Assessing the Response of Patients with Alzheimer Disease to Cholinesterase Inhibitors

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Introduction

The advent of cholinesterase inhibitors (CI) as regular prescription drugs for the treatment of Alzheimer disease (AD) in mild to moderate stages has created opportunities for a proactive role among primary care practitioners with interest in a geriatric practice. The Canadian Consensus Conference on Dementia original report,1 and its update,2 clearly support the role of primary care physicians in the diagnosis and treatment of AD. A new challenge is the assessment of response to CI in individual patients. This review will examine the evolving expectations of response to treatment since 1986, when tacrine was first described as an effective drug,3 and will conclude with current realistic goals at therapeutic doses of donepezil, rivastigmine and galantamine—improvement in apathy peaking after three months of therapy and one year of stability for cognitive, functional and behavioural symptoms, followed by a decline parallel to natural history.4

Responders in Randomized Clinical Studies

The early descriptions of the response to CIs such as tacrine, included ‘return to playing golf,’3 which set treatment expectations to a return to previous complex activities. A Canadian double-blind multicentre study did not find such dramatic effects.5 However, an increase in Mini Mental State Score (MMSE)6 was found after four weeks of treatment, associated with an increase in spontaneity of speech and in initiative for activities of daily living; a loss of behavioural spontaneity was noted by caregivers upon termination of the CI. The next randomized studies in the US followed the guidelines of the Food and Drug Administration: a measure of cognition and a global impression of change based on interview.7 One study8 showed improvement in cognition using the Alzheimer’s Disease Assessment Scale, cognitive subscale (ADAS-cog)9 but failed to demonstrate improvement on a clinical global impression of change (CGIC). Two other clinical trials10,11 showed improvement on both ‘primary outcomes,’ and the publication of these two studies introduced the notions of: (1) patients improving by four points or more on the ADAS-cog—described as ‘comparable with reversing six months of disease progression’;10 and (2) patients improving on the CGIC.11

This brief historical review provides the basis for understanding why ‘responder analysis’ in the subsequent studies with second generation CIs, including donepezil, rivastigmine, mirtifonate and galantamine, were focused on how many patients improved by four points or more on ADAS-cog and how many were improved on a global impression of change. The number needed to treat to achieve one patient with a four-point improvement on ADAS-cog ranges from four to 13 depending on the study and dose of CI.12

Over time, additional outcomes were introduced with the requisite sensitivity to change to allow a demonstration of stabilization of activities of daily living (ADL) up to one year,13 delay of emergence of behavioural and psychological symptoms of dementia (BPSD) in mild stages of AD,14 and improvement of some of these BPSD in moderate to severe stages of AD.15

Finally, two placebo-controlled studies of one year duration demonstrated that for patients on a CI, the improvement on MMSE peaks at three months, with a slow return to the starting point at the end of the year,16 and significantly delays the further loss of functional abilities.17

Taken together, these findings suggest that postponing or slowing decline in the domains of cognition, functional ability, behaviour, caregiver burden and resources utilization should be given a high priority over cognitive enhancement in future randomized clinical trials, clinical practice and decision-making about health care budgets.4

Responders in Clinical Practice

The primary care practitioners deal with one patient at a time, ideally with a reliable caregiver providing feedback on the patient’s cognitive abilities, activities of daily living and behaviour in the days to weeks preceding each visit. Expectations from the patient and caregiver may differ from that of the health professional,18 and all must understand that CIs are not a cure for AD. For most patients who tolerate therapeutic doses, CIs provide a stabilization of symptoms rather than a dramatic but short-lived ‘improvement in memory.’ They are not a substitute for, but are part of the comprehensive management of AD, which includes a good clinical diagnosis, patient and caregiver education, and monitoring for loss of ability to drive and caregiver burn out.19

Here are some practical tips on the use of CI and assessing response to treatment at the office:

- treat concomitant disorders first, such as depression, nutritional deficiencies, hypothyroidism; then reassess;
do a good baseline assessment of cognition (using the MMSE supplemented by clock test in patients with minimal or borderline impairment), ADL, mood and behaviour (using a semi-structured interview);

- write down two or three specific (but realistic) expectations from both the patient and the caregiver for abilities they want to improve or maintain over one year;

- show a cautiously optimistic attitude;

- start low and go slow, especially in small body weight women;

- write down the first few words of impression from the caregiver (and hopefully the patient) at the next follow-up visits (a caregiver diary may help);

- repeat the assessments at 6-month intervals; the MMSE may not be very sensitive for measuring improvement, but can help demonstrate stabilization or slower decline over time (operationally defined as two or fewer points lost per six months within the 10 to 26 severity range).

Using this approach, responders in clinical practice will be patients who tolerate a therapeutic dose of a CI (eg. donepezil 5 or 10mg QD, rivastigmine 3–6mg BID, galantamine 8–12mg BID) and are stable over one year, many having demonstrated an increased awareness to daily events and initiative to perform ADL, peaking at three months. A slow decline is to be expected after one year, and it is not currently recommended to stop a CI until reaching a severe stage of AD. Switching among CIs is possible but more evidence on the safety and benefit of this procedure is needed before formal guidelines are issued.

The Future
There are a number of clinical trials being initiated using an ‘add-on’ design, in order to test the safety and efficacy of agents that could modify the disease process.20 Patients on stable doses of a CI and interested in participating in such research can be referred to sites of the Consortium of Canadian Centres for Clinical Cognitive Research (C5R) and other participating sites.

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