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Updates

New Developments In Treatment: Didanosine (ddI), Foscarnet, And Trimethoprim-Sulfamethoxazole

Studies of two previously investigational drugs, didanosine and foscarnet, and new data on prophylaxis against *Pneumocystis carinii* pneumonia (PCP) further advance treatment of human immunodeficiency virus (HIV) disease and associated opportunistic infections.

Didanosine (ddI), an Alternative Antiretroviral Agent

Didanosine (ddI, 2′,3′-dideoxyinosine, [Videx™]), like zidovudine (AZT, [Retrovir™]), inhibits the replication of HIV. Didanosine is the second antiretroviral drug to be approved for use against HIV. Results of Phase I studies, as well as information from expanded access and open label programs in the United States, France, and Britain, suggest that didanosine might be effective in slowing the progression of HIV disease. These studies, however, use surrogate laboratory markers of HIV disease (CD4+ lymphocyte counts and p24 antigen levels) rather than clinical endpoints (opportunistic infections, hospitalizations, mortality) as measures of possible therapeutic benefit. Clinical efficacy, therefore, is not yet established. Nevertheless, based on modest improvements in key laboratory values, the United States Food and Drug Administration (FDA) has approved didanosine for use by prescription on a noninvestigational basis (9 October 1991).

Toxicities of didanosine include painful peripheral neuropathy, severe pancreatitis, hepatitis, abdominal cramps, and diarrhea. Because the drug is prepared with a buffer to facilitate absorption, it should be administered 2 hours apart from other drugs (such as ketoconazole, dapsone, tetracyclines, and quinolone antibiotics) whose absorption is impaired by buffered products.

Didanosine can be used in patients who do not tolerate zidovudine or who have failed treatment with zidovudine. Because didanosine has minimal hematologic toxicity, it is a logical alternative for those patients who develop anemia or other hematologic toxicity while receiving zidovudine. The clinical and laboratory parameters indicating "failed therapy" with zidovudine are less clear. Persistently falling CD4+ lymphocyte counts, new or progressive opportunistic infections and malignancies or persistent generalized symptoms and signs, such as fevers, weight loss, and inanition, can be interpreted as "failed therapy." Another indication for didanosine usage (although not

FDA-approved) is patient desire to try this alternative antiretroviral agent. Insufficient efficacy information is available regarding combined zidovudine plus didanosine therapy and additional toxicity will occur, so combination therapy cannot be recommended on a scientific basis at this time. Because the studies have not been published, the best single source of information on didanosine at this time on administration, toxicities, and drug interactions is the package insert.

Foscarnet for Cytomegalovirus Retinitis

Foscarnet (trisodium phosphoformate [Foscavir™]), like gancyclovir (Cytovene™), is effective in arresting cytomegalovirus (CMV) retinitis. Unpublished studies have indicated that survival in foscarnet-treated patients averaged 12 months, whereas survival in gancyclovir-treated patients averaged 8 months. It has been postulated that foscarnet's non-CMV antiviral activity might be responsible for the improved survival in the foscarnet group. Another possible explanation for the longer life expectancy in the foscarnet-treated patients in this study is that gancyclovir-induced neutropenia limited concomitant zidovudine administration.

On the basis of this information, gancyclovir and foscarnet can both be considered first-line agents against CMV retinitis. Foscarnet has substantial nephrotoxicity requiring frequent monitoring and dosage adjustments. Therefore, gancyclovir is the preferred agent for patients with established renal insufficiency. Coadministration of gancyclovir and zidovudine frequently causes neutropenia. When severe neutropenia occurs, the combination of either gancyclovir plus didanosine or foscarnet plus zidovudine is recommended. Both gancyclovir and foscarnet are administered intravenously, either in the hospital or via indwelling catheters at home. The stability of the foscarnet preparation and the need to administer it via an infusion device present special problems for home administration. Because the studies on foscarnet have not been published, the best single source of information at this time regarding administration, toxicities, and drug interaction is the package insert.

Trimethoprim-Sulfamethoxazole, First Choice Treatment for Prophylaxis against PCP

Trimethoprim-sulfamethoxazole (TMP-SMX [Bactrim™, Septra™]) is a more effective agent than aerosolized pentamidine in prophylaxis against *Pneumocystis carinii* pneumonia (PCP) and is now recommended as the first-line agent. This recommendation is based on studies showing impressive benefit from TMP-SMX in preventing PCP, whereas aerosolized pentamidine appears to be associated with late treatment failure (especially upper lobe disease and extrapulmonary pneumocystosis). Both drugs are associated with important side effects. TMP-SMX causes rash, fever, hepatitis, and bone marrow toxicity. Aerosolized pentamidine administration can cause bronchospasm, pancreatitis, and hypo- and hyperglycemia and possibly is responsible for some cases of pneumothorax. Data on dapsone prophylaxis are not as extensive, but the drug appears to be effective. Dapsone toxicities include methemoglobinemia, hemolysis, bone marrow suppression, rash, nausea, and abdominal pain. Trimethoprim-sulfamethoxazole should now be considered the drug of first choice in prophylaxis against PCP with dapsone and aerosolized pentamidine alternative regimens.