

Immune and Viral Response to Isoprinosine in Chronic Fatigue Syndrome

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Background: CFS is a debilitating condition associated with low level activation of the immune system, and impaired cytotoxicity. Isoprinosine induces lymphocyte differentiation, and augments lymphocyte, macrophage, cytotoxic T and natural killer (NK) cell functions, resulting in an indirect host mediated antiviral action.

Objective: To describe the clinical and immunomodulatory effects in patients with CFS treated with Isoprinosine

Methods: We performed a retrospective chart review of patients with CFS (CDC 1994 case definition, history and physical examination), and included those who had evidence of low NK cell cytotoxicity (NKCC) activity (<20%) and no other concomitant immunomodulatory therapy or systemic antivirals that received Isoprinosine between January 2004 and July 2008. The dose schedule for Isoprinosine was 500/1000mg (odd/even weeks), 3 times a day, Monday through Friday, for a 6-month-cycle, repeated according to patient's clinical and laboratory progress.

The clinical assessment was based on a score developed by the principal investigator that qualified the functional status of the patients ranging from 1 to 7, with 1 being a severely impaired function as compared to baseline; 4 as the baseline status at the beginning of the therapy, and 7 being an improved function to a normal status. The immunomodulatory assessment included measurement of whole blood NKCC activity to K 562 erythroid cells, T cell activation measured by flow cytometry (CD2+CD26+, CD4+CD38+, CD8+CD38+, CD4+ HLA DR+, CD8+ HLA DR+, CD8+CD11b expression) and Tumor Necrosis Factor (TNF)- α by ELISA. Also, the pre and post treatment titers of EBV (VCA-M, VCA-G, EBNA-G, EA-G) and HHV-6 (IgM, IgG) were included. Non parametric analysis of variance was used to establish significant difference between the baseline and 6 and 12 months post treatment.

Results: Seventy two patients fulfilled the inclusion criteria, 65 (90.3%) women, mean age of 51 years (range 27 to 82). The onset of CFS was slow in 73.6% and acute in 26.4%, and the mean duration of disease was 13 years. At the time of this analysis follow up data after 6 months of therapy was available in 42 subjects and showed a highly significant increase in the clinical score ($p=0.0001$). There was a 50% increase over baseline in the NKCC activity ($p=0.03$) in 34 patients. The CD4+ CD38+ T cell levels decreased from elevated baseline levels ($p = 0.03$) in 29 patients. Twenty two patients had a clinical follow up at 12 months, 12 of them with immunological evaluation. There was a highly significant difference in the clinical score ($p=0.009$) and in the number of CD4+CD38+ T cells towards normal ($p= 0.002$) and a significant decline in the CD8+ CD38+ T cells ($p= 0.03$). Viral serology before and after 6 months on Isoprinosine was compared in 12 (EBV) and 20 (HHV-6) patients, it did show a trend of viral response as reflected in a significant decrease of VCA M ($p=0.045$) and VCA G ($p=0.003$). No patients developed nephrolithiasis or gout, though GI side effects were common (23 %) and dose adjustment was required in 19%. No serious adverse reactions were reported.

Conclusion: There was a significant improvement in the clinical score of patients with CFS treated with Isoprinosine at 6 and 12 months, with an improvement towards normalization of CD4+CD38 at 6 and 12 months, and CD8+CD38+ at 12 months. NKCC activity was significantly improved and EBV titers (IgM and IgG) decreased significantly after 6 months of therapy. A large randomized trial focused on this immune defined subset would be appropriate.

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