In the Literature

IL-2 Therapy for AIDS


Immune reconstitution in response to HAART is often incomplete, and in addition to having persistent organism-specific deficits, patients may never achieve a normal CD4+ T cell count or normal CD4+/T cell function, despite effective suppression of viral replication. As a consequence, there remains an interest in immunomodulatory therapies that may enhance immune reconstitution. One such approach that has been under investigation for >1 decade is the adjunctive use of recombinant human IL-2, a cytokine that plays a central role in the cellular immune response.

HIV-infected adults with CD4+ cell counts of 50–350 cells/μL who had not previously received a protease inhibitor were treated with indinavir plus 2 nucleoside analogue reverse-transcriptase inhibitors, at least one of which had to be novel to the patient. After 12 weeks of antiretroviral therapy, patients with a plasma HIV RNA concentration ≤5000 copies/mL were randomized to continue to receive antiretroviral therapy (ART) alone (the ART group), to continue to receive ART with a continuous infusion of IL-2 at a dosage of 9 million IU daily for 5 days every 8 weeks (the ART + IV IL-2 group), or to continue to receive ART with IL-2 at a dosage of 7.5 million IU subcutaneously twice daily for 5 days every 8 weeks (the ART + SC IL-2 group). A total of 159 patients were available for analysis.

Forty and 51 patients discontinued therapy before weeks 60 and 84, respectively. Grade 3 and 4 adverse events were more common in the groups receiving IL-2; adverse events included fatigue, fever, chills and sweats, mucocutaneous events, and (especially in the ART + IV IL-2 group) nausea and vomiting.

The primary end point of the study (a >50% increase in the CD4+ cell count at week 60) was achieved by 29%, 81%, and 67% of patients assigned to the ART, ART + IV IL-2, and ART + SC IL-2 groups, respectively. The response in each of the IL-2 arms was superior to that in the ART arm (P<.001 for each comparison). Patients assigned to the IL-2 arms also had significantly fewer AIDS-defining events, with 1 event (Kaposi sarcoma) occurring in the ART + SC IL-2 arm and none occurring in the ART + IV IL-2 arm. Seven events occurred among patients assigned to receive ART alone (Kaposi sarcoma, 2 events; Burkitt lymphoma, non-Hodgkin lymphoma, Castleman disease, Pneumocystis jirovecii pneumonia, and esophageal candidiasis, 1 event each). There were no significant differences between treatment groups with regard to plasma HIV RNA level at week 84.

IL-2 therapy was associated with a general peripheral expansion of CD4+ T cell populations, including both naive and memory/effector cells and populations bearing CD28 (coreceptor for T cell activation), CD25 (α chain of the IL-2 receptor), and CD95 (the Fas receptor that mediates apoptotic signaling by Fas ligand). There were no significant differences between treatment arms with regard to changes in skin test reactivity or in vitro lymphocyte proliferation.

Previous studies found that CD4+ T cell responses to IL-2 therapy were confined to individuals with baseline CD4+ T cell counts of ≥200 cells/μL. In the study by Mitsuyasu and colleagues, although patients with CD4+ cell counts as low as 50 cells/μL were eligible for enrollment, IL-2 therapy was not initiated until patients had received 12 weeks of HAART, at which time the median CD4+ cell counts ranged from 239 to 305 cells/μL. Despite the success in expanding peripheral CD4+ cell populations, IL-2 therapy was not associated with in vitro evidence of enhanced T cell function. Of more importance, however, was the occurrence of fewer AIDS-related serious clinical events among IL-2 recipients. A meta-analysis of previous IL-2 trials also suggested an associated clinical benefit [1]. A definitive answer regarding the potential for prevention of opportunistic infections and malignancies, however, awaits the outcomes of 2 large clinical trials that are currently in progress.

Reference


Casting a NET for Bacterial Killing


It has recently been reported that neutrophils, upon activation by bacteria, become adherent to host cells and subsequently extrude DNA, as well as nuclear histones and cytoplasmic granule proteins, while retaining viability. The DNA forms weblike structures in association with a high concentration of these cationic proteins and enzymes with antibacterial activity. These structures, when formed within infected tissue, function as neutrophil extracellular traps (NETs), which serve to smare and kill bacteria [1]. Clark and colleagues now provide evidence that platelets play a key role in this process, thus contributing to clearance of bacteria from the bloodstream.

A prior observation—that human platelets express Toll-like receptor 4 (TLR4) on their surfaces—suggested that
these cells are capable of detection of infectious microorganisms. Consistent with previous reports that platelets bind to adherent neutrophils in animal models of sepsis, Clark and colleagues found that lipopolysaccharide (LPS) binds to platelet TLR4 and that LPS-treated platelets avidly bind to neutrophils and activate them. Exposure of platelets to plasma obtained from patients with severe sepsis had a similar effect that, on the basis of blocking studies, was found to be dependent on TLR4 activation, as well as on other undefined mechanisms. These effects were reproduced in vivo in a mouse model of endotoxia. Activation of adherent neutrophils by platelets exposed to LPS or to septic plasma led to the formation of NETs, and the ability of NETs to trap bacteria was significantly enhanced by the interaction of platelets with neutrophils. By using fluorescently labeled, intravenously injected Escherichia coli, it was demonstrated that ∼60% of the bacterial cells were trapped at sites where platelets adhered to neutrophils, whereas the remaining adhered to Kupffer cells and neutrophils alone.

Additional studies found that NETs resisted shear and, thus, were capable of functioning in low-flow endovascular sites, including pulmonary capillaries and hepatic sinusoids, where they ensnared bacteria within these small blood vessels. There was evidence, however, that binding of platelets to neutrophils led to endothelial damage. Of interest is that, in the murine model, the development of platelet-neutrophil NETs in hepatic sinusoids was associated with elevation of hepatic transaminase concentrations; this was possibly related to decreased sinusoidal perfusion, suggesting a possible mechanism for the hepatic dysfunction that is frequently observed in patients with severe sepsis.

This study provides a possible answer to the question of where the platelets go in patients with severe sepsis, during which thrombocytopenia, sometimes severe, is a frequent occurrence. Although, in many cases, there is evidence of disseminated intravascular coagulation as a likely etiology, there is no such evidence in other cases. This study suggests that the sequestration of platelets in association with NETs may account for low platelet counts in some patients.

Platelet TLR4 binding and activation and binding to adherent neutrophils occurs at higher concentrations of LPS than are required for direct activation of neutrophils. This suggests that the mechanism described here is only activated in conditions of severe sepsis as a means of enhancing clearance of bacteria from the bloodstream. Because the recruitment of platelets to this process significantly enhances bacterial trapping in NETs, the process can be considered one of ratcheting up the innate immune system to deal with more-serious, potentially life-threatening challenges. Because ratcheting up to this level has potential downsides, including thrombocytopenia and local endothelial and hepatic injury, such a 2-step system seems wise in allowing a modulated response to infection. It also suggests the possibility that the adverse effects could be favorably modulated by TLR4 antagonists.

Reference

First US National Survey of Human Papillomavirus (HPV) Prevalence


Of 1921 self-collected vaginal specimens obtained from women aged 14–59 years from throughout the United States, 26.8% were found to contain HPV DNA by PCR. There was a statistically significant increase for each year of age from 14 to 24 years, followed by a gradual decrease. The genital wart–associated viruses HPV-6 and HPV-11 were detected in 1.3% and 0.1% of women, respectively, whereas the oncogenic types (HPV-16 and HPV-18) were detected in 1.5% and 0.8%, respectively. Overall, 3.4% of subjects were infected with ≥1 HPV type included in the quadrivalent HPV vaccine (Gardasil; Merck).

Influenza B Resistant to Oseltamivir


In a prospective study from Japan, reduced susceptibility of influenza B virus was identified in 1 (1.4%) of 74 children infected with this virus after treatment with oseltamivir, and the reduced susceptibility was associated with a defined mutation in the viral neuraminidase. Separately, variants with reduced susceptibility to this drug were identified in 7 (1.7%) of 422 influenza virus isolates recovered from individuals who had not received a neuraminidase inhibitor. Three of the 7 patients may have been infected as the result of contact with siblings who had been shedding resistant virus.

Intravenously Administered Polyclonal Immunoglobulin in Sepsis


A meta-analysis of 20 randomized, controlled trials found evidence that the administration of polyclonal intravenous immunoglobulin to patients with sepsis was associated with improved survival (risk ratio, 0.74; 95% CI, 0.62–0.89), compared with placebo administration or with no intervention. Severe sepsis or septic shock, administration of immunoglobulin to patients with sepsis at a dose of at least 1 g/kg, and receipt of therapy for ≥2 days were strongly associated with improved outcomes. However, the authors note that most of the trials that they evaluated were performed before the use of activated protein C and the general acceptance of early goal-directed therapies, and they indicate the need for a large, prospective, randomized trial.