

## **IL2 THERAPY:**

### **LOW DOSE DAILY vs. HIGH DOSE INTERMITTENT REGIMENS**

#### **What is the Difference Between the Two Regimens?**

The main differences between these two treatment regimens are systemic toxicity and the changes effected in the immune system.

Low dose IL2 has been devised to avoid all of the systemic toxicities of IL2. Low dose IL2 therapy (i.e. 2 million Units/day) is ~ 5-10-fold lower than the high dose regimens. The highest, Maximum Tolerable Dose (MTD), i.e. 15 million Units/day, can lead to severe (Grade III) systemic toxicities, including high, persistent fever (~ 103-105 °F), severe muscle aches, fatigue (bed rest >50% of day) and lethargy (sleeping >50% of day)..

#### **The Mechanisms Responsible for IL2 Toxicity**

The side effects of IL2 therapy are due to the release of secondary cytokines by the initial target cells activated by IL2. Therefore, IL2 itself is not directly toxic, and the only cells influenced directly by IL2 are lymphocytes, because only lymphocytes have IL2 receptors (over the past 20 years several other cells have been reported to express IL2Rs, but they have never been corroborated). The secondary cytokines released by IL2-stimulated lymphocytes are tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), and granulocyte-macrophage colony stimulating factor (GM-CSF). Natural Killer (NK) cells release all of these cytokines when stimulated by high concentrations of IL2, but if lower IL2 doses are used, the release of large amounts of secondary cytokines by NK cells can be largely circumvented.

The secondary, pro-inflammatory cytokines released generate inflammation by causing the leakage of plasma and white blood cells from the blood vessels into the tissues. Ultimately, this leads to the classic signs and symptoms of inflammation, which include redness, swelling, tenderness and fever.

#### **What are the Beneficial Effects of the High Dose Regimen?**

The high dose regimen causes a rapid and marked increase in circulating CD4+ T cells. However, the high dose regimen causes an initial drop in all circulating mononuclear cells, including T cells, B cells, NK cells and monocytes, while the therapy is being administered. After the IL2 therapy is discontinued, usually after 5 days, there is a marked rebound of the concentration of all circulating mononuclear cells and most of

these cells increase to a concentration ~ 10-fold higher than present prior to IL2 administration. Thereafter, the concentration of all of these cells gradually and progressively decreases. Coincident with the marked decrease in circulating cell concentrations, there is also a severe loss of plasma, the fluid portion of the blood, from the blood vessels. With the rebound in cells after the therapy is stopped, there is also a return of the plasma back to the circulation and any fluid gained during the treatment interval is gradually mobilized from the tissues and excreted via the kidneys..

Over the course of the next 7 weeks after the discontinuation of the 5-day IL2 therapy, all of the cell concentrations gradually and progressively fall back toward baseline, which is the concentration at time 0, before the administration of IL2. According to the published data (N. Eng. J. Med. 332:567, 1995; 335:1350, 1996; J. Infect. Dis 175:781, 1997), all of the lymphocytes and monocytes, except the CD4+ T cells, return to the baseline concentrations. The CD4+ T cells do not return completely to the baseline count, so that with repeated doses every 8 weeks, there is a gradual and progressive increase in the concentration of circulating CD4+ T cells. Accordingly, for those individuals with low CD4+ T cell concentrations, the benefit of repeated cycles of high dose intermittent IL2 therapy is an acceleration of the return of normal concentrations of circulating CD4+ T cells.

### **What are the Potential Benefits of the Low Dose IL2 Regimen?**

Low dose daily IL2 administration leads to a progressive increase in circulating CD4+ T cells, especially of the naïve subset, and in addition, leads to an increase in NK cells. There is also a reproducible increase in circulating eosinophils. As well, after 24 weeks of daily low dose IL2 therapy, there is a significant improvement in *in vivo* cell-mediated immunity to common environmental antigens and to routine vaccines, as assessed by skin tests compared to baseline (i.e. time=0) tests (Proc. Natl. Acad. Sci. USA 93:10,405, 1996).

Normally, IL2 receptors are expressed only on mature, peripheral T cells that have recently received activating signals via their antigen receptors. Therefore, for the most part, the most responsive T cells are those in the lymph nodes and spleen, and that are circulating in the blood and lymphatics. However, IL2 receptors are also expressed on immature T cells in the thymus, and clinical trials have now shown that new, "naïve" T cells increase in the circulation as a consequence of low dose daily IL2 therapy (HIV Clinical Trials 1:1, 2000).

Perhaps the most dramatic effect of low dose daily IL2 therapy is the increase seen in the concentration of circulating NK cells. All NK cells express IL2 receptors. However, only ~10% of NK cells express the same kind of high affinity IL2 receptors that are expressed by T cells, while ~ 90% of NK cells lack expression of 1 of the 3 receptor chains, so that they do not bind IL2 with the same high affinity as do T cells. The IL2 receptors that are expressed by NK cells are probably really receptors for IL15, which is now thought to be the major cytokine that promotes NK cell maturation.

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Recent experiments in experimental animals have shown that IL2 is crucial for the responsiveness of CD8+ T cells, which are the principle cells responsible for eliminating viral infections and leading to long-lasting immunity. IL2 stimulates the proliferation of CD8+ T cells that are challenged by viral infections, and IL2 also augments the capacity of CD8+ T cells to kill virus-infected cells, and to secrete antiviral cytokines such as IFN- $\gamma$  and TNF- $\alpha$ . Now, our own experiments in HIV+ subjects indicate that when viremia recurs upon supervised treatment interruption, there is a marked increase in circulating CD8+ T cells coincident with a marked decline of plasma HIV concentrations (HIV Clinical Trials 1:16, 2000).

## **Why Use IL2 Therapeutically?**

IL2 is the major survival, growth and differentiation factor for T cells (Science 240:1169, 1988). Only antigen-activated T cells produce IL2, and it targets only lymphocytes, primarily T cells, but it also activates B cells and NK cells. Thus, in contrast to other drugs, IL2 is a natural hormone, normally manufactured by the body when the immune system is activated to respond to invasion by foreign microbes. Accordingly, there are 2 potential indications for the use of IL2 for the treatment of HIV infection.

One indication for IL2 therapy is as a general stimulant of the immune system. Although the new antiviral drugs effectively suppress viral replication, they do not accelerate the recovery of the immune system. Therefore, there is a need for agents to accelerate immune system recovery, and IL2 is really the only cytokine presently available for human use that targets T cells. Since the major pathology of HIV infection is manifest by the loss of CD4+ T cells, it is logical to test IL2 to ascertain whether it can correct the immunodeficiency.

The second potential use for IL2 in the treatment of HIV infection is to boost HIV-specific immunity. It is clear that IL2 functions normally to promote the proliferative expansion of HIV-activated killer lymphocytes, both NK cells and CD8+ killer T cells. If there is even a relative deficiency of the capacity to produce IL2, the magnitude of the expansion of killer cells will be abbreviated, and there will result a paucity of killer T cells that are so important for combating infections by microbes that reside inside cells. Therefore, IL2 is a natural choice for an immune-based therapy (IBT).

## **How Does One Obtain IL2?**

The FDA has not yet approved IL2 for the treatment of HIV infection. Consequently, it is now only available through experimental clinical trials. There are 2 international phase III trials ongoing that are presently open to volunteers. One trial is sponsored by the NIAID, called *Espirit*, is open to individuals with  $> 300$  CD4+ T cells/ $\mu$ L (see [www.espiritstudy.org](http://www.espiritstudy.org)), and the other trial, termed *SILCAAT*, is sponsored by the Chiron Corporation (Emeryville, CA), and is open to individuals with  $< 300$  CD4+ T cells/ $\mu$ L (see [www.silcaat.com](http://www.silcaat.com)). Both of these trials are long-term trials (i.e. several years)

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designed to test whether the high dose (15 million U/day) and intermediate dose (9 million U/day) intermittent IL2 treatment regimens can prolong the time interval to the progression to AIDS-defining illnesses compared with antiviral therapy alone.

At the Weill Medical College of Cornell University and The New York Presbyterian Hospital, a new trial is now open to volunteers, which is designed to test whether low dose daily IL2 therapy with or without vaccination with the canarypox HIV vaccine (ALVAC, vCP1452) can prevent or attenuate viral relapse when antivirals are interrupted (see the "Follow" section, this website for the protocol & consent form). This trial is open to individuals who have CD4+ T cell concentrations  $\geq$  400 cells/ $\mu$ L, and who have plasma HIV concentrations < 50 molecules/mL. This trial requires a minimum 6-month commitment on the part of the volunteer. All individuals are scheduled to undergo a supervised treatment interruption.