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NATURAL KILLER CELL CYTOTOXITY AND COURSE OF ILLNESS IN DEPRESSED MOOD

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SUMMARY

There is now some evidence that depressed mood is associated with activation of the immune system. First, we evaluated, within a cross-sectional design, NKCA (in vitro) in 49 subjects meeting inclusion criteria either for a major depressive episode, for dysthymia, or for "double depression". We found that recent and long depressive episodes (dysthymia) are associated with a lower immunodepression. Second, we compared two subset of subjects: 14 patients meeting criteria of major depression to 14 healthy controls. The data show a significant improvement in major depression when compared to controls througout a treatment combining supportive psychotherapy and 8 mg Reboxetine™.

Key words: *depression - killer cells - immune system - natural killer cell Activity - reboxetine*

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Objective

There is now some evidence that depressed mood is associated with activation of the immune system. The aim of this study is to highlight the effects of the course of illness on changes in natural killer cell activity (NKCA), and to compare a subset of patients meeting criteria for major depression to healthy controls.

Methods

We evaluated, within a cross-sectional design, NKCA (in vitro) in 49 subjects meeting inclusion criteria either for a major depressive episode, for dysthymia, or for "double depression".

Ethics: all subjects (patients and healthy controls) signed written informed consent relating to the experimentation, which had previously been submitted to the local ethics committee.

Fig.1: design

- HAM-D, MADRS, CGI and NKCA were assessed at days –7, 0 and 21 of treatment in depressed patients and at days 0 and 21 in healthy controls.
- A 7 days placebo wash-out was performed in patients switching from a prior treatment.

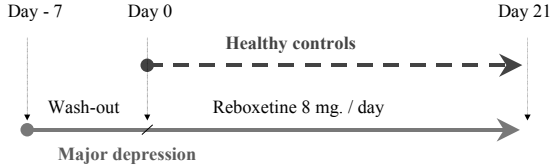

Figure 1. Design

Laboratory testing: we evaluated NKCA (in vitro), lymphocytes phenotypes, interleukin 2 and 6 before (day-7, day 0) and during (day 21) treatment with the specific noradrenaline reuptake inhibitor (NARI) reboxetine (Edronax ® 8 mg/day) within a 21 days comparative pilot study design. K562 cells incubated with 0.2 mCi 51Cr (sodium chromate) were used as target cells. Peripheral blood lymphocytes were added as effectors cells at various effectors / target ratios *Natural Killer Cell Activity:* NK cytotoxic assay was performed according to the classical method. K562 cells incubated with 0.2 mCi 51Cr (sodium chromate) were used as target cells. Lymphocyte phenotypes were analyzed using flow cytometry assays. Purchased monoclonal antibodies included anti-Leu-5b(anti-CD2) anti-Leu-4 (anti-CD3) for pan-T cells, anti-Leu-3 (anti-CD4) for helper T cells, anti-Leu-2a (anti-CD8) for cytotoxic T cells, rIL-2R1 (anti-CD25) for human r IL-2 receptor, anti-Leu-11 (anti-CD16) for Fc receptor on NK cells and neutrophils, anti-Leu-19 (anti-NKH1-CD56) for NK cells and cytotoxic T cells, and anti-Leu-16 (anti-CD20) for B cells. HAM-D, HAM-A, BDI, NEWCASTLE Scale, ERD (Wildlocher) were also collected. Course of illness was assessed by recording number and duration of previous and present episodes, and by the "distinct quality" of the present episode.

Patients: From the initial sample of 49 patients showing various forms of depression, 14 patients with major depression, according the DSM IV criteria, were treated with reboxetine 8 mg /day and compared to 14 untreated sex, age, tobacco, alcohol and caffeine use-matched healthy control voluntary subjects.The average age was 40.53 ± 10.01 (min= 23, max=62). There were 35.7 % men (n=10) versus 64.3 % women (n=18).

In a second time two groups (healthy controls and major depression) were contituted according to the above mentioned criteria. There were no stastistical differences in average age, sex ratio, civil status, even if more subjects from from the control control group were keeping their job (p=0.06) instead of being out of activity. Caffeine use, but not nicotine (p=0.222), was somewhat more present in patients with major depression (p = 0.06).

Results

a) Among others findings (not mentioned here), duration (months) of the present episode appeared to be significantly (Anova: F=2.396, df=5, p<0.05) associated with NKCA, in such a manner that contraries meet together (= U-curve-like results) (see table I). On one hand, the shorter (or "recency" of) the episode, the better the average residual NKCA. On the other hand, the longer the episode, the better the average residual NKCA. Medium-length episodes (2 to 5 months) were associated with the lowest average NKCA.

Similar results (p<0.05) were observed when comparing dysthymia to single major episodes, and when comparing chronic condition, exacerbation of a chronic condition, recurrence, distinct and first episode.

b) Furthermore, when comparing the "major depression group" (n=14) treated by 8 mg Reboxetine to healthy controls (n=14) through a 21 days schedule, we observed a significant improvement in patient's NKCA at day 21 versus control's NKCA at day 21 (fig 2). These observations are differently illustrated by means figues 3 and 4.

Table 1. Average natural killer cell activity (% lysis)

Duration of present episode	Nb subjects	Average natural killer cell activity (% lysis)	Standard deviation
0 to 1 month	4	11.25	6.76
≤ 2 months	4	11.75	9.39
≤ 3 months	8	8.13	7.03
4-5 months	7	5.81	3.82
6-11 months	8	11.25	6.45
> 12 months	18	14.22	6.91

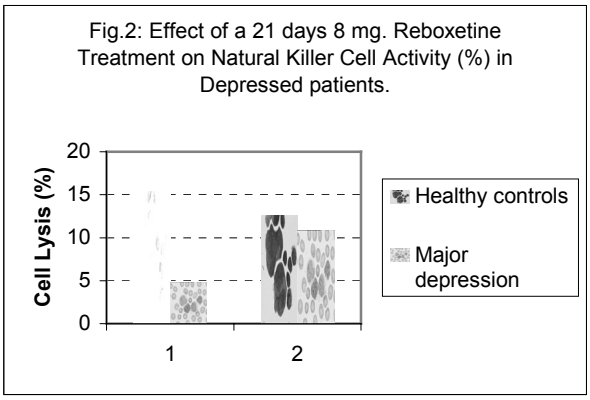

Figure 2. Effect of a 24 day 8mg Reboxetine Treatment on Natural Cell Activity (%) in Depressed Patients

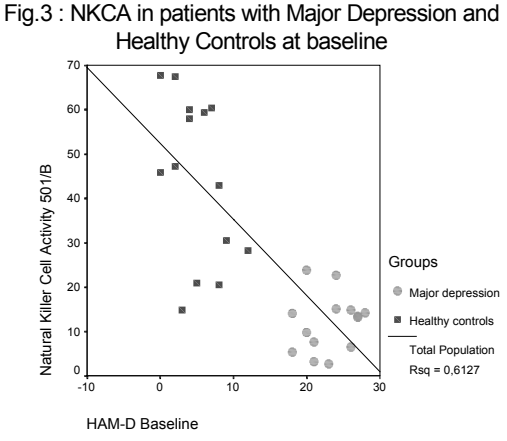

Figure 3. NKCA in patients with Major Depression and Healthy Controls at baseline

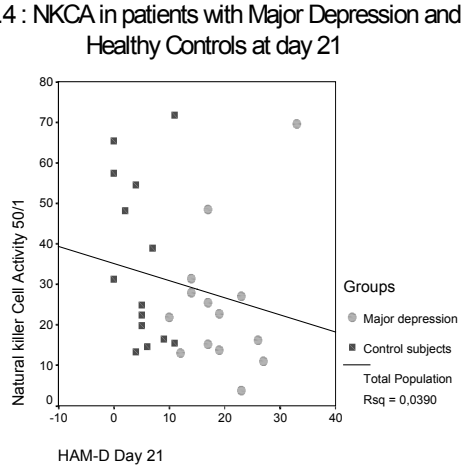

Figure 4. NKCA in patients with Major Depression and Healthy Controls at day 21

A discriminant analysis including temporal indicators allowed a 80 % of correct reclassification of patients showing immunodepression (< pct33) versus patients with preserved NKCA (Wilks' Lambda=0.57, p=0.006).

Discussion

Recent and long depressive episodes (dysthymia) are associated with a lower immunodepression. The growing research investigating cellular immunity as well as hypersecretion of pro-inflammatory cytokines in mood disorders should carefully take the course of illness into account.

The data obtained in the present study support the results of previous studies, according to which depressed patients are less immunocompetent. Depression has thus an impact on the normal function of the immune system. The novelty is that treatment by combined reboxetine 8 mg /day and supportive psychotherapy may have immune-enhancing properties, inducing a possible reversibility of the above-mentioned defects.

This may be relevant for the treatment of co-morbidities in the liaison-psychiatry setting.

Further studies however should be done to provide deeper understanding of the possible mechanisms underlying the reduced NK-Cell activity in depressed subjects and its reversibility by means of reboxetine and supportive psychotherapy.

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