Acyclovir

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Acyclovir is sold under the trade name Zovirax and is licensed for the treatment of herpes simplex (genital herpes), chicken pox and shingles (zoster). It is widely used by people with HIV to treat infections such as herpes simplex, shingles, hairy leukoplakia (HLP), herpes, human herpes virus 6 (HHV-6) and Epstein-Barr virus (EBV).

What Does the Research Show?

Acyclovir's use against herpes is well documented. Acyclovir does not rid the body of the herpes simplex virus (HSC), but it reduces its severity or slows its growth by inhibiting reproduction of the virus. Acyclovir has been shown to be very safe and effective against both shingles and herpes infections.

Acyclovir's effectiveness against other viral conditions is not as strong, but there is some evidence to support its use. A study of patients with oral hairy leukoplakia (OHL) reported that high-dose acyclovir caused the OHL lesions to shrink in most patients. OHL is an infection common for people with HIV that causes the formation of fuzzy or "hairy" sores in the mouth and on the tongue. For more information, read Project Inform's publication, *HIV and the Mouth*, available at 1-800-822-7422 or *www.projectinform.org*.

The study also concluded that the drug greatly reduced the patients' levels of Epstein-Barr virus, which some believe is a cause of hairy leukoplakia. Anecdotal reports of the use against OHL are almost universally positive, although relatively high doses and long treatment are required.

To date, no studies have shown acyclovir as being effective in fighting HIV infection or reducing the side effects of AZT, despite early claims of this nature.

Analysis of the Multicenter AIDS Cohort Study (MACS) has shown that people on acyclovir had a 40% longer survival compared to those that did not take acyclovir. However, acyclovir was not able to prevent cytomegalovirus (CMV), a virus in the herpes family of viruses that is the leading cause of blindness among people with AIDS. An average dose of 600–800mg per day was used. Survival benefit was not prolonged by higher doses of acyclovir but by longer duration of use.

Results from a cytomegalovirus (CMV) prevention study comparing valacyclovir (Valtrex, 2 grams four times/day) to two different doses of acyclovir (400mg twice/day and 800mg four times/day) showed an increased death rate in the group taking valacyclovir. The study (called ACTG 204) enrolled 1,200 people with CD4+ cell counts below 100.

There were fewer cases of CMV disease in the group taking valacyclovir compared to the groups on acyclovir. However, this might be because more people who were taking valacyclovir dropped out of the study because of increased side effects. There were significantly more cases of neutropenia and increased serum creatinine levels in the group that used valacyclovir, while there was a higher incidence of thrombocytopenia in the group on low-dose acyclovir.

Valacyclovir (Valtrex) is approved for treating herpes simplex and herpes zoster. Much higher levels of acyclovir are achieved in blood with this formulation. However, HIV-positive people should be cautious with valacyclovir because of severe side effects resulting in death have been reported among people with advanced stage HIV disease using high doses (8 grams/day) of the drug.

Famciclovir (Famvir)—which is very similar to acyclovir—is another drug approved to treat zoster. Famciclovir has a longer half-life and requires less frequent dosing (500 or 750mg three times a day).

What About Side Effects?

While standard uses of acyclovir seldom result in significant side effects, many HIV-related uses of the drug require higher doses that sometimes cause minor problems. Some people experience short-term side effects, such as nausea, vomiting and headaches. Still fewer report diarrhea, dizziness, anorexia, fatigue and a medication taste in the mouth. All of these effects are quite uncommon at standard and low doses.

In HIV-related use, acyclovir is often used in a long-term manner quite different than that employed in treating herpes. It is this type of use which is least well understood. Side

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effects reported in long-term use include: headaches, diarrhea, bone marrow toxicity and nausea; less frequent effects include rashes, insomnia, fatigue, fever and muscle cramps. Long-term, high dose users sometimes report the onset of neuropathy symptoms, such as tingling in the fingers and toes, which seem to disappear quickly when the dose is lowered or interrupted. Overall, acyclovir is well-tolerated with minor toxicities.

A few researchers are concerned that long-term continuous use of acyclovir might cause the development of new strains of herpes that are resistant to acyclovir. Some have already reported such mutations, but others question whether this is necessarily due to using acyclovir. From the patient's point of view, such a concern would have to be weighed against the benefits of controlling infections. Several drugs have been shown to work against herpes which has become resistant to acyclovir. These include IV foscarnet (Foscavir), oral trifluridine and IV cidofovir (Vistide). Although the side effects of foscarnet and cidofovir are well documented, long-term toxicity data for these other compounds are relatively unknown.

How to Get It?

Any physician can prescribe acyclovir for use orally, intravenously (injection into the veins) or topically (on the skin). It is covered by most insurance plans. To avoid insurance disputes, however, the physician should make a point of writing the prescription for an approved use, such as herpes. Prescriptions for use against OHL are seldom contested.

GlaxoSmithKline, the maker of acyclovir, has a patient assistance program for people who do not have insurance. Additionally, people who take high-dose acyclovir on a regular basis may also qualify for the acyclovir price cap. Doctors can call 1-800-722-9294 for more information on either of these programs

How to Use It?

For control of herpes simplex infection, patients need only follow the standard directions provided with the prescription. To treat the occurrence of herpes simplex, typically 400mg every 8 hours (total dose 3,200mg/day) for 10–14 days is used. Higher doses are used for recurrent cases of herpes simplex. HIV-experienced doctors can usually recommend an effective dosage for non-standard uses such as OHL and shingles. In general, many doctors suggest the following:

For OHL: High doses are required, typically 800mg five times a day (total dose 4,000mg/day) for two to three weeks when lesions are present. When the lesions regress, long-term therapy can be continued at doses as little as 1,200mg per day.

For shingles: High doses are usually required. This usually means a dose of 800mg five times a day until the problem has cleared for several days.

Long-term, preventive use of acyclovir: When herpes and other infections are dormant, 800–1,200mg daily is considered sufficient for preventive therapy.

Acyclovir users must remember that reports of dosage are not firm recommendations, since they are based largely on observations by patients and doctors. Thus, they are not as precise as the results of studies and may not always be right. When using any drug in an unapproved or unstudied manner, neither the manufacturer nor the doctor can offer risk-free guidance. However, persons who have frequent or severe recurrences can be given daily suppressive therapy with oral acyclovir or oral famciclovir. Valacyclovir also is an option.

Commentary

Use of acyclovir makes the most sense in the presence of the infections for which its activity has been proven—herpes simplex, hairy leukoplakia and Epstein-Barr virus. This makes it relevant for a large percentage of HIV-infected people since these infections are very common. Several studies have now shown that chronic use of acyclovir resulted in a survival benefit.

The Bottom Line

Pros:

- Direct resolution of unpleasant infections such as shingles, HLP and herpes.
- Usually reimbursable by insurance.
- Possible survival benefit.

Concerns:

- Resistance to acyclovir is becoming more common.
- Some side-effects which might add to a weakened patient's burden.
- Not effective in preventing CMV.

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