Maturation inhibitor reappears

In order to create new copies of itself, HIV infects cells of the immune system called CD4+ T-cells. Once inside these cells, HIV can take control and transform the cells into mini virus factories.

Anti-HIV drugs work by interfering with vital viral replication processes (steps in the creation of new viruses). Specifically, most of these drugs interfere with viral enzymes. Although there are more than 20 approved therapies for HIV, many are chemically related to each other and can generally be placed into the following main groups:

- reverse transcriptase inhibitors
- protease inhibitors
- co-receptor blockers
- integrase inhibitors
- fusion inhibitors

Because many of these drugs are in the same chemical families, if HIV becomes resistant to one drug in a family, or class, it may have varying degrees of resistance to other drugs in the same family. This is called cross-resistance and it can limit future treatment options. Cross-resistance highlights the need for new effective therapies.

First bevirimat

Researchers in the United States have developed a novel anti-HIV compound called PA-457, also known as bevirimat dimeglumine. This drug belongs to an emerging group of anti-HIV medicines called maturation inhibitors. Bevirimat is the first drug in this class.

This drug has had a chequered history. It was initially developed by Panacos Pharmaceuticals Inc. with promising preliminary data reported. However, further development of bevirimat then stalled for several years as Panacos encountered problems. The main issue was that in a significant proportion of HIV positive volunteers HIV unexpectedly appeared to be resistant to bevirimat. This is odd because HIV maturation inhibitors have never been used in clinical trials before, so researchers were mystified about this finding. A possible explanation for this unexpected viral resistance is that in some people HIV has naturally developed mutations that can render maturation inhibitors ineffective from the start.

Myriad takes control

Panacos then sold the drug to another company, Myriad Pharmaceuticals Inc., based in Salt Lake City, Utah. Myriad renamed bevirimat MPC-4326 and also is developing HIV maturation inhibitors of its own, which are code-named MPC-9055 and MPC-461359. Of these three drugs, MPC-4326 (bevirimat dimeglumine) is the furthest along in clinical development.

MPC-4326 was originally developed in a liquid formulation. However, a tablet formulation is now used in clinical trials. To move forward with MPC-4326, Myriad has to find a way to predict which HIV positive people have preexisting resistance to this drug. Information in the public domain suggests that Myriad is developing a relationship with the Belgian diagnostics company Virco BVBA to develop a test for maturation inhibitor resistance. Virco appears to have developed a genotypic resistance test that can detect resistance to MPC-4326. Using this assay, a reanalysis of a limited number of blood samples from previous clinical trials suggests that in some people who are not resistant to MPC-4326 significant decreases in viral load (about 1.26 log) are possible.

In the coming months, hopefully the ability of researchers to interpret the results of this assay will improve. A phase 2b clinical trial of MPC-4326 is planned for North America later this year in treatment-experienced HIV positive
Results from previous clinical trials of MPC-4326 suggest that the drug is generally well tolerated. Headache is the most common side effect and even this was mild in severity.

Many anti-HIV drugs are broken down in the liver or kidneys by different enzymes. An advantage of MPC-4326 is that it is not processed by the more common pathways in the liver that often lead to significant drug-drug interactions. MPC-4326 is processed in the liver by the same class of enzymes (called UGTs) that metabolize some other anti-HIV drugs such as raltegravir (Isentress). Very little of MPC-4326 is processed by the kidneys. This means there are few other HIV drugs that will change the way MPC-4326 is processed in the body. Additionally, laboratory studies suggest that MPC-4326 does not inhibit the liver enzyme cytochrome P450 3A4 which processes many anti-HIV drugs. Therefore there is a low likelihood for MPC-4326 to affect the processing of other anti-HIV drugs and consequently have little impact on the levels of other anti-HIV drugs in the body.

REFERENCES:


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