IL-2 Fails in Two Large Studies

February 10, 2009 By David Evans

It's finally official: Proleukin (interleukin-2, IL-2), a long-studied experimental immune-based therapy for HIV, simply doesn't work. When compared with antiretroviral (ARV) therapy alone, Proleukin plus ARV treatment failed to protect people against developing an opportunistic infection or death, despite generating greater increases in CD4 counts. The news was presented Tuesday, February 10, at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal.

Proleukin, manufactured by Novartis Pharmaceuticals and approved for the treatment of kidney cancer and melanoma, is a synthetically generated version of an immune signaling molecule called interleukin 2, or IL-2. When CD4 cells release IL-2, it causes other CD4 cells to multiply. For more than 15 years, researchers have studied IL-2 as a treatment to boost CD4 counts in people living with HIV. However, no one has until now been able to definitively show whether these additional CD4 cells protected people against HIV disease progression, such as AIDS-related diseases and death.

The two studies presented at CROI, called ESPRIT and SILCAAT, examined the effect of Proleukin in two different populations. ESPRIT looked at the drug in people who were on ARV treatment with a CD4 count greater than 300. SILCAAT looked only at people on ARV therapy with CD4 counts between 50 and 299. Both studies were conducted internationally.

Marcelo Losso, MD, from the Hospital José María Ramos Mejía, in Buenos Aires, presented data from the ESPRIT study. In total, the study enrolled 4,111 people with HIV in 25 countries. All of the participants were taking ARV therapy, and 80 percent had a viral load of less than 400 copies when they entered the study. Participants were randomized to either add Proleukin to their ARV regimen or continue taking ARV treatment alone. The average CD4 count among participants in both groups at the start of the study was 457.

Over nearly seven years of follow-up, people taking Proleukin had a CD4 count that was, on average, 153 cells higher than people not taking Proleukin. However, there was no meaningful difference in the rates of death, opportunistic infections or non-AIDS-related serious health events, such as traditional cancers or cardiovascular disease. Unfortunately, people taking Proleukin did have a higher risk of developing a serious side effect, which most commonly included fever, malaise, psychiatric problems and blood vessel problems.

The results of SILCAAT, presented by Yves Levy, MD, from the Hôpital Henri Mondor, in Créteil,

France, were nearly identical to those in the ESPRIT trial. SILCAAT included 1,695 patients, whose average CD4 count at the start of the study was 202. The primary difference from ESPRIT, given that people in SILCAAT had much lower CD4 counts at the trial's initiation, was that people taking Proleukin only gained, on average, 57 more CD4 cells than people not taking Proleukin. There was, however, no benefit in terms of opportunistic infections or death.

There was a trend toward a greater number of side effects in people taking Proleukin, but this did not reach statistical significance in SILCAAT, meaning that the difference was small enough to have occurred by chance.

Both Losso and Levy concluded their presentations by saying that the CD4 gains produced by Proleukin do not appear to be as protective against disease progression and death as the CD4 gains conferred by ARV therapy alone. They hypothesized that CD4 cells generated by Proleukin may not be functional enough, or that the drug may cause some as yet unidentified damage to the immune system that outweighs whatever benefit it provides in terms of CD4 increases.

Levy commented at the end of his presentation that SILCAAT retained blood samples from a large proportion of the patients and that if funding can be found for future studies, they might help explain why Proleukin didn't diminish illness and mortality.

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