Original article

Comparing treatment effects in a clinical sample of patients with probable Alzheimer's disease treated with two different cholinesterase inhibitors

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Abstract. *Background:* The aim of this study was to compare the effect of treatment with different cholinesterase inhibitors (ChEIs) on mental status and every day function in a natural outpatient clinic setting, so that this evaluation could more realistically reveal the effects which are likely to be observed in patients attending ordinary dementia clinics rather than in the context of a randomised controlled drug trial. *Methods:* Long term outcome of treatment with the ChEIs donepezil and rivastigmine was retrospectively evaluated in 147 patients with a clinical diagnosis of probable Alzheimer's disease of mild to moderate level of severity who had been monitored for a period of nine months. Measures included Mini Mental State Examination, Activity of Daily Living and Instrumental Activity of Daily Living scales. *Results:* Response rate was similar to that of other published clinical trials on ChEIs. Patients who responded well to treatment with ChEIs better maintained their improved performance. *Conclusions:* Treatment with both ChEIs resulted in improved performance in those patients responding to therapy. Greater response was observed in previously untreated patients who had a shorter disease history but overall the findings in this unselected clinical sample confirmed that patients gain some benefit from intervention with ChEI treatment. (www.actabiomedica.it)

Key words: Alzheimer, dementia, donepezil, rivastigmine

Introduction

Alzheimer's disease (AD) is by far the most common type of degenerative dementia. Although the aetiology of the disease is mainly unknown, some of its neuropathological and neurochemical consequences have been clearly established. In the last decade, advancements in knowledge on the biochemical disorders caused by AD in the cholinergic system of the brain has led to the development of cholinesterase inhibitor (ChEI) treatment that appears to alleviate the symptoms caused by the disease. Clinical benefits in cognitive and neuropsychiatric symptoms have been established in large scale multi centre studies of current ChEIs (i.e. donepezil, rivastigmine and galantamine) (1-6). The evidence obtained so far suggests that all these drugs are equivalent in alleviating the symptoms of AD, despite differences in pharmacokinetics or pharmacodynamics. Limited evidence is available from direct comparisons of the effect of these drugs, except for their side effects (7, 8). Reviews of available evidence conclude that all of them have a comparable positive effect and safeness, despite differences in tolerability and elimination half life. Neuroimaging studies have all reported comparable increases in regional cerebral blood flow or metabolism in re-

sponders to treatment, although the topographic distribution of these increases includes a variety of locations (9-13). Evidence of a neuroprotective effect has also been published suggesting that ChEI treatment might slow down disease progression (14, 15). No comparisons of the effects on mental status and activities of daily living of the different drugs have been carried out in which the patients' degree of response to the drugs was also a factor in the assessment of the outcome measures. A recently published study used a design and methods similar to the ones adopted in this study (16). Patients were classified into responders and non responders, with no grading of the extent of their response. No difference between the two drugs was found in any of the measures.

This study retrospectively evaluated the cognitive profile and instrumental and daily living activity abilities of patients who had been assessed in an outpatient clinic for cognitive disorders and monitored following treatment with a ChEI for a period of nine months.

The aims of this retrospective study were, therefore, to evaluate the effect of the different drugs used, and to assess the degree of individual response to treatment by evaluating changes from baseline and its influence on long term outcome. Interactions between all the variables of interest were also investigated.

Methods

Sample

One hundred and forty seven patients (mean age 74.9, SD 6.9; mean education: 5.4, SD: 2.6) fulfilling clinical criteria (17) for a diagnosis of probable mild to moderate AD were included in this study. Among the original sample of 165 patients, 16 interrupted the study for significant gastrointestinal side effects. Out of the remaining subjects, none experienced adverse events during the study period. These patients were treated with ChEI and monitored over a period of nine months amongst the series of sequential referrals in the Centre for Cognitive Disorders at the University of Parma (Italy). The sample included 100 women and 47 men. One hundred and nine patients were treated with donepezil and 38 with rivastigmine. Treatment was titrated according to published protocols up to individual patient's maximum tolerated dose. It was assigned by the physicians and was based on their clinical judgment which took into account the clinical profile of each patient.

Material

Scores of those instruments which have been specified by the Italian national guidelines (Cronos Project) for the monitoring of ChEI treatment were available. These included the assessment of general mental status with the Mini Mental State Examination (MMSE) (18) and the assessment of general every day function with the Activity of Daily Living (ADL) and the Instrumental Activity of Daily Living (IADL) scales (19). Available assessments had been carried out at baseline, and after three and nine months of treatment with ChEI therapy. Since this study was retrospective and included the evaluation of data which are part of the routine clinical protocol adopted for patient monitoring in the clinic, no additional ethical approval or consent from patients was, therefore, necessary.

Evaluation of response to treatment

Response to treatment was evaluated in each patient after three months. The evaluation of the treatment response was based on the observed increase/no change/decrease in MMSE scores from baseline. Four classification categories were set: good responder (≥2 points), responder (>0, ≤2), unchanged (=0) and non-responder (<0). A score improvement greater than two points was set for a classification as good responder, since a change in score of up to two points on the MMSE is potentially in the range of changes observable as a result of practice effects on repeated assessment with this test. An average increase of 1.12 (±0.47) points was observed in patients with AD tested four times in six weeks (20). Following these criteria, 34 (23.1%) patients were classified as good responders, 40 (27.2%) met criteria for responders, 21 (14.3%) had unchanged scores at reassessment whereas 52 (35.4%) showed a decrement in performance and were classified as non responders.

Statistical analysis

Group comparisons were carried out on the baseline and nine month data. Data from subgroups obtained by classifying patients according to their degree of response after three months of treatment were analysed only at baseline and at nine months. No analysis was carried out on the three month data since the scores at this stage were used as the guide for evaluating the response level. Data were analysed with analysis of variance. Post-hoc analyses were carried out whenever appropriate. Analyses of the nine month follow up were carried out using difference scores obtained by subtracting baseline scores from follow up scores. This manipulation should minimise the potential impact of differences in baseline scores between patients of different levels of severity.

Results

Patients treated with donepezil represented 74% of the sample while those treated with rivastigmine were only 26% of the sample. There was a tendency amongst the clinicians, therefore, to choose donepezil as the most appropriate treatment in the majority of cases.

Baseline analysis

There was no significant difference in MMSE scores at baseline between patient groups treated with different ChEIs ($F_{(1,145)}$=0.35, n.s.) (Table 1). A significant difference in the baseline MMSE scores was observed between patients who fell in the different treatment response categories ($F_{(3,143)}$=2.80, p=0.04) (Table 2). Post-hoc analysis with the Fisher test showed that a significant difference was present between the mean baseline MMSE scores of 'good responders' (p=0.01) and 'responders' (p=0.02), and those of 'non responders' with this latter group having higher baseline scores. When treatment with different ChEIs was factored in together with treatment response classification no significant difference in baseline MMSE scores was, however, found ($F_{(3,139)}$=1.97, n.s.).

Table 1. Baseline mean values (and standard deviations) of MMSE, ADL and IADL scores in patients treated with donepezil or rivastigmine

Measure	Donepezil	Rivastigmine
MMSE	18.90 (4.16)	18.45 (3.72)
ADL	5.02 (1.28)	5.05 (1.23)
IADL	3.65 (2.25)	3.58 (2.07)

Table 2. Baseline mean values (and standard deviations) of MMSE, ADL and IADL scores in patients who had different response to treatment

Measure	Good responders	Responders	Unchanged	Non-Responders
MMSE	17.76 (3.57)	18.12 (3.57)	18.62 (3.99)	20.02 (4.47)
ADL	5.35 (1.18)	4.72 (1.22)	5.43 (0.93)	4.88 (1.41)
IADL	3.71 (2.38)	3.17 (2.23)	4.00 (1.97)	3.79 (2.14)

No significant difference was found between baseline scores of patients treated with different drugs ($F_{(1,145)}$=0.02, n.s.) (Table 1) nor among those showing a different type of response ($F_{(3,143)}$=2.51, n.s.) (Table 2). The analysis of IADL scores showed no significant difference between scores of patients treated with different drugs ($F_{(1,145)}$=0.03, n.s.) (Table 1) nor among scores of patients with different types of response ($F_{(3,143)}$=0.87, n.s.) (Table 2).

Follow-up analysis at nine months

When treatment with different ChEIs was taken into account the variations in MMSE scores showed a significant difference between donepezil and rivastigmine treated patients ($F_{(1,145)}$=4.99, p=0.03) with rivastigmine treated patients showing greater stability in MMSE scores than the donepezil group (Table 3). No significant difference in ADL score variations was present ($F_{(1,145)}$=1.30, n.s.) whereas for IADL score variations, the difference was statistically significant ($F_{(1,145)}$=4.99, p=0.03). Once again rivastigmine treated patients showed more stable scores than those treated with donepezil (Table 3).

Further statistical comparisons were carried out with the patients rearranged in subgroups classified on the basis of their response to treatment as evaluated three months after ChEI therapy commencement. A significant difference was present only for MMSE ($F_{(3,143)}$=18.92, p<0.0001) (Table 4). Post-hoc compari-

Table 3. Nine month follow up mean values (and standard deviations) in variations in MMSE, ADL and IADL scores of patients according to treatment with donepezil or rivastigmine

Measure	Donepezil	Rivastigmine
MMSE	-0.84 (3.23)	-0.32 (3.46)
ADL	-0.22 (1.12)	0.00 (0.70)
IADL	-0.68 (1.51)	-0.08 (1.15)

Table 4. Mean (and standard deviations) MMSE, ADL and IADL variation scores at the nine-month follow-up of patients who had different response to treatment independently of the drug used

Measure	Good responders	Responders	Unchanged	Non-Responders
MMSE	1.76 (2.70)	-0.07 (3.28)	-0.76 (2.14)	-2.79 (2.72)
ADL	-0.09 (1.11)	-0.25 (1.19)	-0.09 (0.77)	-0.17 (0.94)
IADL	-0.12 (1.47)	-0.55 (1.60)	-0.57 (1.47)	-0.75 (1.27)

sons with the Fischer test showed that all subgroups were significantly different from each other ($p<0.01$) with the exception of 'responders' versus 'unchanged'. No significant difference between subgroups of patients with different response to treatment was observed for ADL ($F_{(3,143)}=0.18$, n.s.) and IADL ($F_{(3,143)}=1.34$, n.s.).

Discussion

This retrospective study compared the effect of treatment with different ChEIs on mental status and every day function in patients with mild to moderate AD. The findings indicate that patients who responded to treatment with ChEIs better maintained their improved performance. A significant enhancement was observed in both MMSE scores and IADL scores of rivastigmine treated patients, but the changes were only marginal and non significant in the donepezil treated group. The classification according to the level of response allowed a better characterisation of the effect of the drugs and revealed only a marginal advantage of rivastigmine for the degree of drug benefit maintenance over time. The observed changes and the proportion of patients responding to the drug in this study were comparable to those of other published studies (see for example reference 21) indicating that the investigated sample was representative of a typical population with AD, which is the most frequent target audience of treatment with ChEIs. The procedure of treatment allocation by the clinician in charge should ensure ecological validity to the study, since presumably, the sample and procedure of treatment allocation is similar to those of most outpatient clinics for AD. The proportion of patients not responding (who showed unchanged or decreased scores) to the drug was also similar to that reported in other published clinical studies (see for example reference 21) and was much higher than that obtained in small group studies of carefully selected, and probably less heterogeneous, groups (9, 13).

To the best of our knowledge this is the first independent study that considers the effects of ChEI therapy in AD in a natural clinical setting in which the degree of response to treatment is taken into account. Recently, the results of a large scale randomised controlled study of 'typical' AD have been published (22). That study assessed the efficacy of donepezil in a typical placebo controlled double blind randomised trial in which patients crossed over from active to placebo treatment in the course of the 48 weeks of treatment. The study concluded that the effect of treatment with donepezil was marginal and not cost effective. These conclusions are questionable for several reasons. AD is a progressive degenerative disease and conventional drug designs, although valid and rigorous methods for the establishment of treatment efficacy in other pathologies, might not be fully adequate for a disease such as AD. This kind of design might potentially interfere with the natural history of the disease (23). Very little is known on the actual effects of ChEI treatment on AD progression. Although drug trials have reliably established a symptomatic effect, some indication is available that the effects of these drugs may extend beyond a symptomatic benefit (14, 24, 25). Without a clear understanding of the effects of ChEI treatments on the progression of the disease it cannot be readily assumed that cross-over designs do not alter the neurobiological status of participants and influence, therefore, the assessment of drug efficacy.

After nine months of observation good responders were still performing at a level which was higher than baseline. The maintained improvement in these

cases was marginally larger in the subgroup treated with rivastigmine.

These data do not provide conclusive evidence of a difference between the two drugs and, although there was some indication that patients treated with rivastigmine showed greater improvements, several limiting factors (i.e. difference in sample size, absence of genetic profiling, psychometric limitations of the measures, etc) do not warrant any conclusion on what might be the reason behind the marginal differences observed in this study. A combination of cognitive and biological outcome measures might be better suited for this kind of assessment. Further longitudinal research including serial evaluation of disease progression with neuroimaging, online assessment of treatment effect with pharmacological MRI, when this techniques will be refined enough to be used in human routine assessment, as well as post-mortem studies are needed in order to fully understand the effects of the different ChEIs on neuropathology and clarify whether treatment with any of the existing ChEIs might have a positive influence on disease progression.

Acknowledgements

This paper is dedicated to the memory of Dr. Ezio Nonis who prematurely and suddenly died before completion of this manuscript.

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Accepted: 20th October 2006
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