An exploratory study to investigate the effect of minocycline on depressive symptom relapse after response to ketamine in patients with therapy resistant major depressive disorder (TR-MDD)

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INTRODUCTION

Repeated intravenous (IV) administration of sub-anesthetic doses of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine (KET) induces antidepressant effects in up to 70% of patients with TR-MDD[1]. However, such effects are transient and chronic repeated administration of KET is impractical.

AIM

Potential strategies to prolong KET-induced antidepressant effects include alternative glutamatergic modulators, which show downstream effects similar and/or complementary to KET but are devoid of acute psychotomimetic effects[2]. The tetracyclic antibiotic minocycline (MIC) penetrates the blood-brain-barrier (BBB) and has anti-inflammatory properties by which it may modulate glutamatergic neurotransmission[3]. Therefore, we investigated whether MIC could prevent depressive relapse after successful response to IV KET in TR-MDD.

METHODS

Patients with TR-MDD according to DSM-IV (IDS-C30 score ≥ 34) were included in a blinded, randomized, placebo-controlled, exploratory study. The Montgomery-Åsberg Depression Rating Scale (MADRS) was administered at baseline and throughout the treatment phases. KET 0.5mg/kg was administered IV six times during a 12-day open-label treatment period, concomitantly with oral MIC 200mg/day. Patients with MADRS total score reductions of ≥ 50% compared to baseline during day 7 to 12 or ≥ 40% on day 12 were considered responders to KET. Responders were subsequently randomized to either continuation of MIC 200mg/day or placebo (PLA) up to day 54 or until depressive relapse. Relapse was defined as a MADRS total score increase to ≥ 30 at any of the scheduled assessments during treatment. Non/partial-responders to KET could opt to participate in an open-label MIC arm of the same duration.

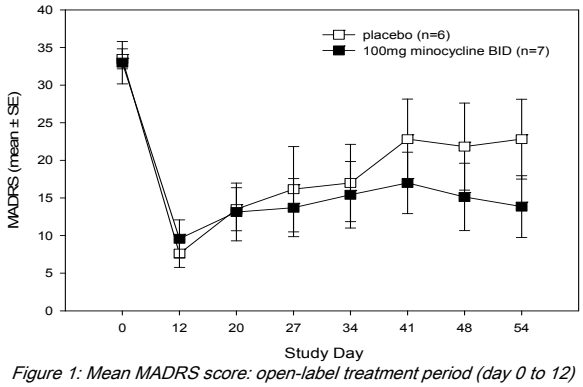

Figure 1: Mean MADRS score: open-label treatment period (day 0 to 12) with subsequent randomization to either MIN or PLA (day 12 to 54)

RESULTS

Twenty-nine patients (55% female, mean age 51 [range 23 – 74] years old, mean MADRS [SD] = 33 [5.00]) received KET and MIC during the open-label phase. On Day 12, the mean MADRS decreased compared to baseline (-15.6 [10.62]; n=26) *(Figure 1)*. Fourteen (54%) patients met response criteria (mean MADRS on Day 12 = 8.9 [5.5]) and were randomized to either PLA (n=7) or MIC (n=7). Five of 15 patients who failed to meet response criteria continued open-label treatment with MIC. On day 54, three patients randomized to PLA and one to MIC had relapsed *(Figure 2)*. No clinical benefit was observed upon open-label treatment with MIC in KET non/partial-responders. Both treatments were well tolerated: during open-label KET treatment dissociative symptoms (41.4%) and headache (37.9%) were the most common adverse events; MIC treatment caused gastrointestinal symptoms in 20% of all patients.

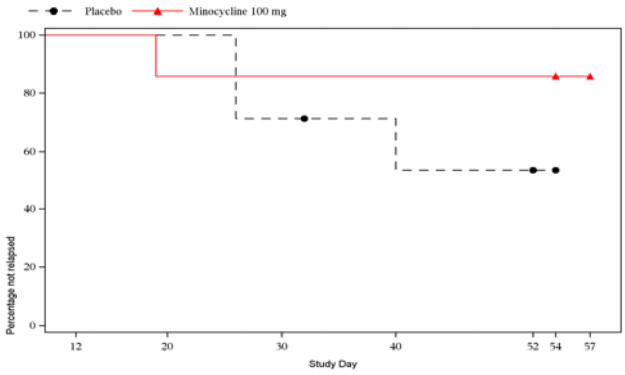

Figure 2: Kaplan-Meier plot of relapse (relapse=total MADRS score >=30) by treatment from day 12 to 54 (closed black circles=placebo; red triangles=minocycline)

CONCLUSIONS

- 50% of patients with TR-MDD responded to repeated intravenous administration of KET combined with orally administered MIC during two weeks.
- fewer responders who were randomized to MIC met relapse criteria compared to those responders randomized to PLA during the subsequent 6 weeks.
- these preliminary results provide some support for further evaluation of central anti-inflammatory/glutamatergic modulation in mood disorders as strategies to prolong KET's antidepressant effects.

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