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Efficacy & Safety Of An Immunomodulatory Ayurvedic Medicine As A Pre-haart Option: 5-year Longitudinal Multicentric Study

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BACKGROUND

The huge success of modern chemotherapeutics in overcoming infectious diseases, by inhibiting life cycles of various pathogens, has resulted in focusing efforts on the similar lines in HIV therapeutics as well. Thus efforts have being focused on inhibiting the HIV life cycle with the use of ART. While ART has substantially improved the survival rates with reduction in morbidity & mortality, however a combination of host & viral factors including the phenomenal rates of viral replication, the development of long lived reservoirs of HIV early during primary infection & the inability of total viral suppression, in addition to long term toxicities have resulted in a cure being elusive with the use of ART. This has resulted in guidelines recommending deferring initiation of HAART till CD4 counts cross below 200 mark, especially in resource limited settings.

It is now recognized that host factors together with viral factors determine the pathogenesis of HIV disease - the complex events that lead to the destruction of an HIV infected person's immune system. This realization that "host factors" including the specific immune response to the virus, non-specific factors and the individuals genetic make-up are as important to the HIV disease process as the intrinsic virulence of the virus itself. This has opened up the possibilities of manipulating these host factors in favor of the host and against the HIV in an attempt to impede HIV disease progression, and forms the basis of immune based and immune modulating therapies in the management of HIV disease.

Traditional Indian system of medicine describes a number of drugs of herbal origin which have now been documented to have immunomodulating & immunopotentiating activities. These herbs have been shown to differentially modulate the cytokine profile, by inducing and amplifying the effects of certain cytokines like IL-2 while at the same time inhibiting others like TNF-α. Earlier studies documented immune boosting & increase in CD4 counts with an ayurvedic medicine (Reimun) in ART naïve HIV patients. We therefore thought of assessing long-term role of REIMUN in preserving the immune function as a pre-HAART option.

METHODS

Study design:	Multi centric, open labeled non-comparative sequential observational study
Settings	Tertiary referral centres
Study Population:	355 ART naive HIV +ve patients of either sexes between 18 to 50 years with CD4 counts between 500-200 cells/mm^3 opting to receive Reimun (Immunomodulatory ayurvedic medicine), Hb > 7 gm%, Karnofsky Performance Score (KPS) > 60. Pregnant & lactating mothers excluded.
Study Assessments:	Clinical examination, blood chemistry, renal & liver function tests X- ray chest, USG, CD4 lymphocyte enumeration.
Outcome measures:	
Primary:	Serial CD4 counts quarterly in 1st six months & six monthly thereafter.

Secondary: Clinical assessment, Occurrence & severity of O.Is Karnofsky Performance Score Fall in CD4 counts < basezline Death Safety & tolerability

Study Treatments: All patients initiated on Reimun- A 3 tabs o.d. & Reimun- B 3 tabs o.d. Patients developing O.Is received standard treatments.

RESULTS

The improvement in the clinical status was apparent with a sense of well being, amelioration of dry cough, pruritus and anxiety. There was improvement in the appetite. Patients with rapid loss of weight showed a significant weight gain varying from 7 to 10 Kgs in body weight. The gain in weight was maximum in the first 2 months, with mean weight gain 5.3 Kgs by third month ($p<0.05$), after which weight stabilized.

The hematocrit response was good with normalization of hemoglobin. Hemoglobin increased from mean value of 9.2 gm% at baseline to 11.8 gm% by the sixth month, reaching a normal value of 12.1 gm% at the end of 1 year and remaining stable at the end of the study with mean value of 12.2 gm% ($p< 0.05$).

The mean Karnofsky Performance Score also improved from 72 at the time of entry in the study to 88 at the end of the study period. Over 5 years study period 22 patients were lost to follow-up, 6 patients developed herpes zoster, 14 episodes of oral candidiasis and 7 cryptosporidiosis. 16 patients reactivation of TB, 8 of these patients died. All other patients responded to standard therapies for Ols.

The post therapy increase in the CD4 lymphocytes was very impressive. Immunological improvement was seen co-relating with the clinical improvement & the mean increase in absolute CD4 count was 47, 62, 168, 121, 138, 98 & 81 cells at 3 (n=355), 6 (n=342), 12 (n=350), 24 (n=330), 36 (n=324), 48 (n= 318) & 60 (n= 312) months above the baseline value respectively ($p<0.02$). Patients with higher CD4 counts at baseline showed rapid and higher increments. Some of the patients went on drug holidays due to financial constraint. These cases showed a decline in CD4 counts which was restored on resumption of therapy. Percentage of CD4 lymphocytes also increased significantly over the baseline values throughout the study period in favor of Reimun. 17 patients though showed fall in the CD4 lymphocyte counts.

No adverse reaction to the study medication was reported.

DISCUSSION

The role of cytokines in HIV disease has been increasingly recognized after the demonstration that 2 groups of cells exists amongst the CD4 helper lymphocytes, namely, the Th-1 & Th-2 cells. The Th-1 cells preferentially secrete IL-2, IL-12 & INF-γ , which stimulate the cellular immune reactions. The Th-2 cells produce primarily IL-4, IL-6 & IL-10, and thus stimulate the humoral immune reactions. Subsequently it has been established that the Th-2 cytokine profile favored the development of AIDS in HIV infected patients, whilst the Th-1 cytoline profile inhibited the progression to AIDS. Cell culture experiments, have demonstrated that certain pro-inflammatory cytokines secreted by immune system cells, such as TNF-α& IL-6, can boost the replication of HIV are also thought to be responsible for the wasting, weight loss and severe cachexia seen in HIV patients. Other cytokines such as IL-10 inhibit HIV replication in macrophages & inhibit IL-6 or tuberculosis induced HIV replication, in part by blocking the activity of TNF-α & IL-6. In-vitro data suggests that the presence of or absence of certain cytokines influence the relative rate of replication of different strains of HIV. Thus the cytokine microenvironment is thought to regulate differentially the replication of different strains of HIV.

HIV associated immune deficiency is now thought to be due to both HIV-mediated suppression of generation of new immune cells as well as due to accelerated destruction of CD4 bearing

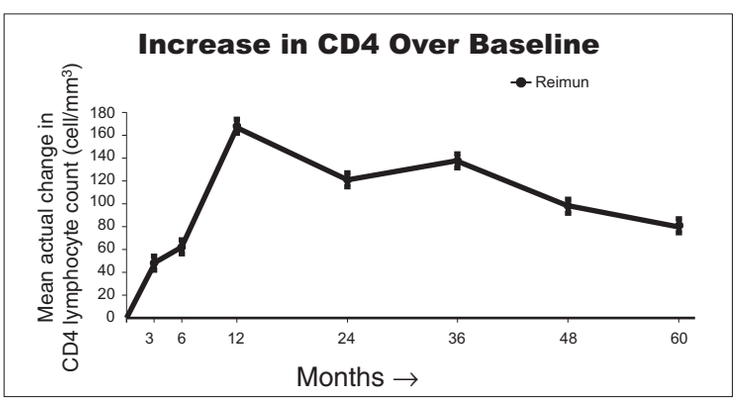
immune cells. Studies have demonstrated that HIV infection suppresses multi-lineage hematopoiesis before effects on thymopoiesis are observed and appears to have profound negative effects on systems of T-cell production.

Thus it is being increasingly recognised that "host factors" including the specific immune response to the virus, non-specific factors and the individuals genetic make-up are as important to the HIV disease process as the intrinsic virulence of the virus itself. Host factors together with viral factors determine the pathogenesis of HIV disease - the complex events that lead to the destruction of an HIV infected person's immune system.

The various individual drugs in Reimun have been reported to stimulate and revitalize the bone marrow-thymus axis. Individual phytochemicals probably induce a cytokine profile that favors the host and opposes the viral effects and impedes the HIV disease progression. Withania somnifera in Reimun is reported to increase the bone marrow cellularity and stimulate the proliferation of the pluripotent stem cells. Angelica galuca, Tinospora cordifolia & Astralagus membranacaus have been shown to increase the secretion of various hematopoetic growth factors like Epo, GM-CSF, & ILs, especially IL-2 which is the T-cell growth factor. The increase in hemoglobin & CD4 counts with Reimun could be in part due to these actions. Allium sativum, Curcuma longa & Glycerrhiza glabra enhance the production of cytokines like IL-10 which interferes with HIV replication, or enhance production and biological effects of beneficial cytokines like INF-γ & IL-2. These drugs also decrese the production & biological effects of harmful cytokines like IL-1 & TNF-α . The significant weight gains and the overall improvement in the clinical status and the reduced incidence of opportunistic infections is probably a reflection of the above said actions.

Reimun not only arrested the CD4 decline in 95 % of cases but also showed a significant and sustained increase in the CD4 cells which was probably responsible for prevention of opportunistic infections in majority of cases.

The increments in CD4 counts due to Reimun may be primarily due to its immuno-modulatory effect. We feel, that the various ingrediants of Reimun having different cytokine modulatory activity, have a primary effect on restoration of immune system. The sustained increase in CD4 counts probably reflect the augmentation of broad immune response as is seen with the use of cytokines. This broad immune response protects the patients from opportunistic infections, stimulates their appetite and leads to weight gain.



Baseline Characteristics	
Age, Y	
Mean	38
Range	21 - 50
Sex (No.)	
Male	221
Female	134
Primary Risk Factor	
Heterosexual Contact	351
Homosexual	3
Transfusion	1
CD_4 Cell Count cells/mm^3	
No. of Subjects	355
Mean	324 $\pm$ 86
Range	221 - 477
Opportunistic infections	
Tuberculosis	73
Herpes zoster	42
Candidiasis	83
Cryptospora / Isospora	36
Karnofsky score (mean)	72
Hb gm % (mean)	9.2

CONCLUSIONS

Reimun safe & well tolerated without any significant untoward effect, showed sustained clinical as well as immunological improvement over study period. Reimun appears to be a useful pre-HAART treatment option in preserving immune function.