INOSINE PRANOBEX IN THE COMBINATION THERAPY OF HIV INFECTION

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Inosine pranobex (InPx) enhances the functions of various immune cells, including T and B lymphocytes, natural killer cells (NK), and monocytes-macrophages (1), depending, at least in part, on an increased cytokine production (1). InPx has also antiviral activity against RNA- as well as DNA-viruses. Recently, the antiretroviral activity of InPx has been shown (2). Furthermore, InPx does not increase HIV production by activating CD4+ lymphocytes with proviral RNA (2).

Preliminary data in patients with the AIDS-related complex (ARC) as well as with persistent generalized lymphadenopathy (PGL) showed that InPx could restore immune function (1). Furthermore, the InPx ability to improve HIV infection course was suggested (1).

Recently, two multicenter, controlled trials assessed InPx treatment in the early stages of HIV infection to delay progression toward overt AIDS and to restore host's immunocompetence (3,4). In the Italian trial (3), none of the subjects receiving InPx (4 gr per day throughout 3 months)was "de novo" diagnosed to have an AIDS-defining condition, such as tuberculosis, P. carinii pneumonia or Kaposi's sarcoma. However, by using the Centers for Disease Control (CDC) classification system, a comparable progression rate from CDC group II toward more advanced stages (groups III and IV) was observed in both InPx- and placebo-treated patients. Finally, in both groups a trend toward a reduced CD4+ cell counts was found throughout the study period.

In the Scandinavian trial (4), HIV+ patients were stratified into three subgroups according to their CD4+ cell count (200, 200-500, 500 x 10 per liter) and randomly assigned to receive either InPx (3 gr per day throughot 6 months) or placebo. No significant difference was found between InPx- and placebo-treated groups in the number of patients whose condition progressed from CDC group II or III to CDC group IV (without AIDS) or in the number who acquired any of the disease defining group IV, but that are not considered indicative of AIDS, with the exception of thrush.

The progression rate to overt AIDS was always more marked in the placebo group, irrespective of CD4+ cell count at entry into the study. The progression to AIDS was associated (P 0.001) with treatment group and lower CD4+ cell count at baseline. CD4+ cells decreased during the study period, although no significant difference was found between patients receiving either InPx or placebo.

Both trials indicate that InPx treatment doses not result "in vivo" into an increased frequency of CD4+ lymphocytes, which are the main target of HIV infection. However, these data do not rule out the possibility that InPx could act "in vivo" in HIV-infected patients by enhancing the function of the remaining T cells as well as the NK activity.

InPx proved to affect "in vivo" the clearance rate of AZT (5), suggesting

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that the concomitant administration of InPx to AZT-receiving HIV+ patients could allow to reduce both AZT dosage and AZT-related toxicity. In fact, the assay of plasma AZT levels in HIV+ subjects also receiving InPx showed both higher mean peak and higher mean nadir level as compared to patients receiving AZT only (5). Furthermore, after 7 days of treatment AZT plasma levels were significantly higher in patients receiving both drugs than in those receiving AZT only. However, the mechanisms accounting for these effects remain to be established.

The combination treatment of HIV infection with both InPx and AZT has several potential advantages, such as lower AZT dosage and a longer interval period between administering AZT to obtain sustained plasma levels as well as a potential to enhance residue immune function resulting from InPx treatment.

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