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The Potential Role of Interleukin-2 in Patients with HIV Infection

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Abstract

Interleukin-2 (IL-2) is a T cell derived cytokine that leads to a sustained expansion of the CD4+ T cell pool when given as 5-day cycles approximately every 8 weeks. An extensive series of phase I/II studies have been carried out and have leaded to the initiation of two phase III trials that are currently enrolling patients in 23 countries. Studies of the mechanisms of action have revealed that IL-2 is capable of inducing the polyclonal proliferation of CD4+ and CD8+ T cells, even in the absence of expression of the high affinity IL-2 receptor. While IL-2 leads to a 6-fold increase in T cell proliferation and a 2-fold increase in T cell death, the primary mechanism of action leading to expansion of the CD4+ T cell pool appears to be an increase in CD4+ T cell survival. While early work focused on the ability of IL-2 to exert these effects in patients with relatively early stages of HIV infection, more recent work, in the setting of HAART, indicates that these effects may be seen at all stages of HIV disease. The results of the phase III studies should provide an answer to the question of whether or not this is a strategy that will be of clinical benefit.

Key words

Interleukin-2 (IL-2). HIV. CD4 T lymphocytes. Clinical trials. Immunology.

Introduction

HIV infection is characterized by an immunodeficiency reflected in the depletion of CD4+ T cells occurring in a setting of immunosuppression and/or polyclonal activation reflected in the viral load[1]. A simplified view of patient management from the perspective of the laboratory-based physician is to keep the CD4 count as high as possible for as long as possible, and to keep the viral load as low as possible for as long as possible. A simplified view from the perspective of the clinic-based physician is to keep the patient as healthy as possible for as long as possible. Integrating these two perspectives is one of the great challenges facing HIV therapeutics as we enter the 21st century.

The addition of highly active antiretroviral therapy (HAART) to the therapeutic armamentarium has dramatically changed our ability to treat patients with HIV infection and, in addition to lowering the viral load, has led to a substantial degree of recovery of the immune system as evidenced by the striking decreases in AIDS-related complications[2]. No such success has been seen with therapeutic strategies that directly target the immune system; however, much work is ongoing in these areas. The purpose of this review is to examine the potential role of interleukin-2 (IL-2) in expanding and main-

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taining the CD4+ T lymphocyte pool of patients with HIV infection.

Mechanisms of action

IL-2 is a T-cell derived cytokine with a molecular weight of 15,000 daltons that induces the activation, proliferation and differentiation of T, B, and NK cells. It was previously referred to as T cell growth factor. The product most commonly used in clinical trials in patients with HIV infection is a recombinant protein expressed in *E. coli* (Proleukin™, Chiron Corporation, Emeryville, CA, USA). This product has been licensed in some countries for treatment of metastatic renal cell carcinoma and melanoma. It is available under an expanded access program in France for patients with HIV infection and CD4+ T cell counts under 200 cells/mm^3.

IL-2 is a molecule that plays a central role in the regulation of the immune system. Classically, resting T cells upon encountering their cognate antigen express the alpha chain (CD25) of the high affinity IL-2 receptor (alpha, beta and gamma chains). The high affinity IL-2 receptor binds IL-2 leading to T cell proliferation and differentiation. Several studies are underway examining the ability of exogenously administered IL-2 to enhance HIV and hepatitis C virus (HCV) specific immune responses[3]. Thus far there are no indications in patients that the administration of exogenous IL-2 is able to enhance an ongoing antigen-specific response. In addition to these effects on antigen-specific immunity, IL-2 also appears to play an important role in T cell homeostasis. In this scenario, IL-2 binds to cells expressing the intermediate affinity IL-2 receptor (beta and gamma chains). Following this interaction cells undergo cell division and express CD25[4]. When administered by intermittent intravenous infusion or subcutaneous injection for 5 days, approximately every 8 weeks, IL-2 leads to an expansion of the CD4+ T cell pool with a preferential expansion of cells of naïve phenotype[5]. This effect appears to be the net result of an immediate increase in proliferation; an immediate increase in cell death and a long-term increase in CD4+ T cell survival. The majority of the current studies evaluating the potential role of IL-2 in patients with HIV infection have used this latter approach.

IL-2 in patients with CD4 counts >200 cells/mm^3

IL-2 was first studied in patients with HIV infection in 1983. The earliest attempts used continuous infusions of IL-2 for periods of up to 8 weeks. During these studies a transient increase in CD4+ T cell counts was noted that peaked at approximately 1 week and then declined despite the continued administration of IL-2. Based upon these observations, studies administering IL-2 as a 5-day infusion every 8 weeks were initiated[5]. Subsequent work has demonstrated that this regimen is the optimum duration and interval for IL-2 therapy during the induction phase of treatment[6]. Similar results were then generated for intermittent subcutaneous therapy[7]. Initial doses were in the range of 12-18 million international units (MIU) over 24 hours. Studies of subcutaneous dosing have indicated that increases in CD4+ T cell count can be seen with doses as low as 1.5 MIU bid with peak responses seen in the range of 4.5-7.5 MIU bid for 5 days every 8 weeks[8-10]. Following several cycles of IL-2, increases in CD4+ T cell numbers can be maintained with less frequent cycles.

The first studies with IL-2 in HIV-infected patients were performed before the advent of potent antiretroviral treatments. In the first report of successful enhancement of CD4+ T cell numbers with IL-2, a total of 25 patients received IL-2 by continuous intravenous infusion over 5 days every 8 weeks[5]. Overall, 60% of those with CD4 >200 cells/mm^3 at baseline had a greater than 50% increase in CD4+ T cells following IL-2. This report was followed by another randomized, controlled trial of intermittent IL-2[11]. In this second study, 60 patients with CD4 counts >200/mm^3 were included[2]. They were randomized to receive antiretroviral therapy alone (typically dual nucleosides) or antiretroviral therapy + IL-2. After one year of follow-up, those patients receiving IL-2 had an increase in their CD4 counts of 488 cells/mm^3 (114% increase from baseline) compared to a decrease of 58 cells/mm^3 (14% decrease) in the control arm. Side effects were common in both of these studies and although the immunologic results were impressive, they came at the cost of frequent grade III or IV side effects. While bursts of HIV replication were noted in some of the patients at the end of IL-2 administration[5,12], these bursts were often transient in nature and, based upon the findings of the randomized controlled trial, did not lead to a sustained increase in plasma HIV-RNA levels.

The recognition of these bursts of virus have led to the decision by most investigators to utilize IL-2 only in the setting of antiretroviral therapy. A single, small trial of 36 patients, however, has noted that one can administer IL-2 to patients with CD4+ T cell counts above 300 without antiretrovirals and achieve a modest increase in CD4+T cell count without an adverse effect on plasma HIV-RNA levels[13].

The high degree of adverse events associated with intravenous administration of IL-2 quickly led to the study of subcutaneous IL-2. In one trial, in which all participants received antiretroviral therapy (nucleoside analogues), comparing intravenous IL-2 to subcutaneous IL-2, the mean increase in CD4+ T cells was 564 cells/mm^3 in the subcutaneous group, 676 CD4+ T cells in the intravenous group, and 55 CD4+ T cells in the control group[14]. Adverse events were milder in the patients treated by subcutaneous route. Similar results have been reported by other authors[15-17]. The main advantages of subcutaneous administration are that is has comparable efficacy, a lower number of adverse events, and is easier to administer.

The introduction of HAART provided the opportunity to study the impact of IL-2 in the setting of more potent antiretroviral treatment. A randomized, con-

trolled trial compared subcutaneous IL-2 plus antiretroviral therapy to antiretroviral treatment alone in 82 patients[18]. Overall, 88% of the patients in this study were receiving HAART with a protease inhibitor. After 1 year of follow-up, patients treated with IL-2 had a 384 cell increase in their CD4 counts (112% of baseline) compared to a 64 cell increase in the control group. At the end of the study, a higher fraction of patients in the IL-2 group had a viral load of <50 copies/ml than those taking antiretrovirals alone (67% *vs.* 36%). However, these differences disappeared when only patients receiving protease inhibitors were analyzed.

In the largest completed study of IL-2 to date, 511 patients were randomized to received IL-2 plus antiretroviral therapy or antiretrovirals alone. Patients assigned to receive IL-2 were randomized to receive either 4.5 MIU bid or 7.5 MIU bid for 5 days every 8 weeks[19]. Patients who were randomized to receive IL-2 had an increase of 221 cells/mm^3 greater than the control group. Of note, CD4 increases were comparable between the two IL-2 groups and there were no significant changes in viral load in any of the groups during the time of the study. In this trial, it was also found that the lower the nadir of CD4+ cells prior to study entry, the less likely the person was to experience a robust CD4+ T-cell increase in response to IL-2 therapy. Patients whose CD4+ T cell counts had been 250 or lower had less robust increases than those with nadir counts between 250 and 400. Subjects with nadir counts 400 and above were most likely to achieve CD4+ cell count increases to above 1,200 following three courses of IL-2 therapy.

In preparation for a phase III trial of IL-2 in patients with HIV infection and CD4+ T >300 cells/mm^3 named the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (the ESPRIT study), three identical randomized controlled trials were carried out in Bangkok, Buenos Aires, and Houston, in patients with CD4+ T cell counts >350 cells/mm^3[3,9,10,20]. All 3 studies compared the effects of three different doses of IL-2 (1.5 MIU bid; 4.5 MIU bid; and 7.5 bid) plus antiretroviral therapy versus antiretrovirals only. In each of these trials patients receiving IL-2 had a significant rise in baseline CD4 counts relative to control patients. In the Argentinean study, mean increases from baseline for patients assigned to IL-2 were 210 cells/mm^3 compared to 29 cells/mm^3 for patients in the control group. Similar results were reported in the Thai study, in which the time-weighted mean change from baseline at week 24 was 252 cells/mm^3 for the combined IL-2 arms versus 42 cells/mm^3 for the control group. A pooled analysis of these data was presented by Arduino, et al. at the 8th Retrovirus Conference in 2001[20]. After three cycles of IL-2, the mean CD4 difference between IL-2 and control groups were 605 cells/mm^3 for patients in the 7.5 MIU dose cohort, 339 for patients in the 4.5 MIU dose cohort, and 66 for patients in the 1.5 MIU dose cohort. The differences between the 1.5 and the control group were not statistically significant in the pooled analysis; however, were significant in the separate analyses of the Thai and Argentinean studies. The percentage of grade III-IV adverse events was 13.5% in those receiving 7.5 MIU bid, 11.1% in those receiving 4.5 MIU bid, and 5.6% in those receiving 1.5 MIU bid. This figure was 2.8% in the control groups. Thus, treatment with IL-2 needs to be somewhat individualized to maximize potential beneficial effects on CD4 count while minimizing the development of adverse events.

Taken together these data strongly suggest that, in patients with CD4 counts above 200 intermittent administration of IL-2 can lead to a pronounced, sustained increase in CD4+ T cell counts without a significant change in viral load. There are few data that provide information as to whether or not these increases will be of clinical benefit. The best published data bearing on this question come from a pooled analysis performed of 157 patients from the first three randomized clinical trials using continuous intravenous infusion of IL-2 plus antiretrovirals versus antiretroviral therapy only[21]. After 2.5 years of follow-up, and based on the original assignments, 9 patients initially randomized to the arms with IL-2 were noted to have developed AIDS-defining events or died, while this figure was 16 among patients allocated to antiretroviral therapy only (p=0.22). As noted above, the ESPRIT study is an ongoing, multicenter, international trial designed precisely to address the potential clinical benefit of IL-2 in HIV-infected patients with CD4 counts >300/mm^3. To achieve this goal, the ESPRIT study will need to enroll approximately 4000 patients and follow them for an average of 5 years.

IL-2 in patients with CD4 counts <200 cells/mm^3

Patients with low CD4 counts (<200 cells/mm^3) did poorly when treated with IL-2 in the pre-HAART era[5]. Side effects were noted to be more prominent and CD4 count increases were less pronounced. For this reason few studies of IL-2 were conducted in patients with low CD4 counts during this time. With the advent of HAART, however, there was renewed research interest in this group of patients and several studies have been completed with encouraging results.

ACTG 328 was a randomised, controlled trial of intermittent IL-2 in 204 protease inhibitor-naïve patients with CD4 counts between 50-350 cells/mm[22]. Patients initially received HAART alone for 12 weeks. If their plasma HIV-RNA was <5000 copies/ml, they were then randomized to continue HAART alone, to continue HAART plus receive intravenous IL-2, or to continue HAART and receive subcutaneous IL-2. Crossover from iv to sc IL-2 was allowed after three or six cycles and took place in 75% of patients initially in the iv arm. The median daily dose of IL-2 was 9 MIU per day in both the iv and sc arms. The median change in the CD4 count was +97 cells/mm^3 for patients who received HAART alone, +309 cells/mm^3 for patients who received iv IL-2 plus HAART, and +240 cells/mm^3 for patients who received sc IL-2 plus HAART. Both

IL-2 arms had a significantly greater rise in CD4 counts when compared to HAART alone. There was no significant difference in the percentage of patients with viral loads <50 copies/ml in the three arms. There were five AIDS-defining events in the HAART alone arm and one in each of the IL-2 arms. The overall event rate was too small for the difference to be of statistical significance. This trial clearly demonstrated that, in combination with HAART, IL-2 could increase CD4 counts in patients with relatively advanced HIV infection.

Finally, a particularly important clinical question is whether IL-2 has any role in patients who do not have a significant rise in their CD4 counts despite treatment with HAART. Arno, et al.[23] studied 25 patients on a PI-containing regimen who had CD4 counts <250 cells/mm^3 and plasma HIV-RNA <500 copies/ml for at least 24 weeks. Patients were randomized to receive intermittent subcutaneous IL-2 plus HAART or HAART alone. Patients initially received 3 MIU of IL-2 bid. The dose was later reduced to 3 MIU once a day because of concerns of toxicity. The study showed that at 24 weeks, the group receiving IL-2 plus HAART had a greater increase in CD4 counts (mean of +105 cells/mm^3) than the group receiving HAART alone (mean of +30 cells/mm^3). However, these figures reflected only patients who tolerated the treatment: only 8 of 13 patients in the IL-2 plus HAART arm completed the study compared with 10 of 12 in the control arm.

A similar French study, known as ILSTIM or ANRS 82, was a randomised, controlled trial of IL-2 therapy in patients with HIV infection who, despite long-term suppressive anti-HIV therapy, had not achieved a CD4+ T cell count above 200 cells/mm^3[24]. At 24 weeks following randomization, 81% of those randomized to receive IL-2 had CD4+ T cell counts above 200 cells/mm^3, whereas this was only seen in 33% of those randomised to continue HAART. These later data formed the basis for the French government to approve IL-2 therapy for people with CD4+ T cell counts below 200 cells/mm^3 under a temporary authorization program (ATU).

Taken together, these data indicate that IL-2 may be able to produce increases in CD4+ T cell counts in patients with CD4+ counts under 300 cells/mm^3 and formed the basis for the phase III clinical endpoint study entitled Subcutaneous Interleukin-2 in Combination with Active Antiretroviral Therapy (SILCAAT). This trial is planned to enrol 2000 patients with 5 years of follow-up.

Side effects of IL-2

IL-2 administration is invariably associated with some degree of side effects. Fortunately, the majority of these events diminish following the completion of the 5-day cycles. The main adverse effects of IL-2 therapy include flu-like symptoms (fever, fatigue, muscle aches), redness or tenderness at the injection site, fluid retention, mood swings, irritability, insomnia, confusion, dry skin, rash, nausea and vomiting. Some tips to limit such adverse events include maintaining adequate hydration and prophylactic use of anti-emetics.

In addition, patients with HIV infection appear to be more prone to develop hypothyroidism under IL-2 therapy. In the CPCPRA study of IL-2, the incidence of hypothyroidism in the control group was 5% compared to an incidence of 10% among patients randomised to IL-2. Therefore, HIV-positive subjects receiving IL-2 should be monitored for signs of hypothyroidism.

Cytokines such as IL-2 and interferon-alpha can be associated with severe depression and have been associated with suicides. For these reasons, patients should be carefully screened for depression prior to the administration of IL-2 and individuals with a history of depression should be monitored closely for recurrence of symptoms during IL-2 cycles.

Conclusions

The intermittent administration of IL-2 can lead to a significant sustained increase in the CD4+ T cell count in patients with HIV infection, in association with a significant degree of side effects. The primary mechanism of action appears to be a prolongation of CD4+ T cell survival. The degree of CD4 T-cell increase is related to the nadir CD4+ count and the dose of IL-2 administered. Once CD4+ T cell numbers have increased with IL-2, they can often be maintained with less frequent cycles of IL-2 every 8 weeks. The results of a pooled analysis of the first 3 randomised controlled trials of IL-2 as well as the body of data looking at the CD4 counts at which opportunistic illnesses occur, suggest that the CD4+ T-cell increases seen with IL-2 are of functional T cells. The true clinical impact of these increases is currently being determined in two phase III studies, SILCAAT and ESPRIT.

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References

1. Sereti I, Lane H. Immunopathogenesis of HIV: implications for immune-based therapies. Clin Infect Dis 2001;32:1738-55.
2. Palella F, Delaney K, Moorman A, et al. Declining morbidity and mortality among patients with advanced HIV infection. N Engl J Med 1998;338:853-60.
3. Xu J, Whitman L, Lori F, Lisziewicz J. Methods of using interleukin 2 to enhance HIV-specific immune responses. AIDS Res Hum Retroviruses 2002; 18:289-93.
4. Sereti I, Gea-Banacloche J, Kan M, Hallahan C, Lane H. Interleukin 2 leads to dose-dependent expression of the alpha chain of the IL-2 receptor on CD25-negative T lymphocytes in the absence of exogenous antigenic stimulation. Clin Immunol 2000;97:266-76.
5. Kovacs J, Baseler M, Dewar R, et al. Increases in CD4 T lymphocytes with intermittent courses of interleukin- 2 in patients with HIV infection. A preliminary study. N Engl J Med 1995;332:567-75.

6. Miller K, Spooner K, Herpin B, et al. Immunotherapy of HIV-infected patients with intermittent interleukin-2: effects of cycle frequency and cycle duration on degree of CD4 T- lymphocyte expansion. Clin Immunol 2001;99:30-42.
7. Davey R, Chaitt D, Piscitelli S, et al. Subcutaneous administration of interleukin-2 in HIV type 1-infected persons. J Infect Dis 1997;175:781-9.
8. Davey R, Chaitt D, Albert J, et al. A randomized trial of high- versus low-dose subcutaneous interleukin-2 outpatient therapy for early HIV type 1 infection. J Infect Dis 1999;179:849-58.
9. Losso M, Belloso W, Emery S, et al. A randomized, controlled, phase II trial comparing escalating doses of subcutaneous interleukin-2 plus antiretrovirals versus antiretrovirals alone in HIV-infected patients with CD4+ cell counts >/=350/mm^3. J Infect Dis 2000;181:1614-21.
10. Ruxrungtham K, Suwanagool S, Tavel J, et al. A randomized, controlled 24-week study of intermittent subcutaneous interleukin-2 in HIV-1 infected patients in Thailand. AIDS 2000;14:2509-13.
11. Kovacs J, Vogel S, Albert J, et al. Controlled trial of interleukin-2 infusions in patients infected with the HIV. N Engl J Med 1996;335:1350-6.
12. Kovacs J, Imamichi H, Vogel S, et al. Effects of intermittent interleukin-2 therapy on plasma and tissue human immunodeficiency virus levels and quasi-species expression. J Infect Dis 2000;182:1063-9.
13. Youle M, Fischer M, Nelson M. Randomised study of intermittent subcutaneous interleukin-2 therapy without antiretrovirals versus no treatment. XIII International AIDS Conference. Durban 2000 [abstract].
14. Levy Y, Capitant C, Houhou S, et al. Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: a randomised controlled trial. ANRS 048 study group. Lancet 1999;353:1923-9.
15. Witzke O, Winterhagen T, Reinhardt W, et al. Comparison between subcutaneous and intravenous interleukin-2 treatment in HIV disease. J Intern Med 1998;244:235-40.
16. Hengge U, Goos M, Esser S, et al. Randomized, controlled phase II trial of subcutaneous interleukin-2 in combination with HAART in HIV patients. AIDS 1998;12:F225-F234.
17. Simonelli C, Zanussi S, Sandri S, et al. Concomitant therapy with subcutaneous interleukin-2 and zidovudine plus didanosine in patients with early stage HIV infection. J Acquir Immun Defic Syndr 1999;20:20-7.
18. Davey R, Murphy R, Graziano F, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: A randomized controlled trial. JAMA 2000;284:183-9.
19. Abrams D, Bebchuk J, Denning E, et al. Community Programs for Clinical Research on AIDS Randomized, Open-Label Study of the Impact of Two Doses of Subcutaneous Recombinant Interleukin-2 on Viral Burden in Patients With HIV-1 Infection and CD4+ Cell Counts of 300/mm^3: CPCRA 059. J Acq Imm Def Synd 2002;29:221-31.
20. Arduino R, Nannini E, Rodrigues-Barradas M. Meta-analysis of the CD4 cell response to 3 doses of subcutaneous interleukin-2 (scIL-2) across 3 vanguard studies. 8th CROI. Chicago 2001 [abstract].
21. Emery S, Capra W, Cooper D, et al. Pooled analysis of 3 randomized, controlled trials of interleukin-2 therapy in adult HIV type 1 disease. J Infect Dis 2000;182:428-34.
22. Mitsuyasu R. A randomized, controlled phase II study of HAART with intermittent IL-2 by continuous IV or subcutaneous routes in HIV-infected patients with CD4 counts 50-350 cells/mm^3: ACTG 328-results at 60 weeks. 5th International Conference on Drug Therapy in HIV Infection. Glasgow 2000 [abstract].
23. Arno A, Ruiz L, Juan M, Jou A, et al. Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with ≤ CD4 T cells and undetectable plasma virus load. J Infect Dis 1999; 180:56-60.
24. Katlama C, Chouquet C, Autran B, et al. ILSTIM (ANRS 082). 7th CROI.