Perspective

Approaches to Immune Reconstitution in HIV Infection

Ongoing studies to identify antigen-nonspecific strategies for enhancing immune reconstitution in individuals with HIV infection include those focusing on the use of interleukin (IL)-2, human growth hormone, and IL-7. IL-2 has been shown to induce substantial CD4+ T-cell increases in HIV-infected patients receiving potent antiretroviral therapy. Although those with CD4+ cell counts greater than 300/μL have shown the greatest gain in CD4+ cells, IL-2 has also increased CD4+ cells in those with initial CD4+ cell counts of less than 200/μL. Ongoing phase 3 trials are evaluating whether these increases in CD4+ cell count are associated with improved clinical outcomes. A small study of human growth hormone suggests that the hormone can reverse thymic involution and improve thymic T-cell production in HIV-infected individuals. Larger studies are ongoing. IL-7 affects T-cell production and function at several stages of T-cell development. Animal studies indicate that administration of IL-7 is associated with marked increases in CD4+ cell counts, and human trials may be possible within the next 2 to 3 years. The mechanism of CD4+ cell increases—eg, expansion of peripheral cells versus enhanced de novo production in the thymus—may affect the potential immunologic and clinical benefit derived from these increases. Additional study is necessary to refine approaches to enhancing immune reconstitution in HIV infection. This article summarizes a presentation made by Laura A. Napolitano, MD, at the May 2003 International AIDS Society–USA course in San Francisco.

Overview

CD4 + T-cell decline in HIV infection can occur as the result of direct or indirect destruction of CD4 + T cells in the peripheral immune system. In addition, infection and destruction of developing CD4 + progenitor cells within the thymus gland may cause reduced synthesis of new CD4 + T cells. Given the normal biologic process of thymic involution, which results in greatly reduced de novo production of T cells in adult life, there is thus high potential for impaired new T-cell production in individuals with HIV infection. With the availability of potent antiretroviral therapy capable of limiting HIV replication, increased attention has been given to strategies for enhancing T-cell production to preserve or restore immune function in HIV-infected patients. Potential pharmacologic strategies include the use of interleukin (IL)-2, human growth hormone, or IL-7.

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Interleukin-2

IL-2 is a central regulator of T-cell function that is produced by activated T cells. This cytokine induces proliferation of T lymphocytes (CD4 + cells more than CD8 + cells), promotes maturation and cytotoxicity of CD8 + T cells, stimulates the immune response to eliminate viruses and intracellular organisms (the T_H1 response), regulates the intensity of the immune response (eg, influences the number of activated cells and their removal through apoptosis), and potentiates the function of antigen-presenting cells (that stimulate function of T cells), natural killer cells, and B cells.

IL-2 treatment in HIV infection has been evaluated in a large number of studies over the past 2 decades. Experience with IL-2 treatment in HIV-infected patients can be summarized as follows. In the pre-potent antiretroviral era, IL-2 treatment was predominantly assessed in patients receiving single or dual nucleoside reverse transcriptase inhibitor antiretroviral therapy. Its use was associated with consistent improvement in CD4 + counts, with increases of approximately 200 to 500 cells/μL compared with controls being observed. No CD4 + cell count increases in patients beginning IL-2 treatment with CD4 + cell counts less than 200/μL were observed. Increases in plasma HIV-1 RNA levels and worsening of clinical status were also observed in some patients beginning treatment at CD4 + cell counts less than 200/μL. In more recent studies, IL-2 administration along with initiation of potent antiretroviral therapy has been found to augment CD4 + cell count response by approximately 100 to 600/μL compared with antiretroviral therapy alone. When given together with potent antiretroviral therapy, CD4 + count increases are also observed in those patients with initial counts less than 200 cells/μL. In general, IL-2 does not appear to have a major effect on HIV-1 RNA levels in those taking potent antiretroviral therapy. However, transient increases in plasma HIV-1 RNA level have been observed during IL-2 treatment in some studies, and small declines in plasma HIV-1 RNA level (< 1 log copies/mL) have also been reported.

Overall, IL-2 treatment results in large, sustained increases in CD4 + cell counts. The gains in the CD4 + cell count consist predominantly of increases in naive CD4 + cells (those not yet exposed to their antigen) versus memory cells (those so exposed). The expansion of the naive CD4 + cell pool appears to be attributable primarily to the proliferation and increased survival of existing naive cells in the peripheral circulation and lymph nodes. In most studies, IL-2 does not appear to stimulate the generation of new naive cells by the thymus, although the data are mixed. Currently, there are insufficient data to indicate whether the CD4 + cell count increases seen with IL-2 treatment actually improve immunity against recall antigens or HIV, include the generation of T cells that have normal function, or improve clinical outcomes. Use of IL-2 is approved in Europe for treatment for patients with persistently low CD4 + cell counts despite virologic suppression under

antiretroviral therapy, but IL-2 is not currently approved by the Food and Drug Administration for use in HIV disease in the United States. Important data on the potential clinical benefits of IL-2 treatment are expected from 2 ongoing phase 3 studies: the ESPRIT study in patients with initial CD4+ cell counts of 300/μL or higher and the SILCAAT study in patients with initial CD4+ cell counts of 50 to 299/μL

During initial studies in the 1980s, IL-2 was administered by continuous intravenous infusion at a dose of 18 million international units (MIU) per day for 5 days every 8 weeks. Administration in this form was associated with frequent moderately severe toxicities, including severe flu-like syndrome, fever, bone marrow toxicity, hypotension, phlebitis, gastrointestinal toxicity, renal insufficiency, and dermatologic reactions. Subsequently, subcutaneous administration of IL-2 was found to result in reduced (but still considerable) toxicity. Dosing of IL-2 in trials generally now consists of subcutaneous administration of 9 to 15 MIU per day (4.5 or 7.5 MIU twice daily) for 5 days every 4 to 8 weeks. In some cases, when IL-2 therapy leads to a prolonged increase in the CD4+ cell count, the dosing interval can be extended to 12 months or longer. IL-2 doses of less than 6 MIU per day appear to be less effective at increasing CD4+ cell counts. Because side effects of IL-2 are much decreased at these lower doses, some studies are still investigating the potential benefits of long-term, low-dose IL-2 therapy.

Human Growth Hormone

Human growth hormone (GH), which is produced in the anterior pituitary gland, acts directly or via insulin-like growth factor-1 (IGF-1) to regulate metabolism and tissue growth. Demonstrated effects of GH and IGF-1 include increases in lean body mass, lipolysis, and protein synthesis. GH also has important effects on the immune system. GH deficiency is associated with thymic hypoplasia in rodents (but not in humans), and animal studies have shown that GH and IGF-1 treatment in aging rodents reverses thymic atrophy and enhances T-cell production. Further, both factors have been shown to augment immune reconstitution in immunodeficient rodents.

Based on these findings in animal studies, Napolitano and colleagues performed a small study in HIV-infected adults to determine if GH treatment might enhance T-cell production. Five HIV-infected male patients participating in a study of GH treatment for HIV-related fat accumulation were assessed for changes in the thymus and in thymopoiesis at 3-month intervals during treatment with doses of 1.5 to 3.0 mg of GH per day for 6 to 12 months. A group of 7 HIV-infected persons participating in observational studies who had similar characteristics as the group receiving growth factor were also studied for comparative purposes. The 5 GH-treated patients had a mean age of 52 years, baseline (pre-GH treatment) plasma HIV-1 RNA level ranging from less than 50 to 5700 copies/mL, and baseline CD4+ counts ranging from 254 to 853 cells/μL; 4 of the 5 were on protease

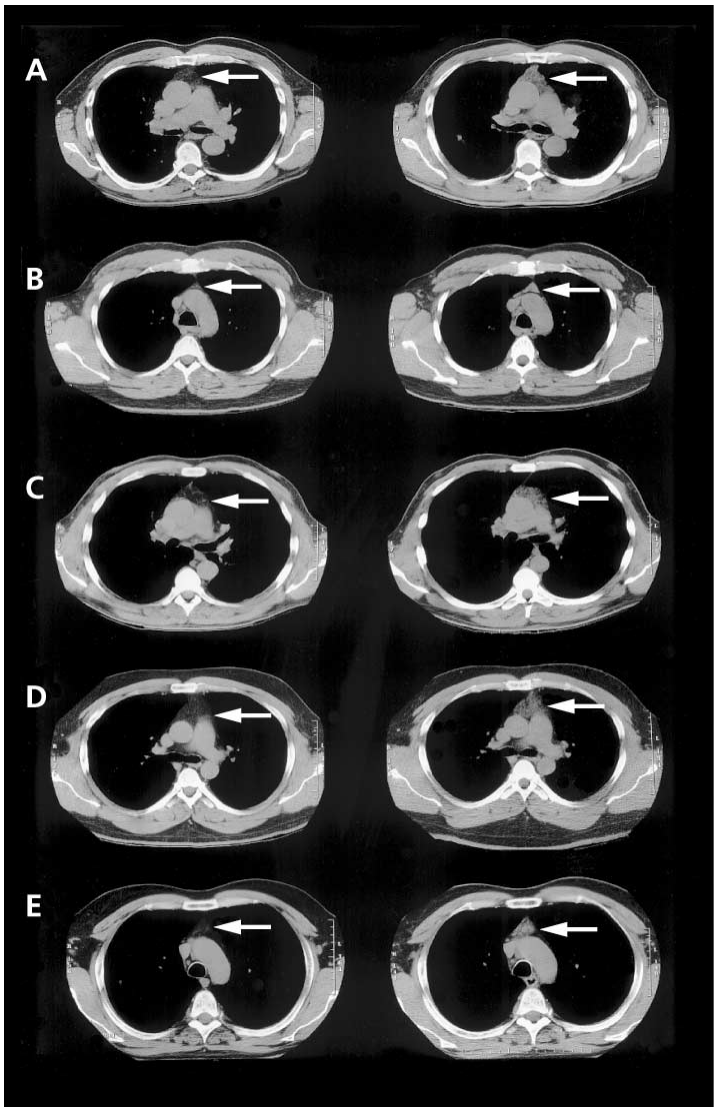

Figure **1.** Reversal of thymic atrophy by growth hormone. Thymus computed tomography scans were performed at baseline and 6 months after initiation of growth hormone (GH) therapy in 5 GH recipients (A-E). Prior to GH treatment, the thymus (left column, indicated by an arrow) was seen as relatively low attenuation tissue, nearly black in color, consistent with fat density. After GH treatment (right column) the density of the anterior mediastinum markedly increased. The formerly black, fat-density tissue was replaced by higher attenuation tissue consistent with cellular thymus. Adapted with permission from Napolitano et al, *AIDS,* 2002.

inhibitor-containing triple-drug therapy and 1 was receiving dual nucleoside reverse transcriptase inhibitor therapy. All 5 patients who received GH exhibited reversal of thymic atrophy during GH treatment, with computed tomography images that were consistent with regeneration of thymic tissue to produce a thymus resembling that typically found in adolescence (Figure 1). In the GH-treated group, thymic density and volume were both increased. Along with the reversal of thymic atrophy, a significant increase in circulating naive CD4+ T-cell percentage was observed in treated patients (Figure 2). Re-involution of the thymus was observed in 2 patients who underwent repeat computed tomography imaging after stopping GH therapy, but increases in naive CD4+ cell percentage persisted. During treatment, no significant changes in total CD4+ cells, total CD8+ cells, memory T-cell subsets, natural killer cells, or B cells were observed. Increases in CD4+ cell count were observed in some patients after discontinuation of GH, but no conclusions regarding such increases could be made in the absence of a true randomized control group. The specific targets of GH in the human immune system are not well understood; however, it appears likely that GH enhances T-cell production by stimulating bone marrow progenitors and facilitating their engraftment in the thymus. Overall, the findings in this small study suggest that GH treatment may enhance thymic function and suggest that de novo CD4+ cell production may be inducible in some HIV-infected individuals. GH treatment is associated with significant toxicities, including arthralgias, myalgias, edema, diabetes, and carpal tunnel syndrome. Additional studies of GH in the setting of immune reconstitution in HIV infection are under way, including a single-center study at the Gladstone Institute of Virology and Immunology at the University of California San Francisco and a multicenter study conducted by the AIDS Clinical Trials Group.

Interleukin-7

IL-7, which is produced by stromal cells of the thymus, bone marrow, and lymph nodes, is an essential regulator of lymphopoiesis that acts on both T cells and B-cell progenitors. The importance of IL-7 on T-cell production has been demonstrated in rodent models such as the IL-7-receptor knockout mouse, which exhibits massive reductions in thymus, spleen, and lymph node cellularity, with thymocyte levels approximately 1% of those seen in normal mice. IL-7 has effects on T-cell production at many stages of development in the bone marrow, thymus, and periphery: it stimulates expansion and export of progenitor cells from the bone marrow, inhibits apoptosis and enhances proliferation of developing thymocytes, and stimulates proliferation and enhances cytotoxicity of mature T cells. It is also believed to play an important role in T-cell homeostasis, with it being proposed that increased levels of IL-7 are part of a homeostatic response designed to increase T-cell production. Supporting lines of evidence include the findings that circulating IL-7 levels are increased in lymphopenia and that cellular production of IL-7 is increased in lymphocyte-depleted lymph nodes. The potent effects of IL-7 on T-cell development and homeostasis have made it an attractive therapeutic candidate to increase T-cell production during immunodeficiency.

IL-7 has been shown to promote T-cell production in several animal models of immunodeficiency. Murine studies demonstrate that IL-7 enhances immune reconstitution after myeloablation or T-cell depletion. In primate studies in simian immunodeficiency virus-infected or -uninfected cynomolgus monkeys and baboons undergoing bone marrow transplantation, IL-7 administration has resulted in marked increases in circulating CD4+ T cells, splenomegaly, and lymphadenopathy. The primate studies suggest that IL-7 induces expansion of existing T cells but that it does not appear to stimulate new T-cell production by the thymus. Additional animal studies are ongoing.

IL-7 therapy has not yet been administered to humans, although human trials of IL-7 may be possible within the next 2 to 3 years. Because laboratory studies have shown that IL-7 can enhance HIV replication, the use of IL-7 in HIV disease will need to be pursued with caution.

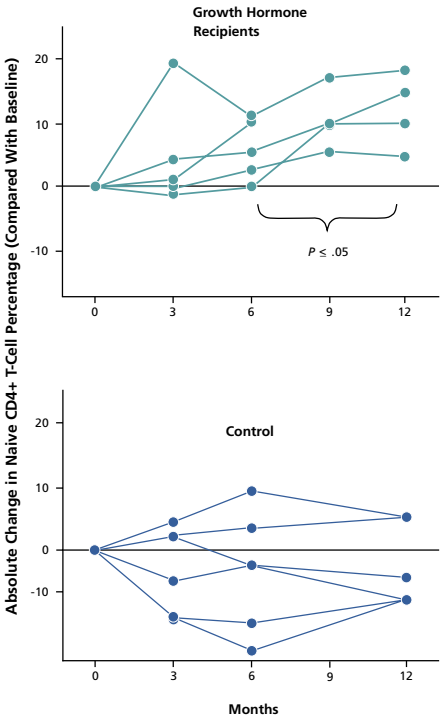

Figure **2.** Absolute change in naive CD4+ T-cell percentage in patients receiving human growth hormone and those not receiving growth hormone (control). Adapted with permission from Napolitano et al, *AIDS,* 2002.

Immune-based Therapies: Further Considerations

Exploration of immune-based therapies for the treatment of immunodeficiency is growing, but there is still much to be learned about the specific effects of these therapies on the recovery of the immune system. Laboratory and animal studies suggest that several potential therapies are capable of increasing de novo T-cell production by the thymus or expanding the numbers of existing T cells. Whereas IL-2 appears to predominantly act by increasing mature CD4+ T-cell populations, GH may act by stimulating new T-cell production by the thymus, and IL-7 may stimulate both de novo T-cell production and mature T-cell expansion. It is possible that the mechanism of T-cell increases may matter to efforts to promote immune system reconstitution in HIV-infected individuals. The normal T-cell repertoire consists of approximately 1 x 10^8 unique T-cell receptors. With HIV-related T-cell deple-

tion, much of this diversity can be lost (Figure 3). Expansion of existing T cells in the periphery increases the number of mature cells with existing antigen specificities, whereas de novo T-cell production by the thymus can replace elements in the T-cell receptor repertoire that are lost during HIV infection. It remains unclear, however, what the clinical consequences of differences in site and mechanism of T-cell increases might be. Ongoing studies will help to answer these and related questions and contribute to refining efforts to enhance immunologic reconstitution in HIV-infected persons.

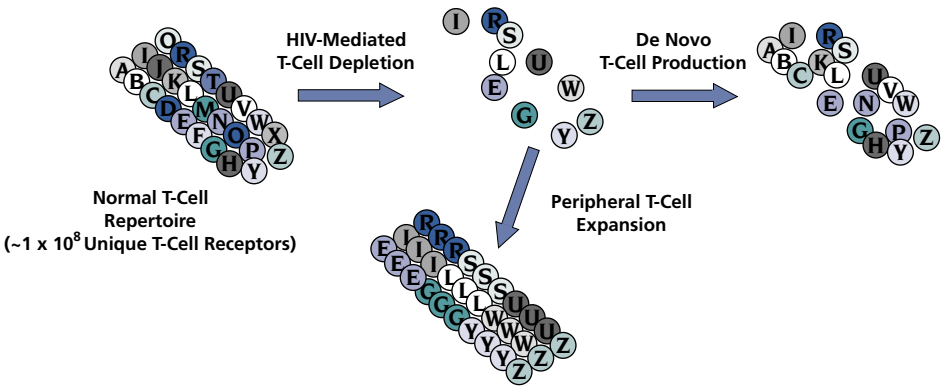

Figure **3.** The source of T-cell increase affects T-cell diversity and antigen recognition. Losses in T-cell receptor repertoire due to HIV infection are not replaced by expansion of peripheral mature CD4+ T cells but can be replaced via de novo synthesis of T cells in the thymus. Figure courtesy of Dr Laura Napolitano.

Conclusion

Several regulators of T-cell production and function, including IL-2, GH, and IL-7, are being considered as potential immune-based therapies during HIV infection. IL-2 induces significant gains in CD4+ T cells in most HIV-infected patients in numerous studies. In preliminary studies, GH appears to reverse thymic involution and enhance T-cell production in some HIV-infected adults. IL-7, not yet studied in humans, appears to play an important role in T-cell production and homeostasis and may have future potential for the treatment of lymphopenic conditions.

These immune-based therapies offer several theoretical advantages in the management of HIV disease, such as improved immune restoration (increased CD4+ T-cell gains with effective antiretroviral therapy); improved immune preservation (delayed CD4+ T-cell decline); improved immune response against HIV or other antigens; improved breadth of the T-cell repertoire; enhanced response to vaccination; and decreased opportunistic infection. However, these therapies also carry significant toxicities, and it remains to be determined whether these agents will offer any advantages beyond those provided by effective antiretroviral therapy alone. Additional clinical and immunologic investigations are ongoing to determine whether immune-based therapies provide clinical benefits to individuals infected with HIV.

Presented by Dr Napolitano in May 2003. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Napolitano in September 2003.

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Suggested Reading

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