Original Research

Sirolimus Augmentation of Esketamine Treatment in Treatment-Resistant Depression: A Pilot Evaluation

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Abstract

This pilot study investigated whether oral sirolimus augments the antidepressant effects of intranasal esketamine in patients with treatment-resistant depression (TRD) unresponsive to esketamine alone. Patients received sirolimus 6 mg orally two hours prior to esketamine treatment for two treatments, taken 28 days apart. Depression severity was assessed using the MADRS, PHQ-9, and HAM-D scales at baseline, 8-, and 16-week intervals. Two-tailed t-tests showed directionally favorable but non-significant improvements at 8 weeks and 16 weeks. One-tailed t-tests, justified by a directional hypothesis, indicated significant improvements at 8 weeks. Despite significant limitations, these findings suggest that sirolimus may enhance esketamine's short-term antidepressant effects, consistent with prior studies indicating that mTORC1 modulation prolongs ketamine's therapeutic benefits. A larger, randomized controlled trial is needed to confirm these preliminary results.

INTRODUCTION

Ketamine has emerged as a rapid-acting antidepressant medication, providing symptomatic relief of depression-related symptoms for many patients with treatment-resistant depression (TRD). The S-enantiomer of ketamine, esketamine, has been approved for the treatment of TRD and for acute suicidal ideation, expanding therapeutic options for patients who are unresponsive to traditional antidepressant medications. Despite its efficacy, the durability of ketamine's antidepressant effects remains limited, often waning within weeks of administration and requiring ongoing maintenance therapy for sustained symptomatic relief [1].

Preclinical studies have identified activation of the mechanistic target of rapamycin complex 1 (mTORC1) as a key downstream pathway involved in ketamine's mechanism of action in depression, putatively by the induction of prefrontal glutamate neurotransmission, leading to activation of synaptic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate (AMPA) receptors, subsequent increases in brain- derived neurotrophic factor (BDNF) levels, TrkB receptor stimulation, and mTORC1 activation, ultimately resulting in increased synaptogenesis with accompanying cognitive and behavioral adaptions in the setting of TRD [2, 3].

Despite this uneasy consensus, prior studies represent a range of conflicting findings across treatment modalities (e.g., IV or intracortical ketamine, intranasal esketamine) and *in vivo* settings (rodent models, human patients). For example, initial rodent studies found that intra-cortical inhibition of mTORC1 via sirolimus blocked ketamine's antidepressant-like effects [4]. However, a recent human study by Abdallah *et al.* [2] demonstrated that pre-treatment with oral sirolimus did not attenuate ketamine's effects but instead prolonged its antidepressant benefits. Further investigation by Averill *et al.* [5] corroborated these findings but found no effect of sirolimus on ketamine's anti-suicidal effects, suggesting a possible mechanistic divergence between ketamine's antidepressant and anti-suicidal actions.

Given these findings, we sought to investigate whether sirolimus augmentation of esketamine would enhance and/or prolong antidepressant effects in patients with TRD who

had not previously responded to esketamine therapy alone. In this study, we contribute to the existing discourse by testing a novel combination of intranasal esketamine (as against other formulations) augmented by oral sirolimus, a combination that has not, to our knowledge, been represented in the existing literature.

METHODS

Study Design:

This was a retrospective per protocol chart review consisting of 18 patients diagnosed with TRD. Patients took sirolimus 6 mg orally two hours prior to scheduled esketamine treatment. Sirolimus was taken for two doses 28 days apart. Patients were eligible for this study if they had not achieved remission or relapsed into a major depressive episode (by DSM-5-TR criteria) despite ongoing maintenance therapy with intranasal esketamine. There were no limitations ion the number, frequency, nor dosing of maintenance esketamine treatments, nor on additional treatments beyond esketamine.

Outcomes:

Depression severity was evaluated using three validated scales: the Montgomery-Åsberg Depression Rating Scale (MADRS), the Patient Health Questionnaire-9 (PHQ-9), and the Hamilton Depression Rating Scale (HAM-D). Scores were collected for the treatment group at baseline (immediately prior to the first sirolimus-augmented esketamine dose), and at 8- and 16-week time points shortly prior to esketamine treatment.

Statistics:

We employed paired-sample t-tests comparing baseline scores to 8-week and 16-week follow-up scores. Both two-tailed and one-tailed t-tests were performed. The one-tailed analysis could be justified based on a review of current literature, which supports an *a priori* directional hypothesis that sirolimus enhances esketamine's antidepressant efficacy. Effect sizes were calculated using Cohen's *d*. Statistical significance was defined as $p < 0.05$.

RESULTS

Following a two-tailed t-test analysis, none of the results met conventional thresholds for statistical significance, although all showed directionally favorable changes and moderate effect sizes (Figure 1). At 8 weeks: MADRS: Mean change −6.39 ($p = 0.053$), Cohen's $d = 0.49$; PHQ-9: Mean change −2.83 ($p = 0.066$), $d = 0.46$; HAM-D: Mean change −2.78 ($p = 0.063$), $d = 0.46$. At 16 weeks: MADRS: −4.22 ($p = 0.19$), $d = 0.32$; PHQ-9: −2.28 ($p = 0.16$), $d = 0.35$; HAM-D: −2.56 ($p = 0.099$), $d = 0.41$. See Table 1 for summary statistics.

By one-tailed analysis, results suggest that sirolimus augmentation may provide short-term clinical benefits in TRD when combined with esketamine. At 8 weeks: MADRS: $p = 0.0265$ (significant); PHQ-9: $p = 0.033$ (significant); HAM-D: $p = 0.0315$ (significant). At 16 weeks: MADRS: $p = 0.095$ (not significant); PHQ-9: $p = 0.08$ (not significant); HAM-D: $p = 0.0495$ (marginally significant). See Table 2 for summary statistics using a one-tailed analysis.

Figure 1

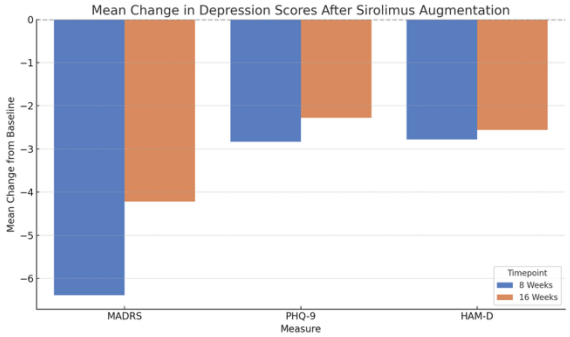

Table 1

8 Weeks	Mean Δ [95% CI]	p-value	Cohen's d	t-statistic
MADRS	-6.39 [-12.87, 0.09]	0.053	0.49	-2.08
PHQ9	-2.83 [-5.88, 0.21]	0.066	0.46	-1.96
HAM-D	-2.78 [-5.79, 0.23]	0.063	0.46	-1.95

Table 2

16 Weeks	Mean Δ [95% CI]	p-value	Cohen's d	t-statistic
MADRS	-4.22 [-10.80, 2.36]	0.19	0.32	-1.35
PHQ9	-2.28 [-5.54, 0.99]	0.16	0.35	-1.47
HAM-D	-2.56 [-5.65, 0.53]	0.099	0.41	-1.74

DISCUSSION

This pilot investigation sought to explore whether pretreatment with sirolimus could enhance the antidepressant effects of intranasal esketamine in patients with TRD. Under a two-tailed analysis, trends toward improvement were seen across all outcome measures at both 8 and 16 weeks, although results did not reach statistical significance. When an *a priori* directional hypothesis was considered, a one-tailed analysis demonstrated significant improvement at 8 weeks on all three measures.

These findings, and the justification of a one-tailed t-test, as warranted by a prior directional hypothesis, are consistent with the prior work by Abdallah *et al*. [2] and others [5], which found a prolonged antidepressant effect of ketamine following sirolimus pretreatment in humans, and support the potential of mTORC1 modulation to sustain ketamine's therapeutic impact. The present results extend this possibility to esketamine, a more accessible and widely used (in this case, intranasal) treatment modality.

However, several methodological limitations must be considered. This per -protocol study was significantly underpowered (estimated power ~0.13), limiting our ability to detect small-to-moderate effects with confidence. The absence of randomization and placebo control introduces bias and limits causal inference. Differences in esketamine dosing frequency compared to IV ketamine protocols used in earlier research may have also masked potential effects. Additionally, differences in delivery route (nasal vs. intravenous) may alter pharmacodynamics and influence the interaction of these medications with sirolimus. Finally, justification of a one-tailed t-test as warranted by an *a priori* directional hypothesis is itself based on a literature with mixed results concerning the effects of sirolimus, and animal studies have showned that intracerebroventricular injection of sirolimus effectively blocked ketamine-induced synaptogenesis and behavioral responses that were taken to represent antidepressant effects in rodent models of depression [4].

In spite of these limitations, this exploratory analysis suggests the potential for sirolimus as an adjunct to esketamine-based therapy in TRD. No doubt, a larger, randomized controlled trial is warranted to confirm these preliminary findings.

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