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Is It Possible to Treat Vascular Dementia?

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Abstract

Randomized controlled trials of primary and secondary prevention of vascular dementia demonstrate real effects on the cause or progression of disease (disease-modifying treatment). These strategies lead to a reduction in all cerebrovascular risk factors, in particular hypertension. Such treatment may prevent dementia by reducing stroke and possibly by other mechanisms that remain undetermined, such as those involved in neurodegeneration and cell death. Curative treatment of vascular dementia, particularly given recent studies on cholinesterase inhibitors (rivastigmine, donepezil and galantamine) and memantine, is still ineffective. There is insufficient evidence to support widespread use of these drugs in vascular dementia. Particular considerations should be taken into account in clinical trials. Vascular dementia is a heterogeneous disease with different subtypes and mechanisms. Therefore, well-designed, adequately powered trials accounting for this heterogeneity, with better clinical definitions and an assessment and detection of cognitive and global changes specific to vascular dementia, are needed.

The Three Main Objectives in the Treatment of Vascular Dementia

Prevention

Before Stroke (Primary Prevention)

One of the most promising lines of research involves trials of preventive treatment in individuals with multiple risk factors: smokers, diabetics, atrial fibrillation, cardiac and hypertensive patients. In addition, recent epidemiological studies suggest that primary prevention of dementia in such patients should be applied from midlife. A retrospective cohort study was carried out, involving 8,845 participants from a health maintenance organization undergoing health evaluations between 1964 and 1973, between the ages of 40 and 44. Midlife cardiovascular risk factors included total cholesterol, diabetes, hypertension, and smoking. Diagnoses of dementia were ascertained from medical records between January 1994 and April 2003. The authors identified 721 participants (8.2%) with dementia. Smoking, hypertension, high

cholesterol, and diabetes at midlife were each associated with an increase in risk of dementia of between 20 and 40% (fully adjusted Cox proportional hazards model: HR 1.24, 95% confidence interval (CI) 1.04–1.48 for hypertension, HR 1.26, 95% CI 1.08–1.47 for smoking, HR 1.42, 95% CI 1.22–1.66 for high cholesterol, and HR 1.46, 95% CI 1.19–1.79 for diabetes). A composite cardiovascular risk score was created using all four risk factors and was associated with dementia in a dose-dependent fashion. Compared with participants having no risk factors, the risk for dementia increased from 1.27 for having one risk factor to 2.37 for having all four risk factors [1]. In this study, the presence of multiple cardiovascular risk factors at midlife substantially increased risk of late-life dementia in a dose-dependent manner. It thus remains to be shown that interventions targeting these risk factors – giving up smoking; control of diabetes, hyperlipidemia and obesity; carotid endarterectomy for symptomatic patients with 70–99% carotid stenosis; anticoagulants for atrial fibrillation; aspirin for patients at high primary risk and antihypertensives – would allow reduction of the risk of later development of dementia. Only a few studies of intervention exist. In the SHEP study [2], treatment of isolated systolic hypertension in individuals over the age of 60 years led to a 36% reduction in the incidence of stroke. The SYST-EUR trial [3] reported a 42% reduction in the overall incidence rate for stroke using antihypertensive treatment in a similar population. It is not known whether treatment of hypertension can prevent vascular dementia. In the same trial, in elderly people with isolated systolic hypertension, antihypertensive treatment was associated with a lower incidence of dementia (vascular but also Alzheimer's disease) [4]. Their findings suggested that if 1,000 hypertensive patients were treated with antihypertensive drugs for 5 years, 19 cases of dementia would be prevented. In the Study on Cognition and Prognosis in the Elderly, elderly patients with mildly to moderately elevated blood pressure, who received angiotensin receptor blocker candesartan-based therapy, had a slightly larger reduction in blood pressure than patients receiving placebo. This was associated with a modest, statistically nonsignificant reduction in major cardiovascular events and a marked reduction in nonfatal stroke. However, cognitive function was well maintained in both treatment groups in the presence of substantial reductions in blood pressure [5]. More recent analyses suggested that candesartan-based treatment improved cognitive function and quality of life in old and very old patients with mild to moderate hypertension [6, 7]. In the Rotterdam study, subjects taking antihypertensive medication at baseline (n = 2,015), who were then followed for a mean of 2.2 years, had a reduced incidence of dementia (adjusted relative risk, 0.76; 95% CI, 0.52–1.12). This reduction in risk was most pronounced for vascular dementia (adjusted relative risk, 0.30; 95% CI, 0.11–0.99) [8]. Thus, there seems to be clear prognostic benefits of treatment that lowers blood pressure in hypertensive patients.

Randomized controlled trials addressing interventions to minimize other risk factors mentioned above, such as warfarin treatment in atrial fibrillation or carotid endarterectomy, based their study end-points on the prevention of strokes and not the prevention of dementia. This is also true for the study of statins. Statins have been

shown to prevent both incident and recurrent cerebral ischemic stroke [9–11]. Given the benefit of preventing recurrent stroke, it would seem reasonable to treat vascular dementia patients with statin therapy to prevent stroke. To date, however, there is no evidence that statin therapy reduces the risk of incident dementia. A post-hoc analysis of the Cardiovascular Health Study revealed a trend towards reduced cognitive decline in patients treated with statins, but there was no change in the risk of incident dementia in this cohort [12–13]. Similarly, two other prospective cohort studies also failed to show a reduction in dementia associated with statin use [14–15]. A large randomized controlled trial in Australia, the ASPirin in Reducing Events in the Elderly trial, is currently ongoing; this study is investigating the use of 100 mg of aspirin for the primary prevention of major adverse events and vascular dementia [16].

After Stroke or Silent Cerebral Ischemia (Secondary Prevention)

This deals with early management of acute stroke, preventing recurrent stroke and reducing the progression of vascular-related changes in the brain by treating vascular risk factors. The Perindopril Protection Against Recurrent Stroke Study [17] showed that active treatment by an angiotensin-converting enzyme inhibitor, used alone or combined with a diuretic, was associated with a reduced risk of dementia and cognitive decline in patients with recurrent stroke. In addition, an active blood pressure-lowering regimen stopped or delayed the progression of white matter hyperintensities detected on cerebral MRI in patients with cerebrovascular disease [18].

Curative Treatment

Once dementia has begun, new infarcts need to be prevented and its progression needs to be slowed down. A variety of treatments for vascular dementia have been tested. These include agents which affect cerebral blood flow. Meyer et al. [19] report encouraging results from a randomized clinical trial testing 325 mg of aspirin per day in 70 patients with vascular dementia. Daily aspirin treatment improved cognitive performance and reduced or stabilized the decline in cerebral perfusion in this group of patients. The authors stated that this treatment also improved quality of life and independence in daily activities. Nimodipine treatment has also been suggested for vascular dementia. This drug exerts its vasoactive effects by dilating mostly small and collateral cerebral vessels and improving blood supply to underperfused areas. In an open trial [20], cognitive function was found to stabilize in 31 patients treated with a daily dose of 90 mg nimodipine for up to 1 year. However, it is very difficult to draw any firm conclusions in the absence of randomized placebo-controlled studies of large populations. In a double-blind, placebo-controlled study [21], 112 patients were treated with nicergoline, a thrombolytic, vasoactive ergot alkaloid. Nicergoline improved vigilance and information processing in the neuropsychological assessment of patients with degenerative and vascular dementia. Several studies have investigated

the use of pentoxifylline, which has been approved for use in peripheral vascular disease (intermittent claudication) and is reported to have a 'hemorheological' mode of action, i.e. it is thought to affect the microcirculation, increasing capillary blood flow and thereby improving tissue oxygenation [22, 23]. These studies suggested that the treatment may be beneficial but the differences between patients receiving treatment and those given the placebo were small and often not statistically significant. Another drug which may be effective is propentofylline [24–26], which strongly inhibits the potentially neurotoxic actions of activated microglia (free radical formation and transformation into brain macrophages). This drug may inhibit the progressive neurodegenerative process in dementia; however, randomized, double-blind placebo-controlled trials are required to establish whether this drug is effective. Long-term benefits have not been consistently demonstrated for any of these drugs. A recent Cochrane review (meta-analyses of 29 studies; total participants = 4,247) on *Ginkgo biloba* extract, concluded that the evidence that *Ginkgo* has predictable or clinically significant benefit for people with dementia (all etiologies) or cognitive impairment is inconsistent and unconvincing [27].

Recent evidence supports the involvement of the cholinergic system in vascular dementia, similar to that seen in Alzheimer's disease (AD). The mechanism of action of cholinesterase inhibitors in vascular dementia should, however, be investigated further [28, 29]. Several studies have tried to determine the effect of cholinesterase inhibitors on vascular dementia, but the results are also limited and inconsistent. A recent meta-analysis of randomized controlled trials concluded that cholinesterase inhibitors and memantine produce small benefits in cognitive function and do not necessarily have clinical significance in patients with mild to moderate vascular dementia [30]. According to the authors, there are insufficient data to support widespread use of these drugs in vascular dementia. The trials meeting the selection criteria for this meta-analysis included three donepezil (307, 308, 319) [31–33], two galantamine (GAL-INT-6 and 26) [34, 35], one rivastigmine (VantagE) [36], and two memantine trials (MMM300 and 500) [37, 38], comprising 3,093 patients on the study drugs and 2,090 patients on placebo (table 1). Cognitive effects on the Alzheimer's Disease Assessment Scale were significant for all drugs, ranging from a mean difference of –1.10 (95% CI –2.15 to –0.05) for rivastigmine to –2.17 for 10 mg daily donepezil (95% CI –2.98 to –1.35). Only 5 mg daily donepezil had an effect on the Clinicians' Global Impression of Change Scale [odds ratio 1.51 (95% CI 1.11–2.07)]. No behavioral or functional benefits were observed, except for a difference of –0.95 (95% CI –1.74 to –0.16) on the Alzheimer's Disease Functional Assessment and Change Scale for treatment with 10 mg daily donepezil. The main outcomes of these trials are described in table 2. Strengths of this meta-analysis include the exclusion of biased studies and the inclusion of unpublished results from three trials not included in previous reviews:

(1) The GAL-INT-26 study, which is now published, showed that galantamine was effective for improving cognition, including executive function, in patients with vascular dementia, with good safety and tolerability. However, improvement in

Table 1. Characteristics of patients from randomized controlled trials for cholinesterase inhibitors and memantine for vascular dementia

Trial	Design and patients							Characteristics of vascular lesions, %					
	Length weeks	Inclusion criteria [44–49]	Patients	Mean age	Males %	Mean MMSE	Mean ADAS-cog/11	Cortical only (single/ multiple infarcts)[1]	Sub-cortical only (lacunes)[1]	Cortical and sub-cortical[1]	White matter only	Extensive white matter[1]	Combined with AD lesions
Donepezil 307 [31] 5 and 10 mg/day	24	probable or possible VaD [44] MD excluded	603	73.9 (7.37)	55	21.3 (4.25)	20.7 (10.4)	18–21	33–36	17–23	18	…	–
Donepezil 308 [32] 5 and 10 mg/day	24	probable or possible VaD [44] MD excluded	616	75.0 (7.44)	60	22.3 (4.31)	20.1 (10.0)	25	35	20	15	…	–
Donepezil 319 [33] 5 mg/day	24	probable or possible VaD [44] MD excluded	974	73.0 (9.36)	59	23.0 (–)	…	…	…	…	…	…	–
GAL-INT-6 [34] 24 mg/day	24	probable VaD [44] or MD [45]	592	75.1 (7.00)	53	20.5 (3.63)	22.8 (9.18)	39–46	40–47	7–8	…	64	48
GAL-INT-26 [35] 16 and 24 mg/day	26	probable VaD [44] MD excluded	788	72.3 (8.87)	64	20.3 (3.90)	22.7 (9.50)	41–46	31	…	…	52	–
VantagE [36] 6 to 12 mg/day	24	probable VaD [44, 46] MD excluded	710	72.9 (8.32)	61	19.2 (4.01)	23.3 (9.88)	…	…	…	…	69–72	–
MMM300 [37] 20 mg/day	28	probable VaD [44, 47] MD excluded	288	76.4 (6.68)	53	16.9 (2.52)	21.0 (9.15)	34–37	…	…	…	76–79	–
MMM500 [38] 20 mg/day	28	probable VaD [44, 48, 49] MD excluded	548	77.4 (6.94)	61	17.6 (3.25)	25.7 (11.0)	28–29	…	…	…	…	–

Figures in parentheses indicate SD. … = Data not available; VaD = vascular dementia; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; ADAS-cog/11 = Alzheimer's Disease Assessment Scale-Cognitive subscale; mixed dementia = vascular dementia and Alzheimer's disease.
[1]Two results correspond to results in the treated and placebo groups respectively.

Table 2. Outcomes of randomized controlled trials for cholinesterase inhibitors and memantine for vascular dementia

Trial	Cognitive outcomes (ADAS-cog/MMSE)			Clinicians global outcomes (CGIC/CIBIC-plus)		Functional scales/behavior	
	treatment	placebo	comments	treatment	placebo	treatment vs. placebo	comments
Donepezil 307 [31] 5 and 10 mg/day	Improvement	Decline	Only 10 mg differed from placebo Post-hoc analyses suggested greater improvement in patients with cortical and multiple territorial lesions compared to those with predominantly subcortical lesions	Tendency to improve	No change	Not significant (ADFACS)	Only 5 mg was significantly associated with improvement or no change versus decline in global scores Only 10 mg differed from placebo in functional scales
Donepezil 308 [32] 5 and 10 mg/day	Improvement	Decline	Only 10 mg differed from placebo Post-hoc analyses suggested greater improvement in patients with cortical and multiple territorial lesions compared to those with predominantly subcortical lesions	Tendency to improve	No change	Not significant (ADFACS)	Only 5 mg was significantly associated with improvement or no change versus decline in global scores Only 10 mg differed from placebo in functional scales
Donepezil 319 [33] 5 mg/day	Tendency to improve	No change	Additional tests of frontal executive function did not improve detection of treatment effects	…	…	No significant (disability assessment for dementia)	
GAL-INT-6 [34] 24 mg/day	VaD: improvement MD: slight improvement	VaD: improvement MD: slight improvement		All cohort: improvement VaD: no change	No change	No significant (disability assessment for dementia; NPI)	
GAL-INT-26 [35] 16 and 24 mg/day	Improvement	No change	Post-hoc analyses suggested greater improvement in patients with cortical and multiple territorial lesions compared to those with predominantly subcortical lesions	Tendency to improve	No change	No significant (ADCS-ADL; NPI)	Post-hoc analyses suggested greater improvement in patients with cortical and multiple territorial lesions compared to those with predominantly subcortical lesions

Table 2. Continued

Trial	Cognitive outcomes (ADAS-cog/MMSE)			Clinicians global outcomes (CGIC/CIBIC-plus)		Functional scales/behavior	
	treatment	placebo	comments	treatment	placebo	treatment vs. placebo	comments
VantagE [36] 6 to 12 mg/day	Slight improvement	Slight decline	Additional tests of frontal executive function did not improve detection of treatment effects	Slight decline	Slight decline	No significant (ADCS-ADL; NPI)	
MMM300 [37] 20 mg/day	No change	No change	Larger effects in subgroups that predominantly had small vessel disease, and with MMSE<15, due to decline in placebo group	No change or tendency to improve	No change	No significant (NOSGER)	
MMM500 [38] 20 mg/day	No change	No change	Larger effects in subgroups who predominantly had small-vessel disease, and with MMSE<15, due to worsening in placebo group	…	…	No significant (NOSGER)	

… = Data not available; MD = mixed dementia (VaD and AD); ADAS-cog/11 = Alzheimer's Disease Assessment Scale-Cognitive subscale; CGIC = clinician's global impression of change; CIBIC-plus = clinicians' interview-based impression of change with caregiver's input; ADFACS = AD functional assessment and change; ADCS-ADL = AD Cooperative Study ADL inventory; NPI = Neuropsychiatric Inventory; NOSGER = Nurses' Observation Scale for Geriatric Patients.

performing daily activities in patients on galantamine was similar to that observed in patients receiving placebo [35].

(2) The VantagE study, which is now published, showed that rivastigmine was not consistently effective in probable vascular dementia. The efficacy in terms of cognitive outcome was based on effects in older patients likely to have concomitant AD pathology. This is consistent with previous findings suggesting that the putative cholinergic deficit in vascular dementia probably reflects the presence of concomitant AD pathology [36].

(3) The Donepezil 319 study remains unpublished [33].

The findings of this recent meta-analysis are not inconsistent with earlier reviews of rivastigmine, galantamine and memantine. Previous Cochrane reviews have concluded that there was insufficient evidence to support the use of these three drugs (galantamine, rivastigmine and memantine) in patients with vascular dementia [39–41]. However, results in the meta-analysis for donepezil differ from an earlier review of

the Cochrane Database [42] and from a manufacturer-sponsored review [43]. This is mainly due to the inclusion of the unpublished trial (trial 319), which substantially attenuated the global effects observed for the 5 mg dose [from –0.24 (95% CI –0.40 to –0.08) to –0.15 (95% CI –0.26 to –0.04)]. At the same time, the risk of death was significantly higher with donepezil than with placebo in trial 319. The evidence of a smaller effect size for cognitive and global outcome, the suggestion of increased mortality with 5 mg donepezil, and the lack of overall benefit with the 10 mg dose, suggest that a guarded position on the use of donepezil for vascular dementia should be adopted.

Currently, there is not enough evidence to recommend cholinesterase inhibitors and memantine as treatment for vascular dementia. Regulatory approval for the treatment of vascular dementia with these drugs has not been acquired in most parts of the world, despite some positive but small effects observed in clinical trials.

Several important factors should be considered for the interpretation of clinical trials for vascular dementia:

The Heterogeneity of the Disease Itself

The trials included patients with clinically heterogeneous cerebrovascular disease and by design could not address whether particular patient subgroups might have benefited. Patients with vascular dementia varied widely in terms of type, location, and extent of cerebrovascular disease. Divergent processes (e.g. single large-vessel lesion or multiple infarct, diffuse leukoencephalopathy and/or lacunes) are potentially included and clinical presentation and progression may differ, and may respond differently to the drugs tested. Additional heterogeneity both within and between trials may result from different choices of diagnostic imaging methods. For example, trials relying to a greater degree on MRI than CT scans may have been more likely to identify patients with smaller lesions and white matter disease (table 1). Consequently, individual patient analyses are needed to identify subgroups of patients with vascular dementia who might benefit from a treatment.

The High Prevalence of Mixed Pathology, Especially in the Elderly

Vascular lesions coexisting with AD lesions may lead to the detection of small effects in the vascular dementia trials, due to effects on comorbid AD, specific subtypes of vascular dementia, or a combination of both.

Selection of Tools Specific to Vascular Pathology

The ADAS-cog test, used in AD trials, essentially provides a composite score of memory, language and orientation. It does not assess attention and the range of executive dysfunction or subcortical impairment associated with vascular dementia.

The Trial Length

The trials lasted 6 months and were designed to specifically assess symptomatic rather than neuroprotective effects.

Physiotherapy can avoid complications of motor function (scarring, ankyloses and retraction of the tendons), increasing the patient's level of independence. Speech therapy is also beneficial. Rehabilitation is often limited by progression of the dementia. At this stage of the illness, simple practical measures such as avoiding falls are very effective. It is also of utmost importance to ensure that the drug treatment does not provoke hypotension.

In general, the management of patients with vascular dementia is similar to that of other dementia patients. If possible, the patient is cared for at home, isolation of the subject is avoided and close attention is paid to the prescription of drugs. Behavioral problems, secondary depression, intercurrent affections and metabolic problems are treated and the patient is made a ward of court if necessary. Family support is encouraged and most importantly, the patient's future is considered.

Conclusions

Vascular dementia is potentially preventable by treating risk factors very early in midlife. It is vital to reduce all cerebrovascular risks, especially hypertension. Curative treatment of vascular dementia is still ineffective, although a number of drugs are currently under investigation. Well-designed and adequately powered trials that account for the heterogeneity of vascular dementia are needed. These trials should use optimal clinical definitions (stratifying by pathology/mechanisms for example) and more specific tools for the detection of cognitive and global changes in vascular dementia. They should allow for the extensive post-hoc analyses required in patients with significant medical and psychiatric comorbidity. The support of carers in the patient's family is essential if elderly patients are to be cared for in the community. This involves assessing the social integration, occupational activity, leisure activity, economic problems and family conflicts associated with sharing the responsibility of caring. By focusing on these aspects we should be able to develop successful intervention strategies to treat vascular dementia.

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