Integrase inhibitor raltegravir makes its mark

For nearly 14 years, the pharmaceutical company Merck has been inventing and testing a new group of anti-HIV drugs called integrase inhibitors. As their name suggests, these drugs work by interfering with HIV’s ability to integrate itself into and take over a target cell.

Along the long path of drug discovery and development, several integrase inhibitors that have performed well in the lab have failed in clinical trials. So it is encouraging that the Merck drug raltegravir (Isentress, MK-0518) has entered the final stage of testing before approval for sale.

At the 14th CROI Dr. David Cooper from Australia presented interim results from two ongoing studies of raltegravir in heavily treatment-experienced PHAs. A preliminary analysis of the trials so far shows that raltegravir can be a very effective part of combination therapy.

Study details
The code names for the studies are Benchmark 1 and Benchmark 2. These are two identical trials. Benchmark 1 has enrolled volunteers from Europe, the Asia/Pacific region and Peru. Benchmark 2 has enrolled volunteers from North and South America.

Both studies are randomized and placebo-controlled. Raltegravir is used at a dose of 400 mg twice daily, together with the best combination of anti-HIV agents as suggested by resistance testing.

The average profile of participants at the start of the study was as follows:

- 13% female, 87% male
- age – 46 years
- CD4+ count – 150 cells
- viral load – 50,000 copies
- at least 90% of participants had AIDS
- many participants had been taking anti-HIV medications for about 11 years
- 21% of participants had not previously used T-20 (enfuvirtide, Fuzeon)

Results—Overall
Because the two studies have identical designs, the results have been very similar. Raltegravir is clearly superior to placebo. So far, only results from the first four months of the studies have been released.

Results—CD4+ counts and viral load
On average, participants who received raltegravir gained 80 extra CD4+ cells. Placebo recipients gained only 30 additional cells.

On the other hand, changes in viral load were more dramatic, with about 60% of raltegravir users achieving a viral load below the 50-copy mark. In contrast, about 30% of placebo recipients had their viral load fall below this level.

Among raltegravir users, viral load fell, on average, 100-fold (or 2 logs) below pre-study levels. In the group who received placebo, decreases in viral load were more modest, averaging about 1 log or 1/10 of pre-study levels.

As is often the case in studies with treatment-experienced PHAs, the more drugs in a regimen that are active against HIV, the better the result. In these studies, adding additional medications, such as the following, enhanced raltegravir’s effectiveness:

- T-20
Raltegravir appears to be slightly less effective when used at very low CD4+ counts (less than 50 cells) or high viral loads (more than 100,000 copies). Keep in mind that these are interim results and the final picture of raltegravir’s effectiveness awaits completion of the study.

**Resistance**

Analysis of samples of HIV taken from participants whose raltegravir-based regimens failed is ongoing. So far, analysis of samples from 32 out of 41 PHAs on such regimens suggests that mutations to raltegravir have developed. Specifically, two key mutation pathways have been identified:

- N155H
- Q148K/R/H

Much more work on exactly how HIV develops resistance to raltegravir must be done so that other key mutations can be identified. Eventually these will have to be added to the genotypic resistance tests commonly in use in high-income countries. Researchers are concerned that resistance to raltegravir may also result in resistance to the experimental integrase inhibitor elvitegravir (GS 9137). This possibility of cross-resistance among integrase inhibitors requires further study.

**Side effects**

Every drug has side effects. However, according to the data released by Merck, there does not seem to be any side effect specifically caused by raltegravir. Indeed, Dr. Cooper said that the medication was well tolerated. A small proportion of participants who received raltegravir reported fatigue. Further study of raltegravir will be needed to find out if this is indeed a side effect.

There have been a small number of deaths in Benchmark 1 and 2 to date. In a study population in which at least 90% of participants had AIDS, the “few deaths” that did occur, according to the presenter, were due to complications from life-threatening infections, liver cancer and lymphoma.

**REFERENCES:**


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