The CD4 Solution?

Now that HAART-for-life is a bust, IL-2 -- the immune-boosting drug that gets a rise out of your CD4 cells -- has been reborn. After years of testing and a dose adjustment or two, some docs say it's ready for prime time.

October 1, 2000 By Lark Lands, PhD and Doug Allen

Larry Bruni, MD, thinks he already knows what the U.S. government is spending $43 million to find out: whether the synthetic version of the immune-regulating protein interleukin-2 (IL-2, marketed by Chiron as Proleukin), an expensive drug approved in the '80s for treating kidney cancer, can boost immunity and slow -- even stop -- HIV disease. Based on seven years of experience giving IL-2 to hundreds of patients in his Washington, DC practice, Bruni believes that it can. And a number of other HIV specialists around the country agree.

But just down the road from Bruni's office, researchers at the National Institute of Allergy and Infectious Diseases (NIAID) are enrolling 4,000 HIVers in a five-year trial to be carried out at 210 sites in 18 countries -- the largest drug trial in the history of federal AIDS research -- to study the question. The trial carries the upbeat name ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial), and is supposed to give a definitive answer on IL-2's worth. The problem is that small trials have already shown that IL-2 can raise CD4 counts -- often far more than HAART alone -- but there's been no definitive, long-term trial data showing that the end result is prevention of AIDS-defining illnesses and death.

Isn't it only logical, you might ask, to presume that higher CD4 counts would equal longer life? Well, they might -- but we don't know for sure whether these IL-2-boosted CD4 cells are identical to those normally produced by the body, with the same ability to counter HIV and other infectious agents. There are laboratory indications that they are, but only cold, hard data will satisfy researchers and the FDA.

So we're all glad they're doing the trial, right? There you go being logical again. It's true that an early objection to IL-2 -- that it could activate infected CD4 cells, causing them to churn out virus and thus boost viral load -- has been eliminated by the drug's use in conjunction with HAART. But there are still a number of scientific and practical reasons that both researchers and treatment advocates have objected to the trial. For HIVers contemplating IL-2 therapy, the only important issue is the dose.

"I think ESPRIT is using the wrong dose," says Kendall Smith, MD, chief of the Division of

Immunology at New York Presbyterian Hospital and professor of medicine at Cornell University. And Smith knows his IL-2 science. He was, after all, the first to identify the IL-2 molecule and its receptor (the area on the cell surface that binds to it). Based on his many IL-2 studies -- from basic-science pharmacology to multiple trials in HIVers -- he believes that daily low doses of IL-2 achieve the best effects. In his trials, 40 participants added to their HAART regimens subcutaneous (under the skin) injections of 2 million international units (MIU) of IL-2 daily, continuing that dose for at least a year. For those who had side effects (other than welts at injection sites), the daily amount was reduced by 25 percent.

Smith's research has shown that this low dose provides a blood concentration sufficient to saturate the IL-2 receptors on T cells (both CD4s and CD8s), thus promoting the cells' growth. It does this without having much effect on the IL-2 receptors of natural killer cells (NKs, which kill virus-infected cells and tumor cells), since they mostly require a higher blood concentration for effect. And that's a good thing: Higher doses of IL-2 cause it to bind to the body's billion or so NK cells, sparking massive production of tumor necrosis factor (TNF), a chemical that causes most of IL-2's obnoxious side effects (such as fatigue and flulike symptoms). Because about 10 percent of NK cells will bind to IL-2 at low concentrations, a sufficient number of them will grow to counter the usual HIV-caused loss of these important immune cells without incurring TNF nastiness. In other words, the low dose promotes the return of both the T cells and the NK cells without causing all the miserable symptoms of higher doses. In addition, Smith's findings indicate that daily low doses of IL-2 will prevent apoptosis, the programmed cell death considered a major cause of immune-cell loss in HIVers.

By comparison, both the ESPRIT trial and most other current IL-2 trials use much higher doses of 9 to 15 MIU daily, usually given in five-day cycles repeated every eight weeks. NIAID officials argue that their high-dose regimen offers different benefits from Smith's approach. "One's not better than the other -- they just do different things," says Clifford Lane, MD, clinical director of NIAID and a longtime IL-2 researcher. "If you give IL-2 for five days every eight weeks, you get an expansion of the CD4 pool. If you give daily IL-2 at low doses, you get an expansion of the natural killer cell pool."

Smith believes that the NIAID approach of occasionally flooding the body with large doses of this cytokine (a cell-produced chemical) is far less likely to approximate the effect that IL-2 would normally have. It is naturally produced in tiny amounts, mostly by activated CD4s and some CD8s. In addition to boosting the number of new T cells and NK cells and activating the NKs, IL-2 indirectly activates monocytes (which destroy foreign matter) and ensures normal performance of antibody-producing B cells. No wonder it's key for maintaining immunity. But in HIV disease, its production goes downhill, especially as CD4 cells decrease.

This Doc's a Believer

I think that that everybody living with HIV should be getting IL-2," Larry Bruni says. "It is an integral part of fixing the immune dysfunction of this disease." Saying that "higher doses cause much more suffering and are not necessary to produce good results," he splits the difference on dosing, recommending a moderate level of 4.4 MIU twice daily for five days, followed by an eight-

week break; he halves that dose if side effects are too troubling. In his experience, this approach makes injecting IL-2 tolerable for most.

Typically, his patients report feeling OK for the first couple of days, and then having worsening fatigue on days three through five, often accompanied by flu-like symptoms (fever, body aches and chills), nasal congestion and depression. Since the fifth day is almost always the worst, Bruni has his patients start their IL-2 cycles on Tuesday so that they can be home resting on Saturday and recovering on Sunday. The result is that "most people make it through their work week or, at most, use one or two sick days, and then go back to work the following Monday feeling fine." In a small percentage of people, the fatigue and depression may linger. If necessary, Bruni recommends antidepressants like Prozac.

Because research has shown that dosing with IL-2 dramatically decreases body levels of vitamins (especially A, B-6, beta-carotene and folate) and minerals (especially magnesium and potassium), Bruni makes sure all his patients are taking potent multiple-vitamin/mineral and antioxidant supplements. Based on German research showing that IL-2's ability to boost CD8 cell proliferation and activation is dependent on glutathione (an antioxidant), Bruni recommends additional N-acetyl-cysteine (NAC), alpha-lipoic acid and vitamin C, the nutrients that boost glutathione production. He says that the result is a better response to the drug and fewer side effects.

But whether or not an IL-2-taker uses nutrients to minimize toxic effects, Bruni says: "No one begs you for another round of IL-2. They keep doing it because of the end results." In his experience, those include substantial increases in both CD4s and CD8s, and, in about half of those given the drug, a tendency toward normalizing the CD4/CD8 ratio (a measure of immune health; normal is greater than 1). On average, it takes three cycles (six months) for the immune system to fully respond, but then, he says, "in those who start with at least 400 CD4s, most [90 percent] will easily have over 1,000 within the first year. Maybe 7 percent will have a lesser increase, and 3 percent won't respond during the first year. In those who start with CD4s between 250 and 300, it may take a year to start seeing good results, but within two years most will be above 500." In those with CD4 cells below 150, Bruni terms the response rate "disappointing."

Smith's lower daily dosing results in a slower but steady increase in CD4s, usually a gain of about 10 cells monthly. That will continue to increase into the normal range (600 or higher) over time. The natural killer cells will increase more rapidly, with a gain of about 80 cells per month for the first several months of IL-2 use. Because most HIVers will have a count of around 100 NK cells to start with, by the third or fourth month they'll likely plateau at 400 (on the high end of normal). Smith recommends that people stay on daily IL-2 until their CD4s reach the normal range, after which they can continue on HAART alone unless their counts again decline.

One point most IL-2 experts agree on: Any immune-based therapy would be best used before CD4-cell diversity is lost. The problem is that there isn't just one type of CD4 cell; there's an alphabet soup, with each "letter" programmed to respond to a specific antigen (invader). As your CD4 count drops, you may lose all the cells of a certain letter type. IL-2 acts like a copy machine for all the letters left, but it can't help you recreate the ones already lost. No one is sure exactly when the

letters start disappearing, but most believe that it's more likely when the count drops below 400. Bruni thinks that using IL-2 prior to this point gives the best hope of maintaining the full immune repertoire.

Saved by the Reborn CD4s?

Overall, the results Bruni has seen in his patients have led him to believe that the gained cells are fully functional. "If the CD4 cells are 800, they're a real 800, and each of them works as well as any other CD4 cell," he says. Though accomplished by different means, Bruni adds, "it's the same kind of immune reconstitution you see with HAART." He bases this opinion on the continued good health of his IL-2-treated patients. They don't develop opportunistic illnesses at the higher-than-normal levels you would expect if those CD4 cells weren't functional. And many report improved overall quality of life.

A Brand-New Man

That's certainly the story of longtime IL-2 taker Ed New, 51, a senior budget analyst for the Nuclear Regulatory Commission in Washington, DC. Diagnosed during his Army days back in 1989, New spent years with serious fatigue, swollen lymph glands, headaches, constantly plugged sinuses and a pessimistic outlook that left him feeling, he says, "I'm HIV, so I can't do this and I can't do that and I don't have great expectations for the future." IL-2 lightened and brightened all that.

After years of monotherapy -- first AZT, then ddI -- that didn't stop his CD4s from dropping to an all-time low of 277, in 1995 he became a guinea pig in one of the earlier NIAID IL-2 trials. From a pretreatment CD4 count of 378, his cells jumped to 594 after the first cycle, then into the 600s after the next couple, and finally up to more than 1,000. Now they usually bound above 1,000 in the month after each cycle, and then gradually drop back to between 800 and 900 within about five months. If the CD4s drop below 800 twice, he does another round, which, on average, now means about one IL-2 infusion every 10 or 11 months.

The initial 18-MIU intravenous dose (then the NIAID standard) caused New severe side effects, including crushing fatigue, flulike symptoms, fluid retention (including his swollen "old-lady" ankles), severe skin peeling and, on at least one occasion, unconsciousness. His hospital roommates during the early days of the trial experienced the rest of the long list of side effects, including shortness of breath (due to fluid retention in the lungs), diarrhea, nausea, vomiting, loss of appetite, weakness, low blood pressure, dehydration, neuropsychiatric problems (including, for some, memory loss so severe that they couldn't remember their names or serious depression that lasted weeks after the treatment), blood-vessel leakage, and liver and kidney dysfunction.

To lessen side effects, the researchers gradually decreased New's dose, eventually dropping to 6 MIU intravenously, given for only three days, and then, switching to subcutaneous dosing in March 1999, settling on 7.5 MIU, divided into two doses, for five days. With this dosing, he says he feels "a little blah" on the first day and gets chills and fever (up to 103 degrees) on the second, along with nasal congestion, fatigue -- "I sleep a lot" -- and a bump at the injection site that remains for up to a month. To head off blood-mineral imbalances and dehydration, he drinks plenty of fluids,

including V-8 for potassium.

Smith says that all these side effects are unnecessary: “Patience is a virtue. You can get the good results you want with no side effects by simply taking IL-2 longer with lower doses. And we can afford the waiting time because of HAART. Call it the kinder, gentler IL-2 approach.”

Side effects or no, Ed New says IL-2 therapy is worth whatever it takes to get the end results. “All the HIV miseries I used to live with are gone,” he says. “And IL-2 has given me hope. I think like a person with a future instead of a person whose life is limited.” While he believes that the HAART regimen he eventually went on (well after the IL-2 had raised his CD4s) has contributed, he says that it’s the two together that have kept him in prime health. “I’m a complete believer in IL-2,” he says. “I will continue it until the day they announce a cure.”

MY, WHAT A BIG TRIAL IL-2 HAS! WILL IT WORK

When NIAID launched its five-year ESPRIT megatrial of IL-2 plus HAART vs. HAART alone, many hailed it as a long overdue step toward funding much-needed immune-based therapy research. But critics raised troubling questions ranging from dosage to bang-for-buck and more. Consider:

Cost: Why spend so much on IL-2 when other promising but understudied immune-based therapies—everything from therapeutic vaccines to the hormone DHEA to herbal combinations—go begging?

Design: Will the varying cycle lengths (after six months he fixed schedule gives way to physician discretion) make data analysis impossible? And is five years long enough to see the real differences in diseases progression between those on HAART alone and those who will take it with IL-2?

Practicality. ESPIRIT will require 2, 000 HIVers with CD4s above 300 to self-inject, for five days every eight weeks, high-dose IL-2 plus down their tricky HAART regimens. Will enough healthy HIVers sign on to this rigorous side effect-prone therapy to fully enroll the trial? The University of Colorado’s Robert Schooley, MD, says, ‘You could be holding breath for a long time.”

Missed Opportunities. The trial’s size could yield important knowledge about new cell tests that might better measure immune changes, so why aren’t the samples of all participants’ cells (instead of a limited number) being stored? Brenda Lein, director of Project Immune Restoration at Project Inform, says, “ESPRIT is useless in terms f answering the question of immune markers.”

Bur NIAID official Jack Killen defends the trial. “It’s taking big risks,” he acknowledges,” but it’s an important study that’s been through an enormous amount of scrutiny.”

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