Vitamin E increases effectiveness of AZT, lowers toxicity

AIDS UPDATE by Sean Hosien

ANTI-HIV DRUGS
A.AZT+Vitamin E

The toxic effects which AZT can have on the bone marrow are well documented, the drug inhibits the growth of bone marrow cells resulting in anemia. The development of anemia can often lead doctors to stop prescribing the drug in affected patients while their bone marrow recovers. To speed recovery of the bone marrow several therapies have been used with mixed results. The most useful appears to be EPO (erythropoietin) a natural substance produced by the body. EPO is still an experimental drug and supplies of it are scarce and expensive so researchers are looking for cheaper and more accessible ways of relieving anemia. Scientists at Tulane University School of Medicine, New Orleans, have been conducting experiments with AZT and vitamin E in an efforts to find ways of countering the toxic effects of AZT. Vitamin E has been shown to stimulate the growth of T-cells as well as cells of the bone marrow in previous experiments.

In test tube experiments conducted at the University, scientists have found that the addition of increasing doses of vitamin E appeared to protect the bone marrow cells from the toxic effects of AZT. Another result of the experiments was that the reseachers found vitamin E enhanced the anti-HIV effect of AZT. At the highest concentration of vitamin E the anti-HIV effect of AZT was increased 14 times. The form of vitamin E used in the study was d-alpha-tocopherol. 31st Annual meeting of the American Society of Hematology, Atlanta, 1989. Abstract #630.

Studies on the absorbtion of vitamin E in normal human volunteers reveal that a single oral dose of 800 mg of vitamin E will result in blood levels 24 hrs later that are higher than those used in these experiments (American Journal of Clinical Nutrition 1984;40:240-245). Since vitamin E is fat-soluble it does accumulate in the body and should human trials of AZT and vitamin E take place, they will probably not require subjects to take the vitamin on a daily basis.

French study
Alzheimers drug for AIDS

As HIV is known to infect brain cells, it is not surprising that in advanced HIV infection brain damage occurs. In alzheimer's disease—where dementia also occurs—researchers suspect that a virus is at the root of the problem. Because of the similarity between certain features of HIV-related dementia and those of alzheimer's disease, French doctors have began testing a drug used to treat alzheimer's disease in HIV infected people.

At the Paul Brousse hospital, Vilejuif, France, doctors have enrolled 9 subjects (8 males, 1 female, 7 subjects had AIDS and 2 had ARC) in a trial of THA (tetrahydroaminoacridine). THA was given as a daily dose of 150 mg for two weeks. The dose was then increased to 200 mg/day. The people in the trial were allowed to use antibiotics and anti-fungal agents for treatment of their opportunistic infections when necessary. Five subjects with AIDS had used AZT previously to this trial but stopped because the drug caused severe bone marrow toxicity. One person did receive AZT with THA but only for the first 2 weeks of the trial.

The administration of THA is thought to have led to stastically significant increases in the average level of white blood cellsas well as the avgerage level of T4-cells (from 65 cells at the beginning of the trial to 159 cells by the end of the second month. Levels of the HIV protein p24, an indirect indicator of viral replication, decreased in 8 of the subjects. After one month p24 could not be detected in in 4 patients (2 with ARC and 2 with AIDS).

Three people experienced side effects such as nausea and vomiting at the beginning of the trial (2 subjects) or at the point where dosage was increased (1 subject) but these side effects disappeared without treatment in the first 2 cases. The third case required a dose reduction to 150 mg/day. No bone marrow or liver toxicity were observed. The clinical course and symptoms of the syndrome were not altered during this short period.

THA may exert its effects due to several factors. Test tube studies show that it inhibits an essential viral enzyme. It may also help CD4-cells (also called T4) in ways not yet fully understood. A long term American study of THA in patients with alzheimer's disease resulted in some beneficial effects and the side effects were not serious (New England Journal of Medicine 1986;315:1241-1245). In the American study THA was made by Aldrich chemicals, Milwaukee.

The French doctors caution that it is too early to tell if these results will continue in the long term. Indeed AZT often causes improvement in the CD4-cell count, p24 antigen and Beta-2- microglobulin levels in patients, but by the sixth month of treatment the patient's blood values have often returned to pre- treatment (baseline) levels. Long term studies of THA in HIV+ people are planned. The Synthese et Recherche company in Anthony, France purified the THA used in the study. International Journal of Clinical Pharmacology, Therapy and Toxicology 1989;27(8):408- 410.

II IMMUNE BOOSTERS
A. Tagamet raises T4 count

Tagamet is the brand name of the drug cimetidine, an anti-ulcer drug available in Canada. Research over the past decade has shown that cimetidine has a broad range of beneficial effects on the immune system. Cimetidine's effect on T4-cells may be of interest to HIV infected people and their doctors. Scientists at the University of Essen, West Germany, have conducted much research with cimetidine. Their most recent results show that the effects of the drug appear to be related to the length of time and dose used.

In a six week study, 12 subjects were given a total of 1600 mg/day of cimetidine orally, taken in three divided doses per day for the first three weeks. The drug was well tolerated with no side effects reported. No toxicity was detected. Within 7 days of cimetidine administration a significant increase in the amount of macrophages and B-cells were found (compared to baseline values) but three weeks after the last dose was taken levels of both these types of cells had declined to their baseline values. A similar pattern was seen in the levels of T4 cells (also known as CD4 cells). Cimetidine also caused an increase in the response of white blood cells to various foreign proteins such as tetanus, tuberculin and candida.

Previous controlled studies of cimetidine in healthy volunteers using a lower dose (800 mg/day) showed that the drug caused increases in the T4/T8 ratio and decreased the level of T8 cells.In the study discussed here (1600 mg/day) cimetidine did not cause a decrease in the T8 count nor did an increase in the T4/T8 ratio occur. The exact mechanism by which high dose cimetidine helps increase T4 cells is unknown. But giving subjects high doses of the drug resulted in statistically significant increases in the T4-cell count. The T4-cell count did not immediately decline when administration of the drug ceased. The researchers concluded that because of the increase in T4 cells seen, the drug should be used in clinical trials with patients suffering from severe immune deficiencies. International Journal of Clinical Pharmacology, Therapy and Toxicology 1989;27:458-462.

While none of the subjects in the above study reported side effects occasional diarrhea can occur in patients using the drug. Serious reactions to cimetidine are rare according to the Canadian Compendium of Pharmaceutical Specialities. Long term administration seems to be well tolerated. A previous trial of cimetidine in 33 ARC patients given 1200 mg/day for five months with an interruption of 3 weeks after 3 months has been reported to cause increases in the level of T4 cells, weight gain and a reduction in fevers. Clinical Immunology and Immunopathology 1988;48:50-60.

A more recent report of the use of cimetidine as an immunomodulator comes from Israel where researchers have used the drug to treat a form of inherited immune deficiency called CVI (common variable immunodeficiency). This disorder occurs mainly in young adults who usually have the following: lower than normal levels of antibodies, recurrent bacterial infections and chronic stomach infections. Patients often suffer from cancers as well. Patients with CVI are often treated with infusions of antibodies. The patient who was treated also had low levels of T4 and B-cells and an abnormal T4/T8 ratio. He was given 1200 mg/day cimetidine given as a divided dose three times per day for six months. While there were no changes in the number of white blood cells, the treatment resulted in a reduction in the number of lung infections and no need for antibiotics during the period of therapy. Journal of Allergy and Clinical Immunology 1989;84:753- 761.

III TESTING
Neopterin and HIV disease

Since the early part of the 1980's researchers have been looking for a reliable method to use in predicting how soon their patients with HIV infection will go on develop AIDS. Since HIV is thought to primarily affect CD4-cells (also known as T4-cells) levels of these cells were monitored in patients. Unfortunately levels of CD4-cells can be affected by incidents other than HIV infection and the proportion of these cells is not always an accurate measurement of the degree of immune suppression. Several years ago scientists found that levels of the chemical Beta2 microglobulin in the blood might be a good index of the state of the immune system, and indeed research has shown that this is the case. Researchers have found that when the levels of the various 'markers' of the immune system are taken together (such as CD4-cells, Beta2 microglobulin, HIV p24 antigen and the CD4/CD8 ratio among others), they collectively provide a better picture of what is going on in the HIV infected patient. However, many of these tests are expensive and not easy to perform and the utility of some tests, such as p24 antigen, are being seriously questioned. If a marker could be found which more easily and accurately reflected the state of the immune system, then physicians could make better decisions about patient care and treatment. Onesubstance which appears to do that is neopterin.

Neopterin is a chemical produced by macrophages. The macrophages are stimulated to produce neopterin by interferon-gamma produced by activated T-cells. Chronic exposure to several infectious agents is thought to result in elevated levels of interferon- gamma and consequently elevated neopterin levels. Neopterin can be detected in the urine as well as blood samples of patients.

Several studies on neopterin and HIV disease progression have been conducted, most of which have taken place in Europe. In this issue of TreatmentUpdate we report on two recent studies one from the USA and the other from Austria.

Researchers at the St. Luke's-Roosevelt Hospital Centre, New York, have conducted a study on over 300 subjects, of which 283 were HIV+, to find out their blood levels of various substances including neopterin. They found that as HIV infection worsened the level of neopterin rose. It was lowest in non-HIV infected controls. HIV+ asymptomatic subjects had the next highest level, above them were subjects with persistently swollen lymph glands (PLS) and subjects with AIDS had the highest levels. Interestingly, HIV+, asymptomatic injection drug users had a higher average level of neopterin than HIV+, asymptomatic gay men or even people with PLS. Journal of Clinical Microbiology 1989;27:1919-1923.

Scientists at the University of Innsbruck, Austria, have conducted much of the pioneering work on neopterin. In a recently published study, they discussed the relevance of neopterin samples obtained from the urine of patients. A group of randomly selected 68 HIV+ (the fact that they were HIV antibody positive was only proven several years later when the samples were retested with the newly invented HIV antibody ELISA) subjects with persistently swollen lymph glands were enrolled in a study between 1982-83. They were regularly monitored and measurements such as the CD4, CD8 and uninary neopterin levels were taken.

The researchers found that the overall rate of progression to AIDS in this group during the period 1983-88 was approximately 30%. The level of neopterin, which rises as HIV infection worsens, was the best single predictor for disease progression. Statistical analysis showed that the CD4-cell count by itself was not statistically significant in predicting disease progression. But when neopterin and CD4-cell counts were considered together, then their predictive value was significant. The researchers found that subjects with neopterin levels higher than normal are 5 times more likely to deveolp AIDS compared to subjects with a value below normal. When the subjects with high neopterin values and low CD4/CD8 ratios were followed up they were found to have an even greater progression to AIDS compared to other subjects. Clinical Chemistry 1989;35:1746-1749.

Neopterin is easy to obtain (no invasive or particularly sophisticated techniques are needed) and measure, using test kits. Because it is accurate and relatively inexpensive (compared to T-cell counters)some scientists see neopterin becomming an increasingly important test. Neopterin could be used not only for patient care/management but also to help determine the efficacy of anti-viral agents. One type of neopterin test kit (called Neopterin RIA-cid) is made by Henning-Berlin, West Berlin, West Germany. Plans are underway to make test kits available in Canada by late Spring, 1990.