How Promising Is It? Notes From The VRX496 Conference Call (the first gene therapy for HIV)

August 12, 2008 By Peter Staley

There has been much interest, and some inevitable hype, in the first potential gene therapy approach for treating HIV, VIRxSYS Corporation's VRX496. On July 24th, the company held a web conference call to describe its latest research on this therapy, but there have been few public reports of what was said on that call.

As a primer, here is Tim Horn's description of how VRX496 is supposed to work (from http://www.aidsmeds.com/articles/hiv_vrx496_gene_therapy_1667_14007.shtml):

> Gene therapy involves introducing genetic material into a person?s cells to turn specific functions on or off. In the case of HIV, turning off certain CD4 cell functions may help protect CD4 cells from becoming infected with HIV or from producing new virus. Alternatively, gene therapy might be used to turn on certain CD4 cell functions, potentially causing HIV-infected cells to self-destruct or to begin producing HIV so that standard HIV medications can go to work.

Gene therapy is complicated, as a gene cannot be directly inserted into a person?s cell. It must be delivered to the cell using a vehicle, or ?vector.? The vectors most commonly used in gene therapy are viruses, given that they have a unique ability to recognize certain cells and insert their DNA into the cells. In gene therapy?as well as vaccine research using this approach?developing a vector involves replacing the genes in the virus that cause disease with those that are intended to have the desired effect on cells.

VRX496, developed by VIRxSYS Corporation, is the first to use HIV itself as a vector?HIV that has had its genetic material removed, leaving only its outer shell (envelope). The envelope is then fitted with therapeutic material called antisense.

The antisense molecule is the mirror image of the gene responsible for producing new envelopes for the virus. When the modified CD4 cells are given back to the patient, the antisense gene is permanently integrated

into the cellular DNA. When the virus starts to replicate inside the host cell, the antisense gene prevents the production of the envelope (env) gene, thereby shutting down HIV replication.

Richard Jefferys, Coordinator of the Michael Palm Basic Science, Vaccines & Prevention Project with TAG, the Treatment Action Group, kindly agreed to let me post his notes from the July 24th conference call, including his must-read “subjective commentary” at the end. Thanks, Richard!

Here are his notes:

VIRxSYS Call Notes

Presenters

Gary McGarrity, PhD, Executive Vice President of Scientific Affairs, VIRxSYS

Carl June, MD, Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania

Background

VRX496 is a lentiviral vector designed to make an ?antisense? gene that can bind to, and disrupt, the envelope gene of HIV. The vector also interacts with HIV in a way that causes more of the antisense gene to be produced in HIV-infected cells than in uninfected cells. VRX496 is delivered by taking a sample of a person?s own CD4 T cells, expanding them in the lab, and introducing the vector which is reportedly taken up very efficiently ? Carl June stated that there is typically an average of 1-3 vector copies per CD4 T cell. The CD4 T cells are then reinfused, most common dose has been ~10 billion cells but both higher (20 & 30 billion) and lower (number not given) are being studied.

Data Presentations

The first report of a 5 person phase I study was published in PNAS several years ago: http://www.pnas.org/content/103/46/17372.full

Participants had failed two prior ART regimens and had

CD4s >150 and viral loads >5000. The paper takes pains to suggest that VRX496 administration was associated with viral load reductions but this interpretation is complicated by receipt of ART and two individuals changing their ART regimens mid-study. 4/5 participants showed CD4 increases of around 60%. On the call they showed long term follow up slides out to around 4.5 years and viral loads are low in all participants although there have likely been additional ART modifications.

Carl June (who was diligent about disclosing that he has no consultancy or other financial relationship with VIRxSYS) then described the extremely preliminary phase II data from a trial conducted by VIRxSYS (not June?s group at University of Pennsylvania). Participants were required to have failed 1 ART regimen and have CD4s >150 and viral load >5000. No viral load reductions were seen. In a slide reporting CD4 count changes, a total of eight participants were listed, but one had no data available and two others dropped out

(according to a follow up email, one because they were taking ARVs after saying they weren?t and the other because they were traveling from Europe and could not continue to do so). Of the remaining five (three on ART, two not), three showed CD4 count increases ranging from 21-52% at 12 months after a single infusion (in one case though, no increase had been seen at the 9 month timepoint). Data was then reported up to an additional 6 months after a second infusion for two of these individuals (neither on ART), showing fluctuating CD4 counts that ranged from 38-110% above baseline. There?s also a dose escalation arm to this study evaluating single-dose of 10, 20 or 30 billion CD4 T cells but no data was reported from that cohort.

Carl June stated that gut biopsies have shown ?good persistence? of CD4 T cells containing VRX496 in the gut-associated lymphoid tissue (GALT). The vector has also been detected in around 0.01-2% of peripheral blood CD4 T cells expressing a marker that is associated with trafficking to the GALT (the marker is called alpha4-

beta7 integrin).

Gary McGarrity believes that the vector is decreasing HIV fitness because VRX496-resistant virus loses large sections of the envelope gene, and therefore the HIV envelope cannot bind to CD4 anymore. Evidence for this has been seen in a lab study (http://jvi.asm.org/cgi/content/full/78/13/7079). They showed sequences from three participants in the phase II studies and some of these sequences (maybe around half) showed deletions in the env gene. McGarrity argued, not very convincingly, that viral load changes weren?t seen because the deletions don?t affect HIV?s gag gene, which is what the viral load test measures.

Data were also presented from three study participants suggesting that their virus was less fit after VRX496 therapy, but this data was generated by Eric Arts whose laboratory viral fitness test has also shown that HIV subtype C is ?less fit? than subtype B (http://jvi.asm.org/cgi/content/abstract/77/2/1021).

Rather awkwardly, there is no evidence that subtype C is less pathogenic than subtype B and one study has suggested that people infected with subtype C have higher, not lower, viral loads (http://jvi.asm.org/cgi/content/full/73/5/4393). These data would appear to call into the question the relevance of this fitness test.

Data was shown from one person suggesting that their HIV had become more homogenous (less genetically diverse) two months after receiving VRX496, but unless this is something that turns out to be consistent among recipients it seems completely uninterpretable.

The company is currently designing a phase IIb trial in collaboration with a ?world class medical advisory board? that includes Steve Deeks, Brigitte Autran, Mike Lederman and others. They hope to have this trial design finalized by the fall of this year.

In terms of safety, the company has 110 patient-years

of follow-up and no serious adverse events have been reported although there are some transient transfusion-like symptoms at the time of CD4 T cell infusion. Phase I trial participants are being followed for 15 years as per FDA requirement.

There?s one other phase I/II trial being conducted by Carl June?s group which involves people on ART with CD4s >350 and viral loads

Gary McGarrity also offered a brief description of their lentiviral vaccine vector, VRX1023. It has the advantages of being able to carry many different genes (up to 10kb of genetic information); these can be genes that make copies of HIV proteins and/or genes that make adjuvants (like cytokines or toll-like receptors). Immunity to the vector ? a problem with vaccines like Merck?s Ad5 ? does not appear to be an issue because antibodies against the vector envelope (which is derived from Vesicular Stomatitis Virus type G or VSV-G) do not affect the vector?s ability to induce immune responses. He stated that the mouse immune response data has

been very encouraging and non-human primate studies are underway. If these studies show promise they hope to have phase I human trials underway within a year.

Q&A

I asked about whether they?re going to include a control arm in the phase IIb in which people just get the CD4 infusions without the vector, as Carl June has previously reported that this can increase people?s CD4 T cell counts (http://www.nature.com/nm/journal/v8/n1/full/nm0102-47.html). They haven?t decided yet. Carl June acknowledged that at least some of the CD4 count effect is likely resulting from the infusions, but he thinks the virological evidence suggests that both the vector and the infusions are contributing.

Nelson asked about duration of follow up for the phase I trial (~4.5 years) and whether quality of life endpoints will be assessed in future studies, Carl June responded

that he is collaborating with QOL researchers at Jacoby Medical Center so that this will be part of future trials. Nelson also asked if any instances of immune reconstitution syndrome have been seen, they said no.

Subjective Commentary

In terms of VRX496, a lot seemed to be being extrapolated from very limited data (this is probably an understatement!). The inferences about viral load reductions that were made based on the phase I trial have fallen by the wayside, which has led to this dubious idea that viral load is unchanged because the vector is increasing the proportion of ?unfit? viruses, but you?d think this would still ultimately impact viral load levels if it is indeed happening. The CD4 increase data is mainly from just two people in the phase II trial and it?s more than a little unclear if the reported CD4 increases are much different from those reported by Carl June in his study of CD4 T cell infusions alone. While it seems possible that the approach could benefit people that are

running out of ART options in setting where these types of infusions are feasible, I think there?s a long way to go to really establish what the vector is doing.

In terms of the VRX1023 vaccine, it?s obviously early days but the vaccine field could sure use some new vector approaches that don?t have issues with pre-existing immunity.