A promising second-generation integrase inhibitor is steadfastly progressing through clinical trials. Dolutegravir, made jointly by pharmaceutical companies Shionogi and ViiV Healthcare and formerly known as “GSK572,” is being evaluated both for first-line HIV therapy and for use by treatment-experienced people. This article reviews study results presented at recent HIV/AIDS conferences and elsewhere.

Integrase Inhibitors

After HIV enters a cell, in order to make more copies of itself it must convert its genetic material, ribonucleic acid (RNA), into the same form as the human cell’s genetic material, deoxyribonucleic acid (DNA). HIV’s integrase enzyme binds to the newly created viral DNA and inserts it into the human cell’s own DNA, enabling the cell to start producing viral proteins—the raw material for new copies of HIV.

As the name suggests, integrase inhibitors work by inhibiting the activity of the integrase enzyme, thereby preventing the viral DNA from being integrated into the host cell’s genetic material and blocking this stage of HIV replication.

In a presentation at the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention in 2009, researcher Jay Lalezari showed a slide with a promising title: “Integrase Inhibitors: Future Cornerstones of HIV Therapy.” His talk cited studies showing that integrase inhibitors are very well tolerated, and mentioned past clinical trials in which half of the treatment-experienced participants with no active drugs in their antiretroviral background regimen still saw their viral load drop below detectable levels while taking integrase inhibitors.

Currently, only one integrase inhibitor—raltegravir (brand name Isentress)—is approved for HIV treatment. The drug class is poised to expand, however: Two experimental integrase inhibitors, elvitegravir and dolutegravir, are currently in advanced human trials.

Elvitegravir requires a “boosting” agent to reach full potency against HIV and is being studied as part of Gilead Sciences’ once-daily, single-pill coformulation known as the “Quad” pill. (See “News Briefs,” page 6, for more information.)

Unlike elvitegravir, dolutegravir does not require boosting. The drug is being tested for use by treatment-naive and treatment-experienced individuals, and recent reports at HIV-related conferences and in medical journals highlight the investigational drug’s strengths and its potential as a new addition to the HIV treatment armamentarium.

Dolutegravir in Development

At the XVIII International AIDS Conference, held July 18 to 23, 2010, in Vienna, Austria, data were presented from two Phase Ib clinical trials of dolutegravir (then referred to by its study name, GSK572).

In the SPRING-1 study, 205 antiretroviral-naive participants were randomized to receive either 10, 25, or 50 mg GSK572 twice a day or a twice-daily 600-mg dose of efavirenz (Sustiva), in addition to a background antiretroviral drug regimen.

After 16 weeks of treatment, participants in the GSK572 groups saw significantly greater drops in viral load, more rapid viral suppression, and bigger CD4 cell gains. At least 90% of participants taking the study drug achieved undetectable viral load (below 50 copies/mL),
compared with 60% of those taking efavirenz. In addition, 18% of participants taking efavirenz reported mild or moderate drug-related adverse events, compared with only 4% to 8% of those taking the study drug.

Also described at the conference, the VIKING study first assessed GSK572 in a small cohort of only 27 individuals, all with prior antiretroviral drug exposure and with HIV bearing resistance to the integrase inhibitor raltegravir. These highly treatment-experienced individuals started the trial with lower CD4 cell counts than those in the SPRING-1 study, and roughly 60% had been diagnosed with AIDS.

VIKING participants in this early cohort began the study with a once-daily 50-mg dose of GSK572 for ten days in addition to their background regimens, none of which contained active drugs. After this ten-day period, background regimens were “optimized” to include drugs active against each participant’s virus, and treatment with GSK572 continued. By day 11 of the study, 78% of these participants saw their viral load drop to below 400 copies/mL; the average decrease was 1.45 log. (See sidebar below to learn more about log changes.)

However, pre-existing resistance mutations to raltegravir caused variation in participants’ responses to the study drug. A second VIKING cohort enrolled 24 participants, also with virus bearing resistance mutations and with poor response to their current treatment regimen; however, these individuals’ regimens were optimized to include at least one active drug at day 11 of the study, and 50 mg GSK572 was given twice daily rather than once daily as in the first cohort.

Results from this study group were presented at the 18th Conference on Retroviruses and Opportunistic Infections, held February 27 to March 2, 2011, in Boston. In Cohort II, an impressive 96% of participants saw their viral load decline to below 400 copies/mL or experienced reductions of at least 0.7 log. Everyone in this second cohort responded to the study drug, even though participants in Cohort II had HIV with extensive integrase inhibitor resistance mutations. As in previous studies, GSK572 was well tolerated, with mild to moderate diarrhea as the most commonly reported adverse event. (One individual experienced two serious adverse events unrelated to the study drug.)

Further Questions

In addition to assessing efficacy and safety in larger populations and over greater periods of time, advanced clinical trials must address concerns about resistance mutations as dolutegravir progresses through the pipeline.

In the VIKING cohorts, with heavily treatment-experienced individuals, response to dolutegravir varied according to the resistance mutations seen in the participants’ virus. At the Vienna conference, researchers reported that VIKING Cohort II participants whose HIV bore the raltegravir-resistance mutations N155 and Y143 did successfully suppress the virus, but only a third of those with the Q148 mutation, also linked with integrase-inhibitor resistance, had a virological response to treatment with the study drug.

An article published in the April 7, 2011, online edition of the Journal of Antimicrobial Chemotherapy reported that two other integrase mutations, T124A and T124A/L101I, were found in HIV from 39% of study participants whose raltegravir-based regimen was failing, and in 25% of participants who were new to integrase inhibitors. The authors concluded that the presence of these mutations may limit people’s response to raltegravir and promote the development of new mutations conferring resistance to dolutegravir. Further study is needed regarding the effects of these and other resistance mutations on the efficacy of second-generation integrase inhibitors.

What’s Next?

The VIKING study is ongoing, as is SPRING-2, a Phase II trial evaluating 50 mg once-daily dolutegravir versus 400 mg twice-daily raltegravir for 48 weeks. Other clinical trials
involving dolutegravir are currently enrolling. (See “Open Clinical Trials,” page 54, for more details.)

The Phase III SAILING study aims to enroll at least 688 treatment-experienced (but integrase inhibitor–naive) individuals and will pit once-daily dolutegravir against twice-daily raltegravir; participants will also receive an investigator-selected background regimen that includes at least one active drug.

A new fixed-dose combination, known as 572-Trii, is under investigation in the SINGLE study. In this Phase III trial, participants will take once-daily 572-Trii, which contains 50 mg dolutegravir plus abacavir/lamivudine (Epzicom), or will receive tenofovir/emtricitabine/efavirenz (Atripla) once daily.

Conclusion

With more people living longer with HIV, there is increasing emphasis on tailoring active and tolerable antiretroviral treatment regimens for life-long therapy. Unfortunately, activity in the drug development pipeline has been slow in recent years; until the May 2011 approval of rilpivirine (see “News Briefs,” page 4), three years had passed since the Food and Drug Administration (FDA) last approved an antiretroviral drug for the treatment of HIV.

FDA approval of dolutegravir depends, of course, on the drug’s performance in current and future trials and is a long way off, but the expansion of the integrase inhibitor drug class would be a welcome development, indeed.

Reilly O’Neal is the editor of BETA.

Selected Sources


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