DEMENTIA NEWSLETTER *for* PHYSICIANS

Vol. 3, No. 1 OTTAWA Spring 2003

A Publication of the Dementia Network of Ottawa

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Aricept: Across the Spectrum of Dementia

By Dr. Bill Dalziel
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Aricept was the first cholinesterase inhibitor (CI) approved in Canada in August 1997. It remains the most studied CI with the greatest depth and breadth across the spectrum of dementia including differing severity of disease and etiology.

Multiple randomized controlled studies (RCT) of up to one year duration have shown the benefits of Aricept therapy in mild to moderate Alzheimer's (MMSE 10-26) in such treatment parameters as cognition, activities of daily living (ADLs), global clinical impression, time to reach a defined level of functional decline (72% longer with Aricept—357 days versus placebo 208 days), and delay in LTC placement by almost two years.

The benefits of Aricept therapy have also been seen in moderate to severe Alzheimer's (MMSE 5-17) in treatment parameters including cognition, function, behavioral problems, and most importantly in caregiver time spent (approximately one hour less per day compared to placebo). Another study showed benefit in patients after LTC placement in cognition, global function, and behavioral problems, particularly aggression and agitation. This emphasizes the point that CIs should not be discontinued simply because someone has entered a nursing home with respect to control of behavioral problems.

Benefits have also been seen in patients with Lewy Body Dementia (case series, not RCT), dementia associated with Parkinson's Disease (a single small RCT) and most recently in a large RCT in vascular dementia. The positive results in vascular dementia coupled with Reminyl's positive study on mixed Alzheimer's / vascular dementia

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Aricept (continued from page 1)

extends the CI class beyond therapy for Alzheimer's alone.

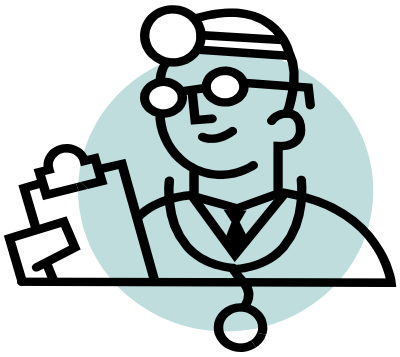
Aricept has similar contraindications and GI toxicity to the other CIs (nausea, diarrhea, bloating, anorexia, and vomiting) but these are generally mild and limited to 1-2 weeks duration. A significant advantage with Aricept is that it is dosed once a day and that the initial dose (5 mgm daily) is a clinically effective dose (as opposed to the initial dose of Reminyl and Exelon). Most patients should be pushed to 10 mgm daily. Dosing is recommended in the morning to avoid the side effect of sleep disturbance and/or nightmares that can be seen with Aricept. Other side effects may include headache, dizziness and cramps.

Pharmaco-economic studies have generally shown Aricept to be cost neutral or slightly cost beneficial, mostly due to delay in long term care placement. Few drugs used clinically are ever cost neutral.

Because it is the most commonly used CI, there have been several small studies looking at the benefits of switching from Aricept to either Exelon or Reminyl. If the patient is switched because of initial non-tolerance or lack of response at 3-6 months follow-up, the switching studies have generally shown a positive benefit in up to 50% of patients. This certainly reinforces the fact that standard of care now in dementia is a trial of one CI and if there is lack of response or intolerance there should be a trial of a second CI. The other scenario in switching is when the patient has initially responded but after a few years the family feels the patient is deteriorating. This is usually due to the fact that the patient's disease has progressed and the speed of progression is higher in moderate dementia than mild dementia.

Usually I try to explain this to families and avoid switching. If these patients are switched, great care must be given to avoid the crash that can be seen when discontinuing a previously effective CI. Use a bridging strategy of initiating the second CI and rapidly titrating it to the minimal clinical effective dose while weaning off the first CI.

In summary, Aricept remains the most popular CI in Canada with the greatest range of studies across the spectrum of dementia.



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Anna Byszewski, Bill Dalziel, Tony Guzmàn, Barbara Power, Tilak Mendis and Inge Loy-English.

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- improve your recognition, diagnostic assessment and treatment of dementia
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- improve your knowledge on monitoring for the benefits of acetycholinesterase therapy
- improve your understanding of the Alzheimer Society's programs and services available for patients/ caregivers/family members

To find out more information, please call: 523-4004

Vascular Dementia (VD)

By Dr. D.A. Guzmàn, M.D., FRCPC, Director, Memory Disorder Clinic

The concept of Vascular Dementia is vague and is currently in a state of flux. It consists of cerebrovascular disease in dementia. There are several types.

A. Dementia associated with multiple cortical (+ or -) subcortical infarcts (*multi-infarct dementia*—MID)
B. Dementia with strategic infarcts (*e.g.,* thalamus, angular parietal gyrus)
C. Subcortical Vascular Dementia—with multiple basal ganglia and white matter lacunes and/or extensive periventricular and white matter lesion

Clearly, imaging is very important in making the diagnosis.

INCIDENCE

Incidence depends on the definition. In the "Nun Study" only 3 of 118 autopsies on demented individuals revealed changes diagnostic of "Vascular Dementia". Other autopsy studies have also shown very low prevalence in more "typical" general populations—e.g. 2 to 7 %. On the other hand, clinically, it is generally accepted that about 20% of all cases of dementia are vascular (VD). It may well be that most of these also have some Alzheimer's disease.

DIAGNOSIS

Multi-Infarct Dementia (MID) can generally be diagnosed and/or suspected with imaging studies and the Ischemic (Hachinski) Index.

Subcortical Vascular Dementia can also be identified by using the Hachinski Index. On the other hand, it is usually of gradual onset and there is no history of strokes. There are often no sudden clinical changes. Imaging is extremely important in subcortical dementia. One finds lacunes in basal ganglia and deep grey matter. Accurate diagnosis is difficult. If one starts by looking at the research criteria used for the identification of patients with Probable Vascular Dementia one gets a better feel of this. The criteria most often used are those of the NINDS-AIREN (National Institute of Neurological Disorders and Stroke and the Association internationale pour la recherche en neuroscience). They require evidence of dementia (memory and two other domains), evidence of cerebrovascular disease (CVD) from neuro-imaging and physical examination and a probable or possible relationship between the dementia and CVD. *Subcortical Vascular Dementia* is difficult to fit in unless one gives more weight to the imaging findings and less to the relationship between CVD and the dementia. The onset is almost always gradual, there may be no focal neurological signs and the most prominent findings are personality changes.

Strategic Infarct Dementia is a different issue that is again diagnosed predominantly through imaging.

MANAGEMENT

Prevention

Dementia with cerebrovascular disease is amenable to preventive management of its vascular component. The risk factors are age, hypertension, diabetes, atherosclerosis, alcoholism, ApoE4, left ventricular hypertrophy, and, of course, strokes. The management of risk factors and the use of the "statin" drugs have been shown to decrease the incidence of dementia.

Cholinesterase Inhibitor Therapy in Vascular Dementia

The rationale for the use of cholinesterase inhibitors in VD is that there is a decline in cholinergic markers (e.g. ChAT, Ach) in CSF in VD and in AD. The changes in VD are related to the effect of the vascular lesions on the cholinergic system and its connections. All three companies producing the currently marketed cholinesterase inhibitors (Janssen-Ortho, Novartis, and Pfizer) have already had some experience in clinical trials on patients with dementia and CVD. More extensive trials restricted to participants with probable vascular dementia are now being conducted using donepezil (Aricept®), galantamine (Reminyl®), or rivagistamine (Exelon®).

Donepezil—A 24-week trial with 616 participants randomized to donepezil or placebo in probable VD showed significant improvement in cognitive function. Placebo participants on cognitive testing did not

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Vascular Dementia (VD)

(continued from page 3)

decline below baseline. *Alzheimer's Disease Functional Assessment of Change Scale* (ADFACS), a functional scale, remained over baseline in treated participants, but dropped below baseline in placebo participants.

Galantamine— A galantamine trial of 6 months duration was carried out with 592 randomized participants. It included probable VD (40%) and mixed dementias (60%). The VD group showed significant improvement in cognition compared to baseline at 6 months. Improvement over baseline was larger in the VD than in the mixed group. VD placebo group did not cross baseline. A new study using galantamine in probable VD is now under way.

Rivastigmine—A clinical trial was carried out with 699 participants randomized. It included patients with AD with and without vascular risk factors. VD patients were excluded. The results showed that those with vascular risk factors but not VD (determined by the Hachinski index) displayed better cognitive, activity of daily living (ADL) and disease variety responses than those without vascular risk factors. However, both groups responded to rivastigmine. A larger probable VD trial using rivastigmine is currently underway.

NOTE: Probable VD studies are hard to carry out because patient selection is very strict and potential participants are difficult to find.

SUMMARY

1. Vascular Dementia is probably less common than usually stated (at least on the basis of autopsy correlations). Mixed Dementia (VD-AD) is probably much more common than usually believed.
2. Prevention is important—especially **strict control of all vascular risk factors**. The use of "statin drugs" probably indicated. Lipids should be particularly targeted.
3. The course of Vascular Dementia is probably worse than the course of Alzheimer's disease. In clinical trials, however, patient selection is such that those chosen are in a stable condition and therefore the Vascular Dementia controls in those studies show less deterioration than those in Alzheimer's disease. This is not a true reflection of reality.
4. Cholinesterase inhibitors will have an important role in Vascular Dementia. Currently they should be used in cases of mixed Vascular/Alzheimer dementia. They are not, at this time, approved for the management of Vascular Dementia.

THANK YOU

The Dementia Network of Ottawa would like to thank Novartis, Janssen-Ortho, and Pfizer for sponsoring this edition of the Dementia Newsletter for Physicians.

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