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**LOW DOSE NALTREXONE IN THE TREATMENT
OF ACQUIRED IMMUNE DEFICIENCY SYNDROME**

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Please Note: The following paper describes the first clinical trial of naltrexone in a low dose. Since 1988, it has become apparent that low dose naltrexone has a broad range of therapeutic uses beyond that in HIV/AIDS. In addition, its optimal adult dosage, rather than the 1.75mg at bedtime described below, has been found to be 4.5mg. For further information, please visit <http://www.lowdosenaltrexone.org>.

Summary

Low dose Naltrexone, an opiate antagonist, was used in doses of 1.75mg qhs in a double blind placebo controlled study as an immunoenhancing agent in the treatment of 38 patients with AIDS. The naltrexone group showed a significant drop in their pathologically elevated levels of serum alpha interferon (alpha IFN) during the 3-month double blind period compared with the placebo patients ($p < .01$) after which the placebo patients were transferred to naltrexone. Of the 38 patients then on naltrexone 23 showed a marked decline in alpha IFN levels (from means of 144.9 i.u. to 11.0 i.u. over a 12-month period) and 15 did not show such a decline. In the course of the study 19 of the 23 who showed a decline in alpha IFN survived while only 2 of the 15 who did not survived ($p < .01$). The 23 in the former group had 8 major opportunistic infections while the 15 in the latter group had 19 ($p < .01$). No side effects were noted. Low dose naltrexone holds promise as an immunoenhancing treatment for AIDS.

Keywords: acquired immune deficiency syndrome, opiate receptors, alpha interferon, endorphins.

Low Dose Naltrexone in the Treatment of AIDS

There is general agreement amongst AIDS researchers and clinicians that the most effective approach to AIDS, ARC and milder HIV related immunodeficiency syndromes will probably be a combination of antiviral and immunoenhancing treatments.

In the light of recent evidence suggesting that the endorphinergic system plays an important role in the homeostatic regulation of immune function, we have developed and tested an immunoenhancing treatment approach using low dose naltrexone.

Human T-cell rosette formation is enhanced by Met-enkephalin and this effect is blocked by prior or simultaneous treatment with naloxone, a narcotic antagonist (1, 2), thus demonstrating that T-cells have functionally important opiate receptors. Other studies have shown that the following functions involve opiate receptors and/or are facilitated by endorphins: lymphocyte blastogenesis (3, 4), T and B cell cooperation (5), lymphocyte mitogen responsiveness (6), in vitro antibody response to sheep RBCs (7), natural killer cell activity (8), expression of cell surface markers involved in lymphocyte activation (such as OKT10, IL2 and Ia receptors) (9), monocyte chemotaxis (10), and macrophage cytotoxicity (11). Studies indicating that virus infected lymphocytes produce beta-endorphin (12), and that both Interleukin I and Interleukin II stimulate pituitary synthesis of beta-endorphin (13), suggest that the central nervous system and the immune system have complex endorphinergic feedback loops that may be important in homeostatic regulation of immune function (14, 15).

Endorphinergic system involvement in homeostatic regulation of immune function raises the possibility that disturbances in this system may contribute to the pathophysiology of AIDS, and that endorphinergic upregulation might have an immunoenhancing effect in the treatment of AIDS. These possibilities led us to consider the use of low doses of naltrexone in patients with AIDS as a means of upregulating endorphinergic function in order to enhance immune function.

Several groups have demonstrated that the opiate antagonists naltrexone and naloxone, either after single doses or after chronic administration, provoke substantial increases in opiate receptor sensitivity which often last several days (16, 17, 18, 19). In connection with this, Zagon and his co-workers carried out a series of experiments to determine the role of opiate receptors and endorphins in modulating tumor growth using a mouse neuroblastoma model (20, 21). They demonstrated that a single high daily dose of naltrexone (10 mg/kg) enhances tumor growth and decreases survival time whereas a single low dose (0.1 mg/kg) per day prevents the development of the tumor in two-thirds of the mice injected with tumor cells, and prolongs survival time in those who develop it. Zagon et. al. theorize that endorphinergic modulation of tumor growth is inhibited by a high dose of naltrexone because it produces an around-the-clock blockade of tumor opiate receptors. The single low daily dose produces a blockade lasting only 3 to 4 hours,

allowing the supersensitivity to endorphins produced by an increase in opiate receptors to be unmasked approximately 20 hours a day. Normal or increased levels of endorphins have an antitumor effect for the period the drug is not present. It is not clear whether the opiate receptors involved in these findings are on the tumor cells or on cells of the immune system with the immune system playing a mediating role. Plotnikoff demonstrated that treatment with leu-enkephalin protected mice against a challenge with leukemia cells and, without additional enkephalin, against a rechallenge with the same cells. He concluded that the protection was mediated by the immune system (22). Narcotic antagonists have also been shown to stimulate pituitary beta-endorphin production (23), raising the possibility that one may be able to increase endorphin production as well as receptor sensitivity with naltrexone.

In view of the aforementioned studies, we investigated (using a double blind, placebo control methodology) the efficacy of low dose naltrexone (1.75mg/day) in the treatment of AIDS.

Patients and Methods

Sample. Fifty-six patients with AIDS were admitted to the study from July 30, 1985 to January 15, 1986. Recruitment methods included referrals from private physicians, an announcement of the study criteria in a local gay newspaper, and referrals from study participants. The study excluded patients using narcotic drugs (because of interference with the therapeutic action of naltrexone), pregnant women and individuals enrolled in other studies within the preceding six weeks. Regardless of recruitment source, a patient was admitted to the study only after telephone consultation with his private physician who continued to provide primary care. The original study sample consisted of 54 homosexual or bisexual men and two male former I.V. drug users. Thirteen patients were rapid dropouts, discontinuing their contact with the study within the first two weeks of involvement. Another five patients attended irregularly and dropped out within 3 months, thus providing us with insufficient data for inclusion. Thereby the study sample consisted of 38/56 of the initial recruitment respondents. Of the 18 dropouts, 10 had Kaposi's sarcoma, and 8 had previously had major opportunistic infections. Twelve of the 18 had been assigned to placebo and 6 to naltrexone. The 38 patients in the study sample had a mean age of 38.4 years with a range of 26 to 46. Thirty-four were white, 3 were black and one was Hispanic. Of the 38 patients in the study sample, 29 had Kaposi's sarcoma (K.S.) while 6 previously had a major opportunistic infection (O.I.) and 3 had both O.I. and K.S. The mean time from AIDS diagnosis to admission was 7.6 months. This sample demonstrated significant immunosuppression, with 31/38 patients having an absolute T4 count on admission of less than 300/ml.

Method. Upon admission, the patient was given a complete explanation of the study, including the procedure of random assignment to naltrexone or placebo. All participants signed informed consents, approved, as was the study, by the Institutional Review Boards of the SUNY-Health Science Center at Brooklyn and the New York City Health and Hospitals Corporation. We conducted a thorough medical history and physical exam, and a briefer physical exam and a follow-up history on each subsequent visit. Patients

returned weekly for 12 weeks, biweekly for the next four to eight weeks and monthly thereafter.

Random assignment was accomplished by a statistician, not involved in the study. Only the pharmacist knew the actual assignment identification for both the naltrexone and placebo groups. The control period was planned to last 12 weeks because of our hesitation in giving a placebo for very long to patients with such a short life span. At the end of that interval the principal investigator directed the pharmacist as previously planned to switch placebo patients to naltrexone. The study then followed both groups on naltrexone to the present.

The study pharmacist compounded the naltrexone by grinding 50mg naltrexone tablets (Trexan, DuPont), and dissolving seven such tablets in 3000 cc. of a heavy cherry syrup. The syrup was dispensed in unit dose bottles, with 15 cc. (containing 1.75mg naltrexone) in each bottle. Placebo patients were given identical bottles containing 15 cc. of the cherry syrup. No difference in taste was noted by patients or staff members between the two preparations. The patients were told to take the medication at bedtime or between 4:00 a.m. to 5:00 a.m. (to facilitate the early morning rise in hypothalamic-pituitary activity, generally called the "Dawn phenomenon" (24)).

Data collection. Admission laboratory tests included CBC and Differential, Urinalysis, SMA 18, Syphilis Serology, HIV Serology, T-cell subsets and serum alpha interferon (alpha IFN) levels. Heparinized white blood cells were frozen at -180°C for future viral assays and immunologic studies. Blood was drawn monthly for T-cell subsets, CBC and Differential, alpha IFN levels and the frozen cell bank. The T-cell subsets and HIV studies were done by the New York City Department of Health, Bureau of Laboratories (courtesy of Roger Enlow, M.D.). The IFN related activity was determined by Elena Buimovici-Klein, M.D., using a previously described micro method (25).

Results

Twenty-two of the randomly assigned patients in the study group of 38 were assigned to naltrexone and 16 to placebo. A review of the laboratory tests in both groups during the 3-month double blind control period showed only a change in serum alpha IFN levels in the naltrexone group from an admission level of 175.9 international units (i.u.) (SD = 85.04) to a level of 109.1 i.u. at 3 months (SD = 75.32, $t = 4.15$, $p < 0.01$). The alpha IFN levels in the placebo group were 147.2 i.u. on admission and 142.9 i.u. at 3 months.

After 3 months the placebo patients were switched to naltrexone and we have followed both groups since. Since the naltrexone appeared to lower the alpha IFN in the pooled data we followed the alpha IFN levels overtime in all 38 patients on naltrexone (the entire group after the first 3 months). We noted that, using a decrease of 2 serial dilutions in alpha IFN levels (75%) as significant (as is standard in interferon research), all patients whose alpha IFN level decreased by this amount continued to show a sequential decline, in most cases reaching and plateauing at a level of 8 i.u. Twenty-three of the 38 study

patients showed such a drop while on naltrexone and 15 did not. For convenience we have elected to call the first group, showing the alpha IFN drop, group A, and the second, group B. These group assignments, by definition, could be applied only retrospectively and were not involved in the initial blind coded patient assignment to placebo and naltrexone groups. Using the time of admission as a reference point, mean time since AIDS diagnosis was 6.6 months and 9.1 months for group A and group B respectively. Of the 23 patients classified in group A, 20 had K.S. prior to admission while 3 had pneumocystis carini pneumonia (P.C.P.). Of the 15 patients classified in group B, 9 had K.S., and 6 had O.I.s as the basis of the diagnosis of AIDS. As of December 17, 1986, 19 in group A and 2 in group B have survived and continue in the study with a mean duration on naltrexone of 12.5 months and 12.1 months for these 2 groups respectively.

Group A had a significantly lower alpha IFN level and higher Hct, T4 absolute count and T4/T8 on admission as compared with group B. There was in addition a high inverse correlation between admission alpha IFN levels and the absolute number of T4s ($r = -.61$, $p < 0.01$) in group A while group B showed a low, nonsignificant correlation ($r = -.20$).

In the course of their time in treatment with naltrexone group A showed a decline in alpha IFN levels from 144.9 i.u. (SD = 81.66) to 11.0 i.u. (SD = 8.37, $t = 7.42$, $p < .01$). Group B showed a mean level of 230.9 i.u. on admission (SD = 66.63) and 201.9 i.u. (SD = 82.67) at the time of data analysis ($t = 2.63$, $p < 0.05$).

During the course of the study, the 23 patients in group A experienced significantly less O.I.s ($\chi^2 = 9.82$, $p < .01$) than the 15 patients in group B. There were 8 O.I.s in the 23 patients in group A and 19 O.I.s in the 15 patients in group B. Of the 8 O.I.s in group A, 4 were mild brief episodes of P.C.P., 3 treated on an ambulatory basis; all 4 resolving with treatment within 48-72 hours. Three of these 4 episodes occurred before the patient's alpha IFN level had decreased from the admission level. All of the other 23 O.I.s in both groups were life-threatening and in fact, 17 were fatal. In addition to the significantly higher rate of O.I. occurrences in group B, there was also a significantly higher death rate ($\chi^2 = 8.84$, $p < .01$). As of December 17, 1986, there were 13 deaths (86%) in the 15 patients in group B and 4 deaths (17%) in the 23 patients in group A.

It should be mentioned that at the beginning of the study none of the patients were on prophylactic antibiotics to prevent P.C.P. During the 4 months preceding the data analysis, 5 patients were started on prophylactic antibiotics by their private physicians. Thus the patients in the study were without such protection during more than 90% of the patient months on naltrexone.

Of the 2 surviving patients in group B, one developed pulmonary K.S. in his 9th month on naltrexone and is presently quite ill. The second, who is feeling well and in stable condition, showed a drop in IFN from an admission level of 32 i.u. to 12 i.u., which just falls short of the drop of two serial dilutions we required for inclusion in group A. The 3 patients in group A whose original diagnosis followed a major O.I. have all survived and none have developed K.S. The 16 surviving patients in group A with K.S. have shown varied patterns in the status of their K.S. lesions. Two have experienced

aggressive progression in particular since starting chemotherapy. The rest have shown either stabilization or mild, slow progression. One, whose K.S. was stable, stopped naltrexone for 10 weeks during a hypomanic episode, and returned to the study with a considerable increase in the number and size of his lesions.

No side effects of naltrexone were noted in the course of the study. This was anticipated as the only side effects noted in narcotic addicts on 50 mg/day are mild depression, irritability and insomnia.

Discussion

The results indicate that 61% (23/38) of AIDS patients in this study treated with low dose naltrexone respond with a marked decrease in serum alpha IFN levels. This decrease appears to result in changes in immune function that provide relative protection to this group from progression and death (in the time frame of this study) and/or is a marker for such protective changes. The clinical protection has not yet been accompanied by a rise in T4 absolute numbers or in the T4/T8.

In an effort to determine the factors distinguishing the two groups, we reviewed and compared all of their admission characteristics. We found significant differences in time since diagnosis (6.6 months for group A, 9.1 months for group B), the admission alpha IFN level (145 i.u. vs. 226 i.u.), the mean Hct (43.1 vs. 37.8) and the absolute numbers of T4s (224 vs. 114). These results suggest that patients with a shorter history and less evidence of progression are more likely to respond to low dose naltrexone. The responding group, however, did include several patients with a two-year history since diagnosis on admission, and several with extremely low T4s (below 50).

The information already available about the physiology and pathophysiology of alpha IFN suggests that its reduction is the crucial factor in patient stabilization in our study. A number of studies have shown that alpha IFN in an acid labile form is elevated in most patients with AIDS and that in prospective follow-up studies of high risk groups it rises significantly 6 to 18 months before AIDS develops and once it rises it remains elevated (26, 27, 28). (Alpha IFN is usually absent in normal subjects. It generally rises to a level of 8 to 24 i.u. for a few days after an ordinary acute viral infection, then returns to zero). Some researchers have suggested that continuously elevated alpha IFN levels contribute to the pathophysiology of the disease and may have a negative prognostic significance (27, 28, 29). Of particular interest in this regard is the evidence that alpha IFN is an endorphinergic agonist, 800 times more potent than morphine (30, 31). In addition the alpha IFN induced enhancement of natural killer cell activity is blocked by naloxone, raising the possibility that for some of its functions interferon works by activating opiate receptors (32). Opiate receptors, like other receptors, decrease in number and sensitivity in the presence of high levels of the receptor specific agonist. Therefore the high levels of alpha IFN in AIDS may reduce lymphocyte (and precursor cell) opiate receptor sensitivity. In addition, elevated alpha IFN levels might send a false endorphinergic signal to the hypothalamus reducing hypothalamic production of corticotropin releasing factor (CRF) (the peptide which simultaneously regulates beta-endorphin and ACTH

production and release from the anterior pituitary). This would disturb hypothalamic-pituitary endorphinergic correction of immune system dysfunction.

In addition, there is considerable evidence in the literature indicating that high levels of alpha IFN have a potent immunosuppressive effect, particularly on T helper cell numbers and function (33, 34, 35, 36, 37). Our finding of an inverse correlation between the admission alpha IFN and T4 absolute number (in group A) is of particular interest in this regard.

The evidence that increasing levels of acid labile alpha IFN have a negative prognostic significance in AIDS, and our finding that lowering it to physiologic levels is associated with relative clinical stabilization, raises the possibility that elevated alpha IFN may be a major pathogenic factor in the development of AIDS in people who are already HIV infected and immunosuppressed.

The means by which low dose naltrexone reduces alpha IFN is unclear and may be quite complex. Five sub-types of opiate receptors have been discovered in recent years. Recent studies have suggested that the Mu and Delta opiate receptors are allosterically and functionally linked. Mu receptor activation inhibits Delta receptor access to its natural ligands: met-enkephalin and beta-endorphin (38, 39, 40). The Delta receptor has been shown to upregulate immune function while Mu receptor activation in general down-regulates immune function (5). Alpha IFN is a Mu agonist (31). Thus at high levels it may tonically inhibit Delta receptor availability, causing immunosuppression. Naltrexone in low doses is a pure Mu antagonist; in higher doses it blocks Delta receptors as well. Low dose naltrexone may in part enhance immune function by blocking Mu activation by alpha IFN. Blocking Mu activation should release Delta receptors on cells of the immune system to respond to endogenous met-enkephalin and beta-endorphin. In addition, the naltrexone may be triggering an increase in CRF production and beta-endorphin release (41).

The mechanism by which the enhanced immune function would lower alpha IFN is not clear, since little is known about the mechanisms of the induction of high levels of acid labile alpha IFN in patients with AIDS.

It is possible that other immune enhancing effects of the endorphinergic upregulation that are presumably produced by naltrexone may contribute to clinical stabilization. The high degree of correlation between alpha IFN levels and clinical outcome suggests however that the alpha IFN decrease is a crucial factor in the low dose naltrexone response. Since elevated levels of acid labile alpha IFN (as well as immunoglobulins, beta-microglobulin and T suppressor cells) are characteristic of several autoimmune disorders (42, 43), it is possible that low dose naltrexone corrects an autoimmune process. Further studies of the factors involved in the elevation of alpha IFN in AIDS, its role in the pathophysiology of the disease, and of the mechanisms of action of low dose naltrexone in producing clinical stabilization will be necessary before these questions can be answered. Our results reinforce the possibility that the serum alpha IFN level is a good marker for following the course of AIDS and for assessing patient response to new treatment approaches. Our

results also suggest that further studies of endorphinergic function and dysfunction in AIDS may yield an expanded understanding of the pathophysiology of the disease and development of effective immune modulating treatment approaches.

Addendum

In the 8 months since the above data was analyzed, another 2 patients in group A have died. As of August 24, 1987, 17 of the 23 patients in group A have survived. The mean time since diagnosis for these patients is 28 months and the mean time on naltrexone is 21 months.

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