Interleukin-2 (IL-2) is a naturally-occurring immune system signaling molecule that promotes lymphocyte generation. Intravenous recombinant IL-2, called aldesleukin, has FDA approval for use in patients with metastatic renal cell carcinoma and metastatic melanoma. Aldesleukin also is being investigated as a treatment for hematologic malignancies, chronic viral infections such as hepatitis C and HIV, and graft-versus-host disease following bone marrow transplantation.

In patients infected with human immunodeficiency virus (HIV), there is a reduced endogenous production of IL-2 and a defect in lymphocyte IL-2 receptor expression, responsible in part for the characteristic reduction in CD4+ cell counts. While some patients may experience a sustained control of HIV viral load with antiviral therapy, the CD4+ cell counts do not recover. This situation may be referred to as “immunologic non-response.” Therefore, exogenous IL-2, in conjunction with antiretroviral therapy, has been investigated as a technique to increase CD4+ cell counts, preserve immune function, and, it is hoped, decrease the incidence of opportunistic infections. In addition, it has been proposed that IL-2 in conjunction with combination antiretroviral therapy may be a useful approach for purging HIV from the latently infected CD4+ cells.

Interleukin-2 therapy as a treatment of HIV is considered investigational.
Rationale

In HIV-infected patients, the critical outcome of IL-2 therapy is a documented reduction of HIV-associated opportunistic infections, HIV-associated malignancies, and/or improved survival. Although there are data to show that the use of IL-2 is associated with an increase in CD4 counts, there are inadequate data to confirm that this results in the outcomes defined above. As an example of the reported literature, in 1996 Kovacs and colleagues published the results of a controlled trial, which randomized 60 HIV-infected patients to receive either IL-2 plus antiviral therapy or antiviral therapy alone. (1) IL-2 was administered every 2 months for 6 cycles of 5 days each, starting at a dosage of 18 million IU per day. In patients treated with IL-2, there was a significant increase in the CD4 count compared to a decrease in the CD4 count in the control group. There were no significant differences between and within groups of serial measurements of viral load. No clinical outcomes were included in this study.

The Kovacs study required hospitalization for intravenous IL-2 administration; significant toxicities were reported. Therefore, research has also focused on different dose schedules, including subcutaneous administration to decrease the toxicity and permit outpatient therapy. For example, in 2000, Davey and colleagues reported on a study that included 82 HIV+ patients with baseline CD4 counts of 200-500/mm-3 with a baseline viral load of less than 10,000 copies/mL. (2) The patients were randomly assigned to receive a combination of subcutaneous IL-2 in combination with antiviral therapy or antiviral therapy alone. The IL-2 protocol included 5-day courses every 8 weeks at a starting dosage of 7.5m IU twice a day, a regimen that has now been used in multiple trials. The main outcome measures included CD4 counts, CD4 cell percentages, and HIV viral loads. Intermittent therapy with IL2 and antiretroviral therapy produced a substantially greater increase in CD4 cells. A variety of other studies focusing on patients with different CD4 levels using different dosages and schedules of IL-2 have also reported that the use of IL-2 is associated with an increase in CD4 cell counts. (3-10)

Trials with clinical endpoints will be necessary to determine whether improvements in these intermediate outcomes will translate into improved clinical outcomes. Two large-scale randomized trials looking at final health outcomes are currently underway. The ongoing ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) is a randomized international 5-year 4,000-person study of IL-2 in HIV+ patients with early asymptomatic disease. (11) The goal of the study is to evaluate and compare the effectiveness of subcutaneous IL-2 therapy in conjunction with antiretroviral therapy compared to antiretroviral therapy alone. Patient selection criteria include an absolute CD4 cell count ≤ to 300/mm-3, without evidence of active clinical disease for at least 1 year. All patients must be receiving combination antiretroviral therapy at the time of randomization. After an initial 3 cycles of IL-2, given for 5 consecutive days every 8 weeks, additional cycles are given at the discretion of the treating physician, based on the patient's CD4 counts. The primary endpoint is new or recurrent disease progression. The SILCAAT trial, initiated in 1999, is an international study of 1,400 HIV+ patients with CD4 counts between 50 and 299 cells/mm-3 and a viral load of less than 10,000 copies/ml who will be randomized to receive antiretroviral therapy with and without additional IL-2. Therefore, in contrast with the ESPRIT study, the SILCAAT study focuses on HIV+ patients with lower CD4 counts. The primary endpoint is time to the first AIDS-defining
event. In 2002, the study was withdrawn when it was unable to achieve its primary endpoint: time to first AIDS-defining event or death.

Other Information

There is currently no Medicare policy regarding the use of IL-2 for treatment of HIV infection.

2005-2007 Update

A literature search was performed using MEDLINE for the period of 2004 through July 2007. While studies continue to show that use of IL-2 can increase CD4 counts, the clinical impact of this change is still unknown. Thus, the policy statement is unchanged. Results from the Phase III randomized trials noted above have not been published. Results from the AIDS Clinical Trials Group 328 Study reported on effects of IL-2 in patients with moderately advanced HIV infection who were also receiving highly active antiretroviral therapy (HAART). (12) In this study, 204 patients who were treatment naïve (or had only received reverse transcriptase inhibitors), with CD4 counts from 50 to 350 per microliter, and who were virologic responders, were randomized to receive only continued HAART therapy or the addition of intravenous (IV) or subcutaneous (SC) IL-2. At week 84, median increases in CD4 were 459/microliter, 312/microliter, and 102/microliter in the IV IL-2, SC IL-2, and HAART only groups, respectively. Increases of greater than 50% at week 60 (primary endpoint) were achieved in 39 patients (81%) and 32 (67%) in the IV and SC IL-2 arms, respectively, compared with 13 (29%) in the HAART arm (P <0.001). Treatment with IL-2 did not increase plasma HIV RNA levels. There were fewer new AIDS-defining events in the IV and SC IL-2 groups than in the HAART group: 0, 1, and 7, respectively. Drug-related adverse events were more frequent with IL-2 treatment. The authors comment that whether IL-2 produces long-term clinical benefit will be answered by large, ongoing clinical trials.

2008 Update

Results from induction phase of the ESPRIT study noted above showed a dose related response to treatment with IL-2 and increases in CD-4 counts. However, it is important to note that toxicity was much higher at the higher doses of therapy. (13) To date, final results of the ESPRIT study with final health outcomes have not yet been published in the peer-reviewed literature.

Currently, a new drug BAY 50-4798 is being investigated for the treatment of HIV “immunologic non-response.” BAY 50-4798 is an IL-2 mutein with a 2700-fold greater affinity for the IL-2 receptor. Since it activates fewer natural killer cells, it is thought to have a better tolerability profile. In a phase I/II randomized, placebo-controlled trial, 32% of patients in the BAY 50-4798 treatment arm versus 14% in the placebo arm discontinued the study. (14) Of the withdrawals in the treatment arm, 60% were due to adverse events. At the end of the 6-month study, patients receiving placebo had an 8-cell drop per cubic millimeter of blood, while patients in the highest dose treatment group had an 18-cell per cubic millimeter gain in blood count. Given the uncertain impact of this treatment on clinical outcomes, the policy statement remains unchanged; this treatment is considered investigational.

2009 - 2010 Update

This policy was updated with a search of the MEDLINE database through January 2010. Results from the combined Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected
Patients with Low CD4+ Counts under Active Antiretroviral Therapy (SILCAAT) study and the Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT), noted above, have been published. (15) These randomized, controlled trials were open label because of well-known side effects of interleukin-2 (IL-2) which made blinding impossible. In the SILCAAT study, 1,695 adult HIV-infected patients with CD4+ cell counts of 50 to 299/μl and HIV RNA levels < 10,000 copies/μl were randomly assigned to receive intermittent, subcutaneous IL-2 plus antiretroviral therapy (n =849) or antiretroviral therapy alone (n =846). In ESPRIT, 4,111 adult HIV-infected patients with CD4+ cell counts of at least 300/μl and no evidence of active clinical disease were randomly assigned to receive either intermittent, subcutaneous IL-2 plus antiretroviral therapy (n =2071) or antiretroviral therapy alone (n =2040). The primary endpoint of both studies was new or recurrent opportunistic disease or death from any cause. Secondary end points included the number of patients experiencing grade 4 clinical events, defined as potentially life-threatening events requiring medical intervention, excluding opportunistic diseases.

Over a median follow-up period of 7 years in the SILCAAT study, the CD4+ cell count was on average 53 cells/μl higher in patients receiving IL-2 plus antiretroviral therapy. In ESPRIT, over a median follow-up period of 7.6 years, the CD4+ cell count was on average 159 cells/μl higher in patients receiving IL-2 plus antiretroviral therapy. Neither study showed a reduction in the primary end point with the addition of IL-2 to antiretroviral therapy by intention-to-treat analysis. Hazard ratios for IL-2 plus antiretroviral therapy were 0.91 (95% confidence interval [CI], 0.70 to 1.18; P = 0.47) in the SILCAAT study and 0.94 (95% CI, 0.75 to 1.16; P = 0.55) in ESPRIT. The incidence of grade 4 events did not differ between the 2 study groups in the SILCAAT study (hazard ratio for IL-2 = 1.10, 95% CI, 0.90 to 1.34, P = 0.35) but did differ in ESPRIT (hazard ratio for IL-2 = 1.23, 95% CI, 1.07 to 1.41, P = 0.003). The authors note that this may indicate a possible mechanism for a negative effect of IL-2 on clinical outcome in patients with higher CD4+ cell counts, related to greater pro-inflammatory effects of IL-2 in patients with higher CD4+ cell counts, increased T-regulatory cells, or both.

To investigate the effects of IL-2 when used alone in patients with HIV, Molina and colleagues (16) randomized 130 asymptomatic, HIV+ adults with CD4+ cell counts of 300-500 cells/μl (and therefore ineligible to receive anti-retroviral therapy) to receive either intermittent, subcutaneous IL-2 (n =66) or no treatment (n =64). No attempt to blind study participants was described. Patients were followed for 96 weeks to compare the rate of progression to the primary study end point, defined as a decrease in CD4+ cells to < 300/μl, the initiation of anti-retroviral therapy for any reason, the occurrence of an AIDS-defining event, or death. Fewer patients in the IL-2 group than in the control group reached the primary study end point (23 (35%) vs. 37 (59%), p = 0.008), and time to the primary end point was significantly shorter in the control group (data not shown). However, the Data Safety Monitoring Board halted the study after 4 patients developed lymphoma, 3 patients in the IL-2 group and one patient in the control group. Further, an accompanying editorial by Kuritzkes (17) suggests that delaying the initiation of anti-retroviral therapy may not be beneficial for patients.

Currently, Clinicaltrials.gov lists no additional trials on the use of BAY 50-4789 in HIV+ patients.

Summary
The large randomized SILCAAT and ESPRIT studies indicate that the addition of IL-2 to antiretroviral therapy in HIV-positive patients with high or low CD4+ cell counts does not improve clinical outcomes. Based on studies to date, the medical policy statement remains unchanged, and IL-2 therapy as a treatment of HIV is considered investigational.
References:


13. Fox Z, Davey R, Gazzard B et al. Predictors of CD4 count change over 8 months of follow up in HIV-1-infected patients with CD4 count '> or = 300 cells/microL who were assigned to 7.5 MIU interleukin-2. HIV Medicine 2007; 8(2):112-23.


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<tr>
<td>HCPCS</td>
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