Promising Prospects

Protease inhibitors offer antiviral power, but require careful choosing

April 1, 1996 By Tim Horn

Finally some genuinely good news for beleaguered PWAs -- especially those whose CD4 cells have dropped through the floor and whose options have run out. The new class of protease inhibitors being developed by a gaggle of drug companies offers antiviral power unmatched by any of the previous generation of nucleoside analogues (AZT, ddI, ddC, d4T and 3TC). And so far, most have far fewer side effects (such as moderate stomach upset and transient increases in liver enzymes) than the older drugs, some of which subject PWAs to everything from peripheral neuropathy to white blood cell depletion.

Although one drug was approved last December and two others may be approved by the time you read this, it will take more than the preliminary studies done so far to learn just how effective and safe these products really are, especially in the long term. (Most protease inhibitor studies showing good antiviral activity are based on measures of increased CD4 count and reduced viral loads; the latter is often viewed as correlating with better health.)

Scientists are still studying to what extent the virus may develop resistance to these drugs. More troublesome, researchers are trying to unravel concerns about cross-resistance -- a mutation induced by one drug that might prevent a person's viruses from being treatable by other protease inhibitors. Consistent adherence to dosing schedules and instructions about meal timing are crucial in postponing resistance. Clinical trials so far show that combining a protease inhibitor with one or more nucleosides increases the antiviral power of both and delays onset of resistance. Lab research suggests that combinations of protease inhibitors may work even better, but inter-company studies needed to establish this have yet to start. And as is typical in this industry, none of these drugs have been tested in enough women or children to determine whether the benefits and toxicities are different in these populations.

Here are the highlights of what's known about the four protease inhibitors from which PWAs will be able to choose this year (several other companies have products in earlier stages of development):

Saquinavir (Invirase) from Hoffman-La Roche:
The only protease inhibitor approved at press time (for use in combination with nucleosides, for people with advanced HIV infection). Taken alone, its antiviral activity appears limited and short-lived. But in combination with AZT, ddC or both, it has shown more significant activity for as long as a year. Side effects seem rare, but only four percent of the drug is absorbed by the body. (It is

important to take saquinavir after a full fatty meal, and a preliminary study suggests grapefruit juice may increase absorption; lactose-intolerant PWAs may want to take it with Lactaid to prevent diarrhea.) A new and hopefully better-absorbed formulation is being tested. Because of concerns about possible cross-resistance, some physicians suggest that those with stable health consider waiting for approval of one of the other protease inhibitors.

Indinavir (Crixivan) from Merck & Co.:
In clinical trials, whether taken alone or in combination with AZT, ddI or 3TC, indinavir has shown the best antiviral activity of the protease inhibitors -- with some small studies even showing most people's viral loads falling to undetectable levels. But resistance to indinavir seems to produce cross-resistance to ritonavir and possibly to saquinavir. And one study found three percent of those taking indinavir developed kidney stones. (High water intake with the pills may reduce this risk.) No food should be eaten an hour before or two hours after taking the drug.

Ritonavir (Norvir) from Abbott Laboratories:
While its antiviral activity appears stronger than saquinavir and somewhat weaker than indinavir, ritonavir is the first drug shown in a study to actually extend survival time and reduce illness for people with under 100 CD4 cells compared to those taking placebos. But ritonavir is cross-resistant to indinavir. An alcohol-based drug, ritonavir cannot be taken with many drugs often prescribed to PWAs (some antihistamines, antibiotics, antidepressants and drugs for prophylaxis and treatment of opportunistic infections). Its foul-smelling liquid form can also cause intestinal problems. Abbott is currently testing a more palatable soft-gel capsule formulation.

Nelfinavir (Viracept) from Agouron Pharmaceuticals:
This drug has shown significant, prolonged antiviral activity used alone and in combination with some nucleosides. Most trial participants have experienced soft stools or diarrhea. But much less human research has been done on this protease inhibitor than the other three. In test-tube studies, resistance sometimes led to cross-resistance to other protease inhibitors.

Unfortunately, all these drugs look to be exorbitantly priced at a time when reimbursement programs -- public and private -- are retrenching. So study the latest data, discuss the options with your physician and choose carefully.

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