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Evaluation Of Immunopotentiating Activity Of A Herbomineral Formulation PV-150896 In HIV Infection.

A Randomised Double Blind Placebo Controlled Trial.

According to the WHO estimates by 2000 A.D. over 90% of AIDS cases will occur in the third world countries with India facing the largest burden of HIV infection in the world.

In-spite of the intense efforts and massive funding of research the world over, anti-retroviral therapy has as yet met with modest success. In the Indian scenario the restricted availability of these anti-retrovirals coupled with the high costs which make them unaffordable, virtually puts these drugs beyond the reach of most of the HIV infected population in India.

In this backdrop various claims of AIDS cure by practitioners of traditional indigenous medicine offering economical alternative therapies are becoming common and appear attractive. However there is now a growing realisation to scientifically and systematically evaluate such claims by conducting controlled clinical studies by experts.

HIV infection by various mechanisms causes progressive immune depletion. The CD_4 lymphocyte count has been used as a surrogate marker of the immune status. Immune depletion make the patients vulnerable to life threatening opportunistic infections to which the patients ultimately succumb. Therefore in addition to antiretroviral therapy a search is being made for medicines which may potentiate or restore the immune response so that the patients can be protected against opportunistic infections as well as may prolong the life expectancy.

Traditional Indian and Chinese medicine describe a number of drugs with immunomodulating and immunopotentiating activities and include indigenous drugs like Asparagus racemosus[1,2], Trichosanthes spp[3,4,5], Allium sativum[6], Pickrorhiza kuorra, Tinospora cordifolia[7,8], Glycerrhizae glabra[9,10,11,12], Prunella vulgaris[13], Astralagus memberanacaus[14 to 26], Cuccurma longa, Angelica galuca[27], Zingiber officinale[28,29], Achyranthes bidentata[30,31] and others. A number of these drugs of herbal origin have also been individually evaluated in the treatment of HIV and AIDS-related illness[32 to44].

The present study was designed to assess the therapeutic effects of a herbomineral formulation PV-150896 containing aforesaid herbal drugs in HIV infected cases with particular reference to its properties for immune restoration or potentiation.

Methods:

Safety Evaluation :

Before commencing the study PV-150896 was analysed and found to be free of toxic heavy metals or steroids.

Study Sample :

To be eligible for the study patients had to meet all the following criteria - documented HIV infection, age between 20 to 50 years, CD_4 lymphocyte count from 200 to 500 cell/mm^3, Karnofsky performance score 60 and above, Hb gm% at least 7gm%, total lymphocyte counts above 2000/mm^3, having normal renal and hepatic function and able to understand and give written consent.

Exclusion criteria included current peripheral neuropathy, significant cardiac, hepatic, renal or neurological disease, active cancer or intractable diarrhoea or severe malabsorption. Pregnant and lactating mothers were excluded for obvious reasons.

HIV infected patients with CD_4 counts below 200 cells/mm^3 were excluded from the study. It was planned to include these AIDS cases subsequently based on the therapeutic outcome of this study.

Study Design:

Our study was a randomised, double blind, placebo controlled trial on 25 HIV positive patients for one year, carried-out at the Virology OPD, Department of Medicine, Sir J.J.Hospital, Mumbai.

Treatment Regimens:

The 25 patients were randomly assigned to receive either PV-150896 (15 patients) in a dose of 11 tablets a day (2 tablets A and 9 tablets B i.e. 11

tablets) or Placebo (10 patients) in a dose of 11 tablets a day (2 tablets A and 9 tablets B i.e. 11 tablets) for one year. Patients received conventional therapies for opportunistic infections wherever indicated.

PV-150896 and matched placebo was supplied by Pharmaveda, Mumbai, India.

Study Assessment:

After randomisation and initiation of the blinded study the patients were seen monthly for detailed history, physical examination and laboratory investigations for hematological and clinical chemistry evaluations which included liver function tests and renal function tests.

The primary outcome measure was the change from baseline in absolute CD_4 lymphocyte counts during the course of the study. The secondary outcome measures were clinical progression of HIV disease, response to the conventional therapies for preexisting opportunistic infections, percentages of lymphocytes that were CD_4 lymphocytes, improvement in the karnofsky performance score, reduction in opportunistic infections and improvement in clinical status of the patient.

CD_4 lymphocyte enumeration was done on day 0, 30, 60, 90, 180, 270 and 360 by flow cytometry at Speciality Ranbaxy Limited, Mumbai, India. CD_4 lymphocyte enumeration was determined two time before therapy with study medications was initiated and the baseline absolute CD_4 lymphocyte count was defined as the mean of the two values.

Clinical progression of HIV disease was classified according to the criteria from the Centre for Disease Control and Prevention (CDC), namely, A1, A2, A3, B1, B2,B2 , C1, C2, and C3[45].

Toxic effects grades were assigned to clinical and laboratory parameters in accordance with AIDS Clinical Trials Group (ACTG) definitions[46]. The intensity of all other adverse events was graded by the investigators as mild, moderate, or severe.

All diagnoses were reviewed by clinical research personnel who were blinded to the treatment assignments. The criteria for discontinuation of assigned

treatment included serious adverse events, noncompliance or unreliable follow-up.

Statistical Analysis:

Patients were randomly assigned to one of the two treatment groups with the use of random number tables. All analyses were carried-out using the intent to treat population. Baseline characteristics were compared between treatment groups using the Van Elteren test[47] stratified by study centre for continuous variables and using Cochran-Mantel-Herenzel test[48] stratified by study centre for categorical variables. The primary treatment comparison evaluated profiles of absolute CD_4 lymphocyte count in the 2 treatment arms during the entire course of 360 days.

The primary metric for analysis of all immunological and laboratory measures was the area under the curve (AUC) of all postbaseline measurements minus the baseline value (design-based analysis of time-weighted difference average (DAVGT)). This was compared between treatment groups using the Van Elteren test stratified by study centre.

Results:

Out of a total of 25 patients enrolled in the study 15 received PV-150896 (2 tablets A + 9 tablets B daily) and 10 patients recieved placebo (2 tablets A + 9 tablets B daily).

Baseline characteristics are shown in Table 1. There was no statistically significant differences in the baseline characteristics between treatment groups. No major adverse reactions were noticed and all patients completed the study.

Immunological Measurements of Efficacy :

Patients randomised to receive placebo showed progressive reduction in CD_4 lymphocyte counts throughout the 360 day period with mean CD_4 lymphocyte count of 23.46 cells/mm^3, 20.0 cells/mm^3,27.84 cells/mm^3, 30.6 cells/mm^3, 80.79 cells/mm^3, and 90.9 cells/mm^3 below baseline at 30 days. 60 days, 90 days, 180 days, 270 days, and 360 days respectively (Figure 1).

Patients receiving PV-150896 had a mean increase of CD_4 lymphocytes of 58.67 cells/mm^3 46.72 cells/mm^3, 95.81 cells /mm^3,124.58 cells/mm^3, 110.00 cells/mm^3 and 140.33 cells/mm^3 above baseline at 30 days, 60 days, 90 days, 180 days, 270 days, and 360 days respectively (Figure 1).

Figure 1

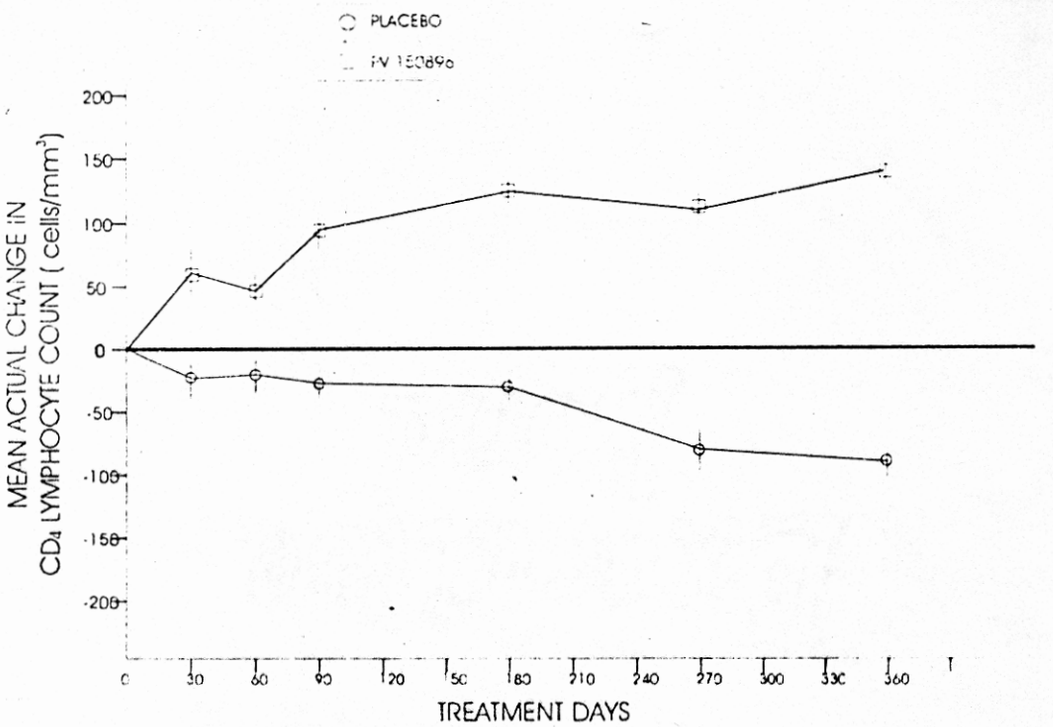
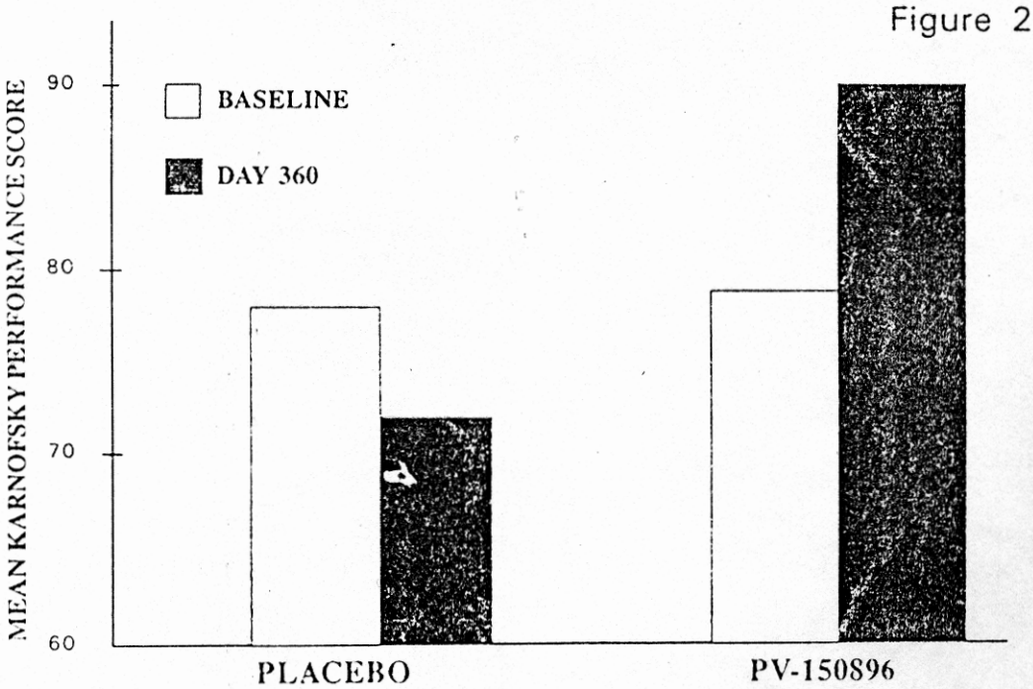


Figure 2



The changes in absolute CD_4 lymphocyte count during the entire study period of 360 days differed significantly ($P < 0.001$) favouring PV-150896 over placebo regimen.

Table-1 Baseline Characteristics of the Treatment Groups (n = 25)*

Characteristic	PV-150896 (n = 15)	Placebo (n = 10)
Age, y		
Mean	38	38
Range	(21-50)	(22-49)
Sex (No.)		
Male	8	5
Female	7	5
Primary risk factor		
Sexual contact	12	8
Homosexual	1	1
Transfusion	2	1
CD_4 Cell count cells/mm^3		
No. of subjects	15	10
Mean	307 ± 86	310 ± 98
Range	212-451	233-480
Opportunistic infections		
Tuberculosis	5	3
Herpes zoster	2	1
Oral candidiasis	6	4
Asymptomatic	2	2
CDC status (No.)		
CDC (A2)	2	2
CDC (B2)	8	5
CDC (C2)	5	3
Karnofsky score (Mean)	88	89
Hb gm%	8.9	9.1

* HIV indicates human immunodeficiency virus, Centres for Disease Control and Prevention.

Percentage of lymphocytes that were CD_4 lymphocytes, the secondary marker for immunological activity, also increased over the baseline values throughout the 360 day period in favour of PV-150896 therapy as compared to placebo therapy ($P < 0.02$, data not shown).

Clinical Assessment of Efficacy :

In the 360 day period 6 patients from the placebo group progressed to a new CDC category or subcategory : 1 from A2 to B2 (oral candidiasis), 2 from B2 to B3 (CD_4 lymphocyte count going below 200 cells), 3 from B2 to C2 (mycobacterial disease).

In the placebo group there were recurrent minor symptoms like persistent dry cough and skin rash. There was no significant weight loss or gain. However mean Hb% was reduced from the baseline value of 9.1 to 7.3 by day 360. The mean Karnofsky performance score was also reduced from the baseline value of 78 to 70 by day 360 (figure 2). Two patients who became infected with pulmonary tuberculosis needed brief hospitalization. The response to conventional therapy for opportunistic infections was barely satisfactory.

There was improvement and reversal in the CDC classification in patients receiving PV-150896 : 2 from A2 to A1, (CD_4 count going above 500 cells), 4 from B2 to B1 (CD_4 count going above 500 cells), 1 from C2 to C1 (CD_4 count going above 500 cells). However one patient progressed from CDC category A2 toB2 (oral candidiasis.)

The observations on clinical features in the patients receiving PV-150896 were encouraging. The patients developed a sense of well being and minor symptoms like dry cough , pruritis & depression disappeared. Anaemia improved as was seen by rise in Hb% from the first month itself reaching a mean value of 13.6 by the third month which further improved by day 360 to 14.3 ($p < 0.001$ when compared with placebo group throughout the study period). Although there was no significant weight gain the patients appetite improved. All patients on PV-150896 responded well to the conventional therapies for the respective opportunistic infections without any major relapse or recurrence of the same or newer opportunistic infection during the study period. The mean Karnofsky performance score was also improved from the baseline value of 79 to 90 at the end of study period (figure 2).

Safety Evaluation:

PV-150896 was well tolerated without any adverse reaction. The liver function test and kidney function tests remained normal throughout the study period.

Comment :

Therapy with PV-150896 produced a significant and sustained improvement compared with placebo in all immunological and clinical assessments without any increase in the ACTG - defined clinical or laboratory assessed toxic effects.

Patients receiving PV-150896 therapy showed a sustained and consistent CD_4 lymphocyte count increase over baseline values over 12 months unlike the placebo group in which the CD_4 lymphocyte showed a sustained decline.

The immuno-restorative effects of PV-150896 are further confirmed by an over-all improvement in the clinical status of the immunocompromised patients infected with HIV as indicated by improvement in the Karnofsky performance score and better response to the conventional therapy for opportunistic infections.

It would be interesting to assess the effect of PV-150896 on quantitative viral lood, which was not done in this study since the test facility was not availble in Mumbai at the time this study was initiated.

In light of the findings of this study, considering the low cost of PV-150896 compared to the expensive antiretroviral therapy, PV-150896 offers an affordable, easily available and safer alternative to the immunocompromised HIV + ve patients.

Since our study population is relatively small, the benefits of this therapy need to be confirmed on larger population.

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