Can valproic acid help flush HIV from hiding?

Researchers in Dallas, Texas, conducted an HIV eradication study and recently published an account of their work. Between 2002 and 2005, four PHAs whose viral load was very low (less than 50 copies) for several years, were enrolled in a study to try to reduce the level of HIV infection of their cells. In addition to their treatment regimens, all participants also received T-20 (enfuvirtide, Fuzeon) and the anti-seizure drug valproic acid. This last medication appears to help release HIV from resting T cells. After three months, researchers found that the level of HIV in resting cells fell significantly in three of the four PHAs. This is the first time that any therapy has appeared to reduce the body’s reservoir of HIV. The news of this development raised hopes that that a route to flushing HIV out of the body may be a possibility if the Dallas protocol were applied for several consecutive years.

However, readers should be cautious in interpreting the results from these and similar studies that are underway. Many issues need to be resolved before researchers can prove that a cure for HIV is indeed at hand. It may take several years before they can be certain about eradication. These and other related issues are explored later in this issue of TreatmentUpdate.

Study details

Researchers recruited four adult participants who had been diagnosed with HIV infection between 1985 and 1999. All of them had been taking HAART for at least two years before entering the study and during that period their viral load was below the 50-copy mark. Having this degree and duration of viral suppression was a requirement for entering this clinical trial.

The CD4+ cell counts of participants at the start of the study and the combinations of HAART used were as follows:

- Participant 1—1,285 CD4+ cells: tenofovir (Viread), abacavir (ABC, Ziagen), d4T (stavudine, Zerit) and amprenavir (Agenerase) boosted with a small dose of ritonavir (Norvir)
- Participant 2—558 CD4+ cells: ddI (Videx), FTC (emtricitabine, Emtriva) and efavirenz (Sustiva, Stocrin)
- Participant 3—350 CD4+ cells: tenofovir, ABC, 3TC (lamivudine, Epivir), efavirenz and nelfinavir (Viracept)
- Participant 4—372 CD4+ cells: AZT, 3TC and nevirapine (Viramune)

Once in the study, participants self-injected T-20 twice daily at standard doses. The purpose of adding T-20 to their regimens was to hopefully intensify the anti-HIV activity of their treatment. After confirming participants’ adherence to this intensified therapy, researchers added another drug, valproic acid, to the regimen. This was taken at a dose between 500 and 750 mg twice daily for three months, at which point the study ended. Valproic acid levels in the blood were monitored to keep them within the range of 50 to 100 mg/L.

Results—Side effects

According to the study team, the four participants tolerated the protocol and adhered to it well.

Participant 4 was taking AZT and his bone marrow was temporarily weakened as he developed less-than-normal levels of red blood cells. This may have occurred because valproic acid can decrease the body’s ability to get rid of AZT.

Results—Viral load

In three of the participants, the intensified treatment regimen was able to keep viral load below the 50-copy mark. Participant 3 developed a minor chest infection after initiating T-20 therapy. His viral load rose to about 75 copies during this illness but then fell back below the 50-copy mark and remained there for the duration of the study.
Misunderstanding viral load results

The currently available tests for assessing viral load generally have a lower limit of 50 copies. There is a common misunderstanding that viral load results below the 50-copy mark are “undetectable.” In reality, these tests can often detect viral loads that are lower than 50 copies but cannot accurately count (or quantify) viral loads that are there. So a more accurate way to refer to the 50-copy limit is to say the viral load is BLQ—below the level of quantification.

Breaking the 50-copy barrier

To be able to accurately assess viral loads less than 50 copies, the study team developed their own test to be used in the lab. It could accurately assess viral loads as low as 1 copy.

Using this ultra-sensitive assay, researchers found that, for the most part, participants 1, 2 and 3 had viral loads as low as 1 copy or less. Participant 4 had viral loads that ranged between 9 copies and 1 copy at different times during the study.

Searching for HIV

Researchers took blood from participants and filtered out the lymphocytes, focusing on CD4+ cells. They maintained and grew these cells in the lab, then stimulated them with interleukin-2 to activate the cells and force HIV out of hiding. Three weeks later, technicians assessed CD4+ cultures for any HIV. In general, during the study, the level of resting T cells with HIV fell by “at least 29%,” according to the researchers. But when participants stopped taking valproic acid and T-20, the number of latently infected CD4+ cells appeared to increase.

In theory, if participants remained on the study regimen for several years, it may have been possible that the pool of resting HIV-infected CD4+ cells could have been removed from the body. However, even this research team notes that there are many issues about this study that need to be explored before they can be certain that HIV infection has been cured. These issues and ideas about different HIV eradication protocols are discussed later in Treatment Update.

REFERENCE:

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