AIDS Treatment News

IL-2: U.S. National Institutes of Health Study Published

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Results of the leading study of interleukin-2 (IL-2), an experimental immune-based treatment for HIV, were published in the NEW ENGLAND JOURNAL OF MEDICINE on March 3. While this research, conducted by H. Clifford Lane, M.D., and 12 other researchers at the U.S. National Institute of Allergy and Infectious Diseases, is an important contribution to developing a new kind of treatment for AIDS, and for other diseases as well, IL-2 is not a treatment that many patients will want to use now.

IL-2 is a substance normally produced in the body which stimulates the growth and development of T-cells and other immune cells. It is also a prescription drug, approved for use in treating metastatic renal cancer. IL-2 treatment can cause serious toxicities, however, because the body's own IL- 2 is produced in small amounts and used locally; but when the same substance is injected, it raises the level throughout the bloodstream, which is not how the body's own IL-2 acts.

At this time IL-2 has serious drawbacks as an AIDS treatment: * It did not work in persons with low CD4 (T-helper) counts; in those with a CD4 count under 200, it seldom showed any benefit, and it also caused more serious side effects than in those with higher counts.

* Even in those with CD4 counts over 200, it did not substantially raise CD4 counts in four out of ten of the patients, for unknown reasons.

* While IL-2 was being administered (usually for five days every two months), it often caused severe side effects, described as worse than a bad case of the flu. Some patients had to spend part of each five-day treatment in bed.

* When IL-2 did work, it greatly raised the CD4 count, and with repeated treatments, the count remained high. But it is not known how well the CD4 cells are working; and there is no proof yet that the treatment provides overall clinical benefit to patients.

* IL-2 also stimulates the growth of HIV. About half the people treated have a large but temporary jump in viral load right after each injection -- even though everyone receiving IL-2 was also taking an anti-HIV treatment, such as AZT or ddI, to minimize this.

* The results so far are based on uncontrolled studies of only a small number of patients.

* IL-2 is expensive.

The main reason why it is unlikely that IL-2 will be widely used at this time is that, at least with the antivirals now available, it does not work for those with advanced AIDS. And those who are doing well enough to use the drug may not want an experimental treatment with considerable drawbacks and no proven clinical benefit yet.

But there are also reasons why this research is important: * When IL-2 does raise CD4 counts, they often went up by several hundred or more, bringing them into the normal range, and keeping them there for a year or longer.
* In the future, when better antivirals (such as protease inhibitors) are available, it is possible that IL-2 may work for patients with more advanced disease. This is because the drug may be failing in more advanced patients because it is stimulating the growth of HIV. So far this is only a theory; it is now being tested in a trial which combines IL-2 with the Merck protease inhibitor.
* It may be possible to use IL-2 in lower doses, or with different dosing schedules, to reduce side effects.
* The IL-2 studies are producing new knowledge about the immune system in HIV disease, knowledge which could lead to a new class of immune-based treatments.
* If IL-2 is indeed improving immune response, that could be useful in many different diseases. For example, a NIAID trial of IL-2 for treating drug-resistant tuberculosis or other refractory mycobacterial infection (in persons without HIV) is now open and recruiting volunteers.
The March 2 Report The information published March 2, which represents the state of IL-2 research as of about a year and a half ago, has basically been known to the AIDS community for some time. A few HIV physicians are already treating patients with IL-2, based on this work.
The article reports on three groups of patients: (1) The first group -- 23 patients in a dose-escalating trial, all with CD4 counts greater than 200 -- received a single course of treatment, a continuous intravenous infusion lasting either five or 21 days. The doses ranged from 1.8 million IU (international units) to 24 million IU per day. The maximum tolerated dose was found to be 18 million IU per day, when the drug was given for five days.
(2) The second group, of ten patients with CD4 count over 200, received a five-day course of intravenous treatment (initial dose 18 million IU per day) every eight weeks. Eight of the ten required dose reductions (to 12 million IU or 6 million IU per day) due to side effects, and two of these eight chose to discontinue the treatment, although they remained in the study for followup.
At the time data was collected for publication, five of the ten had received IL-2 treatment for two years. The average CD4 count (for all ten of these ten patients) went from about 400 to almost one thousand during the first year of treatment; the maximum CD4 increase was over 2200. But four of the ten did not respond -- their count stayed about the same, or even continued to decline.
CD8 counts generally remained stable. An analysis of the cells using 2-color flow cytometry showed that the proportion of CD8 cells positive for HLA-DR was reduced -- which is considered a potentially good sign.
Four of the ten patients showed a consistent increase in viral load (HIV RNA) after each infusion; but then the viral load quickly returned to baseline. There was no corresponding increase in p24 antigen. Another four of the ten had a viral load which remained below the 10,000-copy cut-off value of the test which was used (the Chiron branched DNA); if they had an increase in viral load, it was too small to be detected by the test.

Two of the ten patients developed pneumocystis; both had failed to respond to IL-2, and both had a very high viral load, 555,000 and 435,000 copies per ml. Their last CD4 counts before being diagnosed with pneumocystis were 400 and 31, respectively. There were no other opportunistic infections in these ten patients.

(3) The third group was 15 patients with CD4 counts under 200. Their side effects were more severe, and all 12 who received two or more courses of treatment required dose reduction. One patient, who took trichosanthin (compound Q) several days after an IL-2 treatment without telling the researchers, died two days later "from hypotension and lactic acidosis." Two of the six patients who started with CD4 of 100-200 had increases of at least 50 percent. But none of the six who started with under 100 had CD4 increases, and two of these patients developed opportunistic infections and died, about two and seven months after their last IL-2 treatment. Immunological tests showed that even in those with CD4 count under 100, their cells may have responded to the drug, suggesting that it may have been the virus which was preventing the CD4 count from increasing.

Additional IL-2 Studies Three other studies at NIH of IL-2 in patients with HIV are now recruiting volunteers. One will test IL-2 in combination with strategies to reduce the activity of tumor necrosis factor (TNF), in the hope that this could improve the results of IL-2 treatment by reducing the side effects and/or viral increase which IL-2 can cause. Another is for people with T- helper count over 500, and will test two doses, given subcutaneously instead of intravenously, and every four weeks instead of every eight weeks. The third study is examining different durations of infusion, and different intervals of IL-2 infusion.

Other IL-2 trials include randomized studies in the U.S. and Australia, and also a trial which combines IL-2 with the Merck protease inhibitor.

For information about volunteering for IL-2 clinical trials, call the AIDS Clinical Trials Information Service, 800/TRIALS-A. You can also find out about AIDS-related trials conducted by the National Institute of Allergy and Infectious Diseases by calling 800/AIDS-NIH.

See the topic on aegis.org