

## Cholinesterase Inhibitors in the Treatment of Vascular Dementia

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### Introduction

Vascular dementia is common, and currently there is no accepted therapy aimed at the cognitive symptoms. Prevention of further strokes is, of course, well established.<sup>1</sup> Evidence is accumulating that the cholinesterase inhibitors, proven therapy in Alzheimer disease (AD), may also be of use in vascular dementia (VaD). This paper will summarize that evidence.

### Epidemiology of Vascular Dementia

Vascular dementia can be diagnosed when there is a high degree of suspicion that cognitive impairment and stroke are related. Various criteria exist, which unfortunately do not overlap to any great extent, but all share several features.<sup>2</sup> These include: the presence of stroke, either clinical or found on neuroimaging; the presence of focal neurologic signs, such as asymmetric power or a positive Babinski response; and a characteristic course, with a sudden onset or stepwise progression. For the highest degree of confidence in the diagnosis, a temporal relationship between the stroke and the dementia is required.

In most surveys of older adults, vascular dementia is the second most common cause of dementia in the community, after AD. In Canada, the prevalence of VaD is 1.5% in people 65 and over, and 5.1% for AD.<sup>3</sup> Other surveys have found similar values.<sup>4,5</sup> Mixed dementia, the coexistence of Alzheimer disease and vascular dementia, is seen in about 0.9%.<sup>3</sup> This is more common than would be expected by chance alone.<sup>6</sup> The prevalence of VaD increases with age.<sup>7</sup> It is more common in men than in women. Vascular dementia may be more frequent than AD in Asian communities, although the pattern may be changing to one identical to that of North America and Europe.<sup>8-10</sup>

A report from the Canadian Study of Health and Aging described the outcomes of vascular dementia.<sup>7</sup> It is an important risk factor for both mortality and nursing home placement. Given its frequency and adverse outcomes, VaD is an important public health problem.

### Why should Cholinesterase Inhibitors be Effective in Vascular Dementia?

There are several lines of support for the possible effectiveness of cholinesterase inhibitors in VaD. Cholinesterase inhibitors work by inhibiting the breakdown of acetylcholine, one of the chief neurotransmitters in the brain. There is a loss of acetylcholine in Alzheimer disease, explaining the effectiveness of cholinesterase inhibitors in this condition. There is also a cholinergic deficit in vascular dementia.<sup>11</sup> The relative preservation of

nicotinic receptors in VaD compared to AD argues for a good response to cholinesterase inhibitors.<sup>12</sup>

True vascular dementia may be very rare. Often individuals with a clinical diagnosis of VaD have cerebrovascular disease at autopsy, but also have significant changes associated with AD. A large autopsy series from the United States found that, of 1929 cases, only six could be found who had VaD without coexisting AD.<sup>13</sup> It may well be that much of what is clinically diagnosed as vascular dementia is, in truth, a mixed dementia.

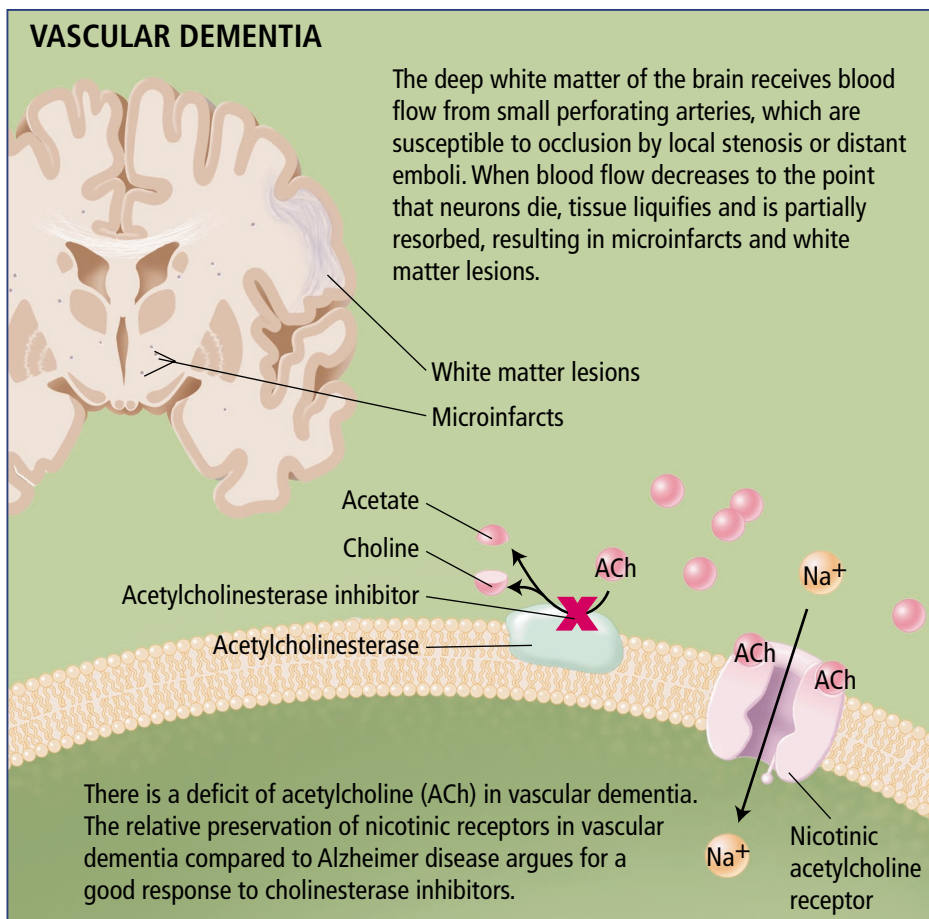
Finally, Alzheimer disease and vascular dementia may be opposite poles of a single disease. It is well-known that vascular risk factors, such as atrial fibrillation and hypertension, increase the risk of AD, regardless of the presence or absence of infarcts.<sup>6,14,15</sup> Stroke also has a dramatic effect on the severity of impairment in individuals with AD, with even small infarcts being correlated with much greater impairment.<sup>16</sup> Taken together, all of the above suggests that vascular dementia is rarely present alone, but rather usually coexists with AD, and even in the absence of AD, a cholinergic deficit is still present.

### Effectiveness of Cholinesterase Inhibitors in Vascular Dementia

There are few published trials of cholinesterase inhibition in vascular dementia. Donepezil was studied in an open-label trial.<sup>17</sup> Eight patients who met criteria for probable VaD were treated with donepezil for six months. All had subcortical disease, without any cortical infarcts. After six months, cognitive testing was stable, and the Clinical Dementia Rating (a measure of the severity of dementia) was slightly improved.

Rivastigmine was used in a small (n=16) randomized controlled trial.<sup>18</sup> The patients all met criteria for probable vascular dementia. All subjects had subcortical VaD, as indicated by white matter changes and lacunar infarcts, but no cortical infarcts. After one year, the treatment group had experienced minimal decline, with a reduction in caregiver stress. The control group had declined in terms of cognition, behaviour and increased caregiver stress. The usefulness of rivastigmine in mixed Alzheimer and vascular dementia is supported by post-hoc results from an Alzheimer disease randomized controlled trial.<sup>19</sup> Subjects with a Hachinski Ischemic Score between 1 and 4 (indicating likelihood of at least some vascular disease) responded to rivastigmine, and did a little better than did those without any concomitant vascular disease.

The largest trial yet published is a randomized controlled trial of galantamine.<sup>20</sup> This trial randomized 592 subjects to galantamine (n=396) or placebo (n=192). Subjects could enter the study if they had AD with evidence of cerebrovascular disease or they met criteria for probable VaD, both of mild to moderate severity. Approximately half of the subjects were in each diagnostic group. The treatment was relatively well tolerated, although 20% of the



galantamine subjects dropped out, compared to 8% of the placebo group. This may relate to the rapid (weekly) dose-escalation used in this trial, compared to the slower (every four weeks) escalation that is used in clinical practice. After six months of treatment, the galantamine group had improved cognition and behaviour, and stable function, when compared to placebo. Although the study did not have sufficient power to analyze each diagnostic group separately, the two groups seemed to have different patterns of response. The probable vascular dementia group improved and remained improved during the six-month study, while those on placebo remained at baseline. The patients with AD with cerebrovascular disease behaved like patients in the Alzheimer clinical trials, with a slight improvement in the treatment group and steady decline in the placebo group. As the accompanying editorial points out, this suggests that the two patient populations may be fundamentally different.<sup>21</sup>

### Summary

Vascular dementia is common and con-

tributes to adverse health outcomes. The relationship between VaD and AD is not yet clear, but considerable overlap exists. This lends a strong theoretical background to the use of cholinesterase inhibitors in vascular dementia. Although the research discussed above is promising, in my view, there is not yet sufficient evidence to recommend cholinesterase inhibitors for probable vascular dementia. As other studies are published in the coming months and years this view will likely change. The galantamine study certainly supports its use in mixed Alzheimer and vascular disease. Additionally, management of vascular risk factors is also important. ◆

Acknowledgements: Dr. Chris MacKnight has received grants and honoraria from Esai, Pfizer, Novartis, and Janssen-Ortho.

### References

1. Gorelick PB, Erkinjuntti T, Hofman A et al. Prevention of vascular dementia. *Alzheimer Dis Assoc Disord* 1999;13(suppl 3):S131-9.
2. Gold G, Bouras C, Canuto A et al. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. *Am J Psychiatr* 2002;159:82-7.

3. Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging: study methods and prevalence of dementia. *CMAJ* 1994;150:899-912.
4. Ott A, Breteler MM, van Harskamp F et al. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam Study. *BMJ* 1995;310:970-3.
5. Stevens T, Livingston G, Kitchen G et al. Islington study of dementia subtypes in the community. *Br J Psychiatry* 2002;180:270-6.
6. Rockwood K. Lessons from mixed dementia. *Int Psychogeriatr* 1997;9:245-9.
7. Rockwood K, Wentzel C, Hachinski V et al. Prevalence and outcomes of vascular cognitive impairment. *Neurology* 2000;54:447-51.
8. Hatada K, Okazaki Y, Yoshitake K et al. Further evidence of Westernization of dementia prevalence in Nagasaki, Japan, and family recognition. *Int Psychogeriatr* 1999;11:123-8.
9. Ikeda M, Hokoishi K, Maki N et al. Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. *Neurology* 2001;57:839-44.
10. Suh GH, Shah A. A review of the epidemiological transition in dementia: cross-national comparisons of the indices related to Alzheimer's disease and vascular dementia. *Acta Psychiatr Scand* 2001;104:4-11.
11. Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Dis Assoc Disord* 1999;13(suppl 3):S115-23.
12. Martin-Ruiz C, Court J, Lee M et al. Nicotinic receptors in dementia of Alzheimer, Lewy body and vascular types. *Acta Neurol Scand Suppl* 2000;176:34-41.
13. Hulette C, Nochlin D, McKeel D et al. Clinical-neuropathologic findings in multi-infarct dementia: a report of six autopsied cases. *Neurology* 1997;48:668-72.
14. Skoog I. Status of risk factors for vascular dementia. *Neuroepidemiol* 1998;17:2-9.
15. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke* 2002;33:1152-62.
16. Snowdon DA, Greiner LH, Mortimer JA. Brain infarction and the clinical expression of Alzheimer disease: The Nun Study. *JAMA* 1997;277:813-7.
17. Mendez MF, Younesi FL, Perryman KM. Use of donepezil for vascular dementia: preliminary clinical experience. *J Neuropsychiatry Clin Neurosci* 1999;11:268-70.
18. Moretti R, Torre P, Antonello RM et al. Rivastigmine in subcortical vascular dementia: a comparison trial on efficacy and tolerability for 12 months follow-up. *Eur J Neurol* 2001;8:361-2.
19. Kumar V, Anand R, Messina J et al. An efficacy and safety analysis of Exelon® in Alzheimer's disease patients with concurrent vascular risk factors. *Eur J Neurol* 2000;7:159-69.
20. Erkinjuntti T, Kurz A, Gauthier S et al. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet* 2002;359:1283-90.
21. Schneider LS. Galantamine for vascular dementia: some answers, some questions. *Lancet* 2002;359:1265-6.