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# DEVELOPMENT OF IMMUNOMODULATORS FOR TREATMENT OF HIV INFECTION

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*ABSTRACT*

*Although considerable attention has been devoted to development of antiviral drugs for therapy of HIV infection, relatively little priority has been directed to correction of the progressive immunologic defect that develops in these patients. We described the development of the therapeutic effect of an immunosupportive biological agent (IMREG-1) derived from human leukocytes. Specifically, IMREG-1 reduced the risk of progression from advanced AIDS-related complex (ARC) based on a randomized double-blinded control trial over a six month period of the laboratory and clinical parameters predictive of a high risk of progression from ARC to AIDS. The comparative value of $CD_4^+$ cell numbers, anergy to recall antigens and symptomatology in assessing risk of progression were also examined.*

The emergence of human immunodeficiency virus (HIV) infection as a major public health problem has led to intensive initiatives to develop therapies to modify the course of disease caused by this retrovirus. Clearly progress has been made in development of drugs such as azidothymidine (AZT) which interfere with proliferation of the HIV virus. Because HIV infection is characterized by progressive immunodeficiency which in its advanced stages is manifested by an inability to respond to antigenic challenges thereby rendering the patient vulnerable to opportunistic infections, there is a clear rationale for developing drugs to modify the immune defect. We describe such a drug which we have termed an "immunosupportive therapeutic."

Several years of research led us to identify and subsequently isolate from human leukocyte dialyzates, an immunoregulatory biologic designated as IMREG-1. This biologic was initially identified by its ability to enhance delayed hypersensitivity reactions to recall antigens (1). Its activity appeared to depend on two small peptides having the sequences Tyr-Gly and Tyr-Gly-Gly, recognizable as the amino terminal ends of the enkephalins. It is of interest to note that these peptides were capable, at dilutions in the femtamolar range, of enhancing delayed type hypersensitivity (DTH) to recall antigens. Recently, we shown that IMREG-1 and the peptide Tyr-Gly were capable of augmenting the production by peripheral blood lymphocytes of $\gamma$-interferon induced by an antigen or mitogenic stimulus (2). We have also demonstrated that both IMREG-1 and the Tyr-Gly dipeptide enhanced the expression of receptors for IL-2 on the $CD_4^+$ lymphocyte subset (3).

Since DTH is a primary index of cell-mediated immune function, and this function is enhanced by IMREG-1, we reasoned that this biologic might be useful in patients infected with HIV virus and with compromised cell-mediated immune function.

**Table 1**
**Occurence of Events in ARC Patients By Treatment Assignment and Weeks on Study**

| Placebo - 1021 Patient Weeks | | IMREG-1 - 2117 Patient Weeks | |
|---|---|---|---|
| Diagnosis | Days to Event | Diagnosis | Days to Event |
| New KS | 32 | | |
| PCP | 41 | | |
| PCP | 69 | | |
| PCP | 83 | | |
| T-Bronch candida | 84 | PCP | 98 |
| PCP | 113 | Periph. Neuropathy | 111 |
| Lymphoma | 139 | PCP | 121 |
| Periph. Neuropathy | 139 | | |
| Periph. Neuropathy | 139 | | |
| Wasting syndrome | 140 | | |
| Encephalopathy | 141 | | |
| PCP | 166 | Esoph. Candida | 154 |

KS = Kaposi sarcoma; PCP = *Pneumocystis carini* pneumonia; T-Bronch candida = tracheobronchial candidiasis; Periph. = peripheral; Esoph. = esophageal

Initial open-label studies in patients with HIV disease gave indications of clinical improvement and improved immunologic function, as measured by several parameters including the return of DTH to recall antigen. The results were of sufficient import to merit a larger placebo-controlled trial.

In November 1986, we initiated a randomized, double-blind placebo controlled trial of IMREG-1 in patients with advanced ARC. The trial was carried out at eight centers in the United States to determine whether administration of IMREG-1 slowed progression of this disease. One hundred and fifty eight patients (141 with ARC and 17 with Kaposi sarcoma), were enrolled in a double-blind randomized placebo controlled trial at eight centers in the United States. Patients at each center were randomized in a 2:1 drug/placebo allocation and were followed for six months or until a preselected endpoint was reached. Eligibility criteria were established to define a group of HIV positive individuals at high risk of developing an AIDS-defining condition in a six month period. These included significantly reduced $CD_4^+$ cells, anergy and other constitutional symptoms, or slowly progressive Kaposi sarcoma (KS) with no other AIDS sequelae. Endpoints were defined as clinical events inclusive of defined progression of disease or, in existing KS patients, rapid progression of KS or occurrence of another AIDS-defining event. Endpoints were initially determined by the treating physician, with final determination of endpoint occurrence being made following case review by the physician-investigators prior to unblinding the study. All statistical analysis was performed using BMDP software on an IBM-AT.

In March 1988, the code was broken and the trial terminated. There were 16 endpoints among ARC patients who completed the protocol--12 out of 37 patients in the placebo group, and 4 out of 69 patients in the drug (IMREG-1) group. Moreover, endpoints occurred earlier in the patients who were in the placebo group *(Table 1)*. These data gave a Relative Risk of reaching an endpoint in the untreated group of 6.6 based on Logistical Regression analysis to adjust for "confounding." The findings led to the conclusion that treatment with IMREG-1 significantly diminished the likelihood of reaching an endpoint ($p < 0.001$).

A rigorous analysis of baseline variables in the patient population indicated

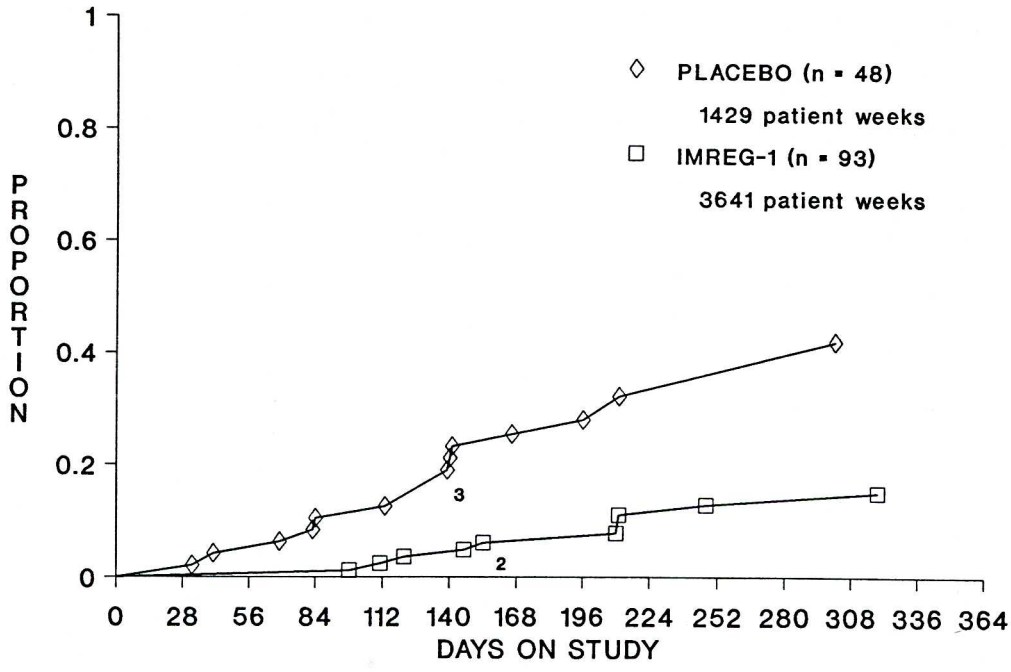


*Fig. 1. Kaplan-Meier probability of experiencing an AIDS-defining or AIDS-related event in patients with AIDS-related complex (ARC) treated with IMREG-1 compared to placebo in a double-blinded randomized placebo controlled trial. Patients who received IMREG-1 had a 15 percent probability of such events in 319 days compared with a 42 percent probability in 301 days for those receiving a placebo, p=0.0005.*

that these were well matched, and that there was no imbalance between the drug and placebo groups. Whereas the treated (IMREG-1) group had twice the number of enrolled patients and therefore a greater opportunity to accumulate endpoints, the patients who received IMREG-1 developed in fact only one-third the number of endpoints as compared to the untreated (placebo) group.

Although patients were not stratified by $CD_4^+$ cell numbers at randomization, post-randomization stratification indicated that in each stratum proportionally more AIDS-defining events occurred in the placebo group than in those treated with IMREG-1.

At the conclusion of the trial protocol, or upon reaching an endpoint, each patient was given the opportunity to receive IMREG-1 for a six-month period. Sixty-four of 93 ARC patients originally assigned to receive IMREG-1 and 30 of the 48 ARC patients originally assigned to receive placebo opted for treatment with open-label IMREG-1. During the open-label continuation protocol patients were not restricted from taking potentially confounding medications, as they were during the placebo controlled trial. Nonetheless, using all available observation time from both the placebo-controlled trial and the continuation protocol, untreated patients demonstrated a 42% probability of experiencing an AIDS-defining or AIDS related event in 301 days. IMREG-1 patients, by contrast, had only a 15% probability of such events in 319 days. This difference was significant at the p=0.0005 level *(Fig. 1)*. The relative risk for these incidence rates demonstrated that it was 3.7 times more likely that untreated patients experienced an AIDS-defining or -related event during the extended observation period.

These results strongly suggest that administration of the immunomodulatory biologic IMREG-1 altered the course of a human disease, i.e., AIDS-related Complex.

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