Assessment on promising Integrase Inhibitor in Antiretro Viral Therapy

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A retrovirus is a germ whose genes are encoded in RNA as a replacement for DNA. Although, like further viruses, retroviruses necessitate to use the cellular machinery of the organisms they infect to make copies of themselves, infection by a retrovirus requires an additional step. The retrovirus genome needs to be reverse-transcribed into DNA by an enzyme called reverse-transcriptase before it can be copied in the usual way. Integration is a distinctive and essential process in the HIV infection cycle and thus represents an attractive antiviral drug target. Integrase inhibitors combined with other classes of drug might contribute to long-lasting suppression of HIV type-1 (HIV-1) replication for many patients. Of the numerous potential integrase inhibitor leads that have been reported, few have reached clinical trials and only one, raltegravir, has been approved for the healing of HIV-1-infected patients. An additional integrase inhibitor, elvitegravir, is currently showing promise in Phase III clinical studies. Once-daily administration of elvitegravir has a comparable antiviral activity to twice-daily of raltegravir in HIV-1-infected patients. Here, we highlight the salient features of elvitegravir: its chemical structure compared with representative integrase inhibitors, mechanism of action, in vitro and in vivo activity against HIV and other retroviruses, and the effect of integrase polymorphisms and resistance mutations on its anti-HIV activity.

Elvitegravir is a promising integrase inhibitor. When elvitegravir is taken with a little dose of the drug ritonavir (Norvir), the concentration of elvitegravir in the blood rises and remains elevated for about a day. The producer of elvitegravir, Gilead Sciences, is also developing another pharmacokinetic (PK) booster called cobicistat, which will be co-formulated with elvitegravir in the future. Presently, raltegravir (Isentress) is the only integrase inhibitor approved by regulatory authorities. Raltegravir is active against strains of HIV that are resistant to several classes of anti-HIV drugs, such as:

- nukes (nucleoside analogues)
- non-nukes (NRTIs)
- protease inhibitors

Elvitegravir is also effectual against such drug-resistant strains of HIV. In a Phase II study that ran for 48 weeks, elvitegravir when taken as part of combination therapy was effective in significantly reducing viral load in treatment-experienced patients. Researchers have also conducted a randomized placebo-controlled study comparing elvitegravir to raltegravir in treatment-experienced people. After one year, elvitegravir was found to be roughly equivalent to raltegravir in its effectiveness. The investigational HIV integrase inhibitor elvitegravir taken once daily continued to perform as well as twice-daily raltegravir (Isentress) at 96 weeks for treatment-experienced people with extensive drug resistance, according to data presented last week at the 19th International AIDS Conference in Washington, DC. HIV integrase inhibitors prevent the virus from inserting its genetic material into a host cell, a necessary step for viral replication. The sole approved drug in this class, raltegravir, has demonstrated long-term efficacy and minimal toxicity, though it has a relatively low barrier to resistance.

Gilead Sciences next-generation integrase inhibitor elvitegravir is used with a boosting agent - either ritonavir (Norvir) or Gilead's novel pharmacoenhancer cobicistat - to enable once-daily dosing. Richard Elion from Whitman-Walker Health presented long term data from a head-to-head phase III randomised controlled trial comparing 150mg elvitegravir once daily or 400mg raltegravir twice daily, both in combination with a fully active boosted protease inhibitor plus a third drug. Study 145 included 712 treatment-experienced participants in Europe, the US and Australia; 702 were included in the efficacy analysis. Just over 80% were men, 60% were white and the average age was 45 years. The mean baseline CD4 T-cell count was approximately 220 cells/mm³, with about 45% having fewer than 200 cells/mm³, and 26% had high viral load (>100,000 copies/mL).

Although all participants had used - and a majority had developed resistance to - at least two antiretroviral drug classes, they were able to construct viable regimens using a ritonavir-boosted protease inhibitor and an active third agent such as etravirine (Intelence), maraviroc (Celsentri or Selzentry) or a nucleoside/nucleotide reverse transcriptase inhibitor. The most frequently used protease inhibitors were boosted darunavir (Prezista) at nearly 60%, lopinavir/ritonavir (Kaletra) at 19% and boosted atazanavir (Reyataz) at 16%. The primary 48-week results, presented at the International AIDS Society meeting last summer in Rome, showed that elvitegravir was well-tolerated and non-inferior to raltegravir in efficacy, with 59% vs 58% of participants in the two arms, respectively, achieving undetectable viral load. Blinded comparison continued through 96 weeks and Study 145 has since moved into an open-label observation phase. By 96 weeks, 41% of elvitegravir recipients and 42% of raltegravir recipients discontinued treatment. The most common reasons were poor adherence (39 vs 34 participants, respectively), withdrawal of consent (30 vs 17), loss to follow-up (29 vs 31), lack of efficacy (17 vs 21), adverse events (11 vs 15) and protocol violations (11 vs 14).

Efficacy of elvitegravir and raltegravir continued to be comparable at 96 weeks, with 48% and 45%, respectively, having HIV RNA <50 copies/mL in an intent-to-treat TLOVR analysis. Virological failure (defined as never suppressed, viral rebound or drug discontinuation due to non-efficacy) was observed in 26% and 29% of participants, respectively. CD4 cell gains were also similar, at approximately 200 cells/mm³. Both elvitegravir and raltegravir were well-tolerated overall and few people discontinued due to side-effects (3% vs 4%, respectively). Grade 2-4 adverse events (68% in both arms), serious adverse events (20% vs 23%, respectively) and grade 3-4 laboratory abnormalities (37% vs 42%, respectively) were generally similar. More elvitegravir recipients reported diarrhoea (13% vs 8%) while more raltegravir recipients had elevated liver enzymes (approximately 2% vs 6%).

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