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INOSINE PRANOBEX IN THE TREATMENT OF HIV INFECTION: A REVIEW

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Abstract — Inosine pranobex (InPx) could prove a valuable and innovative approach to the treatment of HIV-infected patients, since InPx administration has been shown in two multicenter trials to effectively delay the progression of HIV infection to overt AIDS. However, further studies are strongly required to optimize both the dosage of inosine pranobex and the administration schedules. Furthermore, clinical trials evaluating combination therapy of HIV infection with both InPx and zidovudine should ultimately provide an important advance in the management of HIV-infected patients. Our finding that concomitantly administered InPx to zidovudine-receiving patients increased the plasma levels of zidovudine as well as prolonged zidovudine mean half-life during InPx treatment suggests several potential advantages of the combination treatment with both InPx and zidovudine, such as a need for lower zidovudine dosage and a longer interval period between administering zidovudine to obtain sustained plasma levels as well as a potential to enhance residue immune function resulting from inosine pranobex treatment.

Inosine pranobex (isoprinosine, InPx), the paracetamidobenzoic acid salt of *N,N*-dimethylamino-2-propanol : inosine in a 3 : 1 molar ratio, has been shown to enhance the function of various cells of the immune system in several studies both *in vitro* and *in vivo* (Glasky & Gordon, 1986; Binderup, 1985; Exon, Henningsen, Koller & Talcott, 1986). The immunoenhancing properties of InPx seem to be strictly dependent on an increased production of cytokines, notably interleukin-1 (IL-1), interleukin-2 (IL-2), or both (Fischbach & Talal, 1985; Wiranowska-Stewart & Hadden, 1986; Tsang, Sei & Bekesi, 1987; Hershey, Bindon, Bradley & Hasic, 1984). Furthermore, InPx was recently proved to strongly increase the gamma-interferon (IFN) production by mitogen-driven peripheral blood mononuclear cells (PBMCs) (De Simone, Santini & Tzantzoglou, 1991).

InPx has also been reported to augment *in vitro* the expression on the murine splenocyte surface of T-lineage and B-lineage specific molecules, such as theta and CR3 antigens, respectively (De Simone *et al.*, 1991; Touraine, Hadden & Touraine, 1980; Renoux, Renoux & Degenne, 1979a).

Furthermore, InPx is able to enhance mitogen-driven lymphocyte activation and proliferation in both humans and animal models (Morin, Grischelli & Daguillard, 1979; Hadden, Hadden & Coffey, 1976; Renoux, Renoux & Guillaumin, 1979b). The finding that InPx enhances the lymphocyte proliferative response to lectins which act mainly via T-cell enrollment, such as phytohemagglutinin (PHA) and concanavalin A (Con A), or via the recruitment of both T- and B-cells, such as pokeweed-mitogen (PWM), or via only B-lymphocytes, such as lipopolysaccharide (LPS), clearly points out the ability of InPx to recognize various cell targets. However, under different experimental conditions the cell subset which is first driven to activation and proliferation is strongly affected by InPx concentrations in the culture medium. Furthermore, although the mitogen-stimulated activity of suppressor T-lymphocytes has been shown to be both induced and suppressed by InPx in different assays (Touraine *et al.*, 1980; Renoux *et al.*, 1979a: Rey, Cupissol, Thierry, Esteve & Serrou, 1983), the biological significance of these effects remains to be established. Moreover, while the PWM-induced production of IgG-containing peripheral blood lymphocytes was augmented (Hersey *et al.*, 1984), which may indicate inhibition of suppressor cell activity or stimulation of helper activity, the characteristically high immunoglobulin synthesis by patients with systemic lupus

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erythematosus was decreased by *in vitro* incubation with InPx (Nakamura, Miyasaka, Pope, Talal & Russell, 1983). A concentration-related effect has been suggested, due to the enhancement of suppressor T-lymphocyte activity at relatively high concentrations both *in vitro* and *in vivo* (Touraine *et al.*, 1980), while the augmentation of helper T-lymphocyte activity is predominant at lower concentrations. Overall, these data strongly suggest that, at least under *in vitro* conditions, InPx could affect the proliferative response of immune cells via acting on the network of both helper and suppressor T-circuits. However, the mechanisms accounting for the recruitment *in vivo* of either helper or suppressor circuits remain to be established.

The cytotoxic activity of natural killer (NK) cells is strongly increased following the *in vitro* pre-treatment of PBMCs with InPx. This effect, which is independent of gamma-IFN, seems to be strictly related to the blocking by InPx of the inhibitory action on NK activity exhibited by monocytes contaminating the cell suspensions (De Simone *et al.*, 1991). There are no data available about the ability of InPx to affect the lymphokine-activated killer (LAK) cell activity.

Finally, by direct interaction *in vitro*, InPx has been shown to stimulate various indices of metabolic activity of macrophages and monocytes (Joseph, Capron, Tonnel, Gosset & Meunier, 1982; Wybran, 1978; Zerial & Werner, 1981).

Con A-induced monocyte chemotaxis is depressed in cells from cancer patients; *in vitro* exposure to InPx or to 48-h supernatants obtained from mononuclear cells pre-treated with the drug restored chemotaxis to normal or near normal levels (Tsang, Fudenberg, Pan, Gnagy & Bristow, 1983). Furthermore, incubation with InPx *in vitro* stimulated IL-1 production by human monocytes and alveolar macrophages, as reported above (Hersey *et al.*, 1984) and increased the levels of lysosomal enzymes in the latter (Joseph *et al.*, 1982). However, in antigen-driven lymphocyte cultures InPx could not replace the helper function of monocytes on specific lymphocyte proliferative responses (Ballet, Morin, Schmitt & Agragart, 1982).

ANTIVIRAL ACTIVITY OF InPx

InPx exhibits *in vitro* antiviral activity, although to a somewhat lesser degree as compared with other compounds, such as ribavirin, acycloguanosine, foscarnet, zidovudine (AZT), and IFNs (De Simone *et al.*, 1991; Chany & Cerutti, 1977; Muldoon, Mezny & Jackson, 1972; Chang & Weinstein, 1973). InPx is able to inhibit the replication of both RNA-viruses, such as echo, rhino, and polioviruses, and DNA-viruses, such as adeno, herpes, and cytomegaloviruses (De Simone *et al.*, 1991). Furthermore, InPx proved to strongly enhance the *in vitro* PBMC proliferative response following challenge with both herpes and myxoviruses (Morin *et al.*, 1979; Hadden *et al.*, 1976; Pompidou *et al.*, 1985a), demonstrating the ability of InPx to enhance virus-specific immune responses, at least in *in vitro* experiments. In addition, InPx has antiretroviral activity, as shown by the finding of reduced levels of reverse transcriptase as well as of p24 and gp120 antigens in HIV-infected lymphocyte cultures treated with InPx (De Simone, De Marco, Arancia, Tzantzoglou, Paradisi & Sorice, 1989b; Pompidou, Zagury, Gallo, Sun, Thornton & Sarin, 1985b) as compared with control cultures. It has been postulated that InPx exhibits its antiretroviral activity either by inhibiting the transduction of HIV through the helper T-cell membrane or by preventing DNA incorporation into the nucleus. Moreover, in InPx-treated HIV-positive cultures the absolute counts of $CD4^+$ lymphocytes were significantly higher than in untreated lymphocyte cultures (De Simone *et al.*, 1989b). On the other hand, other studies reported that InPx has minimal or even no antiviral activity against HIV (Pompidou *et al.*, 1985b; Schinazi, Cannon, Arnold & Martino-Saltzman, 1988). Furthermore, despite available literature reporting conflicting data about the efficacy of InPx in inhibiting HIV replication, concentrations of InPx above 200 μg/ml seem to result in a strong antiretroviral activity in *in vitro* experiments (Campoli-Richards, Sorkin & Heel, 1986). Clearly, further studies are warranted to better understand the molecular mechanisms accounting for the putative antiretroviral activity of InPx. However, InPx does not increase HIV production by activating $CD4^+$ lymphocytes bearing integrated proviral RNA, as demonstrated by most reports (De Simone *et al.*, 1989b; Pompidou *et al.*, 1985b).

In vivo administered InPx (4 g per day throughout at least 6 days) proved to significantly reduce the sign and symptom scores in both experimental viral infections and human viral diseases, such as hepatitis, herpes and cytomegalovirus infections (De Simone *et al.*, 1991; Muldoon *et al.*, 1972; Chang & Weinstein, 1973; Chany & Cerutti, 1977; Ohnishi, Kosuzume, Inaba, Ohkura, Shimada & Suzuki, 1983). In fact, most studies showed a trend toward a better outcome of patients treated with InPx in

comparison with control patients, as demonstrated by both clinical course and laboratory data as well as by shorter hospitalization and fewer relapses. Furthermore, no consistent toxicity ascribed to InPx has been found in these *in vivo* studies, as demonstrated by the equal number of patients in both InPx and placebo groups who prematurely discontinued their drug. Available reports clearly indicate that the most frequent InPx-related adverse effects occurring during *in vivo* treatment are mild gastric distress and, notably in patients with previously reported acute gout, hyperuricemia and hyperuricuria, due to the degradation of the inosine moiety to uric acid (De Simone *et al.*, 1991) as occurs in the metabolism of natural purine.

EFFECTIVENESS OF InPx IN TREATING HIV-INFECTED PATIENTS

Since it is estimated that more than 5 million people worldwide are currently infected with HIV and the acquired immunodeficiency syndrome (AIDS) may ultimately develop in the great majority of these patients, effective therapeutic regimens are urgently needed. Furthermore, the treatment with AZT, which is the only licensed drug exhibiting effective *in vivo* antiretroviral activity, thus resulting in delaying HIV-related disease progression, is usually associated with often life-threatening side-effects, such as anemia, neutropenia, and bone marrow toxicity, requiring blood transfusion and/or reducing the dose of AZT (Fischl *et al.*, 1987; Volberding *et al.*, 1990).

The goal of an effective treatment of HIV infection should include a strong antiretroviral activity and the enhancement of residue immune function as well as the reduction of both HIV- and drug-related complications usually occurring throughout the disease course. Therefore, either multidrug regimens or treating HIV-infected patients with a single compound with both antiretroviral activity and immunoenhancing properties are required to effectively delay the progression of HIV infection and to prevent the occurrence of both serious infections and cancer.

The administration to HIV-infected patients of a biological response modifier with immunoenhancing properties, such as InPx, could result in an increase of retroviral replication by activating $CD4^+$ lymphocytes bearing integrated proviral DNA. InPx, in spite of the ability of being co-mitogenic for T-cells under *in vitro* conditions, did not prove, alone or in combination with AZT, to enhance *in vitro* HIV production, as reported above. Overall, these data prompted several authors to test the *in vivo* efficacy of InPx in treating HIV-infected patients. Preliminary reports showed that, in patients with the AIDS-related complex (ARC) as well as in HIV^+ subjects with persistent generalized lymphadenopathy (PGL), InPx somewhat restores the immune function, as demonstrated by the enhancement of both T-cell proliferative response to mitogens (Pompidou *et al.*, 1985b; Tsang, Zanjani, Warner & Bekesi, 1986; Tsang, Roboz & Bekesi, 1987; Grieco *et al.*, 1984) and NK cell cytotoxicity (Wallace & Bekesi, 1986; Bekesi, Tsang, Wallace & Roboz, 1987). Furthermore, Wallace and co-workers have also suggested the ability of InPx to improve the course of HIV infection, as evaluated using strict clinical standpoints (Wallace & Bekesi, 1986).

Both the pharmacological properties of InPx and the good tolerance of administration (Jones, Dyken, Huttenlocher, Jabbour & Maxwell, 1982) prompted an assessment, in two multicenter, controlled trials, of the efficacy of administering InPx in the early stages of HIV infection to delay the disease progression and to restore the host's immunocompetence (De Simone *et al.*, 1989a; Pedersen *et al.*, 1990).

In the Italian multicenter trial (De Simone *et al.*, 1989a) 553 HIV^+ patients were enrolled into the study. According to the Centers for Disease Control (CDC) classification system for HIV infection (CDC, 1985), 163 (62%) individuals in the InPx group were classified as CDC group II (asymptomatic infection), 83 (32%) as CDC group III, and only 15 as CDC group IV C2, since they exhibited both oral hairy leukoplakia and candidiasis, whereas in the placebo group 187 (61%), 87 (30%), and 27 (9%) individuals were classified as CDC group II, III, and IV C2, respectively. The two groups were well-matched as far as the demographic characteristics are concerned, such as age, sex, previous treatments, and high-risk behavior for HIV infection. Furthermore, most patients who entered into the study were drug addicts (189 and 213 in InPx-treated and in the placebo group, respectively), whereas only 72 and 79 individuals in the InPx and the placebo groups, respectively, were accounted for by homosexuals, heterosexuals, and hemophiliacs. InPx treatment (4 g per day throughout 3 months) resulted in a slight improvement from a clinical standpoint as compared with untreated patients (Table 1). In fact, none of the subjects completing the trial was "*de novo*" diagnosed to have an AIDS-defining condition such as tuberculosis, *Pneumocystis carinii* pneumonia or Kaposi's

Table 1. Effects of InPx on clinical and immunological parameters

	InPx		Placebo	
	Day 0	Day 90	Day 0	Day 90
HbsAg+	14	14	16	16
p24+	9	9	9	9
CDCII	163	136	178	146
CDC III	83	90	87	96
CDC IV C2	15	35	27	50
Fever	7	6	10	15
Diarrhea	10	7	9	11
Weight loss	9	8	8	7
Minor infections	11	12	2	11*
CD4+/mm^3	538 ± 109	503 ± 141	651 ± 119	618 ± 108
CD8+/mm^3	992 ± 109	881 ± 232**	1008 ± 159	1103 ± 136
CD4+/CD8+	0.55 ± 0.15	0.60 ± 0.21	0.64 ± 0.10	0.56 ± 0.01
CD8+/HNK-1+	201 ± 54	278 ± 114**	234 ± 98	240 ± 138

*$P < 0.02$; **$P < 0.01$.
(Modified from De Simone *et al.*, 1989a.)

sarcoma. Moreover, no increase, and rather a trend towards decrease, in the number of individuals with chronic diarrhea, chronic or recurrent fevers, or minor infections was found in the InPx-treated group. However, by using the CDC classification system to assess HIV infection progression, a comparable progression rate from CDC group II toward more advanced stages (groups III and IV) was observed in both InPx-receiving and untreated patients. Finally, in both groups a trend, although not statistically significant, toward a reduction of peripheral blood $CD4^+$ T-lymphocyte counts was found throughout the study period. On the other hand, in InPx-receiving subjects a reduced frequency of circulating $CD8^+$ cells was found at the end of the study period as compared with pre-treatment values, whereas in control subjects $CD8^+$ lymphocytes were slightly increased. Therefore, the peripheral blood $CD4^+/CD8^+$ cell ratio was higher following InPx as compared with placebo treatment.

Finally, preliminary data indicate that *in vivo* administered InPx, at least under the dosage and duration treatment schedule of this trial, could result in an increased frequency of the $CD8^+$ $HNK\text{-}1^+$ cell subset. However, the biological and clinical relevance of this finding requires further investigation. None of the InPx-receiving patients was withdrawn because of toxicity and/or side-effects reasonably related to the treatment.

The Scandinavian trial (Pedersen *et al.*, 1990) was a randomized, double-blind placebo-controlled study performed to assess the efficacy of InPx treatment in delaying the infection progression in HIV-positive patients in whom overt AIDS had not yet developed. A total of 816 HIV-infected patients, ranging in age from 18 to 75, who were seropositive for HIV antibody on both enzyme immunoassay and immunoblot assay, entered into the study. The presence of AIDS according to the CDC 1985 definition was considered a strict exclusion criterion. Patients were stratified into three subgroups according to their $CD4^+$ cell count (< 200, $200 - 500$, $> 500 \times 10^6$ per liter). Within each subgroup, the patients were randomly assigned to receive either InPx (1 g) or placebo three times daily for a total of 3 g/per day throughout 6 months. The patients in the InPx group as well as in the placebo group were comparable in terms of sex, high-risk behavior, age, body weight, medical history within 3 months of study entry, clinical staging, general well-being according to the visual-analog scale, substrata according to $CD4^+$ cell count, and the mean number of both $CD4^+$ and $CD8^+$ peripheral blood lymphocytes at baseline. Non significant differences between the groups included a lower $CD4^+$ cell count and a higher frequency of thrush, hair leukoplakia, diarrhea, and unexplained weight loss in the placebo group.

The major difference with respect to the Italian study, in addition to the InPx dosage and duration of treatment (4 g for 3 months and 3 g daily for 6 months, in the Italian and in the Scandinavian trials, respectively) was that 82.8% of the patients were homosexual or bisexual, whereas intravenous drug abusers and hemophiliacs accounted for only 10% of the patients enrolled in the trial. The remaining 60 patients were heterosexual and had no identifiable risk factors for HIV infection.

Table 2. Disease progression according to CDC Group at base line

CDC Group at base line	Number of Patients		
	Group II	Group IV without AIDS	AIDS
InPx Group			
CDC II or III	307	62	1*
CDC IV without AIDS		41	1
Total	307	103	2*
Placebo Group			
CDC II or III	288	65	15*
CDC IV without AIDS		50	2
Total	288	115	17*

*$P < 0.001$ in comparison between InPx and placebo groups. (Modified from Pedersen *et al.*, 1990.)

A potentially important bias of the Scandinavian study was the substitution after the study was ended of the CDC classification system for a modified Walter Reed Staging Classification (Redfield, Wright & Tramont, 1986), which was used in the early trial design. The substitution was well reasoned, but could somewhat affect the study conclusions.

AIDS developed in 17 patients (4%) in the placebo group as compared with two (0.5%) in the InPx group ($P < 0.001$) (Table 2). However, no difference could be detected between InPx- and placebo-receiving patients with respect to disease progression according to the modified Walter Reed Staging Classification, the primary end point designated before the study began. Furthermore, no significant difference was found between the two 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 diseases defining group IV, but that are not considered indicative of AIDS, with the exception of thrush, which developed in 11.2% of those in the InPx group and in 15.6% of those in the placebo group ($P = 0.05$).

The progression rate to AIDS was always more marked in the placebo group, irrespective of the $CD4^+$ cell count at entry into the study. *Pneumocystis carinii* pneumonia was the most common AIDS-defining disease, accounting for more than 50% of all cases, which occurred in the patients whose condition progressed to AIDS throughout the study period. The progression to AIDS proved significantly associated ($P < 0.001$) with the treatment group and a lower $CD4^+$ cell count at baseline.

The $CD4^+$ lymphocytes decreased during the study period, although no significant difference was found between patients receiving either InPx or placebo. A decrease to a similar degree in the peripheral blood $CD4^+/CD8^+$ cell ratio was also observed in both groups. Finally, no significant difference between InPx- and placebo-treated patients was found with respect to the absolute $CD8^+$ cell counts.

Adverse events were recorded with equal frequency in both groups. Furthermore, no serious adverse event was recorded throughout the study period.

A supplementary analysis was performed following an optional 24-week open treatment phase (Thorsen & The Scandinavian Isoprinosine Study Group, 1991). Five hundred and ninety-six patients, equally distributed between the randomization groups, accepted open treatment. Within 48 weeks, 10 patients (2.4%) assigned InPx and 27 patients (6.4%) assigned placebo progressed to overt AIDS ($P < 0.005$). Supplementary analysis according to intention-to-treat principles showed similar results. No effect was observed on the HIV-related progressive fall in $CD4^+$ cell count. The number and severity of adverse reactions were low and the types of reaction benign. No major toxicity was observed. Therefore, the open phase of the trial further supports the hypothesis that HIV-positive individuals without overt AIDS could safely and, at least to some degree, effectively be treated with InPx within an observation period of 1 year.

The results of the Scandinavian trial are interesting and provocative; however, the conclusion that InPx could delay the progression of HIV infection to overt AIDS has to be regarded with some caution. In fact, despite a reduced progression rate to overt AIDS in

InPx-receiving patients, the authors were not able to demonstrate the ability of InPx, at least under this treatment schedule, to delay the progression of HIV infection as an absolute rule, as shown by a similar number of patients whose condition progressed from CDC group II or III to CDC group IV without AIDS in both the InPx and placebo groups. Therefore, the efficacy of InPx in treating HIV-infected patients requires further investigation.

Both the Italian and the Scandinavian studies clearly indicate that InPx treatment does not result *in vivo* in an increased frequency of peripheral blood $CD4^+$ lymphocytes, which are the main target of HIV infection. However, these data do not rule out the possibility that InPx could act *in vivo* by enhancing the function of the remaining T-cells as well as the NK activity, as reported by previous studies (Glasky & Gordon, 1986; Binderup, 1985; Exon *et al.*, 1986; Fischbach & Talal, 1985; Tsang *et al.*, 1987a; Pompidou *et al.*, 1985a; Tsang *et al.*, 1986, 1987b; Wallace & Bekesi, 1986; Bekesi *et al.*, 1987). Furthermore, InPx has only to a certain degree antiviral activity against HIV, as described above (Schinazi *et al.*, 1988; Pompidou *et al.*, 1985a), somewhat supporting this hypothesis.

InPx IN COMBINATION THERAPY OF HIV INFECTION

The demonstrated ability of InPx to positively affect the clinical course of HIV infection, in spite of both the slight antiretroviral activity and of not restoring immune function, as shown by the trend toward a decrease of $CD4^+$ cell counts in InPx-receiving patients in both the Italian and the Scandinavian trials, suggests that the administration of InPx together with a compound exhibiting a strong antiretroviral activity, such as AZT, could be more effective than treatment with either alone.

The 3- or 6-month treatment period may be reasonably regarded as short, therefore suggesting a potential bias with respect to the study design of both the Italian and the Scandinavian trials. However, the results of these trials, although preliminary, are encouraging and point out that this approach in treating HIV infection to delay the progression rate to AIDS requires further investigation to optimize both the InPx dosage and administration schedules. Clinical trials comparing InPx with antiretroviral drugs, notably AZT, and combination therapy seem to be warranted.

The recently reported ability of InPx to affect *in vivo* the clearance rate of AZT (De Simone *et al.*, 1988; De Simone, Tzantzoglou, Vullo, Catania & Trinchieri, 1989c) suggests that the concomitant administration of InPx to AZT-receiving HIV-infected patients could be useful in reducing AZT dosage as well as the AZT-related side-effects. The assay of plasma AZT levels in HIV-infected subjects also receiving InPx showed a higher mean peak plasma level as well as an higher mean nadir level of AZT as compared with patients receiving AZT only. Furthermore, following 7 days of treatment with either AZT or AZT plus InPx, we found that the AZT plasma levels were significantly higher in patients receiving both drugs than in those taking AZT only. The area under the plasma concentration – time curve was significantly increased in patients receiving both AZT and InPx as well as the plasma half-life of the elimination phase of AZT was shorter in patients administered AZT only with respect to subjects also receiving InPx. These findings point out that InPx strongly affects *in vivo* the clearance rate of AZT. However, the understanding of the molecular mechanisms accounting for this effect requires further investigation. The report that concomitantly administering probenecid to AZT-receiving patients results in the inhibition of AZT glucuronidation as well as of renal excretion (Wellcome Product Monograph, 1989) could indirectly suggest that InPx may affect AZT metabolism by inhibiting the glucuronidation of the latter. However, further studies are needed to better understand this issue.

The finding that concomitantly administered InPx to AZT-receiving patients increased AZT plasma levels as well as prolonged AZT mean half-life during InPx treatment suggests several potential advantages of the combination treatment with both InPx and AZT, such as a need for lower AZT dosage and a longer interval period between AZT doses to obtain sustained plasma levels as well as a potential to enhance residue immune function resulting from InPx treatment.

The clinical, virologic, and immunologic effects of combination therapy with both InPx (4 g per day) and ribavirin (800 and 1200 mg per day, respectively) for up to 3 months in HIV-culture positive homosexual men have been recently evaluated (Schulof *et al.*, 1990). The patients who entered the study were asymptomatic (CDC group II), or had PGL (CDC group III), or exhibited prior histories of minor HIV-related infections. No patient had ARC symptoms (CDC group IV-A) or AIDS-defining infections or tumors (CDC group IV-C2). However, no evidence was provided in this study that the combination of InPx and ribavirin could lead to any

improvement in the clinical status of HIV-infected patients. The treatment was associated with a generalized lymphopenia affecting all lymphocyte subsets, including $CD4^+$ cells, which was partially reversible after stopping treatment. Since previous trials of ribavirin alone reported similar effects on absolute lymphocyte counts (Roberts, Heseltine & Mansell, 1987; Vernon & Schulof, 1987) as well as ribavirin can concentrate in erythrocytes therefore resulting in shortened red cell survival (Canonico *et al.*, 1984), it is likely that the reduced lymphocyte counts could be due to ribavirin, more than InPx, cellular uptake and direct cytotoxicity.

Furthermore, no improvements were noted in this study in *in vitro* antigen-driven lymphoproliferative responses as well as in NK cell cytotoxicity, which is consistent with previous studies of immunomodulating properties of ribavirin (Peary *et al.*, 1980). Therefore, this trial seems to indicate that the combination therapy with both InPx and ribavirin does not restore *in vivo* the immune competence of HIV-infected patients. However, the small number of the patients entered the study points out that further studies are needed to better understand this issue. Furthermore, whether higher InPx dosage or different administration schedules could result in a better outcome as well as in the recovery of immune functions in HIV-positive subjects also receiving ribavirin remains to be established.

In conclusion, InPx could prove a valuable and innovative therapy for treating HIV-infected patients, since InPx treatment has been shown in two multicenter trials to effectively delay the progression of HIV infection to overt AIDS. However, further studies are strongly required to optimize both InPx dosage and administration schedules. Furthermore, clinical trials evaluating the combination therapy of HIV infection with both InPx and AZT should ultimately provide an important advance in the management of HIV-infected patients.

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