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Combination Therapy With Amantadine And Immunomodulators Potentiates Antiviral Effects In Influenza A Virus-Infected Mice

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Amantadine (Adamantanamine hydrocloride, AMN) is known to inhibit influenza virus replication as well i*n vitro* and *in vivo*, by inhibiting viral uncoating process. On the other hand several studies have reported that this drug is immunosuppressive as measured by inhibition of lymphokine-induced proliferation of cloned murine cytotoxic T- lymphocytes. In our previous studies we demonstrated that thymosin α1 (TH) given in combination with Interferon (IFN) α/β to cyclophosphamide-treated or tumor-bearing immunosuppressed mice, strongly stimulated natural killer (NK) activity, while none of the single agents, when administered at the same doses and at the same time, statistically modulated the NK response. Therefore we have investigated the efficacy of AMN given in combination with TH and murine IFN in animal experimental models of virus infection. Four-weeks old Balb-c male mice were inoculated intranasally with 100 μl of PR8 virus suspension, (1HAU/mouse) and treated with i) saline solution; ii) TH plus IFN;iii) AMN for three days p.i. (20 mg/kg periorally); iiii) AMN plus TH for four days p.i. (200 μg/kg i.p.), followed by a single administration of IFN (30,000 I.U. i.p.). The combination therapy with AMN, TH and IFN significantly increased the mean survival time and the overall survival of mice, as compared to the control group and to the groups treated with AMN alone or TH and IFN. In addition, the study of immunological markers, as CD4 / CD8 lymphocyte FACS analysis and cytotoxic activities (NK and CTL), seems to indicate that the increased mice survival is correlated with improvement of immunological parameters.

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Safety and Efficacy of Intranasal Pirodavir (R77975) for Treatment of Naturally Occurring Common Colds. F Hayden, G Eisen, M Janssens, K Andries, and P Janssen. University of Virginia, Charlottesville, VA and Janssen Research Foundation, Piscataway, NJ and Beerse, Belgium.

Intranasal pirodavir (PIR) is protective against experimental RV illness. This randomized, double-blind, placebo (PLA)-controlled trial determined the therapeutic efficacy of PIR in naturally occurring RV colds of $\leq$ 48 hours duration. Adults (n=201) were randomly assigned to intranasal sprays of PLA or PIR (2mg/dose) 6 times/day for 5 days. In subjects with RV-proven colds (55 PLA, 53 PIR), no important differences existed in gender (% female, 69 vs 64%), mean age (21 vs 20 yrs), or time from colds onset (24 vs 27 hrs). The overall resolution of respiratory symptoms did not differ between the groups ($p \geq 0.2$), and daily individual symptom scores found no differences in favor of PIR. The median durations of illness were 7.0 days for both groups. In contrast, reduced frequencies of RV shedding were observed in the PIR group on day 3 (70% vs 23%, $p<0.001$) and day 5 (38% vs 12%, $p=0.002$) but not after treatment on day 7 (19% vs 21%). An intent-to-treat analysis involving all subjects (101 PLA, 100 PIR) also found no differences favoring PIR. The PIR group had higher rates of nasal dryness, blood in mucus, or unpleasant taste ($p \leq 0.05$) on several study days. In summary, intranasal sprays of PIR were associated with significant antiviral effects but no clinical benefit in treatment of naturally occurring RV colds.