IL-2’s Downfall Might Have Been Inflammation

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The failure of Proleukin (Interleukin-2, IL-2) to demonstrate a clinical benefit in the SILCAAT and ESPRIT studies earlier this year might have resulted because the drug increased immune system inflammation, according to an article published October 15 in *The New England Journal of Medicine (NEJM)*.

Researchers once had high hopes for Proleukin. While there’s no question that the drug raises CD4 cells, early studies failed to demonstrate consistently whether those additional CD4 cells reduced the risk of disease or death in people living with HIV. SILCAAT and ESPRIT, two very large international studies that enrolled 5,800 people with HIV, were designed to prove once and for all whether or not Proleukin-induced CD4 increases translated into clinical benefit. Unfortunately, SILCAAT and ESPRIT researchers reported earlier this year that neither large study found Proleukin beneficial in this regard.

Now, researchers from both studies have published their results in NEJM, along with an analysis of why Proleukin might have failed. They offer two hypotheses: First, that the increased cells themselves have no role in protecting people from opportunistic infections or death, or second, that something about Proleukin is harmful to people with HIV and thus negates the benefits of increased CD4 counts. The authors offer some evidence that the latter might be the more logical explanation.

People receiving Proleukin in both studies were more likely to have serious side effects. In SILCAAT there were more psychiatric and gastrointestinal problems. In ESPRIT there were far more incidences of deep vein thrombosis, a blood clot that forms in blood vessels deep in the body. According to the authors, these increased side effects could be caused by increased immune system inflammation. Certainly a number of studies show that Proleukin increases cell-signaling molecules associated with inflammation, such as D-dimer and C-reactive protein. D-dimer levels were higher in people taking Proleukin in the studies.

The authors state that a link between the elevated D-dimer levels and the increase in blood clots in ESPRIT could explain the failure to show clinical benefit in that study. They conclude that “the mechanisms behind these deleterious effects remain unclear but could be related to the effects of T regulatory cells, greater proinflammatory effects of interleukin-2 in patients with higher numbers of CD4 cells, or both.”

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