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A Risk-Benefit Assessment of Interleukin-2 as an Adjunct to Antiviral Therapy in HIV Infection

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Abstract

Immunomodulation has become a major focus of HIV research in an effort to augment, boost or restore the patient's damaged immune system. Recombinant interleukin-2 is currently being studied in phase II/III trials in HIV-infected patients. Several clinical studies have demonstrated that intermittent regimens are associated with marked rises in CD4+ cell counts without an increase in viral load. Most of these studies employ 5 consecutive days of interleukin-2 therapy by continuous intravenous infusion or subcutaneous injection, repeated every 8 weeks. An alternative strategy is the daily administration of low doses of interleukin-2, but clinical experience with this regimen is limited.

Interleukin-2 administration can adversely affect virtually every organ system, requiring aggressive supportive care. A variety of administration strategies and interventions are being evaluated to minimise toxicity.

Currently, no clinical end-point data are available for interleukin-2 in HIV-infected patients. Until phase III studies are completed, interleukin-2 can be used in the research setting as an immunomodulator and adjunct to antiretroviral therapy. Its potential to activate latently infected cells and promote HIV eradication from reservoir sites is also an important area for further study. If clinical benefit

can be demonstrated, interleukin-2 could be useful as an adjunct to antiretroviral therapy if adverse effects can be minimised and therapy can be given infrequently on an outpatient basis.

Highly active antiretroviral therapy has dramatically changed the management of HIV infection. Combination regimens have sharply reduced the incidence of opportunistic infections and HIV-related mortality.[1] In some cases, these therapies have allowed for the discontinuation of some prophylactic agents. However, the currently available antiretrovirals are associated with numerous problems, including viral resistance, drug-drug interactions and adverse effects, necessitating the need for newer therapies. In addition, it is likely that any effort to eradicate HIV or provide long term virological suppression in the absence of antiretrovirals will require restoration of the immune system through other approaches.

Immunomodulation has become a major research focus in HIV pharmacotherapy. Recombinant interleukin-2 (aldesleukin; Proleukin®, Chiron Corporation) is currently approved by the US Food and Drug Administration for the treatment of metastatic renal cell carcinoma and metastatic melanoma and is under investigation for HIV infection. HIV infection leads to a gradual immunological deterioration manifested by a decline in CD4+ cells and ultimately results in the development of opportunistic infections and other complications. Originally called T cell growth factor, interleukin-2 has numerous effects on the immune system, including the proliferation of CD4+ and CD8+ cells, increased production of interferon-γ and increased activity of natural killer cells.[2,3] HIV-infected patients have a decrease in interleukin-2 production and defects in interleukin-2 receptors.[4] Thus, exogenous administration is being evaluated in a variety of dosages and routes in HIV-infected patients.

Interleukin-2 therapy stimulates the polyclonal expansion of T cells and B cells.[5] Studies examining T cell receptor diversity have shown that interleukin-2 does not restore a damaged T cell repertoire but expands and maintains the available T cell pool.[6] Thus, early intervention with interleukin-2 is more likely to generate a favourable response. As with most immunomodulators, the likelihood of a response improves if treatment is administered in the presence of an intact immune system.

It is difficult to assess the risk-benefit relationship with an investigational agent in which phase III studies have not yet been completed. However, a large body of literature is available for interleukin-2 in the HIV-infected population. This paper describes the adverse effect profile and the immunological benefits of interleukin-2. More importantly, it will attempt to identify those patients who have the greatest likelihood of a response and how to minimise interleukin-2-induced adverse effects.

1. Therapeutic Benefits

The immunological benefits of interleukin-2 have been well documented in several small clinical trials (table I). The antiretroviral regimens varied considerably in these studies. Some trials were performed before the advent of protease inhibitors, whereas others use aggressive highly active antiretroviral therapy regimens. Despite these differences, the randomised studies of interleukin-2 plus antiretrovirals versus antiretrovirals alone clearly demonstrate a significant increase in CD4+ cells in those groups receiving interleukin-2, without a sustained increase in viral load. However, no data are available to date on the clinical end-points of death or progression to AIDS. A meta-analysis of 3 randomised controlled trials demonstrated a trend for improved clinical outcome, with 9 AIDS-defining events in 77 patients receiving interleukin-2 with antiretrovirals versus 16 events in 80 patients receiving antiretrovirals alone.[19] Currently, 2 multinational phase III trials with over 4000 pa-

tients are being planned to demonstrate if interleukin-2 has a significant effect on clinical end-points.

1.1 Continuous Infusion

Interleukin-2 has primarily been studied in HIV-infected patients as a continuous infusion or as a subcutaneous injection administered for 5 consecutive days. Kovacs and colleagues[20] reported a pilot study in HIV-infected patients who received interleukin-2 as a 5-day continuous infusion administered every 8 weeks. Dosages ranged from 6 to 18 MIU/day and were adjusted for toxicity. Patients with CD4+ counts >200 cells/mm^3 demonstrated significant increases in CD4+ cells that were sustained with repeated infusions. However, in 10 out of 12 patients with lower counts (<200 cells/mm^3), poor CD4+ responses were noted and viral load was increased.

These investigators followed this preliminary data with a randomised trial of standard therapy versus standard therapy plus interleukin-2 using the same continuous infusion regimen.[7] Patients with CD4+ counts above 200 cells/mm^3 were enrolled and a double nucleoside antiretroviral regimen was considered the standard of care at the time of the study. At 1 year, patients in the interleukin-2

Table I. Clinical trials of intermittent interleukin-2 in HIV-infected patients

Study	Year	Baseline CD4+ cell count (cells/mm^3) and patient groups	Route, regimen and initial dosage	Follow-up	Change in CD4+ cell count (cells/mm^3)
Studies with continuous intravenous infusion					
Kovacs et al.[7]	1996	CD4+ >200; 30 pts ART + IL-2; 30 pts ART	CIV 6-18 MIU/day × 5 days q8wk	1y	ART + IL-2: +412; ART: –48
Saravolatz et al.[8]	1996	CD4+ 100-300; 81 pts; ART alone or ART + IL-2 for 3, 4 or 5 days	CIV 12 MIU/day q8wk × 1y	1y	3 days: –25%; 4 days: +10%; 5 days +39%; ART –25%
Carr et al.[9]	1998	CD4+ 200-500; 27 pts ART + IL-2; 30 pts ART	CIV 12 MIU/day × 5 days q8wk	1y	IL-2 + ART: +215; ART: –121
Studies with subcutaneous administration					
Davey et al.[10]	1997	18 pts ART	SC 3-15 MIU/day qd or bid × 5 days q8wk	6mo-3y	44% of pts had increase of ≥200
Hengge et al.[11]	1998	CD4+ 200-500	(i) SC 9 MIU/day × 5 days q6wk; (ii) SC 9 MIU/day × 5 days if CD4+ <1.25 × baseline; (iii) ART	1y	IL-2 groups: +100; ART: no change
Levy et al.[12]	1998	CD4+ 250-550	(i) CIV mean 8.8 MIU/day × 5 days q8wk; (ii) SC mean 9.9 MIU/day × 5 days q8wk; (iii) ART	56wk	CIV: +707; SC: +564; ART: +55
Arno et al.[13]	1999	CD4+ <250	SC 3 MIU bid × 5 days q4wk	6mo	IL-2: +105; ART: +30
Wood et al.[14]	1998	CD4+ 200-499; 18 paediatric pts	SC 1 MIU/m^2 or SC 4.5 MIU/m^2 bid × 5 days q8wk	6mo (n = 9)	+75
Davey et al.[15]	1999	53 pts	SC 1.5 or 7.5 MIU/day q4wk or q8wk	6-28mo	Low dosage: +27/mo; high dosage: +116/mo
Davey et al.[16]	1999	CD4+ 200-500; 37pts IL-2 + ART; 41 pts ART	SC 7.5 MIU bid × 5 days q8wk	70% of patients at 1y	IL-2 + ART: +384; ART: +64
Losso et al.[17]	1999	CD4+ >350; 36 pts ART + IL-2; 37 pts ART	SC escalating 1.5, 4.5, 7.5 MIU bid × 5 days q8wk	24wk	Change from baseline above control group: 1.5 MIU +81, 4.5 MIU +354, 7.5 MIU +520
Tambussi et al.[18]	1999	CD4+ 200-500; 60 pts	(i) CIV 12 MIU/day × 5 days q8wk, then SC 7.5 MIU bid × 5 days q8wk; (ii) SC 7.5 MIU/day × 5 days q8wk; (iii) SC 3 MIU/day bid × 5 days q8wk; (iv) ART	1y	Above baseline: (i) 698; (ii) 625; (iii) 726; (iv) 103

ART = antiretroviral therapy; **bid** = twice daily; **CIV** = continuous infusion; **IL-2** = interleukin-2; **MIU** = million international units; **pts** = patients; **qd** = once daily; **qxwk** = every *x* weeks; **SC** = subcutaneously.

group had a significantly higher CD4+ count (+412 cells/mm^3) compared with the control group (–48 cells/mm^3). No differences were noted in viral load, although there was a trend for the interleukin-2 group to have a lower viral burden at the end of the study.

A shorter infusion time was evaluated in a randomised trial. Patients were randomised to receive either a 3-day, 4-day, or 5-day continuous infusion of interleukin-2 plus standard therapy or standard therapy alone.[8] Interleukin-2 therapy was administered every 8 weeks for 6 cycles. As shown in table I, the 5-day infusion period was associated with the largest increase in CD4+ count. No differences in viral load were observed between the groups. Each continuous infusion group received a similar total interleukin-2 dose because of dosage reduction for toxicity. This study suggests that the duration of the infusion is more important than the daily dosage.

1.2 Subcutaneous Injection

The ability to administer interleukin-2 as a subcutaneous injection allows for improved convenience, patient self-administration, outpatient therapy, and potentially fewer infections due to intravenous lines. The pharmacokinetics of subcutaneous interleukin-2 have been evaluated in HIV-infected patients.[10,21] These studies demonstrate that subcutaneous injections can achieve adequate absorption in HIV-infected patients. Furthermore, twice-daily administration of interleukin-2 produces a pharmacokinetic profile that is similar to that of continuous infusion.

Davey and colleagues[15] evaluated low (1.5 MIU twice daily) versus high (7.5 MIU twice daily) dosages of interleukin-2 given either monthly or every 8 weeks in 49 patients with early HIV infection (CD4+ >500 cells/mm^3). All 4 treatment groups experienced significant increases in CD4+ count. At 6 months, the mean increases in CD4+ count were 116.1 cells/month and 26.7 cells/month in the high and low dosage groups, respectively. Long term follow-up in 39 patients showed a mean CD4+ count of 1381 cells/mm^3 at 18 months. This study demonstrated that both low and high dosage regimens resulted in improved CD4+ counts. However, the increase was much more rapid with higher dosages but was also associated with more adverse effects.

A multicentre study of interleukin-2 plus standard antiretroviral therapy versus standard therapy alone has recently been reported.[16] Patients with CD4+ counts between 200 and 500 cells/mm^3 were randomised to receive subcutaneous interleukin-2 at a starting dosage of 7.5 MIU twice daily for 5 days every 8 weeks in combination with antiretroviral therapy, or antiretrovirals alone. At the time of reporting, 70% of patients had received 6 cycles of interleukin-2. The mean CD4+ count in the interleukin-2 group increased from 355 cells/mm^3 at baseline to 739 cells/mm^3, while the control group increased from 341 to 405 cells/mm^3. No differences in viral load were reported, although there was a trend for the interleukin-2 group to have a larger percentage of patients with viral loads below the detectable limit of the assay.

Tambussi and colleagues[18] evaluated whether a greater response could be achieved by initial continuous infusion therapy followed by subcutaneous injection when compared with high or low dosage subcutaneous injection therapy. Patients were randomised to 1 of 4 groups as follows, with each interleukin-2 group receiving concomitant antiretroviral therapy. Group 1: 12 MIU/day continuous infusion for 5 days every 8 weeks for 2 cycles followed by 7.5 MIU twice daily subcutaneously for 5 days every 8 weeks for 4 additional cycles; group 2: 7.5 MIU twice daily subcutaneously for 5 days every 8 weeks for 6 cycles; group 3: 3 MIU twice daily subcutaneously for 5 days every 4 weeks for 12 cycles; group 4: antiretrovirals alone. At 12 months, the CD4+ count above baseline was 698 (group 1), 625 (group 2), 726 (group 3) and 103 (group 4) cells/mm^3. These data suggest that more frequent lower doses of interleukin-2 provide similar CD4+ increases compared to higher dose regimens, and provide a better adverse effect profile. However, interleukin-2 therapy given every 4 weeks may be inconvenient for some patients. This

study also demonstrates that an 'induction' phase with intravenous interleukin-2 is not necessary for a sustained response.

A comparison of continuous infusion and subcutaneous injection routes was performed in patients with CD4+ counts between 250 and 550 cells/mm^3.[12] The mean dosage in the continuous infusion group was 9.9 MIU/day versus 8.8 MIU/day in the subcutaneous injection group. A control group receiving antiretrovirals alone was also included. The median increases in the intravenous, subcutaneous injection and control groups were 707, 564 and 55 cells/mm^3, respectively. Similar to the study described above,[18] administration by continuous infusion did not appear to produce a significantly greater CD4+ response than subcutaneous injection.

Several general points regarding interleukin-2 therapy can be concluded from these studies. Subcutaneous injection is similar to continuous infusion in terms of improvement in immunological parameters. The duration of intermittent interleukin-2 therapy (5 days) appears to be more important than the total dose. Lower dosages of interleukin-2 (3 MIU/day) are still effective at increasing CD4+ counts, although it may take longer to reach the CD4+ target number than it would with higher dosages. Finally, the rise in CD4+ count associated with interleukin-2 therapy plus highly active antiretroviral therapy is substantially greater than the increases observed with highly active antiretroviral therapy regimens alone.

1.3 Low Dosage Therapy

Due to the potentially severe toxicities associated with the dosages of interleukin-2 described in sections 1.1 and 1.2, some investigators have advocated a daily low dosage regimen for improving immune function.[22] It is believed that interleukin-2–mediated stimulation of natural killer cells leads to the production of numerous pro-inflammatory cytokines [such as tumour necrosis factor-α (TNFα) and interleukin-6], suggesting their role in the toxicity and viraemic burst observed during interleukin-2 cycles.[23-26] Since the majority of natural killer cells lack the α chain of the interleukin-2 receptor (CD25), most have a relatively low affinity for interleukin-2 (approximately 100-fold lower than B and T lymphocytes).[27,28] Thus, it has been suggested that low dosages of interleukin-2 (<1 MIU/m^2/day) can generate a B and T cell response while avoiding the stimulation of natural killer cells and its resultant toxic effects.[22]

A limited number of studies have examined this approach. One initial dose-escalation report studied recombinant human interleukin-2 0.18 MIU administered daily by intradermal injection as well as recombinant human interleukin-2 covalently bound to polyethylene glycol (PEG IL-2) 0.036 MIU administered twice weekly by intradermal or subcutaneous injection.[29] On the basis of the promising increases in delayed-type hypersensitivity response and natural killer activity seen after 30 days, a follow-up report examined PEG IL-2 treatment alone at a dosage of 0.036 MIU twice weekly.[30] This study demonstrated improved lymphokine-activated killer cell and natural killer cell activity and a trend toward a CD4+ response in patients with baseline counts above 400 cells/mm^3. However, PEG IL-2 has since been associated with neurotoxicity[31] and the future use of this modified form is uncertain.

A later study by the same group evaluated unmodified recombinant human interleukin-2 given by daily subcutaneous injection for 6 months.[32] In this study, 16 asymptomatic HIV-infected patients (mean CD4+ count 347 cells/mm^3) were analysed, with 10 patients receiving the 'maximal nontoxic dose' of 0.1875 to 0.25 MIU/m^2/day, and 6 receiving ≤0.125 MIU/m^2/day because of toxicity. The interleukin-2 used in this study was supplied by Amgen and was not equipotent to the Chiron product used in the intermittent studies. These toxicities were mild, consisting of fever, myalgia and fatigue in 3 patients, and a worsening of asthma symptoms in 2 others. By 6 months, natural killer cell levels in the higher dosage group were 6 times higher than in the lower dosage group, and these cells exhibited more killing activity. Other parameters such as eosinophil and monocyte levels

and delayed-type hypersensitivity responsiveness increased relative to the lower dosage group. In addition, CD4+ counts rose in the higher dosage group with a mean monthly gain of 28 cells/mm^3/month [95% confidence interval (CI) –2 to 58 cells/mm^3]. In contrast, CD4+ counts decreased in the lower dosage group, averaging a loss of 28 cells/mm^3/month (95% CI –49 to –7 cells/mm^3).

Another set of reports evaluated daily low dosage therapy in a group of patients with AIDS-related malignancies. A phase II report in this series evaluated a 90-day course using a final dosage of 1.2 MIU/m^2/day in 19 patients, with some patients receiving multiple courses.[33,34] Toxicities were modest, with fatigue, myalgia, arthralgia and nasal congestion among the complaints. Although these patients were in advanced stages of infection, no opportunistic infections occurred while on therapy. In addition, they reported a treatment-dependent rise in eosinophils and natural killer cells (343 ± 202%), but no effect on CD4+ or CD8+ subsets or on plasma viraemia.

These studies indicate that daily low dosage subcutaneous interleukin-2 is well tolerated. There appears to be no burst of plasma HIV during administration, in contrast to standard dosage intermittent treatment. Systemic adverse effects are mild and transient, with grade III toxicities occurring only with dosages above 1 MIU/m^2/day. Of note, all of the cited reports describe a significant local reaction at the sites of injection. Issues of proper administration and adherence to this regimen of daily injections were not addressed in these studies.

The efficacy of this regimen is still uncertain. Initial concerns regarding the pro-inflammatory function of stimulated natural killer cells remain unaddressed; however, this role may be augmented during therapy. Natural killer cells appear to be important for host defence against a wide variety of viral infections.[35] Since natural killer cell activity is suppressed during HIV infection, they may be an appropriate target for immune therapy.[2,3] Therefore, the rise in natural killer cell absolute number and reactivity observed in these studies may be beneficial. Other noted changes (such as increased delayed-type hypersensitivity reactivity, *in vitro* blastogenesis, increases in eosinophils, etc.) suggest a strengthening of innate and cell-mediated immunity.[30]

The results of the study[32] demonstrating a rise in CD4+ count during low dosage daily therapy are promising, but should be interpreted with caution. A significant difference was seen only in comparison with a nonrandomised cohort who received a lower dosage, and in fact experienced a loss of CD4+ cells while on therapy. The immunological effects of subcutaneous injection intermittent therapy at higher dosages are similar to those induced by intravenous intermittent interleukin-2 infusions, and appear limited to the CD4+ subset. In contrast, the induction of natural killer cells rather than CD4+ T cells with daily low dosage therapy mirrors the results in cancer patients receiving prolonged (90-day) interleukin-2 intravenous infusions at mid-range dosages (1 to 5 MIU/m^2/day).[36] These observations suggest that the frequency, rather than the route, of administration may influence which cell population will be favoured. Immune modulation outside the CD4+ population has not yet been associated with clinical benefit for HIV infection. Although interleukin-2 given on a daily basis in low dosages produces a unique type of immune stimulation, the clinical benefit of this type of stimulation is unknown.

2. Effects on Viral Load

The potential for interleukin-2 to increase viral replication has been evaluated in a variety of clinical studies. interleukin-2 could theoretically increase HIV replication either by directly activating infected CD4+ cells or by increasing production of pro-inflammatory cytokines such as TNFα and interleukin-6. These cytokines are thought to be cofactors for HIV replication and are released in significant amounts during interleukin-2 therapy.[37]

To date, all randomised studies of interleukin-2 + antiretroviral therapy versus antiretrovirals alone have shown no difference in viral load or a trend

for lower viral load in the interleukin-2 groups. Early studies described transient viral bursts during therapy or a worsening viral load in patients with CD4+ counts <200 cells/mm^3. However, these studies were performed before the release of potent antiretrovirals such as protease inhibitors. The use of highly active antiretroviral therapy in combination with interleukin-2 allows for adequate suppression of replication during immune-activating therapy.

3. Interleukin-2 plus Highly Active Antiretroviral Therapy and HIV Reservoirs

Recent studies have demonstrated that, despite its ability to control viral burden, highly active antiretroviral therapy is unable to eradicate HIV. Enhanced purification and stimulation methods have shown that well suppressed patients on highly active antiretroviral therapy nevertheless maintain a reservoir of latent virus within the resting CD4+ T cell compartment.[38-40] Despite treatment with highly active antiretroviral therapy, approximately 10^7 resting CD4+ T cells remain infected with replication-competent virus, and these latent cells can be infectious upon cell stimulation. This pool appears to exist as early as 10 days after the onset of acute symptoms.[41]

The continued presence of this pool may present a threat to long term viral control, leading to changes in regimen and the eventual exhaustion of available antiretroviral drugs. Other cellular and anatomic viral reservoirs may exist as well, such as in the bone marrow, the brain, the lymphoid tissue of the gut, or in macrophages,[42] In response to these concerns, the use of immune modulators such as interleukin-2 has been suggested as a means to stimulate the latent pool and make them susceptible to antiretroviral therapy.

Studies have shown that these latent viruses can be activated to replicate *in vitro* by the addition of interleukin-2, TNFα and interleukin-6.[43] Notably, *in vivo* levels of these latter 2 cytokines increase during interleukin-2 administration.[44-46] Theoretically, latent HIV may be purged by treating patients with agents that activate viral replication. This activation should lead to HIV-induced cytolysis of these cells. Although this would also lead to viral production, treatment with highly active antiretroviral therapy should render it largely incapable of spreading infection. By induction of viral expression, these cells may also be more susceptible to immune clearance.[43]

Chun and colleagues[47] have addressed this issue retrospectively by examining 14 patients who had received interleukin-2 cycles over an average of 39 months. These patients were shown to have less culturable latent virus compared with 12 non-randomised HIV-infected control participants (mean 0.389 *vs* 1.032 infectious units per million cells). Another similar study reported that, out of 26 patients with viral load <50 copies/ml, 2 patients receiving interleukin-2 had no detectable infectious HIV RNA in peripheral blood mononuclear cells. However, both patients had detectable infectious HIV RNA in lymph node tissue. Although these findings support the concept that interleukin-2 activation in combination with highly active antiretroviral therapy may reduce the latent reservoir, a larger prospective randomised trial will be necessary to confirm these results.[48]

4. Adverse Effects of Interleukin-2 Therapy in Patients with HIV Infection

Administration of interleukin-2 is associated with many systemic adverse effects. Virtually all organ systems can be affected to varying degrees during interleukin-2 therapy. Interleukin-2 stimulates release of various pro-inflammatory cytokines, including interleukin-6, interferon-γ, granulocyte-macrophage colony-stimulating factor and TNFα. The exact mechanism of the adverse reactions associated with interleukin-2 treatment is unclear. However, on the basis of the nature and onset of these reactions, it is generally believed that these effects are probably caused by increased release of endogenous pro-inflammatory cytokines rather than by the exogenous interleukin-2 itself.[49]

The severity of adverse reactions using high dosage continuous intravenous infusion of inter-

leukin-2 (up to 18 MIU/day for 5 to 21 days) in HIV patients in earlier trials[20] had led to exploration of lower dosage continuous infusion[7] and subcutaneous injections as alternative means of drug delivery.[10] In general, the adverse reactions seen with continuous infusion interleukin-2 occur more frequently and are of higher intensity than those with subcutaneous injections. Lower baseline CD4+ count (<200 cells/mm^3) was also associated with more severe reactions to high dosage continuous infusion.[20] Most of the interleukin-2 reactions are dose related, generally transient, and are reversible upon or soon after cessation of therapy. Of note, it is not possible to compare the incidence of adverse reactions reported in different clinical trials as the definitions and the rating of toxicities vary widely from study to study. A summary of the reported adverse reactions is shown in table II.

The most frequently reported adverse effects of interleukin-2 are constitutional symptoms, including fatigue, malaise, fever, myalgia and arthralgia. Fatigue and malaise have been reported in up to 100% of patients receiving both continuous infusion and subcutaneous interleukin-2.[9,15,20,50,51] Fever occurs in 12 to 100% in various studies. During a typical 5-day cycle, the constitutional symptoms most often begin on days 2 to 3, with increase in severity until day 5. The symptoms are usually continuous throughout the cycle with continuous infusion interleukin-2, but with subcutaneous injection they usually peak at 4 hours after injection and gradually subside over the next 4 to 8 hours.[10]

The constitutional symptoms can persist for several days after therapy interruption. Grady et al.[52] assessed the functional status of patients during and after continuous infusion interleukin-2 by a patient survey. At the end of a 5-day course, the Global Fatigue Index significantly increased from baseline ($p < 0.001$), then improved but remained worse than baseline scores at 1 week after treatment. The scores returned to baseline at 1-month follow-up.

Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, anorexia, dyspepsia and abdominal pain have all been reported with interleukin-2 therapy. Persistent symptoms may impair patients' ability to maintain oral fluid intake during their interleukin-2 cycle, which may result in worsening volume depletion.

The most serious toxicity associated with interleukin-2 is capillary leak syndrome, which may result in organ hypoperfusion and hypotension.[53] Capillary leak syndrome is characterised by increased capillary permeability to fluid and protein along with reduced vascular tone. It is more often reported in patients receiving interleukin-2 for the treatment of malignancy, where high dosage intravenous therapy (up to 0.6 MIU/kg every 8 hours) is used. More serious processes associated with capillary leak syndrome include pulmonary oedema, congestive heart failure, hypotension, azo-

Table II. Adverse effects associated with administration of interleukin-2 to patients with HIV infection

Organ system or syndrome	Symptoms
Constitutional symptoms	Fatigue, malaise, fever, chills, rigors, myalgia, arthralgia
Gastrointestinal	Nausea, vomiting, diarrhoea, anorexia, abdominal pain, dyspepsia, stomatitis, mucositis
Capillary leak syndrome	Peripheral oedema, pulmonary oedema, hypotension, oliguria, congestive heart failure
CNS	Headache, insomnia, somnolence, anxiety, depression, mood alteration, dizziness
Renal, metabolic or electrolyte balance	Oliguria, azotaemia, hypomagnesaemia, hypocalcaemia, hypophosphataemia, hyponatraemia
Skin	Local inflammation of injection sites, erythroderma, dry skin, pruritus, urticaria, exfoliative dermatitis
Cardiovascular	Cardiomyopathy, congestive heart failure, hypotension, cardiac ischaemia
Intravenous catheter-related	Thrombophlebitis, line infection
Liver	Increased bilirubin levels, increased transaminase levels
Haematological	Neutropenia, thrombocytopenia
Other	Exacerbation of inflammatory or autoimmune diseases, hypothyroidism, nasal congestion

taemia, angina and cardiac ischaemia. Recognition of early signs of capillary leak syndrome before profound organ compromise is critical to avoid life-threatening conditions and long term sequelae. Milder symptoms from capillary leak syndrome include fluid retention, resulting in peripheral oedema and bodyweight gain. Specific treatment is generally not indicated as these symptoms usually resolve after discontinuation of interleukin-2.

Various CNS-associated symptoms have been reported during interleukin-2 cycles, including insomnia, anxiety, headache, dizziness, mood alteration and depression.

Reduced urine output and electrolyte losses (most commonly magnesium, calcium and phosphate losses) have been associated with interleukin-2 therapy. Renal function and serum electrolyte should be monitored to detect any changes where fluid and/or electrolyte supplementation may be necessary.

Interleukin-2 can cause a constellation of different dermatological manifestations, including erythroderma, pruritus, exfoliative dermatitis, urticaria and localised subcutaneous nodules and erythema at injection sites.

Other transient adverse effects related to interleukin-2 therapy include hyperbilirubinaemia, neutropenia, thrombocytopenia, increase in liver enzyme levels, flare of inflammatory and autoimmune diseases and thrombophlebitis with or without catheter-related infections in patients receiving continuous infusion interleukin-2. Hypothyroidism has recently been reported as a permanent effect from repeated courses of interleukin-2 in up to 10% of patients.[54] Long term levothyroxine therapy has been able to correct the abnormalities in these patients. Cardiomyopathy has also been reported rarely.

The specific adverse effects vary widely between patients and are not predictable. No factors have been identified that might predict a patient's specific symptoms or susceptibility to interleukin-2 effects. Patients receiving the same dosage and duration of therapy may have markedly different adverse effect profiles. However, patients receiving repeated cycles often demonstrate similar adverse effects from cycle to cycle. Similarly, the duration of these adverse effects varies from 1 to 2 days to 2 weeks after a cycle of therapy.

5. Pharmacological Management of Adverse Effects Associated with Interleukin-2

The goal of interleukin-2 therapy in HIV patients is to provide maximal immunological response with manageable toxicities that do not significantly impair the patient's quality of life during and between cycles. Patient education is crucial prior to and throughout interleukin-2 therapy. Patients with a good understanding of the potential adverse effects are more likely to adhere to the preventive measures to be taken to ameliorate some of these adverse effects. A thorough physical examination and laboratory evaluation should be performed before each cycle of interleukin-2 to ensure normal cardiac, pulmonary, hepatic, renal and neurological function prior to initiation of therapy.[55] Comfort measures through pharmacological interventions are an essential part of an interleukin-2 cycle. In a study evaluating supportive regimens given to HIV patients receiving continuous infusion interleukin-2, it was noted that the patients received an average of 10 medications (range 2 to 24) for symptomatic support during a 5-day cycle.[56] At the beginning of each cycle, the patient should be advised to refrain from strenuous exercise and to maintain good oral fluid intake (including electrolyte-containing drinks) throughout the cycle. The patient and/or caregiver should keep an accurate daily log of fluid intake and output, temperature and other symptoms.

Aggressive supportive care is an important component of interleukin-2 therapy. Pharmacological interventions for interleukin-2–induced adverse effects are listed in table III. In most instances, these medications are only necessary for as long as the interleukin-2 reactions last, and can be discontinued within a couple of days after completion of an interleukin-2 cycle. Most adverse effects can be managed on an outpatient basis. A

comprehensive review describing the management of the adverse effects of interleukin-2 can be found elsewhere.[53]

6. Improved Administration Strategies

The symptoms associated with interleukin-2 adverse reactions continue to be a limiting factor for some patients. In some cases, dosage reductions allow the patients to tolerate the therapy; however the immunological response may be diminished. In other instances, patients can tolerate interleukin-2 only with the assistance of numerous supportive medications. Thus, there is a continuous need to search for ways to minimise some of the toxicities associated with interleukin-2 in order for these patients to gain the maximal benefit.

A lengthening of the time between treatment cycles would make a marked impact on patient and prescriber acceptance. Davey et al.[57] recently reported long term (2 years) follow-up data in patients receiving subcutaneous interleukin-2. Following the initial 1 year of therapy (6 cycles), many patients could maintain their elevated CD4+ counts with infrequent 5-day cycles. The investigators reported that the mean interval between cycles was 9 months in this cohort. Thus, after an initial response, patients may only require interleukin-2 therapy once or twice each year. This significantly reduces the inconvenience and cost of therapy. Further clinical experience involves the use of 3-day continuous infusions to maintain the patient's CD4+ count after a good initial response has been achieved.

Table III. Management and prevention of adverse effects associated with administration of interleukin-2

Adverse effect	Management strategy
Fatigue/malaise	Avoid strenuous exercise
Fever, arthralgia, myalgia	Paracetamol (acetaminophen) alternating with ibuprofen; opioid analgesic if needed
Chills and rigors	Pethidine (meperidine) as needed
Hydration	Encourage oral fluid intake or intravenous fluid
Nausea/vomiting	Prochlorperazine or promethazine; granisetron or ondansetron; droperidol
Diarrhoea	Loperamide, diphenoxylate/atropine, codeine phosphate or kaolin/morphine
Capillary leak syndrome	Dosage reduction or discontinuation of interleukin-2; manage associated signs and symptoms with close haemodynamic monitoring if indicated
Insomnia	Diphenhydramine, temazepam, zolpidem
Anxiety	Lorazepam
Electrolyte imbalance	Oral or intravenous magnesium, calcium or phosphate as needed
Dermatitis	Emollients, topical corticosteroids, antihistamines
Nasal congestion	Loratidine, oral decongestants
Hypotension	Fluid replacement with normal saline
Mucositis	Oral hygiene, mouthwash containing local anaesthetic
Hypothyroidism	Thyroid supplementation

A variety of adjunctive therapies has also been investigated in an attempt to attenuate the adverse effects of interleukin-2. Most of these measures target the reduction of pro-inflammatory cytokines that are produced during interleukin-2 infusions. Early efforts specifically targeted TNFα, which increases during interleukin-2 infusions and is associated with numerous adverse effects. A randomised trial attempted to compare the use of thalidomide (an inhibitor of TNFα) plus interleukin-2, a TNFα monoclonal antibody plus interleukin-2 and interleukin-2 alone in a small cohort of HIV-infected patients.[58] The preliminary results of this study failed to demonstrate any beneficial effect when either of these agents was administered during an interleukin-2 cycle.[58] The inability of these therapies to significantly decrease interleukin-2 adverse effects is probably related to their specificity for a single cytokine. It is likely that the toxicities of interleukin-2 are mediated by the effects of a variety of other pro-inflammatory cytokines, including interleukin-1 and interleukin-6. Currently, there is an interest in assessing the role of corticosteroids in ameliorating interleukin-2 related symptoms, since these agents have global suppressive effects on cytokine production. A nonblind trial and a double-blind placebo-controlled randomised trial evaluating the role of prednisone administered during and for 2 days after an interleukin-2 cycle are currently under way.

7. Risk-Benefit Assessment

It is difficult to assess risk-benefit for an investigational drug in which clinical end-point data are not available. Thus, the use of interleukin-2 as an adjunctive therapy for HIV infection should be considered in the context of which patients are likely to get the greatest benefit from improvements in immunological markers. The CD4+ count remains the most important surrogate marker for the risk of developing an opportunistic infection. Measures to increase this value are useful if the adverse effects and inconvenience can be minimised. Thus, interleukin-2 may be an important potential adjunctive therapy pending completion of end-point trials.

Interleukin-2 should currently only be used in the research setting with patients with HIV. When using this agent, it is important to identify patients who are most likely to respond to interleukin-2. This would include patients with good viral suppression and those with CD4+ counts above 200 cells/mm^3. Adverse effects can be minimised by intermittent subcutaneous administration of low to moderate dosages (3 to 7.5 MIU twice daily). In addition, aggressive supportive care should be administered if necessary. Three cycles of therapy separated by 8 weeks should be given initially. If a patient demonstrates a favourable response, additional cycles can be administered. In general, a good response can be defined as a doubling of the CD4+ count or a CD4+ value of >1000 cells/mm^3. For patients on long term therapy, a 'plateau' CD4+ level should be established for each patient above which further cycles should be withheld until the CD4+ count falls below this value. If a patient does not have a response after 3 cycles, further interleukin-2 therapy should be re-evaluated.

Another strategy would be to consider interleukin-2 as a part of a salvage regimen for patients with low CD4+ counts. Patients with counts below 200 cells/mm^3 could be administered potent antiretroviral therapy in an effort to suppress HIV replication and increase CD4+ counts to a level that increases the likelihood of a response to interleukin-2. Once this has been achieved, interleukin-2 can be administered to further increase the CD4+ count to a range that theoretically reduces the risk of an opportunistic infection. The difficulty in suppressing HIV viral load in a highly antiretroviral-experienced patient complicates this approach.

Low dosage daily interleukin-2 therapy may also be an option for some patients who wish to avoid the potentially severe adverse effects of interleukin-2. However, the arguable immunological benefits combined with the inconvenience of a daily injection limits the usefulness of this strategy. Additional clinical trials with this regimen are ongoing and may provide better insight into the role of low dose therapy.

8. Conclusions

The potential licensure and widespread use of interleukin-2 in HIV infection will rely on clinical end-point data from large multicentre phase III studies. Until these data are available, interleukin-2 can be used in the research setting as an agent to augment, boost or enhance the immune system and as an adjunct to antiretroviral therapy. Its potential to activate latently infected cells and promote HIV eradication from reservoir sites is also an important area for further study. Patients should be closely monitored for adverse effects and supportive care medications should be provided. Dosage reductions may be necessary based on patient tolerance and toxicity. Multiple randomised studies have shown that interleukin-2 is effective in raising CD4+ counts without increasing viral load. If clinical benefit can be demonstrated, this agent could be a useful immunomodulator in HIV-infected patients if adverse effects can be minimised and therapy can be given infrequently on an outpatient basis.

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