PD-1 Checkpoint Inhibitor May Delay HIV Rebound

Two out of 11 people who received four doses of budigalimab have maintained viral suppression for a year and a half after stopping antiretroviral therapy.

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Budigalimab, a monoclonal antibody that blocks PD-1, delayed viral rebound or maintained a low viral load in a majority of people with HIV who interrupted antiretroviral treatment, according to results from a small pilot study presented at the European AIDS Conference (EACS 2023) in Warsaw. While these findings are still early, they add further evidence that PD-1 inhibitors might be used as part of a combination strategy for a functional cure.

PD-1 ("programmed death 1") is an immune checkpoint receptor on exhausted immune cells. Normally, it suppresses T-cell activity, preventing the immune system from attacking the body's own tissues (autoimmunity), but some tumors can hijack PD-1 to turn off immune responses against malignant cells. Likewise, people with chronic HIV infection typically have upregulated PD-1 expression and dampened T-cell responses.

Checkpoint inhibitors that block PD-1 can release the brakes and restore T-cell activity. PD-1 inhibitors—monoclonal antibodies such as Keytruda (pembrolizumab) and Opdivo (nivolumab)—are now widely used as cancer immunotherapy. In theory, Routy explained, PD-1 inhibitors could potentially reverse T-cell exhaustion and restore function in people with HIV, and they might also act as a latency reversal agent to push virus out of cells.

Budigalimab (ABBV-181), an investigational PD-1 inhibitor from AbbVie, is being explored as an approach for achieving durable control of HIV without antiretroviral therapy (ART), also known as remission or a functional cure. Jean-Pierre Routy, MD, of McGill University Health Centre in Montreal, presented findings from the first two Phase I randomized trials of budigalimab for people living with HIV, conducted in the United States and Canada.

So far, studies of budigalimab dosed at 250 or 500 milligrams every two or four weeks for cancer treatment have demonstrated safety and efficacy similar to that of approved PD-1 checkpoint inhibitors. But the doses used in the HIV trials are 50 to 100 times lower, Routy noted. In addition, the HIV treatment is finite, whereas cancer immunotherapy typically continues for multiple cycles or until disease progression or unacceptable side effects occur.

The first study, known as M19-972 (NCT04799353), evaluated the safety and pharmacokinetics of a single IV infusion (10 mg) or subcutaneous injection (10 to 20 mg) of budigalimab in 32 people on suppressive ART, with no treatment interruption.

The second study, known as M19-939 (NCT04223804), included a carefully monitored analytical treatment interruption. This study enrolled 41 people on suppressive ART. All but one were men, most were white and nearly half were Latino. The median age was approximately 45 years, they had been living with HIV for about 10 years and they had maintained viral suppression on ART for nearly as long. CD4 counts were high, in the 600 to 900 range. All had typical chronic HIV infection, and none were elite controllers.

In the first stage of the study, 20 participants received two doses of 2 mg or 10 mg budigalimab administered via IV infusion four weeks apart, while five people received a placebo. They stayed on their antiretrovirals for four weeks and were scheduled to stop ART when they received their second dose of budigalimab or a placebo, but two people opted out of the interruption.

In the second stage, 11 people received four doses of 10 mg budigalimab spaced two weeks apart, while five received a placebo. They all stopped ART at the time of their first budigalimab or placebo dose. This group was the focus of the exploratory efficacy analysis.

The study protocol called for participants to restart ART if their viral load reached 1,000 or higher for four weeks, their CD4 count fell below 350 or declined more than 30% from baseline, they experienced HIV-associated symptoms or they became pregnant. The participants or investigators could also decide to restart antiretrovirals at any time.

In both studies combined, budigalimab was generally safe and well tolerated. Overall, about one third of participants experienced treatment-related adverse events, with a slightly higher frequency in the budigalimab groups versus the placebo groups, Routy reported. Three budigalimab recipients experienced mild to moderate reversible immune-mediated side effects (two cases of thyroiditis and one skin reaction), which can occur when immune responses unleashed by checkpoint inhibitors lead to excessive inflammation. There were no serious or severe treatment-related adverse events in any group.

In study M19-939, budigalimab pharmacokinetics varied according to the dose and timing, with the 10 mg IV dose administered every two weeks yielding the highest serum concentrations. People who received the 10 mg IV dose either two times separated by four weeks or four times separated by two weeks achieved “near-complete” PD-1 receptor saturation (meaning receptors were all occupied by the monoclonal antibody), which persisted for eight to 10 weeks, but this did not occur with the 2 mg dose.

Among the 11 people in the second stage who received four infusions of 10 mg budigalimab every two weeks, a few had viral kinetics mimicking those of placebo recipients, but others showed delayed viral rebound (more than 21 days after ART interruption), a lower peak viral load or viral control (HIV RNA maintained below 1,000 copies). The median time to viral rebound was 29 days

in the budigalimab group versus 21 days in the placebo group. “A one-week difference is not that big, but there seems to be some effect,” Routy said.

Six out of nine budigalimab recipients who completed the second stage were considered good responders. In this subgroup, the peak viral load after rebound was around 10,000 copies, compared with around 100,000 copies in the placebo group.

Two of the budigalimab recipients were deemed post-treatment controllers. One patient from Montreal maintained an undetectable viral load for about 50 days after ART interruption, then saw an increase to about 350 copies, followed by a decline and sustained suppression below 100 copies for 19 months, having received their most recent blood test three weeks ago, Routy reported. The second individual, from the United States, experienced a viral load spike around 20 days after treatment interruption, reaching about 700 copies, followed by a rapid decline and sustained suppression below 200 for 18 months.

“Budigalimab administered for finite duration at very low doses was well tolerated in Phase Ib studies of people living with HIV,” the researchers concluded. “Biweekly administration of budigalimab 10 mg IV for four doses led to delayed viral rebound and/or ART-free viral control in six of nine participants completing treatment, with two participants remaining off ART until the end of the study.”

Based on these findings, further studies using the 10 mg dose of budigalimab are warranted. One Phase II trial aims to enroll 140 participants in the United States, Canada, Europe, Brazil and South Africa, according to Routy. Study M19-965 (NCT06032546) will test budigalimab and another investigational monoclonal antibody (ABBV-382) that blocks the alpha-4 beta-7 integrin receptor used alone or in combination.

Researchers and advocates have debated the ethics of treatment interruption trials, recognizing that it is necessary to stop antiretrovirals to see whether an intervention works. As expected, no placebo recipients in this study controlled HIV after stopping ART. While a majority of budigalimab responders had a viral load below 1,000 during much of the treatment interruption period, even a low-level persistent viral load can lead to a host of health problems, and 1,000 appears to be around the level where HIV transmission can occur. Simon Collins, of HIV i-Base, suggested that it would be useful to follow a combined cohort of people who undergo ART interruption in multiple trials in order to have sufficient numbers to understand long-term outcomes.

Collins also brought up the importance of including people of all demographic groups in HIV cure studies, which to date have mostly enrolled white gay men. He urged researchers not to impose upper age cutoffs that would exclude long-term survivors. Sarah Fidler, MBBS, PhD, of Imperial College London, pointed out that regulatory safety requirements regarding contraception and pregnancy can be a barrier to enrolling more women. And while advocates urge the inclusion of people from low- and middle-income countries in cure research, she stressed the importance of safety in areas where frequent monitoring is not easily available.

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