV vectors generally.**
 - **The FDA currently recommends such monitoring for AAV trials**



RAC Recommendations on Trial Design

- **The RAC recommends developing assays to distinguish the gene transfer product from other biological treatments that the subject is receiving.**
- **The potential role of immunosuppression in altering the risks of the gene transfer vehicle and/or gene transfer product should be assessed.**

RAC Recommendations on Trial Design

- **Clinical criteria for deferring administration of the gene transfer vector, especially in safety trials, should be carefully considered in advance and clearly stated in the protocol. Special attention should be given to:**
 - **Screening for signs of active infection prior to dosing**
 - **Obtaining laboratory results prior to dosing**

RAC Recommendations on Trial Design

- **To enhance the safety for participants in gene transfer trials, consider developing medical cards that would include the following:**
 - **A brief description of the vector and a web-based link to find out more information;**
 - **24 hour contact numbers for the study's principal investigator(s) or a designate, and**
 - **A detailed list of samples that should be collected when a study subject seeks medical attention for non-routine care.**

RAC Recommendations on Trial Design

- **Protocols should plan for the additional blood and other samples that may need to be collected if a serious adverse event occurs. This should include addressing the logistics of collection should the subject be under the care of physicians who are not involved with the trial or the subject is unable to provide consent.**
- **The logistics of an autopsy, including a detailed protocol that could be shared with an outside institution, as well as considering mechanisms for transfer of the decedent from an outside institution to the institution conducting the trial, should also be developed in advance.**

RAC Recommendations on Trial Design: Informed Consent

- **In early phase trials it is critical to take steps to prevent therapeutic misconception in the informed consent process.**
- **Investigators need to recognize that their own belief in their study may also lead to therapeutic misconception.**

RAC Recommendations on Trial Design: Informed Consent

- **In cases where the investigator is also the subject's physician:**
 - **The potential conflict of roles should be clearly explained in the consent process.**
 - **The subject should be assured that a decision to not to participate in the study will not impact their relationship with their physician.**

RAC Recommendations on Trial Design: Informed Consent

- **In cases where the investigator is also the subject's physician:**
 - **Consider having a third party involved in the consent process to ensure that the subject understands the different, and possibly competing roles, that the investigator/physician will perform.**
 - **Consider providing the opportunity to enlist an independent physician, not involved in the trial, in the event of a medical complication.**



RAC Recommendations on Trial Design: Informed Consent

- **A discussion of the importance of an autopsy is critical in clinical trials and it may be prudent to involve the family, if possible, in that discussion prior to enrollment.**

RAC Recommendations on Trial Design: Informed Consent

- The *NIH Guidance on Informed Consent for Gene Transfer* provides a resource for information regarding these difficult consent issues

<http://www4.od.nih.gov/oba/rac/ic/>