**Interleukin-2 in Clinical Trials: Other Factors to Be Considered**

To the Editor—Emery et al. [1] did a valuable retrospective evaluation of 3 randomized controlled trials that addressed the clinical benefits of interleukin (IL)-2 therapy in adults with human immunodeficiency virus (HIV) infection. The analysis of the pooled data (median follow-up, 29 months) showed a nonsignificant but relevant 43% reduction in the risk of disease progression and death for subjects randomized to receive continuous infusion of IL-2, compared with those randomized to receive antiretroviral therapy alone (control group), even though 60% of the subjects in the control group received IL-2 after ~1 year in the study. Another remarkable finding was the significantly lower plasma HIV RNA level for patients in the group receiving IL-2, relative to that for patients in the control group. A recent randomized multicenter clinical trial detected a larger decrease in the mean virus load and more likelihood of achieving a virus load of <50 copies/mL in subjects receiving IL-2, compared with subjects receiving antiretroviral therapy alone, at 1 year of follow-up [2].

Phase III trials of IL-2 therapy with antiretrovirals versus antiretroviral therapy alone are currently underway to appraise prospectively the role of IL-2 in HIV treatment. The results of these trials will be critical to defining the future use of IL-2 in this setting. Because the typical side effects of IL-2 therapy make a blinded study impossible, other aspects of the studies might affect the results.

A meta-analysis [3] showed that several types of interventions (educational, behavioral, and emotional) had a weak-to-moderate effect on drug compliance and on outcomes for subjects with chronic diseases. In another study [4], patients with diabetes mellitus who believed that they had participated in the decision-making process were more likely to follow through on treatment decisions than those who did not feel that they were part of the decision-making process. An additional meta-analysis with diabetic patients found that emotional stability, internal and external motivations, perceived benefit, and supportive structure were positively associated with patient compliance [5]. Other factors that might be associated with better outcome include the amount of information and the encouragement that patients receive [6].

Subjects randomized to IL-2 therapy probably will have different experiences than subjects randomized to a control group (antiretroviral therapy alone). Those receiving IL-2 injections might make more-frequent visits to a doctor’s office, as well as periodic phone calls to medical care providers, and therefore might have closer follow-up. This is reasonable to assume, considering the concerns about the side effects of IL-2 therapy. These patients probably will be taught about the risks of receiving IL-2 without being on antiretroviral therapy. The almost universal CD4 cell count expansion seen with moderate-to-high doses of IL-2 certainly can enhance patients’ motivation and drug adherence. Overall, subjects randomized to the group receiving IL-2 will have more interaction and contact with the HIV care team. Therefore, discrepancies between the groups may be attributed to better compliance with antiretroviral drug therapy in the group receiving IL-2 than in the group receiving antiretrovirals alone. Greater drug compliance has been closely related with superior virologic suppression. This eventually may account for the virus load reduction described in prior studies and for the different disease progression risks that may be observed in the ongoing phase III trials.

The indirect effects of IL-2 itself might be considered as part of the intervention, much like an inherent benefit associated with IL-2 therapy. If so, whether these factors affect the degree of external validity of the clinical trials should be considered.

In summary, elements other than the administration of IL-2 may affect the virologic response of and, subsequently, the clinical effect on HIV-infected patients. These factors have been associated with outcome in the treatment of various other chronic disorders. This disparity should be taken into consideration when data from phase III trials of IL-2 therapy are analyzed and may indicate a need to create a better balance between groups.

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**References**


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