



Discussion of Relevant SAEs in Retroviral Vector Studies

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- Reviewed adverse events from all retroviral vector trials in our database
- Adverse events were from expedited submissions, annual reports, and from periodic RAC reviews (such as in 1993 and 1995)



Algorithm

- Searched for any malignancies, myelodysplastic syndromes (MDS) or monoclonal proliferations
- Examined but will not further elaborate on cases that were either consistent with disease process (e.g., Kaposi's sarcoma in advanced HIV+ subjects) or local skin tumors in studies where fibroblasts not transduced/involved



Caveats

- Analyzed was the OBA database which has following limitations:
 - Only includes studies that fall under the *NIH Guidelines* and voluntary submissions
 - Incomplete database, esp. in regard to annual report information
- Combination of all retroviral studies in our database (different routes, transgenes, target conditions, transduction rates, etc.)



Cases Found

- Eight cases that will be discussed further:
 - 4 lymphomas
 - 2 Myelodysplastic Syndromes
 - 1 case of monoclonal lymphoproliferation
 - 1 malignant glioma



Lymphomas

- All occurred in studies where HIV was target illness
 - Mucosal Associated Lymphoid Tissue (MALT) lymphoma
 - Rectal area lymphoma
 - Intestinal lymphoma
 - Nasopharyngeal lymphoma



Lymphoma, Case 1

- HIV/ribozyme/transduced autologous CD4+ cells.
- Mucosal associated lymphoid tissue (MALT) lymphoma noted in H. pylori + subject
- Biopsies of lymphoma analyzed by PCR (looking for vector envelope) and tested for RCR. Negative.
- Infusate of test material (transduced autologous lymphocytes) obtained and PCR/RCR negative as well.
- Successfully treated for infection, with resolution of lymphoma several months later



Lymphoma, Case 2

- HIV/Syngeneic twins/CD4-zeta chimeric receptor/transduced CD8+ cells
- Rectal area lymphoma noted 2-3 weeks after receiving gene transfer product (transduced allogeneic T-cells)
- On pathology, lymphoma noted to be advanced in stage and extension. Strongly suggestive of a pre-existent condition
- Further material not available. Subject died and PI not notified until months later



Lymphoma, Case 3

- HIV/Syngeneic twins/antisense TAR and transdominant Rev genes/transduced lymphocytes
- Four years after receiving last infusion of T-cells, subject found to have diffuse large B-cell lymphoma of large and small intestines
- Biopsy specimens RCR negative and negative by nested PCR (looking for both vector & transgene)
- Serum RCR negative. Two of six samples PCR positive for transgene.



Lymphoma, Case 4

- HIV/Syngeneic twins/CD4-zeta chimeric receptor/transduced CD8+ cells
- Large B-cell lymphoma of nasopharynx noted 4.5 years after last infusion of transduced allogeneic T-cells.
- Treated by local medical doctor. No biopsy specimens available to PI for further analysis.
- RCR-negative when last seen by the PI 1 year ago.



Myelodysplastic Syndrome, Case 1

- Breast cancer/MDR-1 gene/autologous CD34+ cells
- Four years after receiving gene transfer product (transduced autologous PBPCs) subject developed MDS/myeloid leukemia.
- Bone marrow biopsies revealed tetraploid or near-tetraploid karyotypes in majority of cells
- Nested PCR of the bone marrow biopsies (looking for transgene) and RCR testing were negative.



Myelodysplastic Syndrome, Case 2

- Neuroblastoma/IL-2 and lymphotactin genes/allogeneic neuroblastoma cells/vaccine
- One month after receiving last transduced cell vaccine subject developed anemia and thrombocytopenia
- Noted to have MDS with emergence of two different clones on BM aspirates
- Aspirates were RCR negative and well as negative for PCR (looking for both transgenes)



Monoclonal Lymphoproliferation

- HIV/Syngeneic twins/CD4-zeta chimeric receptor/transduced CD8+ cells
- Three months after receiving third course of transduced cells, HIV+ subject diagnosed with monoclonal lympho-proliferative disorder with plasmacytoid differentiation expressing monoclonal lambda light chain
- Subsequently developed lymphoma, noted on analysis of a pleural effusion



Monoclonal Lymphoproliferation (cont)

- All specimens reanalyzed and found to be HHV-8 +. Also, in retrospect, subject diagnosed with multicentric Castleman's disease.
- RCR testing and PCR (looking for vector) done and negative



Malignant Glioma

- Brain tumors/HSV Tk gene/autologous tumor cells
- Subject with metastatic renal cell carcinoma noted to have new onset malignant glioma. Found 3 months after receiving intratumoral injections of transduced cells
- RCR testing of tumor specimens was negative.
- Southern blot and PCR for both transgenes (neoR and TK) also negative.



Conclusions

- Several cases of malignancies/MDS were noted
- Analyses were carried out with RCR testing and PCR testing for transgene/vector
- However, in 2 cases, adequate specimens were not obtained
- Clear instructions for local physicians necessary to ensure appropriate follow-up testing in all cases