The Efficacy of Transdermal Rivastigmine in Mild to Moderate Alzheimer's Disease with Concomitant Small Vessel Cerebrovascular Disease: Findings from an Open-Label Study

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INTRODUCTION

Background

Alzheimer's disease (AD) and **cerebrovascular disease** are leading causes of dementia, with cerebrovascular disease, specifically **small vessel cerebrovascular disease (svCVD)** co-existing in one-third of AD patients worldwide, particularly in Asia, where the number is believed to be even higher at **50%**.

Currently, **cholinesterase inhibitors** such as rivastigmine are the approved treatment for the symptomatic management of cognitive deficits in AD. This inhibitor **reduces the activity of the esterase enzyme** and results in **improved activity of the acetylcholine neurotransmitter**, which reduces cognitive decline in patients with AD. There is also evidence that levels of acetylcholine are also reduced in patients with cerebrovascular disease.

Project Aim

To identify the effectiveness of Rivastigmine Patch in patients with AD having MRI-confirmed svCVD in an open label trial.

Hypothesis

Patients with AD having concomitant svCVD treated with Rivastigmine patch 9.5mg/24 hours will experience improvements in cognition and daily function over a 24 week period.

MATERIALS AND METHODS

Methods

Open Label Study **100** patients diagnosed with AD and MRI-confirmed svCVD were recruited → Rivastigmine Patch **4.6mg/24h** for first 4 weeks → Rivastigmine Patch **9.5mg/24h** subsequently → Cognitive assessments at **baseline**, **16-week mark**, **24-week mark**

Note: Dose adjustments for up to 2 weeks at a time, and for a maximum of up to 2 times, were permitted to address perceived safety or tolerability issues.

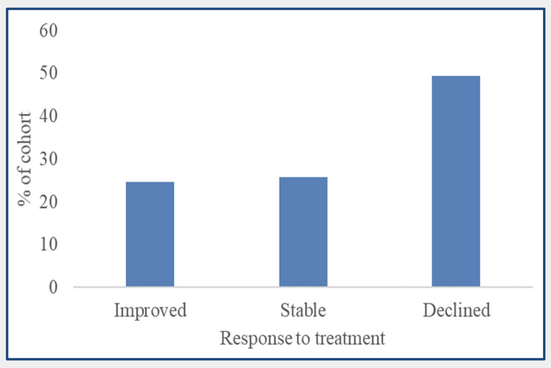
Outcomes

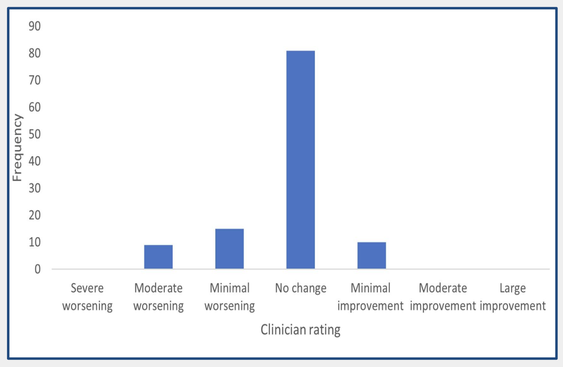
1. Change in global cognition (indexed by **ADAS-Cog**)
2. Clinical-rated impression of change (indexed by **ADCS-CGIC**)
3. Activities of daily living (indexed by **ADCS-ADL**)
4. **Side effects** and safety profile of treatment

Statistical Analysis

- **Intent-to-treat** study design
- All patients with baseline cognitive assessment and received at least one dose of transdermal Rivastigmine were included
- Missing data was imputed using **last observation carried forward (LOCF)**
- Repeated measure analysis, analysis of variance, Tukey's test, and Chi-square test were used to assess outcomes

RESULTS





Change in Global Cognition

- **25%** of the patients experienced a **significant improvement** in cognition (M=–5.08, SD=3.11)
- **27%** of the patients had **stable performance** (M=0.38, SD=0.71)
- **48%** of the patients observed a **decline in performance** (M=6, SD=2.98)

All changes in global cognition were measured **after 24 weeks** of treatment and based on **ADAS-Cog** scoring.

Change in Global Function

- Mean impression of change in global function was reported as **"no change"** for **81%** of the patients
- **"Minimal improvement"** in global function was rated for **5%** of the patients
- **"Worsening"** in global function was rated for **14%** of the patients

All changes in global function were rated **after 24 weeks** of treatment and based on clinician-rated **ADCS-CGIC**.

Interaction between Treatment Response and Severity of svCVD

Overall, there was no interaction effect between Fazekas score (measure of the severity of svCVD) and treatment response on the ADAS-Cog.

Safety Profile

- Treatment was **not associated with any serious adverse events**
- Mild adverse events were observed by **3%**, **10%** and **3%** of the patients at the 8-week, 16-week and 24-week time points respectively
- Most reported adverse event was **contact dermatitis**, which was limited to the site of application of the transdermal patch
- **3 patients deceased** during the study period, but **none of the deaths** were considered to be treatment-related

DISCUSSION

These findings suggest that transdermal rivastigmine may be **useful in delaying cognitive decline** in almost 50% of patients with AD and concomitant svCVD, with minimal side effects.

Favorable effect of rivastigmine in patients with svCVD may be due to its capacity to **modify cardiovascular risk factors**.

- Rivastigmine may have a larger function on cognitive function by attenuating of hypotension, rather than, its enhancing effect on brain cholinergic tone
- Patients with **subcortical dementias** may experience both acetylcholine inhibition activity of rivastigmine, as well as a powerful **butyryl-cholinesterase inhibition effect**

Limitations

- **Lack of control group:** A control group of pure AD or pure vascular disease would have provided insight on whether rivastigmine is superior in treating mixed dementia with svCVD as compared to pure dementia.
- **Cardiovascular risk factors were not accounted for:** Previous research has shown that rivastigmine is sensitive to cardiovascular risk factors.
- **Duration of the study:** The average life expectancy of people with Alzheimer's disease is 10 years after diagnosis as compared to the length of this study.

CONCLUSION

Transdermal Rivastigmine patch is **effective in targeting cognitive impairment** in patients with AD with concomitant mild to severe svCVD with **minimal side effects**.

Future improvements include inclusion of a control group, collection of AD biomarkers and MRI to discriminate pure AD and AD with svCVD as well as determining whether the severity of cardiovascular risk factors affects treatment outcomes.

ACKNOWLEDGEMENTS

The authors of this poster would like to sincerely thank Prof Nagaendran for his guidance on this paper and designing of this poster. The authors of the paper would like to thank National Neuroscience Institute, Singapore, for sponsoring this study.