Can an Immune-Modulating Drug Help Clear the HIV Reservoir?

Ruxolitinib may have contributed to a functional cure after a stem cell transplant without a rare mutation.

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An immunomodulating drug used to treat graft-versus-host disease may reduce the size of the HIV reservoir and reverse immune dysfunction, according to study findings presented at the International AIDS Society Conference on HIV Science (#IAS2023) and at the preceding HIV Cure & Immunotherapy Forum. What's more, ruxolitinib (Jakafi) may be helping to maintain long-term remission in a man who appears to be cured after a stem cell transplant.

"Our Phase II human study with ruxolitinib provides a proof of principle that JAK 1/2 inhibitors, originally developed for inflammatory diseases, can reduce the HIV reservoir," lead study author Monica Reece, a PhD student at Emory University in Atlanta, told POZ. "We have demonstrated that ruxolitinib can reduce the reservoir by reducing the life span of cells harboring latent virus and by blocking inflammation that allows the reservoir to persist."

While antiretroviral treatment keeps HIV replication at bay as long as it continues, the virus inserts its genetic blueprint—known as a provirus—into the chromosomes of human cells, establishing a long-lasting viral reservoir that is unreachable by antiretrovirals and invisible to the immune system. Even when viral replication is suppressed, people with HIV can experience ongoing immune dysfunction and inflammation that contributes to a wide range of health problems, including cardiovascular disease and neurocognitive impairment.

These latent proviruses can lie dormant indefinitely in resting CD4 T-cells in the presence of antiretrovirals, but they usually start producing new virus soon after the drugs are stopped, posing a major barrier to a cure. HIV cure researchers have tried many approaches to kill off latently infected cells, flush out latent virus, permanently silence dormant proviruses or even excise viral genes from host cells.

"The barrier to an HIV cure is that the virus hides inside the DNA of cells," senior investigator Christina Gavegnano, PhD, said in an Emory news release. "The brass ring is an agent that can eliminate these reservoir cells, which would ultimately eliminate HIV from a person's body."

Ruxolitinib Trial

The Phase IIa AIDS Clinical Trials Group A5336 trial enrolled 60 adults living with HIV who were on antiretroviral therapy with stable viral suppression for at least two years and had a CD4 count above 350. Forty participants were randomly assigned to add ruxolitinib to their regimen for five weeks while 20 stayed on antiretrovirals alone.

Ruxolitinib is an oral JAK 1/2 inhibitor that interferes with key steps in the JAK-STAT signaling pathway, which is involved in cell proliferation, immune regulation and inflammation. It is used to treat conditions such as myelofibrosis and graft-versus-host disease that doesn't respond to steroids.

Gavegnano and colleagues have been studying ruxolitinib for more than a decade. Back in 2016, they reported that the drug reduced HIV replication in human macrophages in laboratory studies and improved HIV-related brain inflammation in mice. She later reported that baracitinib (Olumiant), a second-generation JAK 1/2 inhibitor, reduced the number of CD4 cells harboring latent virus in recently infected monkeys.

As previously reported, the main A5336 trial showed that ruxolitinib significantly decreased markers of immune activation and cell survival. Reece and colleagues looked more closely at the effects of the drug on the peripheral HIV reservoir and immune biomarkers associated with HIV persistence. Study participants who received ruxolitinib were classified as having a high viral reservoir (top one third) or a low reservoir (bottom two thirds). They were followed for an additional seven weeks after five weeks on ruxolitinib.

The researchers measured integrated proviral HIV DNA in peripheral blood cells, noting changes over time. They saw a significant decline in proviral DNA from week 5 to week 12 in participants with a high viral reservoir who received ruxolitinib. The reservoir size did not change in ruxolitinib recipients with a low reservoir, while those who did not receive the drug showed a slight increase. Based on the viral decay rate, they calculated that 99.99% viral clearance could potentially be achieved in just under three years.

Participants who received ruxolitinib also showed greater changes in numerous biomarkers related to immune activation and dysregulation, cell survival and reservoir establishment and expansion. Based on these findings, the researchers identified "niche" biomarkers that predicted which individuals are likely to experience substantial reservoir decay when treated with ruxolitinib (BCL/KI67, pSTAT5, CD127 and IL-10).

A limitation of this analysis is that the study team looked only at hidden virus in peripheral blood cells, not in lymph nodes or so-called sanctuary sites such as the central nervous system or gut that are shielded from the immune system.

This study offers evidence that JAK 1/2 inhibitors can reverse immune dysfunction and decrease the size of the viral reservoir in a subset of people with HIV, the researchers concluded. Studies looking at a longer duration of treatment are underway. If these findings are confirmed, ruxolitinib or baricitinib could potentially be used as "a backbone for cure-based eradication strategies," they suggested.

According to Vincent Marconi, MD, lead author of the main A5336 trial, “These data are valuable because they show that JAK inhibitors can contribute to a long-term cure strategy for HIV, but they can also be used to slow the inflammatory process caused by other infectious diseases,” potentially including acute COVID-19 and long COVID.

The Geneva Patient

Ruxolitinib is just one of the many agents that have shown promise as a cure strategy in early studies, but another presentation at the conference gives it added weight.

Asier Sáez-Cirión, PhD, of Institut Pasteur in Paris, reported that a man dubbed the Geneva Patient appears to be the sixth person cured of HIV after a stem cell transplant for cancer treatment. But unlike the other five, he received stem cells from a donor who does not have a rare mutation (CCR5-delta32) that prevents HIV from entering cells.

The man was diagnosed with an aggressive type of sarcoma and underwent chemotherapy and whole-body radiation before receiving the stem cell transplant in July 2018. He developed acute and chronic graft-versus-host disease and was treated with various immunosuppressive drugs, including ruxolitinib. He stopped antiretrovirals in November 2021 and continues to have undetectable HIV 20 months later.

Researchers are still working to learn why this man was apparently cured after a transplant of stem cells without the CCR5-delta32 mutation, while other attempts have failed.

For example, in 2013, Timothy Henrich, MD, now at the University of California San Francisco, and colleagues described two HIV-positive men in Boston who received transplants to treat lymphoma using so-called wild-type stem cells. The Boston Patients generated considerable excitement, as they appeared to be controlling HIV after stopping antiretroviral therapy. But hopes were dashed when they experienced viral rebound three months and eight months after treatment discontinuation.

One factor might be the Geneva Patient’s use of ruxolitinib, which he received for years to manage ongoing graft-versus-host disease. The drug “may have had an impact of reducing the reservoir and the absence of viral rebound,” Alexandra Calmy, MD, PhD, of Geneva University Hospitals in Switzerland, said at an IAS media briefing. Henrich, too, told POZ that ruxolitinib might have contributed to the man’s long-term remission. However, other experts suspect the graft-versus-host reaction itself may have triggered HIV remission.

Stem cell transplants are far too risky for people who do not need them to treat life-threatening cancer, and the intensive and costly procedure is not feasible for most people living with HIV worldwide. But cases like this offer clues that could help scientists develop strategies that lead to a more widely applicable functional cure. Most experts predict that a combination approach will likely be needed, and drugs like ruxolitinib might be part of the mix.

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