

SUMMARY
Workshop on Immune based Therapies in the Treatment of HIV Infection

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Kendall A. Smith

HIV-infected patients, physicians and scientists now all realize that Highly Active Anti-Retroviral Therapy (HAART) cannot cure HIV infection. As well, the chronic, continuous administration of HAART is associated with an ever-increasing incidence of serious side effects that preclude the use of this form of therapy indefinitely. Thus, HAART is now being viewed in the same light as glucocorticoid therapy for rheumatoid arthritis: although effective, the toxicities of the therapy will ultimately severely limit its continuous use.

Accordingly, attention is now turning to immune-based therapies (IBTs). It is well established that the immune system responds to viral infections and is responsible for inhibition of viral replication and destruction of virus-infected cells, eventually eliminating replicating virus, leaving a state of long-lasting immunological memory and protective immunity. Therefore, this workshop focused on how to design clinical trials to determine the effectiveness of therapies designed to boost immunity.

Dr. June Bray, Deputy Director of The Forum organized the workshop and facilitated the discussions along with Scientific Chair, Dr. Alan Landy of The Rush Presbyterian Hospital, Chicago.

Roy Gulick from Weill Medical College of Cornell University detailed the results of HAART compiled to date: ~ 70% response rate within 1 year of therapy, with 20% treatment failures after this time interval. However the numbers are decidedly worse after 2 years of HAART; the treatment failures increase to 60%.

Brenda Lein of Project Inform presented a lucid, informed and comprehensive perspective from the community on the problem confronting the field, i.e. of the best way to monitor IBTs to determine their efficacy so that approval can be gained. While IBTs are in clinical trials, they are not available to the vast majority of individuals infected with HIV. There is a concern that unless investigators and officials can agree as to the surrogate markers and the magnitude of changes in these markers affected by the IBTs, the ultimate approval IBTs will be prolonged beyond reason.

In my presentation I tried to make the following points:

- 1) The immune response is anti-viral.
- 2) Therefore we should monitor the virus to assess the efficacy of IBTs.

- 3) A good way to do so is to administer IBTs together with HAART, followed by the interruption of HAART to determine whether the IBTs prevent or attenuate viral replication. This could be termed a *Diagnostic Treatment Interruption* (DTI).
- 4) The best model for such an approach is Hepatitis C Virus (HCV) infection. In this infection the standard therapies are administered for 48 weeks, followed by discontinuation of therapy, and evaluation of plasma HCV 24 weeks after the treatment interruption.

I presented our data on the DTI of 9 individuals who were chronically infected with HIV prior to receiving HAART, which has just been published in the November/December, 2000 issue of "HIV Clinical Trials" (see the "Investigate" section on this web site). These individuals were treated with at least 3 months of daily low dose IL2, and prior to DTI, they had achieved CD4+ T cell counts within the normal range, and had elevated levels of CD8+ T cells and NK cells. Upon DTI, we found that although there was a relapse of detectable plasma virus in all subjects, the concentration of the virus was controlled by the host antiviral response. After an initial rapid increase, there was a rapid decrease (average 10-fold) in plasma virus concentration, followed by a "trough", which came to a lower steady state.

Coincident with the decline in plasma virus concentration, CD8+ T cells concentrations increased markedly, and then remained elevated while the virus declined and reached a lower plateau. Moreover, the rate and magnitude of the decline in plasma virus correlated with the magnitude of increase in CD8+ T cells, suggesting that a surrogate marker of the host antiviral response could be the concentration of CD8+ T cells.

We repeated the DTI in 4 of the 9 subjects after reinstatement of HAART. The peak plasma HIV concentration was >10-fold lower in 3 of 4 of these subjects, suggesting that the 1st DTI had acted to prime the host response to the virus. In support of this interpretation, the "viral set point" or trough viral load was found to be significantly lower than after the 1st DTI in 2 of these 4 individuals.

The number of volunteers who participated in these studies was small. However, the studies are on-going and thus far 31 subjects have entered the study, while 16 individuals have undergone 1 DTI, and 6 individuals have undergone 2 DTIs. Additional data will be presented at the 8th Conference on Retroviruses & Opportunistic Infections in Chicago in January 2001 (see meeting abstract on this web site).

The most important conclusion that can be made at this time is that individuals who are chronically infected prior to receiving HAART *can* mount a significant antiviral host response, provided they have recovered normal concentrations of circulating CD4+ T cells and have achieved elevated levels of CD8+ T cells and NK cells. Moreover, the way to test for *in vivo antiviral reactivity* is to employ a DTI, then monitor plasma HIV concentrations and lymphocytes over a short-term (i.e. 8-12 weeks).

Michael Lederman from Case Western Reserve University presented a proposal to use vaccination during the administration of IBTs to monitor overall immune responsiveness. He detailed how existing vaccines, such as hepatitis virus vaccines could be used to monitor and quantify antibody, CD4+ T cell and CD8+ T cell responses. Such immunological parameters could be standardized and used to determine differences in IBTs that might have different mechanisms of action. This approach would obviate the need to use different immunological assays for different IBTs. Rather, we should be focused on using established assays of the development of immunity in reaction to common vaccines.

I seconded this idea, and remarked that as we test more therapeutic vaccines for HIV, that we need to use control vaccines for our HIV-specific vaccines. The immune responses to these control vaccines can then serve as indicators of the functional capabilities of the immune system that are independent of its reaction to HIV itself.

Jay Berzofsky of the National Cancer Institute remarked that it would be important to employ vaccines that the majority of individuals had never been exposed to, to measure the primary immune response, and also to use immunogens that would provoke a secondary or memory immune response.

Victor DeGruttola from Harvard School of Public Health discussed statistical methods to optimize the analysis of data gained from clinical trials. In particular, he suggested that when analyzing the data obtained from viral relapse after treatment interruption, that the entire curve should be analyzed by making a rank-based nonparametric comparison of the viral load relapse curves. In this way, the data on the time to relapse, the rate of increase in plasma HIV, as well as the rate and magnitude of the decrease in viral load can be analyzed.

Perhaps the most important presentation of the meeting came from Bill Schwieterman from the FDA. His entire slide presentation is available for those interested, by EM @ scwieterman@cber.fda.gov. In essence, he supported and strongly recommended that investigators consider designing phase I/II trials of different IBTs using the viral and lymphocyte dynamics that occur after antiviral treatment interruption as endpoints. He pointed out that HAART is similar to the use of glucocorticoids for rheumatoid arthritis: effective yet too toxic for continuous use. Therefore, any agents that would facilitate HAART-sparing regimens and still maintain viral latency or low viral loads would be looked upon favorably.

He also stressed that HIV therapy has progressed to the point where it is in a position not too different from that faced by the Hepatitis C Virus (HCV) field. Because continuous interferon therapy is too toxic, the standard therapy for HCV is given for a finite period of 48 weeks, followed by treatment interruption and evaluation for detectable plasma virus 24 weeks later. The FDA has used the surrogate marker of plasma virus to approve the agents presently used for HCV treatment, upon the recommendation of the experts in the field. Therefore, should experts in the HIV field recommend adoption of the DTI approach to testing IBTs, he suggested that the FDA would consider using plasma HIV as

a surrogate marker for IBT approval. In response to this, after breakout sessions the Forum endorsed DTI as a method of testing for HIV-specific host reactivity after IBTs administered during maximal viral suppression while on HAART.