P.2.f.021 Results of a double-blind placebo-controlled study of the antidepressant effects of the mGLU2 negative allosteric modulator RG1578

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Background: Abnormalities in glutamate transmission have been implicated in major depressive disorder (MDD). supported by recent studies demonstrating fast and persistent antidepressant effects of the NMDA antagonist ketamine. It has been hypothesized that aetiologically chronic stress may ultimately lead to a disruption of normal glutamate transmission via excessive autoinhibition through presynaptic metabotrobic glutamate receptors type 2 (mGlu2). mGlu2 antagonists should correct this abnormal state and offer a therapeutic approach. We evaluated the antidepressant effects of the mGlu2 negative allosteric modulator RG1578 in patients with an inadequate response to SSRIs or SNRIs. This compound demonstrated antidepressant and procognitive effects in preclinical models.

Methods: 310 patients with MDD and an inadequate response (inclusion criterion for severity of illness: MADRS $\geqslant$ 25, CGI $\geqslant$4) to up to two antidepressant trials were randomized to double-blind treatment and with placebo (N = 86; female 67%; mean age 46.0±11.2; above 45 years 47%), 5 mg (N = 89; female 70%, mean age=46.9±10.7; above 45 years 61%), 15 mg (N = 88; female 72%; mean age = 46.9±10.9; above 45 years 60%) or 30 mg (N = 47; female 64%; mean age 44.5±13.1; above 45 yers 53%) of RG1578 as an adjunct to ongoing treatment with an SSRI or SNRI. Patients completed 6 weeks treatment without major protocol violations. The primary endpoint (MADRS) was assessed by fully blinded centralized raters. Secondary endpoints included the IDS-SR30, CPFQ, SDS. Effects on cognition were assessed with the CANTAB battery.

Results: At baseline the mean MADRS total score was 31 (±6 [SD]) and the CGI-S 4.4 (±0.7). Compared to historical normative CANTAB data the mean cognitive performance of patients was within normal range with a minority of patients demonstrating deficits exceeding one standard deviation at baseline (placebo group: 8%; 5 mg group: 8%; 15 mg group: 10%; 30 mg group 13%). Between 82% and 88% of the patients completed treatment without major protocol violations. At the end of treatment the decreases in the MADRS total score did not differ significantly between any active treatment arm and placebo (placebo: −11.8±11.2; 5 mg: −12.8±11.2; 15 mg: −11.8±11.2; 30 mg: −13.2±11.2). Response rates were 35% for placebo, 40% for 5 mg, 43% for 15 mg and 47% for 30 mg and did not differ significantly. Remission rates did not differ significantly between treatment arms (placebo 29%, 5 mg 38%, 15 mg 30% and 30 mg 32%. Additional analyses in subgoups of patients defined by sex, geography history of previous episodes, age, family history, baseline cognitive impairment) did not demonstrate any drug effects over placebo. Similar results were observed for all secondary outcome measures. The effects of treatment with RG1578 on cognitive functions did not differ at any dose level from those of placebo. Exploration of RG1578 exposure-response relationship confirmed former results.

Overall treatment with RG1578 was well tolerated and associated with few side-effect related study withdrawals.

Discussion: Adjunctive treatment with RG1578 was not associated with significant antidepressant effects in patients with MDD and inadequate response to antidepressants. No effect on cognitive functions was observed.

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P.2.f.022 Psychiatric disorder and sexual dysfunction: a pilot study

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Purpose of the study: The aim of the study was to evaluate sexual function in patients affected by various psychiatric disorders before and after of the onset of their illness, trying to evaluate the role of psychiatric disorder in the development of sexual dysfunction.

Materials and Methods: The sample includes 48 patients (27 females) with a mean age of 35 years. The mean age at onset of psychiatric illness was 29 years. Thirty-three patients were affected by bipolar disorder, 8 by anxiety disorders, 5 from eating disorders and 2 by psychotic disorder. Sexual function was assessed via the Arizona Sexual Experience Escape (ASEX) while social functioning was assessed via the Work and Social Adjustment Scale (W-SAS). Clinical Global Impression (CGI) was completed by the treating psychiatrist. Each item of ASEX was evaluated through a score ranging from 1 to 6 (e.g. the answers to question 1 were coded from "extremely strong" to "no sex drive",). ASEX questionnaire was modified to evaluate sexual function at T0 (i.e, before the onset of the psychiatric disorder), T1 (at the onset, before starting medication treatment), T2 (after starting a medication treatment). We run a descriptive analysis and evaluated the values for each item of ASEX at T0, T1, T2. An ANOVA repeated measure was conducted for ASEX total score at T0, T1, T2; age was included in the analysis as a covariate.

Results: A reduction of ASEX score over time was observed for: sex drive T0 2,52 (DS 1,203), T1 3,54 (DS 1,368) and T2 3,87 (DS 1,566), sexual arousal T0 2,54 (DS 1,071), T1 3,52 (DS 1,255) and T2 3,75(DS 1,437), erection (males) T0 2,10 (DS 1,788), T1 2,95 (DS 1,146) and T2 3,15 (DS 1,663), lubrication (females) T0 2,77 (DS 1,394), T1 3,38 (DS 1,416) and T2 3,38 (DS 1,525), orgasm T0 2,92 (DS 1,334), T1 3,79 (DS 1,443) and T2 3,94 (DS 1,465). The following mean values were reported for satisfaction achieved with orgasm: T0 2,67 (DS 1,358), T1 3,56 (DS 1,457) and T2 3,73 (DS 1,634). An impairment over time in all items of W-SAS was been reported. A mean value of 3,69 (DS 1,307) was found for CGI, 2,19 (DS 1,249) for overall improvement 5,17 (DS 3,491) for efficacy index (4 point x4 rating scale that assesses the therapeutic effect marked by side effects). A statistically significant difference was found for total ASEX score between T0 and T1. No statistically significant difference was found between T1 and T2, possibly due to the lack of statistical power.

Conclusions: An impairment of sexual function was found from T0 (before the onset of illness) to T2 (after medication treatment). However, only the difference between T0 and T1 reached statistical significance. These preliminary findings identify a worsening of sexual function over time, in patients with psychiatric disorders. Whether the worsening is due to the illness, its treatment or patients' ageing is yet to be determined.