Could Broadly Neutralizing Antibodies Partner With Long-Acting Antiretrovirals?

Specialized antibodies might be used in combination with injectable lenacapavir or cabotegravir.

March 6, 2024 By Liz Highleyman

Broadly neutralizing antibodies, or bnAbs, appear to work well with lenacapavir (Sunlenca) or cabotegravir in long-acting regimens for HIV treatment, but studies are still in early stages, according to two presentations this week at the Conference on Retroviruses and Opportunistic Infections (CROI 2024) in Denver.

Monoclonal antibodies are manufactured proteins that work like natural antibodies made by the immune system. People living with HIV normally produce HIV-specific antibodies, but these mostly target parts of the virus that are hidden or highly variable. However, a small proportion of people make broadly neutralizing antibodies that target conserved parts of the virus that don't change much. These specialized antibodies are being explored for HIV pre-exposure prophylaxis (PrEP), treatment and cure research. But HIV can develop resistance to bnAbs, so they are best used in combination therapy.

Lenacapavir Plus Two bnAbs

Lenacapavir is approved for highly treatment-experienced people with multidrug-resistant HIV. It is administered by injection every six months, but it currently does not have equally durable partners to build a complete twice-yearly regimen. Researchers are exploring whether bnAbs could fill that role.

Joseph Eron, MD, of the University of North Carolina at Chapel Hill, presented new results from a study of lenacapavir plus a pair of bnAbs being developed by Gilead Sciences, dubbed teropavimab and zinlirvimab.

Teropavimab (GS-5423) is derived from a bnAb called 3BNC117 that targets the CD4 binding site on HIV's gp120 protein, which the virus uses to enter cells. Zinlirvimab (GS-2872) is derived from a bnAb called 10-1074 that binds to the V3 loop of HIV's envelope. Both bnAbs were modified to extend their half-life and enable less frequent dosing. More than half of subtype B HIV—the most common type in the United States and Europe—is highly susceptible to both antibodies, and more

than 90% is susceptible to one or the other, according to Eron.

At last year's CROI and in The Lancet HIV, Eron and colleagues reported findings from a Phase Ib trial (NCT04811040) that enrolled people on antiretroviral treatment with an undetectable viral load. They were tested to ensure that their HIV was highly sensitive to both teropavimab and zinlirvimab. Of the 124 people initially screened, 44% met the susceptibility criteria. Others were unable to enroll due to a temporary clinical hold on lenacapavir or for other reasons, leaving 20 people for the analysis. Most were white men, and the median age was 44.

At the start of the study, after discontinuing their existing antiretrovirals, all participants received an oral loading dose of lenacapavir, two subcutaneous injections of lenacapavir and an intravenous infusion of teropavimab (30 milligrams per kilogram). In addition, they were randomly assigned to receive either 10 mg/kg or 30 mg/kg infusions of zinlirvimab. Due to the lenacapavir hold, the study was stopped ahead of schedule at 26 weeks, and participants received only one round of treatment.

Lenacapavir, teropavimab and zinlirvimab remained above therapeutic levels, and 90% of participants in both dose groups maintained viral suppression at six months. The treatment was safe and generally well tolerated.

These findings set the stage for a new cohort of 11 people whose HIV was highly sensitive to either teropavimab or zinlirvimab, but not both. Again, they were on stable antiretroviral therapy with an undetectable viral load, had a current CD4 count above 500 and had never had their CD4 count fall below 350. This cohort was more diverse: About a quarter were women, more than a third were Black and 27% were Latino. The median age was 49, and they had been diagnosed with HIV for a median of 16 years. One person was diagnosed with hepatitis B and excluded from the analysis.

The 10 remaining participants were randomly assigned to the same two regimens as the first cohort. At 26 weeks, they restarted their baseline oral regimen. At that point, eight of the 10 (80%) maintained viral suppression (defined as 50 copies or less), Eron reported this week. But the response differed in the two zinlirvimab dose groups. Only two of the four people who received the lower dose still had an undetectable viral load, compared with all six of those who received the higher dose. No risk factors for viral rebound were identified other than a lower zinlirvimab dose.

One participant in the lower dose group who was sensitive to teropavimab was diagnosed with COVID-19 at the time of viral rebound and regained suppression after resuming an oral regimen. The other was sensitive to zinlirvimab and continued to have a low-level detectable viral load after restarting oral treatment. No treatment-emergent resistance was detected.

Again, treatment was well tolerated, and no one stopped therapy due to side effects. The only treatment-related adverse events were mild injection site reactions related to lenacapavir, such as pain, itching, swelling or nodules. No one experienced infusion reactions from the antibodies.

These results suggest that “more inclusive bnAb sensitivity criteria may be appropriate for treatment studies with [lenacapavir+teropavimab+zinlirvimab] when higher bnAb concentrations are maintained,” the researchers concluded.

Based on these findings, this combination has advanced to a Phase II trial (NCT05729568), according to a Gilead press release. The study will assess the safety and efficacy of multiple doses of the regimen in people with viral suppression.

Cabotegravir Plus One bnAb

In the second study, Babafemi Taiwo, MD, of Northwestern University in Chicago, and colleagues evaluated the safety and efficacy of long-acting cabotegravir plus a bnAb called VRC07-523LS that targets HIV’s CD4 binding site. It too was modified to improve its durability.

The combination of injectable cabotegravir and rilpivirine, sold as Cabenuva, is administered once monthly or every other month. It is currently the longest-acting complete antiretroviral regimen, but other durable partners would be welcome, especially for people whose HIV is resistant to NNRTIs like rilpivirine.

The Phase II ACTG A5357 trial (NCT03739996) enrolled adults with viral suppression for at least two years, no prior treatment switches due to virological failure and a current CD4 count of at least 350. Among the 142 people screened, 36 did not meet the criteria for sensitivity to VRC07-523LS and 31 were excluded for other reasons. The remaining 75 people had a median age of 54. About three quarters were men, half were white, a third were Black and 11% were Latino.

In Step 1, the participants in this open-label study first took oral cabotegravir (Vocabria) plus two NRTIs for four weeks. Those who maintained viral suppression proceeded to Step 2 and received long-acting cabotegravir injections every four weeks and 40 mg/kg infusions of VRC07-523LS every eight weeks. After 48 weeks, they resumed a standard oral regimen. A total of 71 people started Step 2, and 60 finished this step.

All but five participants (7%) maintained viral suppression (defined as 200 copies or less) at 48 weeks. Those five all had cabotegravir and VRC07-523LS levels within the therapeutic range. Three people experienced virological failure after receiving a COVID or mpox vaccine. Two regained viral suppression while staying on the same regimen, but one continued to have a low-level viral load after resuming an oral regimen. One person had an integrase resistance mutation. None developed antibodies against VRC07-523LS.

Treatment was generally safe and well tolerated. Twelve participants had severe (Grade 3) adverse events or discontinued due to events deemed possibly related to treatment. Most of them experienced chills, fatigue, muscle pain or other symptoms possibly related to VRC07-523LS. One person stopped treatment due to a mild infusion reaction.

The combination of a single long-acting bnAb plus injectable cabotegravir “has potential for maintenance of HIV-1 suppression but will require a better understanding of the mechanisms underlying breakthroughs,” the researchers concluded.

While these findings are interesting, injectable cabotegravir and rilpivirine is highly effective, well tolerated and does not require IV infusions. Cabotegravir plus VRC07-523LS given on an every-other-month schedule does not appear to offer an advantage, except, perhaps, for people with NNRTI resistance. For those individuals, a small case series presented by Monica Gandhi, MD, MPH, of the University of California San Francisco, and colleagues suggests that injectable cabotegravir plus lenacapavir could be a feasible option.

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