HIV-infected immunologic non-responders: can we provide a helping hand?

Caryn G. Morse and Joseph A. Kovacs

Laboratory of Immunoregulation. National Institute of Allergy and Infectious Diseases (NIAID). Critical Care Medicine Department. National Institutes of Health (NIH) Clinical Center. Bethesda, MD. United States.

Highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality associated with HIV infection. In most patients receiving HAART, suppression of HIV replication is accompanied by recovery of CD4 T lymphocytes to near normal levels and a substantial reversal of HIV-associated immunologic defects, as is best reflected by the marked decrease in HIV-related opportunistic complications. However, immunologic recovery varies greatly between patients, and a significant proportion of those treated experience only small improvements in CD4 cell counts despite virologic suppression on HAART. These patients, who maintain virologic suppression on HAART but fail to have significant gains in CD4 T-cell counts, are referred to as immunologic non-responders.

Estimates of the frequency of immunologic non-response vary depending on the definition used. Based on a number of cohort studies, 10% to 20% of treated patients fail to have an adequate CD4 count increase (e.g > 100 cells/mm^3 increase over baseline or an increase to > 200-300 cells/mm^3) after 6-12 months of effective HAART[1-7]. Whereas some patients with a poor initial immune response despite virologic suppression will go on to have an immunologic response over time, others will be stalled at a threshold that potentially puts them at increased risk for opportunistic complications. Observational cohort studies suggest that such patients do in fact have a higher rate of new AIDS-defining events or death than complete responders, though these rates are less than is seen in patients who are both immunologic and virologic non-responders[2,6,7].

The pathogenesis of discordant responses is poorly understood. The immunologic response to HAART is influenced by a number of viral, host, and treatment-related factors. Immune recovery depends, in part, on the extent and duration of viral load reduction, although the minimum viral suppression necessary for improved immune function and CD4 recovery is debated. Numerous other factors may influence CD4 T cell and immune recovery, including the degree of immunosuppression at HAART initiation (e.g., baseline CD4 count), duration of infection, baseline viral load, history of opportunistic infection, co-morbidities, and age. Potential mechanisms underlying the low-level regeneration of CD4 cells in immune non-responders include deficiencies in the regeneration of central memory CD4 cells and excessive apoptosis[8]. Increased CD4 and CD8 T cell activation at baseline has also been correlated with poor immune responses to HAART[9].

In one early observational study, no association was found between a specific antiretroviral regimen and the presence of discordant responses[5]. In recent years, however, a number of reports have described CD4 declines or attenuated gains despite viral suppression in patients receiving a combination of didanosine and tenofovir[10]. While co-administration of these two agents has been shown to increase the ddI serum concentration, thereby increasing the risk of ddI-associated toxicities, the exact mechanisms leading to the CD4 effects are uncertain. The effect is diminished when a lower ddI dose is used[11]. Failure to increase CD4 counts may also be associated with additive myelotoxicity of antiretroviral drugs and therapies being administered for the prevention or treatment of opportunistic infection, as, for example, the additive myelosuppression of zidovudine (AZT) and trimethoprim/sulfamethoxazole (TMP/SMX).

It has been postulated that ongoing, low-level viral replication, occurring below the limits of assay detection, may contribute to slowed CD4 T-cell recovery. Consequently, one approach has been to change or intensify antiretroviral regimens in an effort to more fully suppress viral replication and allow immune recovery, though available data do not support this practice.

Alternative strategies aimed at improving the HIV-induced immunodeficiency utilize immune-based therapies. Potential approaches that have been studied over the years include therapy with cytokines such as interleukin-2 (IL-2), IL-12, IL-7, interpheron alpha, interpheron gamma and GM-CSF, as well as cell-transfer approaches using unmodified or genetically modified CD4 or CD8 cells. Immunosuppressive medications aiming to reduce high level immune activation thought to underlie CD4 cell turnover and death have also been studied, including cyclosporine A, anti-TNF monoclonal antibodies (etanercept), and mycophenolate mofetil.

The best-studied and most promising immunotherapy agent for HIV infection that has been investigated to date is IL-2. IL-2 is a cytokine produced by T lymphocytes that is known to promote proliferation and modulate the secretory capacity of lymphocytes, including T, B, and natural killer cells. Numerous randomized trials have demonstrated that intermittent subcutaneous or intravenous administration of cycles of IL-2, in combination with anti-

Potential conflict of interest: The US Government has been granted a use patent for intermittent IL-2 therapy, including J.A. Kovacs as an inventor.

Correspondence: Dr. C.G. Morse.
National Institutes of Health (NIH).
10 Center Drive, MSC 1576.
Bethesda, MD 20892-1576. USA.
E-mail: cmorse@niaid.nih.gov

Manuscript received on October 8, 2007; accepted on October 10, 2007.

retroviral medications, can lead to significant, sustained increases in CD4 T cell number and percentage above that seen with antiretroviral medications alone, without increases in CD8 cell number or plasma viral load[12-15]. The IL-2 induced CD4 count increases result predominantly from peripheral T-cell expansion, as a result of an initial IL-2 induced proliferation of both CD4 and CD8 cells, followed by time/cycle-dependent increased survival of CD4 cells preferentially to CD8 cells[16]. The expanded CD4 cells have a naïve or central memory phenotype and are CD25 (high affinity IL-2 receptor) positive and express FoxP3[16-18]. While the expanded cells have some phenotypic characteristics of CD4 regulatory cells, functional studies do not support this categorization[17].

A small number of trials of IL-2 have focused specifically on immunologic non-responders, who had CD4 T cell counts below 200 cells/mm^3 in the setting of a virologic response[19-22]. In three randomized controlled trials of IL-2 in immunologic non-responders, significant and sustained CD4 cell count gains were consistently achieved in the majority of patients[19-21]. While the CD4 count increases in these cohorts were modest compared to patients initiating IL-2 with higher baseline CD4 counts, in all studies the median CD4 count following IL-2 therapy increased to > 200 cells/mm^3.

In this issue of EIMC, Crespo et al[23] report on a cohort of HIV-infected patients receiving combination antiretroviral therapy without a significant increase in CD4 count despite viral suppression below the limit of detection. In this study, patients with CD4 T cell counts below 200 who had received HAART for a median of nearly 5 years but showed no significant CD4 count increase for at least 12 months despite viral suppression to < 50 copies/mL, received low-dose, intermittent IL-2, consisting of IL-2 cycles (4.5 mIU once a day subcutaneously for 5 consecutive days) every 4 weeks with a planned goal of 6 cycles. The dose and schedule was selected to minimize IL-2 related side effects while optimizing the probability of lasting CD4 gains. While the IL-2 regimen was well tolerated with only mild side effects, such as low-grade fever and mild constitutional symptoms, reported by most patients, four patients did not complete the planned 6 cycles of IL-2 due to toxicity or patient choice. Overall, CD4 cell counts increased by a median of nearly 50 cells, with 8 of 18 participants experiencing a rise in CD4 count to over 200 cells/mm^3. A differential effect was seen however, with 5/18 (27%) participants experiencing < 25% increase in CD4 from baseline. While this was not a randomized trial, the lack of CD4 count increases for a year prior to IL-2 therapy, and the absence of other interventions clearly support that this is an IL-2 effect.

Taken together, these studies suggest that intermittent IL-2 therapy in immunologic non-responders results in beneficial immunologic responses. However, the clinical benefit of IL-2-associated CD4 count increases has not been established to date in any HIV-infected cohort. Given the cost of the drug as well as the substantial adverse effects associated with IL-2 therapy, such as flu-like symptoms that while transient can be debilitating, it is critical to establish if IL-2-related CD4 gains translate into a reduction in HIV-related clinical events. Two large, randomized trials of intermittent IL-2 therapy powered to detect differences in clinical outcomes, are currently ongoing and will hopefully provide a definitive answer to the clinical benefits of this therapy in the next one to two years. The Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) and the Phase III Multicenter Randomized Study of the Biological and Clinical Efficacy of Subcutaneous Recombinant, Human IL-2 in HIV-Infected Patients with Low CD4 Counts Under Active Antiretroviral Therapy (SILCAAT), which have enrolled ~4,100 and ~2,000 patients, respectively, are similar in design but differ in the target population, with ESPRIT enrolling patients with CD4 counts $\geq$ 300 cells/mm^3, and SILCAAT enrolling those with CD4 counts of 50 to 299 cells/mm^3. The completion of these trials is crucial to understanding what role IL-2 may play in the management of the immunodeficiency of HIV infection in immunologic non-responders as well as other HIV-infected patients. While clinical end points remain under investigation, smaller phase II trials aimed at better elucidating the mechanisms and benefits of IL-2 are ongoing and hopefully will lay the groundwork for optimally utilizing IL-2 in the future, assuming clinical benefit is demonstrated. Until that time, though, patients should receive IL-2 only as part of such ongoing clinical trials.

Acknowledgement

This work was supported by the Intramural Research Programs of the National Institute of Allergy and Infectious Diseases (NIAID) and NIH Clinical Center, NIH (US).

References

1. Dronda F, Moreno S, Moreno A, Casado JL, Pérez-Elías MJ, Antela A. Long-term outcomes among antiretroviral-naive human immunodeficiency virus-infected patients with small increases in CD4+ cell counts after successful virologic suppression. Clin Infect Dis. 2002;35:1005-9.
2. Grabar S, Le Moing V, Goujard C, Lepot C, Kazatchkine MD, Costagliola D, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med. 2000;133:401-10.
3. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med. 2003;163:2187-95.
4. Marimoutou C, Chene G, Mercie P, Neau D, Farbos S, Morlat P, et al. Prognostic factors of combined viral load and CD4+ cell count responses under triple antiretroviral therapy, Aquitaine cohort, 1996-1998. J Acquir Immune Defic Syndr. 2001;27:161-7.
5. Moore DM, Hogg RS, Yip B, Wood E, Tyndall M, Braitstein P, et al. Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. J Acquir Immune Defic Syndr. 2005;40:288-93.
6. Nicastri E, Chiesi A, Angeletti C, Sarmati L, Palmisano L, Geraci A, et al. Clinical outcome after 4 years follow-up of HIV-seropositive subjects with incomplete virologic or immunologic response to HAART. J Med Virol. 2005; 76:153-60.
7. Piketty C, Weiss L, Thomas F, Mohamed AS, Belec L, Kazatchkine MD. Long-term clinical outcome of human immunodeficiency virus-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. J Infect Dis. 2001;183:1328-35.
8. Benveniste O, Flahault A, Rollot F, Elbim C, Estaquier J, Pédron B, et al. Mechanisms involved in the low-level regeneration of CD4+ cells in HIV-1-infected patients receiving highly active antiretroviral therapy who have prolonged undetectable plasma viral loads. J Infect Dis. 2005;191:1670-9.
9. Goicoechea M, Smith DM, Liu L, May S, Tenorio AR, Ignacio CC, et al. Determinants of CD4+ T cell recovery during suppressive antiretroviral therapy: association of immune activation, T cell maturation markers, and cellular HIV-1 DNA. J Infect Dis. 2006;194:29-37.
10. Negredo E, Molto J, Burger D, Viciana P, Ribera E, Paredes R, et al. Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load. AIDS. 2004;18:459-63.

11. Karrer U, Ledergerber B, Furrer H, Elzi L, Battegay M, Cavassini M, et al. Dose-dependent influence of didanosine on immune recovery in HIV-infected patients treated with tenofovir. AIDS. 2005;19:1987-94.
12. Davey RT Jr, Murphy RL, Graziano FM, Boswell SL, Pavia AT, Cancio M, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: A randomized controlled trial. JAMA. 2000;284(:183-9.
13. Kovacs JA, Vogel S, Albert JM, Falloon J, Davey RT Jr, Walker RE, et al. Controlled trial of interleukin-2 infusions in patients infected with the human immunodeficiency virus. N Engl J Med. 1996;335:1350-6.
14. Levy Y, Durier C, Krzysiek R, Rabian C, Capitant C, Lascaux AS, et al. Effects of interleukin-2 therapy combined with highly active antiretroviral therapy on immune restoration in HIV-1 infection: a randomized controlled trial. AIDS. 2003;17:343-51.
15. Abrams DI, Bebchuk JD, Denning ET, Davey RT, Fox L, Lane HC, et al. 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 Acquir Immune Defic Syndr. 2002;29:221-31.
16. Kovacs JA, Lempicki RA, Sidorov IA, Adelsberger JW, Sereti I, Sachau W, et al. Induction of prolonged survival of CD4+ T lymphocytes by intermittent IL-2 therapy in HIV-infected patients. J Clin Invest. 2005;115:2139-48.
17. Sereti I, Imamichi H, Natarajan V, Imamichi T, Ramchandani MS, Badralmaa Y, et al. In vivo expansion of CD4CD45RO-CD25 T cells expressing foxP3 in IL-2-treated HIV-infected patients. J Clin Invest. 2005;115:1839-47.
18. Sereti I, Martínez-Wilson H, Metcalf JA, Baseler MW, Hallahan CW, Hahn B, et al. Long-term effects of intermittent interleukin-2 therapy in patients with HIV infection: characterization of a novel subset of CD4(+)/CD25(+) T cells. Blood 2002;100:2159-67.
19. Arno A, Ruiz L, Juan M, Jou A, Balagué M, Zayat MK, et al. Efficacy of low-dose subcutaneous interleukin-2 to treat advanced human immunodeficiency virus type 1 in persons with ≤ 250/μL CD4 T cells and undetectable plasma virus load. J Infect Dis. 1999;180:56-60.
20. Katlama C, Carcelain G, Duvivier C, Chouquet C, Tubiana R, De Sa M, et al. Interleukin-2 accelerates CD4 cell reconstitution in HIV-infected patients with severe immunosuppression despite highly active antiretroviral therapy: the ILSTIM study–ANRS 082. AIDS. 2002;16:2027-34.
21. Marchetti G, Meroni L, Varchetta S, Terzieva V, Bandera A, Manganaro D, et al. Low-dose prolonged intermittent interleukin-2 adjuvant therapy: results of a randomized trial among human immunodeficiency virus-positive patients with advanced immune impairment. J Infect Dis. 2002;186: 606-16.
22. David D, Nait-Ighil L, Dupont B, Maral J, Gachot B, Theze J. Rapid effect of interleukin-2 therapy in human immunodeficiency virus-infected patients whose CD4 cell counts increase only slightly in response to combined antiretroviral treatment. J Infect Dis. 2001;183:730-5.
23. Crespo M, Caragol I, Falcó V, Ribera E, Urban S, Pahissa A. Efficacy of Recombinant Interleukin-2 (rIL-2) in Patients with Advanced HIV-1 Infection and Blunted Immune Response to HAART. Enferm Infecc Microbiol Clin. 2008;26:27-31.