Effect of Percentage of Life-Years from the Start of Major Depressive Disorder on the Therapeutic Response to REL-1017

Poster #5198

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ABSTRACT

Background: Chronicity of depression has not proven to be a reliable predictor of response to standard antidepressant treatments (SATs) or response to placebo. However, early improvements after treatment are generally associated with better outcomes and earlier and more severe first episodes of depression may play a role in the prognosis of MDD. NMDAR channel blockers are emerging as a promising novel treatment for MDD. The mechanism of action of NMDAR channel blockers is related to BDNF and mTor-dependent neural plasticity. REL-1017 (dextromethadone) is a novel safe and well tolerated NMDAR channel blocker that increases BDNF in humans. In a recent Phase 2 study, REL-1017 showed rapid, robust, and sustained therapeutic effects in patients with MDD. We investigated the relationship between percentage of life-years from the start of MDD and therapeutic response to REL-1017.

Methods: We reviewed historical data on the start date of MDD recorded in the database of a Phase 2a study of REL-1017 as adjunctive treatment in patients with MDD who failed 1-3 adequate SATs. The percentage of life-years from the start of MDD was calculated by computing the number of years from the start date of MDD recorded in the REL-1017 phase 2 study database divided by age and multiplied by 100. Patients were then divided as below and above the median value. The MADRS change from baseline (CFB) was compared between REL-1017 and placebo groups by Student' t test for unpaired data.

Results: The median percentage of life years from the start date of MDD for the 62 randomized patients was 23%. At 25 mg and 50 mg doses, patients below the median percentage of life-years were significantly more responsive to REL-1017 vs. placebo. In contrast, among patients above the median percentage of life-years, the response to REL-1017 vs. placebo was not statistically significant.

Conclusion: In this Phase 2 trial, 25 and 50 mg doses of REL-1017 were significantly effective vs. placebo in reducing MADRS scores below the median (23%) for percentage of life-years from the start of MDD. When the same data were analyzed for patients above the median (23%) for percentage of life-years, results did not reach statistical significance at either REL-1017 dose. This differential therapeutic effect related to chronicity of MDD has not been previously reported for monoaminergic drugs, atypical antidepressants or ketamine. The differential therapeutic effects of REL-1017 when administered earlier compared to later in the course of MDD may signal potential disease modifying effects related to neural plasticity. If these preliminary findings are confirmed in ongoing Phase 3 trials, REL-1017 could become first line treatment for patients with recent onset of MDD. In the context of MDD clinical trials, a careful analysis of patients above or below the median for years of life from the start of MDD may signal treatments with potentially disease modifying effects.

INTRODUCTION

- Chronicity of depression has not proven to be a reliable predictor of response to standard antidepressant treatments (SATs) or response to placebo[1]
- Early improvements after treatment are generally associated with better outcomes[2,3]
- Earlier and more severe first episodes of depression may play a role in the prognosis of MDD[4]
- NMDAR channel blockers are emerging as a promising novel treatment for MDD[5]
- The mechanism of action of NMDAR channel blockers is related to BDNF and mTor- dependent neural plasticity[6,7]
- Esmethadone is a safe and well tolerated NMDAR channel blocker [8] with promising preclinical results for treating MDD[6,9]
- Esmethadone increases BDNF plasma levels in humans[8]
- In a recent Phase 2 trial, esmethadone showed rapid, robust, and persistent therapeutic effects in patients with MDD

OBJECTIVE

- To assess whether REL-1017 may be more effective in MDD patients with a lower percentage of life-years from the start of MDD

METHODS

- We reviewed data from a randomized Phase 2a study of REL-1017 as an adjunctive treatment in patients with MDD who failed 1-3 adequate SATs
- Duration of MDD was defined as the difference between age at study enrollment (baseline) and the start date of MDD (years)
- The percentage of life-years since the first diagnosis of MDD was calculated as duration of MDD (years) divided by age at baseline and multiplied by 100
- Patients were stratified into two subgroups, below and above the median value of the percentage of life-years since the first diagnosis of MDD (23%)
- The Montgomery-Asberg Depression Rating Scale (MADRS) change from baseline (CFB) was used to compare REL-1017 vs. placebo
  - Student's t test for unpaired data

RESULTS

- 62 patients with MDD were randomized and treated
- Life-years with MDD: Median 23%; Mean 30%; Range: 2-76%
- There were no significant differences between the 3 groups of treatment for this parameter

Figure 1. Scatter Plot of Percentage of Life-Years with MDD in the 62 study patients

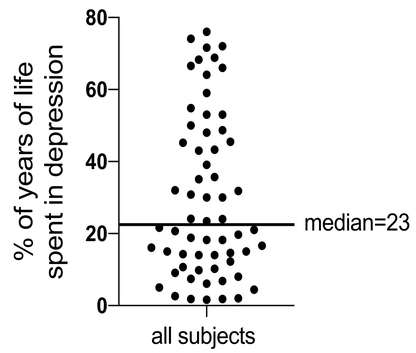
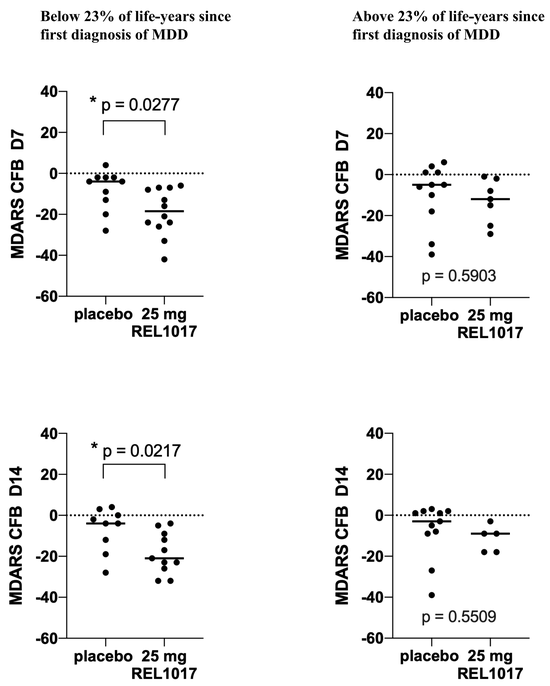
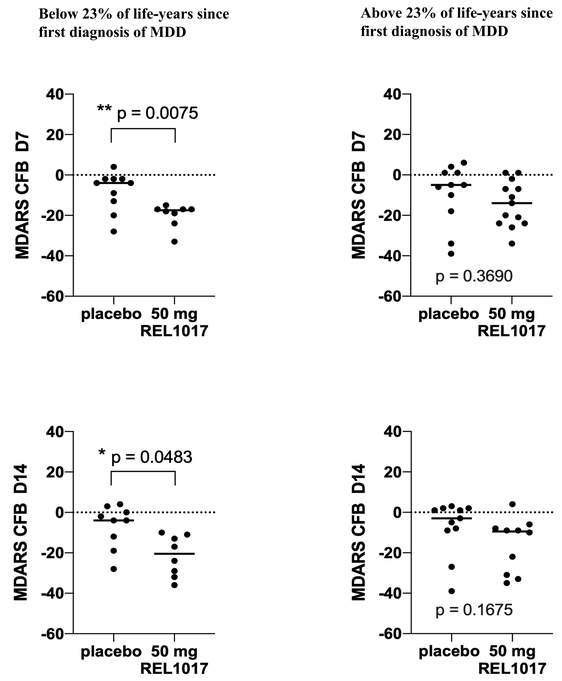


Figure 2. Scatter plots of mean CFB for MADRS at Days 7 and 14 for patients treated with placebo or 25 mg of REL-1017 by median percentage of life-years since first diagnosis of MDD



Horizontal bars refer to the mean percentage life-years since the first diagnosis of MDD

Figure 3. Scatter plots of mean CFB for MADRS at Days 7 and 14 for patients treated with placebo or 50 mg of REL-1017 by median percentage of life-years since first diagnosis of MDD



Horizontal bars refer to the mean percentage life-years since the first diagnosis of MDD

- Patients below the median percentage of life years since the first diagnosis of MDD (≤23%) showed a significant improvement of MADRS mean scores at day 7 (p=.0277) and at day 14 (p=.0217) with REL-1017 25mg vs. placebo (**Figure 2**)
- Patients below the median percentage of life years since the first diagnosis of MDD (≤23%) showed a significant improvement of MADRS mean scores at day 7 (p=0.0075) and at day 14 (p=0.0483) with REL-1017 50mg vs. placebo (**Figure 3**)
- Treatment effects were not statistically significant in patients above the median percentage of life-years (≥23%) since the first diagnosis of MDD (p >0.05 at all time points) with REL-1017 25 and 50mg vs. placebo (**Figures 2 and 3**)

DISCLOSURES

This research was sponsored by Relmada Therapeutics, Inc. Drs. Fava, Pani, Manfredi and Pappagallo are paid consultants for Relmada Therapeutics. Dr. Manfredi is an inventor on esmethadone patents and other patents and patent applications. Research performed by Dr. DeMartin at the University of Padova was funded by Relmada Therapeutics.

CONCLUSIONS

- In this sub-analysis, REL-1017 25 and 50 mg daily was significantly effective in reducing MADRS scores vs. placebo in patients below the median (23%) percentage of life-years since first diagnosis of MDD
- For patients above the median (23%), the improvement from REL-1017 was less and did not reach statistical significance
- This differential therapeutic effect related to chronicity of MDD has not been previously reported for monoaminergic drugs nor for atypical antidepressants and has not been described for ketamine
- Stratification of patients above or below the median percentage of life-years since first diagnosis of MDD may identify treatments with potentially disease modifying effects
- The significant effect of REL-1017, when administered earlier compared to later in the course of MDD during a patient's life-time, may be related to differential neural plasticity effects and may signal potential disease modifying effects
- This finding, if confirmed in ongoing Phase 3 studies of REL-1017, may help the selection of patients with a higher likelihood of response to REL-1017 treatment
- If these preliminary findings are confirmed in larger trials, REL-1017 could become a first-line treatment for recent onset of MDD and other neuropsychiatric disorders that may potentially benefit from NMDAR channel block[10,11]

REFERENCES

1. Papakostas GI, Fava M. Predictors, moderators, and mediators (correlates) of treatment outcome in major depressive disorder. *Dialogues Clin Neurosci*. 2008;10(4):439-51.
2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905–17.
3. Kraus, C., Kadriu, B., Lanzenberger, R. et al. Prognosis and improved outcomes in major depression: a review. *Focus (Am Psychiatr Publ)*. 2020;18(2):220-35.
4. Pereverseff RS, Beshai S, Dimova M. First episode indices associated with lifetime chronicity of depression among formerly depressed participants: an exploratory study. *J Ment Health*. 2020;29(6):677-83.
5. Pochwat B, Pałucha-Poniewiera A, Szewczyk B, Pilc A, Nowak G. NMDA antagonists under investigation for the treatment of major depressive disorder. *Expert Opin Investig Drugs*. 2014;23(9):1181-92.
6. Fogaça MV, Fukumoto K, Franklin T, et al. N-Methyl-D-aspartate receptor antagonist d-methadone produces rapid, mTORC1-dependent antidepressant effects. *Neuropsychopharmacology*. 2019;44(13):2230-8.
7. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329(5994):959-64.
8. DeMartin S, Vitolo O, Bernstein G, Alimonti A, et al. The NMDAR Antagonist Dextromethadone Increases Plasma BDNF Levels in Healthy Volunteers Undergoing a 14-Day In-Patient Phase 1 Study. ACNP 57th Annual Meeting: Poster Session II. *Neuropsychopharmacol*. 2018;43:228–382.
9. Hanania T, Manfredi P, Inturrisi C, Vitolo OV. The N-methyl-D-aspartate receptor antagonist dextromethadone acutely improves depressive-like behavior in the forced swim test performance of rats. *Exp Clin Psychopharmacol*. 2020;28(2):196-201.
10. Boldrini M., Canoll P.D. and Klein R.S. (2021). How COVID-19 affects the brain. *JAMA Psychiatry.* https://doi:10.1001/jamapsychiatry.2021.0500.
11. Masi A., Narducci R. and Mannaioni G. (2019). Harnessing ionic mechanisms to achieve disease modification in neurodegenerative disorders. *Pharmacological Research* 147:104343. https://doi:10.1016/j.phrs.2019.104343.

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