Raltegravir (Isentress)—results after one year

Raltegravir, formerly MK-0518 and to be sold under the brand name Isentress, is a new drug for the treatment of HIV infection. Regulatory authorities in Canada will approve the sale of this drug in the fall of 2007.

Raltegravir represents an important development because it is the first of a new class of anti-HIV agents called integrase inhibitors. These drugs work by interfering with an enzyme essential for creating new viruses. By slowing down or stopping the activity of the integrase enzyme, raltegravir, as part of combination therapy, can significantly reduce viral load. As viral load goes down, CD4+ cell counts rise and health improves.

Raltegravir is active against HIV-1 that is resistant to the following classes of HIV medications:

- nukes (nucleoside analogues)
- non-nukes (NNRTIs)
- protease inhibitors
- fusion inhibitor

Raltegravir is also active against HIV that uses the co-receptors CCR5 or CXCR4.

After six months of treatment in a group of heavily pre-treated volunteers, raltegravir, as part of combination therapy, helped to suppress viral load below the 50-copy mark in as many as 67% of PHAs.

Recently, researchers presented the results of one year of raltegravir exposure in treatment-experienced PHAs during a study called Protocol 005.

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

- 10% female, 90% male
- age – 43 years
- CD4+ cell count – 240 cells
- viral load – 63,000 copies
- 10 years previous exposure to anti-HIV medications

All participants received an optimized background therapy (OBT) based on their treatment history and resistance testing. Participants who did not receive raltegravir received placebo. During the first six months of the study, the trial was placebo-controlled. After this, all participants received raltegravir (and OBT). Initially, raltegravir was given in different doses to different participants. However, after six months, the dose was standardized at 400 mg twice daily.

**Results—Viral load**

During the placebo-controlled part of the study, about 60% of participants who received raltegravir had their viral loads fall below the 50-copy mark. Among volunteers who received placebo and OBT, about 10% had their viral load fall below the 50-copy mark.

After one year, the proportion of raltegravir users with a viral load below the 50-copy mark was 50%.

**Results—CD4+ cell counts**

During the placebo-controlled phase of the study, CD4+ cell counts rose in raltegravir users by at least 100 cells. This was sustained through the next six months of the study. Among people who received placebo and OBT, during
the first six months their CD4+ counts rose by about 25 cells. However, no further increase was noted after the sixth month.

**Focus on resistance**

Researchers found that 33 out of 133 participants (about 29%) who received raltegravir developed treatment failure during the first six months of the study. Most of these participants had detectable resistance mutations associated with raltegravir. Usually, resistance to raltegravir required the presence of at least two mutations.

In this study, factors associated with a reduced risk of developing raltegravir resistance were as follows:

- relatively low viral load (less than 100,000 copies) at the start of the study
- using T-20 (enfuvirtide, Fuzeon) as a new drug in the participant’s OBT

**Complications and side effects**

In this study, raltegravir was generally safe. Side effects that were seen in raltegravir users were also seen in participants who received placebo.

Three participants who received raltegravir had significantly increased levels of liver enzymes in the blood.

There were a total of four serious complications during the study:

- Higher-than-normal levels of lactic acid in the blood and kidney dysfunction occurred in one participant who took raltegravir at a dose of 600 mg twice daily. This person also developed blood poisoning from a bacterial infection and subsequently died.
- Severe inflammation of the pancreas gland (pancreatitis) occurred in one person receiving raltegravir at a dose of 200 mg twice daily. Researchers decided that this was due to the drugs in the OBT.
- A partially blocked artery was seen on a CAT scan in one person who received placebo.
- Accelerated loss of subcutaneous fat (lipoatrophy) occurred in a person who received placebo.

**Cancers**

During the first six months of the study, no new cancers were detected. However, after this time, when all participants received raltegravir, one participant’s lymphoma grew worse while another developed skin cancer.

A large trial comparing the effectiveness of raltegravir-containing combinations to efavirenz-containing combinations in first-line therapy is underway. The results from this study will be helpful for doctors and their patients when making decisions about starting HAART.

**REFERENCE:**

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