Are new drug boosters coming?

Protease inhibitors used in high-income countries mostly include the following:

- atazanavir (Reyataz)
- darunavir (Prezista)
- fosamprenavir (Telzir)
- lopinavir (in Kaletra)
- saquinavir (Invirase)
- tipranavir (Aptivus)

All of these drugs are taken together with a small dose of ritonavir, another protease inhibitor (PI). The purpose of ritonavir is to increase absorption and slow down the breakdown of the other protease inhibitor in the body. The net effect of taking ritonavir with any of these other PIs is that their levels in the blood remain high for prolonged periods, allowing for once- or twice-daily dosing. Drugs such as ritonavir, when used in this way, are called pharmacokinetic (PK) enhancers or boosters.

Ritonavir is also mixed with lopinavir and put into a tablet formulation and sold as Kaletra. These medicines are made by Abbott Laboratories. So far, Abbott is the only company to put an enhancer and PI into one pill—a co-formulation. But other pharmaceutical companies, like Gilead Sciences, are beginning to develop their own boosters to co-formulate with their medicines. Gilead makes several commonly used HIV medicines, such as the following:

- tenofovir (Viread)
- FTC (emtricitabine, Emtriva)
- Truvada (tenofovir + FTC) in one pill
- Atripla (tenofovir + FTC + efavirenz/Sustiva) in one pill

Gilead also has other HIV medicines that it is testing, such as the integrase inhibitor elvitegravir (GS 9137). Elvitegravir needs to be taken with a pharmacokinetic booster in order for it to be taken once daily. Now Gilead has developed its own booster called GS 9530. Gilead hopes to put all of the following drugs into one small pill so they can be taken just once daily:

- tenofovir
- FTC
- elvitegravir
- GS 9530

Unlike ritonavir, GS 9530 has no anti-HIV activity. At a dose of 150 mg, GS 9530 has about the same boosting effect as 100 mg of ritonavir.

Safety

Tested at doses ranging between 50 mg and 200 mg, GS 9350 seems to be well tolerated. This PK enhancer, now entering further stages of clinical testing, does not appear to increase lipid levels in the blood.

Much work remains to be done to understand all of the potential interactions that GS 9350 might have, not just with other anti-HIV agents but also the many medicines that HIV positive people use for the following conditions:

- anxiety
- cardiovascular disease
- depression
diabetes
bacterial and fungal infections

In the works

Gilead plans to compare the effects of its new four-drug co-formulation—its so-called quad pill—against Atripla in 2009. Another study using GS 9350 with atazanavir is also being planned.

Yet another booster

A small corporation, Sequoia Pharmaceuticals Inc., has developed a PK enhancer called SPI-452. They have tested it with the protease inhibitors atazanavir, saquinavir and darunavir. In all cases, SPI-452 was an effective booster and it does not seem to significantly raise levels of bad cholesterol (LDL) or triglycerides in the blood. Side effects reported were generally mild in intensity. In 45 people exposed to SPI-452, side effects included the following:

- headache
- nausea
- upset stomach
- diarrhea

SPI-452 is currently a liquid formulation. Historically, liquid formulations of HIV medicines are not pleasant tasting and have been generally shunned by HIV positive adults. So, to be taken seriously, the company would have to develop a pill formulation of this drug.

The next step would be further clinical trials. Whether other pharmaceutical companies would be interested in testing Sequoia’s PK booster is not yet clear. But what seems likely is that ritonavir’s position as the only PK enhancer for use with HIV medicines seems limited. It will take several years for clinical trials with the PK enhancers mentioned in this report to be completed.

REFERENCES:


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