New Drug Venetoclax Offers Hope to People with HIV

In a study published earlier this week, researchers at the Mayo Clinic in Minnesota say a new drug called venetoclax may be a useful tool in the fight against HIV. The human immunodeficiency virus (HIV) infects CD4 T cells, which are critical in adaptive immunity. When a person contracts a typical infection such as measles, their immune system produces a wide range of T cells to combat the virus. When one T cell is effective against the pathogen, clones of that T cell proliferate and some become long-living memory T cells.

When HIV invades the body and attacks CD4 T cells, some of the infected cells become memory T cells. Current HIV treatments do not affect these infected T cells, which have incorporated viral genes into the host cell’s DNA but are not actively replicating the virus. In the United States, over 1.2 million people are living with HIV infections, the total cost of caring for people with HIV is more than 27 billion dollars annually, and over 21,000 Americans die each year from complications of HIV and AIDS. Ironically, a new promising method of treating HIV involves tricking HIV into reactivating. When HIV reactivates and begins to replicate, a protein called HIV protease is activated and begins to destroy components of the virus and the host. As a result, the cell undergoes apoptosis, which is also known as “cell suicide,” and the number of cells with latent HIV virus decreases. This population of dormant of HIV-infected memory CD4 T cells is regarded as the reason HIV is incurable. These cells contain HIV DNA, but they cannot be killed while they are inactive and non-replicating.

Previous studies examined other drugs that reactivated the HIV from its dormant state, but did not induce replication. Experiments indicated the HIV-infected cells were active and producing HIV proteins, but they were neither replicating nor dying. Researchers proposed two explanations for this phenomenon: either a critical apoptosis protein was not being produced or that protein was being produced but additional proteins were counteracting it. Data published by scientists at the Mayo Clinic supported the latter hypothesis. Memory T cells are designed to withstand stress and challenges from pathogens. Their survival is essential to lifelong immunity. Therefore, memory T cells respond to stress by producing protein that make them much less susceptible to death than other cells in the body.

Venetoclax, the drug tested at the Mayo Clinic on HIV infected cells, was granted breakthrough therapy designation by the Food and Drug Administration in recognition of its good safety rating and ability to target other malignancies. Venetoclax works by targeting an anti-apoptosis protein called BCL-2. After the HIV infected T cells are reactivated, apoptosis begins, and because BCL-2 and similarly functioning proteins have been inhibited, cell suicide occurs. This project was the first demonstration of a pharmacological method of reducing the HIV reservoir in the majority of cases.

Further trials of venetoclax in humans are necessary to examine the incidence of toxicities and side effects in patients, especially the already vulnerable HIV-infected population. One benefit of conducting trials within the HIV-positive population is the current dearth of treatments. This means a good portion of the target population is likely to be willing to participate in drug trials. If approved, the cost of venetoclax must also be considered, as the average person with HIV already spends over $20,000 per year on healthcare and venetoclax should be used in supplementation with traditional antiretroviral therapy (ART) and not in place of ART. Healthcare professionals must also remember that HIV reactivating drugs such as venetoclax will not access and reactivate all the viruses in one round of treatment. Instead, venetoclax would likely be necessary in multiple rounds of treatment similar to chemotherapy for cancer patients.

Reference:

N. W. Cummins et al. (2016). "Prime, Shock, and Kill: Priming CD4 T Cells from HIV Patients with a BCL-2 Antagonist before HIV Reactivation Reduces HIV Reservoir Size." J Virol **90**(8): 4032-4048.

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