Original paper

Cholinesterase inhibitors in the "real world" setting: rivastigmine versus donepezil tolerability and effectiveness study

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Abstract

Introduction: Comparative tolerability and effectiveness of donepezil and rivastigmine in clinical practice using a "real life" sample of patients diagnosed as having mild to moderate Alzheimer's disease and treated in the memory clinic setting have not been properly studied to date.
Material and methods: A retrospective, case records analysis of all patients (N=183) who had been prescribed either drug over the period of 3 years (1998-2000) and were seen for at least 6 months afterwards. Main outcome estimates were: for tolerability the likelihood to achieve recommended doses for both drugs and side effects profiles, for effectiveness clinical global impression of change (CGI) rating at 6 months after dose titration finished.
Results: Numerically, more subjects on rivastigmine than on donepezil dropped out early due to side effects (14.6% vs 11.9%). A maximum approved dose (10 mg for donepezil and 12 mg for rivastigmine) has been achieved by significantly more patients on donepezil than on rivastigmine ($p<0.001$). Side effects profiles of both drugs were similar and equally contributed to the drop-out rate. The response rate defined as at least no change on CGI did not differ between the groups.
Conclusions: Donepezil and rivastigmine are comparably tolerated and of similar clinical benefits in the "real life" population of non-selected patients with mild to moderate AD. The differences in tolerability reported in the randomized controlled trials might be attributed to the fixed schedules of reaching the target dose of rivastigmine.

Key words: cholinesterase inhibitors, tolerability, effectiveness.

Introduction

Cholinesterase inhibitors are the only agents approved for the symptomatic treatment of Alzheimer's disease (AD) type dementia, despite their only minor, yet proven clinical efficacy in both short-term [1, 2] and extension studies [3, 4]. Mean change in scores on the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog), the standard measure of efficacy, is comparable for donepezil and rivastigmine and reaches the difference (vs placebo) of between 1.5 (low-dose donepezil) and 3.8 (high-dose rivastigmine) in the intention-to-treat analyses [5, 6]. Additionally, some functional (as measured by activities of daily living) and behavioral benefits of either donepezil or rivastigmine treatment have been shown.

Tolerability of both drugs according to randomized clinical trials has been claimed as being comparable to placebo. The only published comparative study [7] showed, however, that using the recommended dosing schedules (medications were administered according to recommended, fixed dosing regimens from the respective product labeling available during the time of the study), donepezil was better tolerated with fewer discontinuations due to adverse events. This study has already been heavily criticized for "forced dosing of rivastigmine" being indicated as the potential source of bias and the company marketing rivastigmine has conducted a large-scale randomized study (the EXCEED study) to clear up the issue. However, the results of this randomized, controlled study (demonstrating similar efficacy and safety of both rivastigmine and donepezil) [8] provide only a rough estimate of what is going on in the "real world" setting.

The objective of the present study was to compare the real-life safety and clinical effectiveness of donepezil and rivastigmine in patients with mild to moderate AD treated in the memory clinic setting, thus being under regular clinical care.

Material and methods

The study was retrospective and naturalistic. The records of all patients who had been prescribed either drug over the period of 3 years (1998-2000) and were seen for at least 6 months afterwards were included. In all cases a standard diagnostic procedure was employed to establish diagnosis of either probable (N=116) or possible (N=67) Alzheimer's disease according to the international criteria (NINCSD-ADRDA). Both drugs were introduced in the lowest marketed doses (5 mg/day for donepezil and 3 mg/day for rivastigmine) and patients were seen in one month. The caregivers were always instructed on the possible side effects and encouraged to contact the treating physician in case any new symptom emerged. Dose titration was slow with minimal intervals of one month and the appearance of any adverse reaction was carefully noted. In case of side effects emerging the patients were re-titrated to a maximum previously well tolerated dose and no further dose escalation was undertaken. The main outcome estimate was the likelihood of achieving recommended doses for both drugs (5-10 mg/day for donepezil and 6-12 mg/day for rivastigmine) as measured by the drop-out rates due to unacceptable adverse events emerging in the titration period. Secondary, all side effects appearing in any time between initiating titration and the last observation carried out were noted. For effectiveness, CGI of change and MMSE scores were compared approximately 6 months after the final dose of the prescribed drug had been achieved.

Results

A total number of 196 charts from the University based Alzheimer's Clinic were reviewed. Minimum required information allowed 183 of them (132 women) to be included. Of the final number of patients, 101 (73 women) were initially on donepezil and 82 (59 women) on rivastigmine. The mean age of all patients was 77±6.6 years (on donepezil 76.3±6.1, on rivastigmine 77.9±7.2 years; NS) with mean MMSE score of 17.3±5.2 (17.4±5.2 vs 17.0±5.3, NS). Detailed patients' characteristics are provided in Table I. After having been prescribed the initial dose of either drug, the patients were seen at 4-6-week intervals until the maximum tolerated dose was achieved.

Safety data

Twenty one patients (13.1%) did not tolerate any given dose of either drug (13 on donepezil and 9 on rivastigmine; difference NS). Clinical non-tolerance rate as defined by the percentage of patients who did not tolerate a minimum effective dose (5 mg for donepezil and 6 mg for rivastigmine) was numerically lower for donepezil (11.9%) than for rivastigmine (14.6%), but the difference did not achieve statistical significance (Fischer's exact test, p=0.59). Similarly, there were no differences in the percentage of patients tolerating low (5 mg for donepezil and 3-6 mg of rivastigmine; 87 vs 85%) or high (10 mg for donepezil and 9-12 mg for rivastigmine; 60 vs 58%)

Table I. Demographic characteristics of patients included in the study

Variable	Total sample	Donepezil group	Rivastigmine group	Between groups difference (p-value)
Number of subjects	183	101	82	Not applicable
Fraction of women	0.72	0.72	0.71	0.91 (NS)*
Mean age	77±6.6	76.3±6.1	77.9±7.2	0.46 (NS)**
Mean MMSE score	17.3±5.2	17.4±5.2	17.0±5.3	0.61 (NS)**
Mean disease duration (years)	4.2±0.9	4.4±0.6	4.0±0.8	0.09 (NS)**

** χ^2 test*
*** t-Student test*

Table II. Side effects emerging during the period of at least 6 months of treatment (numbers represent N of patients; in square brackets N of patients experiencing side effects resulting in drop-outs); all differences numerical only

Side effect	Donepezil (N=101)	Rivastigmine (N=82)
All gastrointestinal symptoms	23 [4]	32 [6]
Nausea	12	17 [1]
Vomiting	5 [2]	7 [5]
Diarrhea	2 [2]	2
Constipation	4	5
Headache	14 [5]	7 [1]
Vertigo	2	2
Extrapyramidal symptoms	2 [1]	3 [3]
Muscle cramps	7 [1]	7 [1]
Limb weakness/falling	4 [1]	3 [1]
Sleep disturbance	13 [1]	8 [2]
Alertness/sensorium change	2 [2]	0
Agitation	3 [1]	2 [1]
Cardiac arrhythmia	1 [1]	0
Congestive heart failure aggravation	0	1 [1]

doses of either drug. However, a maximum recommended dose (10 mg for donepezil and 12 mg for rivastigmine) has been achieved by significantly more patients on donepezil than on rivastigmine (60 vs 21%, Fischer's exact test, p<0.001; see the chart).

The most common reasons for drug withdrawal were gastrointestinal disturbances or headache. In 4 cases, there were severe adverse events all leading to hospitalization [two cases of delirium-like state (one with severe parkinsonism) induced by donepezil (10 mg each), one severe congestive heart failure exacerbation on rivastigmine (3 mg) and one cardiac arrhythmia (ventricular extrasystole) on donepezil 5 mg]. We observed numerical (but statistically non-significant) differences in some side effects' frequencies e.g. gastrointestinal symptoms were more common in the rivastigmine group while headache and sleep disturbances in the donepezil group (for details, see Table II). Overall, the frequency of any side effect during the treatment was almost equal in both cases, reaching 71.3% in donepezil and 78% in rivastigmine treated patients (p=0.3). The drop-out rates due to adverse events were comparable as well [14.6% in the donepezil and 22.8% in the rivastigmine group (Fischer's exact test, p=0.4)].

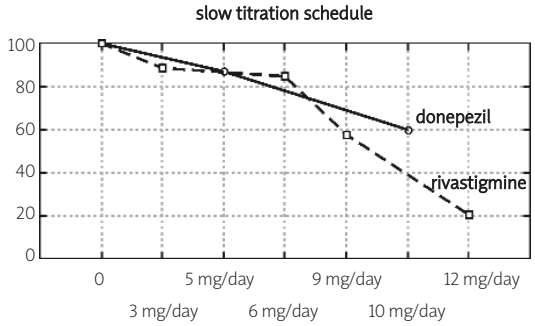

Figure 1. Percentages of patients achieving a given dose of donepezil or rivastigmine

Effectiveness data

MMSE and Clinical Global Impression of Change (CGI-C) scores were calculated at between 6 and 8 months after the maximum tolerated dose had been achieved. Therefore, by definition, the patients who dropped out early and were unable to tolerate minimum effective doses were not included in the analysis which thus comprised 89 patients (out of initial 101) treated with donepezil and 70 (out of initial 82) with rivastigmine. MMSE scores did not change significantly in either group during the 6 month period indicating a possible symptomatic effect of both medications (mean change for donepezil 0.8±0.4; p=0.3 and for rivastigmine 0.6±0.6; p=0.5). However, the extent of improvement as measured by MMSE only just missed statistical significance (Fischer's exact test, two tailed, p=0.015) indicating a marginally better effect for donepezil. Similarly, using CGI scores we were unable to find important differences between the groups. Seventy four percent of patients treated with donepezil and 68.6% on rivastigmine could be classified as responders based on at least "no change" score in CGI (p=0.4). When using more conservative criteria of responding (at least "minimal improvement" score) 39.3% improved on donepezil and 34.2% on rivastigmine (p=0.5).

Discussion

Despite their limited clinical efficacy, cholinesterase inhibitors are the current recommended standard of care for the symptomatic treatment of mild to moderate Alzheimer's disease [9]. Their comparative effectiveness and tolerability is a subject of controversy, since while randomized controlled trials show them to be similar, few open-label studies and laymen press releases (available also in the internet) point to donepezil as the better tolerated drug.

In a retrospective chart analysis of a relatively large population of treated patients we have failed to detect any meaningful differences in tolerability between donepezil and rivastigmine treatments. The non-tolerability of any prescribed dose and discontinuation rates, as well as the profile of side effects were similar. The only exception was the proportion of patients achieving a maximum

recommended dose being roughly three times as high for donepezil (60 % vs 21%). The results disaccord with data from the only comparative open-label study published so far [7]. The differences include: less patients achieving the maximum approved dose of each drug (87.5 vs 60% for donepezil and 47.3 vs 21% for rivastigmine) and a relatively higher discontinuation rate for donepezil (10.7 vs 14.6%) with roughly the same in case of rivastigmine (21.8 vs 24%). The side effects profile reported here is similar to the previously shown in both randomized clinical trials of individual drugs and in the comparative study of Wilkinson et al. (2002). The most common were gastrointestinal disturbances (usually nausea, rarely vomiting or diarrhea) which were slightly more frequent after rivastigmine than donepezil; interestingly, in agreement with most previous reports, they were only occasionally very severe and persistent and thus treatment limiting. Our data are, however, in agreement with the EXCEED study in which both drugs were equally effective and safety measured by adverse events did not significantly vary between the study arms either [8].

One of the reasons for showing no clinically important differences between donepezil and rivastigmine treatments might be a very conservative method of dose titration applied. In fact, when rivastigmine first appeared on the market many clinicians almost immediately felt that dose escalation every 2 weeks is far too fast and, on top of that, very impractical for those who admit a lot of patients. The same was true in our clinic: in the unpublished case series of first 22 rivastigmine treated patients more than 50% dropped-out during the dose titration period experiencing intolerable side effects, mostly vomiting. The company that markets the drug has already changed the recommendations for dose escalation, now saying that the aim is to achieve the maximum well tolerated dose with the acceptable use of slower steps (by means of both longer than 2 week intervals and employing intermediate doses) to reach the final dose. Austrian and French published studies on the use of rivastigmine in clinical routine which have already supported the need for slower dose titration of the drug [10, 11], while a Spanish study with less conservative, "dose forcing" method of titration showed a significantly poorer outcome for rivastigmine [12]. The same is true for the randomized trial of Wilkinson et al. [7], which used a forced titration schedule, showing tolerability difference and the EXCEED study, in which dose titration was more optional and dependent on clinical response, showing no difference whatsoever [8].

Another important factor that may have influenced the outcome in the presented study could be the lack of excluding criteria, making it as close to everyday, clinical practice as possible. Indeed, the only exclusion which really operated was the presence of an unstable, severe AD-nonrelated disorder; as a result, in our study group there were patients typically knocked out of most of the studies, even open in nature (like, for instance, patients with a heart pacemaker or suffering from insulin-dependent diabetes or a well-controlled glaucoma). This broad "all-inclusive" pattern of our patients might be the origin of the relatively low ratios of those who reached higher doses of both drugs.

To conclude, both donepezil and rivastigmine produce side effects in most patients; luckily, they are usually mild and transient in nature, thus not restricting the use of both medications, even in "real life" patients. We might also expect similar effectiveness in patients tolerating minimal recommended doses. There are, however, numerical differences indicating possible overall better profile of donepezil (more patients achieving the maximum recommended dose, slightly less drop-outs due to side effects and marginally more responders) which might be clinically meaningful bearing in mind the necessity of the long-term use of these medications. Interestingly, the financial burden for caregivers and not lack of either tolerability or response has been recognized by Korean investigators as a main predictor of drop-outs during treatment with cholinesterase inhibitors [13].

The differences in tolerability profiles observed by some investigators might most probably be attributed to the forced titration rate [7, 12], since others, implementing a more practical approach to dose titration [8, 10, 11 and the current study], consider rivastigmine equally well tolerated as donepezil.

The impact of sponsoring companies cannot, however, be excluded. Finally, as stressed by the authors of the recent meta-analysis, "there are some data which suggest that differences in study designs and patient populations affect outcomes. Therefore, caution should be taken before making decisions on relative efficacy, safety, and tolerability, because clinical studies may not always be directly comparable" [14].

Conclusions

Cholinesterase inhibitors, donepezil and rivastigmine are comparably effective in the treatment of cognitive deficits of subjects suffering from dementia of Alzheimer's type. Cholinesterase inhibitors are generally well tolerated. If side effects occur, they commonly include gastrointestinal symptoms, headache and sleep disturbances, usually of mild and transient course and not leading to disproportionate drop-outs in the "real life" population. The differences in safety profile between donepezil and rivastigmine observed in some studies are in fact small and may be mostly attributed to the titration schedule.

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