There are no translations available.

A really efficient immunomodulator at every step of seropositivity

Naltrexone (commercial name in France : Nalorex®) is a synthesis molecule. It is an opiate antagonist that acts in competition with morphin and opiates on central and peripheric nervous system opiate receptors and on immune system cells. It has been used as a supporting treatment for drug addicts. In that case, the usually posology used is 50 mg/day.

For years numerous small assays have been carried out for HIV+ patients, and today low dose Naltrexone use (3mg/day at bedtime ; which requires fractionning the 50 mg tablet by the pharmacist), is part of the treatment of 15 000 seropositive patients in USA and Europe, and is prescribed by almost 600 doctors, especially by Dr. Bihari, New York (tel 212 929 4196, Fax 212 229 9371).

Naltrexone use is based on following points :

1. A seric decrease (one third of its normal value) of endorphin (bêta endorphin) is observed for HIV+ patients (Spinazzola F, et al., Riv. Eur. Sci. Med. Farmacol., 1995, 15, 5, 161-165), even if there is no consensus on this fact (Barcellini W, et al., Peptides, 1994, 15, 5, 769-775).

These opiate substances are neurohormones that regulate the immune System by linking to receptors present on some particular cells of the immune system. This regulation occurs by means of a relatively unknown mechanism of cell activation, particularly Natural Killer cells (Gatti G, et al., Brain Behavour and Immunity, 7, 16-28, 1993) and by cellular secretions (cytokines, immunoglobulins).

2. Low dose (3 mg/day) Naltrexone use for HIV+ patients increases endorphin concentrations (bêta endorphin and metenkephalin), whereas high doses (50 mg/day and more) knocks down endorphin secretion
3. Naltrexone also favours Natural Killers cell action and CD8 cytotoxic lymphocytes, which could explain its action in some cancers.

The first assays with Naltrexone alone have been carried out in 1985-1986 by Dr. Bihari in New York (B. Bihari and al., Int. Conf, on Aids, 1989). During a double blind test made for 38 AIDS patients for 3 months, a drastic decrease of opportunistic infections (OI) was observed in the treated group (no OI for 22 patients) versus 5 OI out of 16 patients in the placebo group. At a biological level, lymphocyte response to mitogens is decreased in the placebo group and normal in the treated group, alpha interferon concentration significantly decreases in the treated group but not in the placebo group.

In 1996, a checkup carried out for 158 patients of Dr. Bihari, ten among them being under antiretroviral therapies, shows on the totality of the group a stabilisation of the T4 cell count during 18 months (from an average of 358 to 368/mm3). On this same period, it is observed for the non-treated group a significant decrease of T4 cell count (from 297 to 176 as a mean value). Concerning a larger number of patients, a T4 cell count stabilisation is observed for more than 85% of the patients. Concerning OI and disease, 25/55 and 13/55 are respectively observed in

the non-treated group and only 8/103 and 1/103 in the treated group. In this assay, some patients were treated for 7 or 8 years and the progression stop maintained during all this period. Besides, no side effects were noticed.

Various combinations of treatment with conventional antiretrovirals have lead to numerous assays. Associated with AZT + 3TC, we observe for 19 patients, during 18 months, a significative increase of T4 cell count, mean value raising from 88 to 194/mm3 with for all an increase of at least 30%. Besides, a comparative study with AZT + 3TC, only for 68 patients, provides a very weak increase of T4 cell count (mean value raising from 352 to 392 in 6 months). Finally, with Naltrexone, a better standing and a weight gain (5 to 25 kg in two months !).

Concerning another group of 45 patients, already under AZT + 3TC + Naltrexone, Indinavir was added (800 mg x 3/day) and Nevirapine (200 mg x 2/day). Before this change of treatment, T4 mean cell count was 235 (betwen 5 and 249) and mean viral load was 74 210 copies/ml. Alter one month, 42 out of the 45 patients had an undetectable viral load which remained unchanged. After 7 months, T4 cell mean value increased until 349 and their percentage from 15.2 to 20.4%. A cholesterol increase was observed (159 to 209). Clinical state improved, no OI occured and mean weight gain was 4 kg.

The failure for 3 patients is due to the too low Indinavir plasmatic concentration (inferior to 8M, one hour after administration), which would justify the commercialization of dosage kits of Indinavir to adjust therapeutical posology.

Such a study would be desirable with D4T in place of AZT.

The treatments today recommended by Dr. Bihari are for his patients who were already under AZT + 3TC + Naltrexone (roughly 1/3), AZT + 3TC + Indinavir + Nevirapine + Naltrexone, and for his new patients (2/3 of his patients), Indinavir or Nelfinavir + Nevirapine + Naltrexone. When treatment fails to make viral load undetectable, an increase of the posology is decided (Indinavir 1 000-1 200 mg x 3/day or Nelfinavir 1 000 mg x 3/day).

Naltrexone association with D4T + Indinavir + Delavirdine would be also interesting (Delavirdine being known to increase Indinavir concentration, contrarily to Nevirapine that diminishes it).

On 150 patients followed by Dr. Bihari, only 4% of them showed a therapeutical escape after 13 months, which is much weaker than that observed with classical tritherapies (20 to 50%)*.

These different results fully justify low dose Naltrexone use (3 mg/day at bedtime) at each step of seropositivity and in association with classical tritherapies and particularly lighter bitherapies (Indinavir or Nelfinavir + Nevirapine). The association with morphin and its derived, with codein and in case of alterations of hepatical or renal functions, represent the only situations in which it shouldn't be used. Efficiency of this type of treatment is, to our knowledge, one of the best among all the published therapies. We think it is useful to associate it to different alternative

therapies (vitamine C and E, selenium, glucuronamide, stress control...).

Finally, let's mention that Naltrexone has been experimented with some success in particular lymphomas (which treatments are particularly difficult for HIV+ patients), in pancreas cancer and in numerous autoimmune diseases (with often low endorphin concentration) like multiple sclerosis, rhumatoid arthritis, lupus, Crohn disease, psoriasis, sarcoïdose, polymyositis, allergic asthma.

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* As far as in classical therapies, it is known that the appearence of resistances is more frequent in case of bitherapies (that shouldn't be used any longer) compared to classical tritherapies, and that crossed resistance appearence limitates for the future the number of combinations that can be used, viral loads measurements should be done regularly, especially for the associations proposed by Dr. Bihari.