Therapeutic Approaches to Patients with AIDS

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Abstract

The immune systems of patients with acquired immunodeficiency syndrome are characterized by a profound defect in the number and function of helper/inducer T-lymphocytes, particularly at the level of soluble antigen recognition. Due to this selective yet profound defect in the immune system, these patients are prone to recurrent severe opportunistic infections and Kaposis's sarcoma. While therapies exist for some of these complications of acquired immunodeficiency syndrome, no effective therapies exist for the underlying immune defect of this syndrome. Reviewed here are some of our recent attempts at immune reconstitution in acquired immunodeficiency syndrome, using either whole scale immune reconstitution through the use of lymphocyte transfers and bone marrow transplantation or enhancement of the remaining immune systems with the T-cell derived lymphokines interleukin-2 or immune γ-interferon. In addition, recent advances in the therapy of Pneumocystis carinii pneumonia and disseminated cytomegalovirus disease are discussed.

Patients with AIDS are characterized by the development of opportunistic infections and unusual neoplasms, particularly Kaposis's sarcoma (1–4). These unusual clinical manifestations occur as a result of an immune system which has been struck a tropic retrovirus HTLV-III/LAV (7, 8). This virus is capable of inducing an immune deficiency state in adults unlike any previously described. This complete lack of helper/inducer T-cell function eventually results in an immune system which is incapable of protecting the host from the most indolent of environmental opportunists. These patients have provided clinicians and clinical researchers with a therapeutic challenge of enormous proportion. Despite adequate therapy for many of the infections these patients develop, and despite good regimens for the treatment of Kaposis's sarcoma (discussed elsewhere), no successful therapies are known for the progressive immune defect these patients exhibit, and thus, despite our best efforts at treating the complications of AIDS, these patients generally die within 2 y of diagnosis due to recurrent infection or progressive neoplasm.

Our current therapeutic approach to patients with AIDS is outlined in Table 1. The most important of these is therapy of any treatable opportunistic infections and/or Kaposis's sarcoma. It should be stressed that the therapy for Kaposis's should be dictated by the severity of the neoplastic process, for most of the currently available treatment regimens are somewhat immunosuppressive and may, in the process of diminishing the neoplasm, in fact shorten the patient's life.

While a discussion of the different approaches to the treatment of the infectious complications of AIDS is beyond the scope of this paper, there are two recent observations which we feel are worthy of note. The first of these concerns the treatment of PCP. While 10–14 days of therapy with either trimethoprim/sulfamethoxazole or pentamidine isethionate is usually adequate for treatment of the non-AIDS cases of PCP, it is often far too short for therapy of AIDS-related PCP (9). Our approach is to treat the patient for 3 wk and at that point repeat the bronchoscopy. If organisms are still present, even though there is no way to distinguish live from dead cysts, we continue therapy for an additional 3 wk. At the end of this next 3 wk of therapy, bronchoscopy is again performed and the same algorithm enacted. Although this approach is somewhat difficult for both the patient and the physician, we find that, by continuing therapy until the bronchoscopy is negative, the rate of subsequent relapse is much reduced over historical controls. A controlled trial is currently in progress to test the validity of this hypothesis.

The second infectious complication worth mentioning is disseminated infection with cytomegalovirus. This DNA virus which can be isolated from at least 90% of patients with AIDS appears to be the cause of a wide variety of clinical syndromes ranging from retinitis to pneumonitis to a poorly defined syndrome consisting of fever, weight loss, and diarrhea (10). The importance of recognizing and being able to diagnose cytomegalovirus disease lies in the fact that at least two drugs (DHDP by Syntex and BW759 by Burroughs-Wellcome) which are currently in Phase I testing appear to have substantial clinical efficacy in the treatment of this condition. While it is too early to tell what the ultimate benefit of these drugs will be, they at least provide some hope that this previously untreatable, devastating complication of AIDS can at least be partially controlled.

Whole-scale immunological reconstitution in patients with AIDS has been attempted by ourselves and others utilizing bone marrow transplantation and/or the transfer of peripheral blood lymphocytes (11–14). In our study we were fortunate in that one of our patients had a healthy twin brother who was not a member of an AIDS risk group. We performed a single bone marrow transplantation in combination with the peripheral transfer of $10^{10}$ peripheral blood mononuclear cells every 2–4 wk for approximately 1 yr. Although we were able to demonstrate definite immunological reconstitution in the form of increased numbers of helper/inducer T-cells in the peripheral blood and the new development of a positive delayed-type hypersensitivity reaction to the soluble protein antigen keyhole limpet hemocyanin to which both the donor and the recipient had been immunized, the effects were only transient, and the patient's immune system returned to its base-line state despite the continued adoptive transfer of immunocompetent cells (Chart 1). We feel these data are strong evidence that the AIDS virus is a persistent agent and...
THERAPEUTIC APPROACHES TO AIDS PATIENTS

Table 1

Actual and theoretical therapeutic approaches to AIDS patients

<table>
<thead>
<tr>
<th>Treatment of the opportunistic infections and/or Kaposi's sarcoma</th>
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<tr>
<td>Immunological reconstitution</td>
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<tr>
<td>Bone marrow transplantation</td>
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<tr>
<td>Adaptive transfer of immune competent cells; syngeneic lymphocyte transfusions</td>
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<td>Immunological enhancement</td>
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<td>Cytokines such as IL-2 and interferons</td>
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<td>Immunological adjuvants</td>
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<tr>
<td>Treatment of HTLV-III/LAV directly with viral chemotherapy active against reverse transcriptase-producing viruses</td>
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that attempts at immunological reconstitution that do not include a strategy for inactivation of the HTLV-III/LAV virus will probably not succeed.

If one envisions the human immune system as an army, then clearly the commanding generals of that army are the helper/inducer T-cells, the very cells which are destroyed in AIDS. These cells serve a central role in the generation and the execution of an immune response and modulate not only the response of other T-cells but the responses of B-cells and monocytes as well. It is no surprise therefore that virtually every parameter of immunological function that has been studied in AIDS has been found to be abnormal (15—21). While some of these abnormalities are most likely due to secondary infections with opportunistic agents, particularly the DNA viruses, they all are of potential importance. Thus strategies designed to supplant the need for the helper/inducer T-cell in the generation of an effector function are of sound theoretical foundation. Two such strategies in this regard are the use of IL-2 to enhance cytotoxic T-cell function and natural killer cell function, and γ-interferon to enhance monocyte-mediated killing.

An important factor to keep in mind in the design of immunomodulator trials in patients with AIDS is that they not only represent a heterogeneous group clinically but have varied immune profiles as well. As can be seen in Chart 2, those patients who present with Kaposi's sarcoma alone seem to have substantially higher numbers of peripheral blood T4 cells than those patients who present with an opportunistic infection. This immunological correlate of the overall survival statistics, which also favor those patients with Kaposi's alone, needs to be taken into account when one designs clinical trials. For this reason, all of our immunomodulatory trials have as entry criteria total lymphocyte counts greater than 1000/mm³. As safety data are generated with the use of these compounds in patients with AIDS, one can justify their use in patients with earlier stages of HTLV-III/LAV disease. These earlier patients, with more intact immune systems, may show substantially different clinical responses than definite AIDS patients. In view of the fact that approximately 10% of these AIDS-related conditions may go on to develop AIDS, such trials seem warranted.

Natural killer cells, as well as cytotoxic T-cells, demonstrate a marked enhancement of cytotoxic capability following incubation in vitro in IL-2. This property of mononuclear cells from healthy individuals is also seen utilizing the mononuclear cells from patients with AIDS (22). Based upon these encouraging in vitro observations, we have carried out several Phase I trials of IL-2 in AIDS patients utilizing both natural product IL-2 as well as genetically engineered or recombinant IL-2. Due to the short half-life of this drug, it was administered as a continuous infusion for 5 consecutive days followed by a 2-day rest period. This cycle was repeated every wk for 4 wk. Doses ranged from 250 units per 24-h period to 2,500,000 units per 24-h period. These treatments, carried out predominantly in patients with Kaposi's sarcoma or patients with opportunistic infections and more than 1000 lymphocytes/mm³, while capable of producing sustained serum levels of IL-2 in the range which would have been capable of inducing enhanced cytotoxicity in vitro, have thus far demonstrated no significant clinical or immunological benefit. It should be stressed, however, that dose-limiting toxicities have not yet been reached in these protocols.

γ-Interferon is another T-cell-derived lymphokine which has
potent cell-activating properties. This antiviral/immunomodulatory agent is capable of enhancing monocyte/macrophage la and FcR expression and can enhance monocyte-mediated cytotoxicity and H2O2 release (23). Based upon these in vitro observations, and based upon the fact that α-interferon has been shown to be capable of inducing remissions in 20–40% of patients with Kapo’s sarcoma, Phase I trials are currently under way with the use of this compound. In the studies being carried out at the NIH, doses in the range of 0.001–1.0 mg/m² are being used as either continuous i.v. infusions or daily i.m. injections. Each treatment regimen runs for 10 days followed by a crossover to the alternate route of administration. While peak levels have been observed to be lower in the continuous infusion regimen, toxicity has been substantially greater, with patients unable to tolerate the top dose i.v. for more than 5 days. In contrast, 10 days of i.m. administration produced minimal side effects. No antineoplastic activity has been seen thus far with the use of this drug. A definite enhancement in natural killer cell activity was seen at a dosage range of approximately 0.1 mg/m². It is too soon to tell if either natural product or recombinant γ-interferon will be of any value in attempting to at least partially restore the immune systems of patients with AIDS towards normal.

Thus, we are still quite far from establishing effective immunological enhancement in patients with AIDS. Although in vitro studies with the use of T-cell-derived lymphokines have provided good rationales for in vivo clinical trials, the success of the laboratory experiments has not been mirrored in the clinic. While much remains to be learned concerning the in vivo fate of these compounds and their precise in vivo potential, the results thus far have been far from encouraging. The inability of these compounds to significantly enhance the immune function of these patients, coupled with the dramatic failure of total immunological reconstitution, strongly points to the fact that, unless we are able to develop effective therapeutic strategies to deal with the causative agent of this syndrome, our attempts at immunological reconstitution seem doomed to failure. While currently unsuccessful in this particular area of clinical research, we should not lose sight of the fact that, short of developing immunological cures, we can still significantly improve the outlook for these patients by developing new and better therapies for the neoplastic and infectious complications of this devastating syndrome.

References

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