

SIX AND 18-MONTH CHANGES IN MILD TO MODERATE ALZHEIMER'S PATIENTS TREATED WITH ACETYLCHOLINESTERASE INHIBITORS: WHAT CAN WE LEARN FOR CLINICAL OUTCOMES OF THERAPEUTIC TRIALS?

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Abstract: *Background:* Clinical trials in Alzheimer's disease (AD) include patients benefiting from recent improvements in AD management. *Objective:* To observe the progression of Alzheimer's disease (AD) after 6 and 18 months in patients treated with acetylcholinesterase inhibitors (AChEI) in order to determine the best duration of follow-up necessary to demonstrate the impact of new drugs. *Methods:* Six hundred and eleven patients included in the REAL.FR cohort were treated with AChEI at baseline. We describe the cognitive, functional, behavioural, nutritional and global changes in the 509 and 364 patients who completed 6 and 18 months of follow-up, respectively, and who did not discontinue treatment. *Results:* After 6 and 18 months, we observed a statistically significant change in the MMSE (-0.54 ± 3.13 at 6 months and -2.90 ± 4.10 at 18 months), ADAS-cog (1.58 ± 5.23 and 4.02 ± 6.83), ADL (-0.30 ± 0.79 and -0.84 ± 1.20), IADL (-0.31 ± 0.95 and -0.94 ± 1.20), CDR sum of boxes (0.75 ± 2.03 and 2.65 ± 3.18) and MNA scores (-0.42 ± 2.89 and -0.95 ± 3.57), demonstrating the progression of AD. But on examining these changes, it appears that even if they were statistically significant at 6 months, they do not appear to be clinically relevant or sufficient to allow the observation of the effect of a new drug at this time, whereas such observation would be possible after 18 months. Similar results were obtained in a subgroup of patients who answer to the inclusion criteria of disease modifying trials which confirms the need for having 18 months of follow-up. *Conclusion:* Changes in AD in patients under AChEI treatment are not sufficient to demonstrate the effect of a new treatment at 6 months. However, 18-month trials appear to have the potential to demonstrate clearly the effect of a new drug.

Introduction

Alzheimer's disease (AD) is a chronic, progressive and severe disease which is considered as a major public health problem. During recent years, significant progress has been made with the development of non-pharmacological treatments and social interventions, and with the introduction of symptomatic treatments that have changed the management of AD patients. The two types of symptomatic treatment currently available, acetylcholinesterase inhibitors (AChEIs) and an NMDA receptor antagonist, have demonstrated their efficacy in short-term randomised controlled trials (1, 2, 3, 4). These pharmacological treatments are now widely used in routine clinical practice and seem to have a moderate but beneficial impact on the progression of AD in the general population (5, 6).

The next objective in the treatment of AD is now the development of disease-modifying drugs that would have an effect on the underlying pathophysiological processes and result in long-lasting changes. Unlike clinical trials which generally lasted 6 months for symptomatic treatments (1, 2, 3, 4), a European task force consensus recommended that disease-modifying trials should last 18 months (7). Most of these

clinical trials with new agents for AD are set up with patients who are already treated with AChEIs. It therefore appears very important to have precise knowledge of the evolution of AD patients, taking into account the impact of specific treatments and changes in clinical practice, in order to be able to interpret the results of these disease-modifying trials.

In this context, the objective of this paper is to describe the evolution after 6 and 18 months of follow-up of AD patients treated by AChEIs, using data from the French prospective observational cohort REAL.FR. Thanks to these results, it will be possible to conclude on which of these two durations of follow-up will best enable us to see the impact of new drugs on the progression of AD under current conditions.

Methodology

Study design

REAL.FR is a study set up by the French network on Alzheimer's disease, which includes 16 expert centres in France. The methodology of the study has been described in detail elsewhere (8). Briefly, 686 AD patients were initially recruited in these centres for 4 years of follow-up with biannual assessments. To be included in the REAL.FR study, patients

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had to present a mild to moderate form of AD (Mini-Mental State Examination (MMSE) (9) score between 12 and 26), diagnosed according to the NINCDS-ADRA (10) and DSM-IV (11) criteria. They also had to live in the community and be cared for by an informal caregiver. Patients were included between April 2000 and October 2002.

Data collected

At inclusion, patients underwent a full medical examination including CT scan and thyroid tests. We excluded from the study patients with severe AD, those who were institutionalized at baseline and those with a concomitant disorder which could affect the short-term prognosis. At each visit, a standardized case report form was completed for each patient by a trained, multidisciplinary medical team.

Various aspects of disease progression were assessed with scales commonly used in clinical trials :

1/ cognitive evaluation with administration of the MMSE (9) and the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) (12).

2/ evaluation of the capacity to carry out the activities of daily living, using the Activities of Daily Living scale (ADL) (13) and the Instrumental Activities of Daily Living scale (IADL) (14) for the more complex activities.

3/ evaluation of behavioural disturbance with the Neuropsychiatric Inventory (NPI) (15) where, according to Aalten et al (16), the score obtained by multiplying frequency by gravity of each symptom must be greater than 3 to be considered as clinically relevant.

4/ overall evaluation using the Clinical Dementia Rating (CDR) (17).

At each visit, all current treatments, in particular specific treatments for AD, were carefully recorded. Nutritional status using the Mini-Nutritional Assessment (MNA) (18) and caregiver burden using the Zarit Burden Interview (19) were also assessed.

During follow-up, all events occurring between two visits, in particular admissions to hospital or to institutions, use of new

support or home assistance services, changes among the patient’s family and friends, were carefully recorded together with deaths, entry to an institution where follow-up was not possible, and other reasons for premature discontinuation such as withdrawal of consent, medical problems of patient or caregiver, or loss to follow-up.

Statistical analysis

For this analysis, we selected patients who were treated by AChEI at baseline and all along the follow-up. Patients who stopped taking AChEI treatments were excluded from the analysis. Statistical analysis was performed using SAS 9.0. software. Classic tests were used for means comparison in the case of quantitative variables (Wilcoxon) and comparison of distribution frequency in qualitative variables (McNemar).

In this study the maximum score on the IADL scale was 5 instead of 8 because we withdrew the items food preparation, housekeeping and laundry for which there were a lot of missing data for the masculine patients.

Results

Evolution at 6 and 18 months of patients treated by AChEIs

Among the 686 patients included, 611 were treated by AChEIs at baseline and were selected for inclusion in this study. They were 77.62 ± 6.80 years old, 429 (70.21%) were women and they were specifically treated for AD for a mean duration of 8.92 ± 9.13 months before entry in the study. In accordance with the inclusion criteria, they presented a mild to moderate form of AD with a mean MMSE score of 20.07 ± 4.22 and were all living in the community.

Twenty-seven patients discontinued their treatment during the 18 months: 13 (2.13%) during the first 6 months, 6 (0.98%) between 6 and 12 months and 8 (1.31%) during the last 6 months. Data were obtained for 509 patients at 6 months and 364 at 18 months. Details of follow-up are summarized in figure 1.

Table 1
 Change during the first 6 months (n = 509)

Parameters	n	Baseline Mean ± SD	6 months Mean ± SD	Change Mean ± SD	P Wilcoxon
MMSE (/30)	505	20.23 ± 4.23	19.69 ± 5.04	-0.54 ± 3.13	0.0002
ADAS-cog (/70)	480	16.91 ± 7.23	18.49 ± 8.82	1.58 ± 5.23	<0.0001
CDR sum of boxes (/18)	492	6.28 ± 3.23	7.03 ± 3.70	0.75 ± 2.03	<0.0001
ADL (/6)	505	5.48 ± 0.83	5.18 ± 1.19	-0.30 ± 0.79	<0.0001
IADL (/5)	479	2.57 ± 1.39	2.26 ± 1.44	-0.31 ± 0.95	<0.0001
NPI (freq x grav) (/144)	494	14.92 ± 14.25	15.09 ± 14.56	0.18 ± 13.93	0.4435
NPI (freq) (/48)	495	8.22 ± 6.57	8.25 ± 6.97	0.02 ± 5.74	0.9044
Zarit (/88)	399	21.24 ± 14.97	22.08 ± 16.02	0.83 ± 10.62	0.4567
MNA (/30)	403	24.17 ± 4.05	23.75 ± 3.23	-0.42 ± 2.89	0.0065
Weight (kg)	495	62.87 ± 12.81	62.69 ± 12.87	-0.17 ± 3.08	0.4248

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Table 2
 Change in the score on each item of the ADAS-cog after 6 months of follow-up (n = 480)

Items	Baseline Mean ± SD	6 months Mean ± SD	Change Mean ± SD	P Wilcoxon
1- Spoken language ability (/5)	0.28 ± 0.71	0.31 ± 0.77	0.04 ± 0.67	0.1880
2- Comprehension (/5)	0.41 ± 0.78	0.45 ± 0.88	0.04 ± 0.79	0.3436
3- Word finding difficulty (/5)	0.79 ± 1.01	0.89 ± 1.10	0.10 ± 1.00	0.0325
4- Word recall task (/10)	6.28 ± 1.36	6.36 ± 1.41	0.09 ± 1.11	0.1365
5- Naming objects and fingers (/5)	0.75 ± 0.84	0.85 ± 0.95	0.10 ± 0.68	0.0010
6- Orientation (/8)	2.54 ± 1.90	2.81 ± 1.98	0.28 ± 1.63	0.0002
7- Commands (/5)	0.81 ± 0.95	0.9 ± 1.00	0.09 ± 0.97	0.0624
8- Ideational praxis (/5)	0.49 ± 0.88	0.71 ± 1.07	0.22 ± 0.82	<0.0001
9- Constructional praxis (/5)	1.13 ± 0.93	1.34 ± 1.12	0.22 ± 0.80	<0.0001
10- Word recognition task (/12)	2.91 ± 1.43	3.17 ± 1.66	0.26 ± 1.36	0.0004
11- Remembering test instructions (/5)	0.54 ± 1.23	0.69 ± 1.39	0.15 ± 1.18	0.0115

Table 3
 Change at 18 months (n = 364)

Parameters	n	Baseline Mean ± SD	18 months Mean ± SD	Change Mean ± SD	P Wilcoxon
MMSE (/30)	357	20.27 ± 4.19	17.38 ± 5.88	-2.90 ± 4.10	<0.0001
ADAS-cog (/70)	311	15.73 ± 6.08	19.75 ± 9.01	4.02 ± 6.83	<0.0001
CDR sum of boxes (/18)	344	6.13 ± 3.17	8.78 ± 4.22	2.65 ± 3.18	<0.0001
ADL (/6)	361	5.60 ± 0.68	4.76 ± 1.45	-0.84 ± 1.20	<0.0001
IADL (/5)	338	2.66 ± 1.36	1.72 ± 1.36	-0.94 ± 1.20	<0.0001
NPI (freq x grav) (/144)	352	14.40 ± 14.09	16.08 ± 15.21	1.68 ± 15.62	0.0593
NPI (freq) (/48)	353	8.00 ± 6.55	8.65 ± 7.43	0.65 ± 6.99	0.1640
Zarit (/88)	279	21.06 ± 14.82	23.81 ± 17.76	2.75 ± 13.40	0.0072
MNA (/30)	260	24.10 ± 2.99	23.15 ± 3.18	-0.95 ± 3.37	<0.0001
Weight (kg)	352	62.81 ± 13.00	62.76 ± 12.79	-0.05 ± 4.99	0.4070

Evolution at 6 months

As shown in figure 1, after 6 months of follow-up, 10 (1.64%) patients were deceased, 8 (1.31%) were institutionalised, 14 (2.29%) were lost to follow-up, 17 (2.78%) withdrew their consent and 7 (1.15%) dropped out for other reasons (move to another district, caregiver's health problem). A total of 56 patients (9.17%) prematurely discontinued follow-up during the first 6 months.

Table 1 shows the change in scores of the different scales evaluating cognitive, functional, behavioural, nutritional and global status of the patients. We observed that change was statistically significant on the MMSE, ADAS-cog, ADL, IADL and MNA scores. The mean differences between 6-month and baseline scores for these 5 scales reflected a worsening in patients' status. The change was not statistically significant for weight, NPI or Zarit scores even if it was close to the threshold of significance for the NPI (p=0.0593). Considering the change in MMSE score, we noted that 116 patients (22.97%) showed a significant loss of 3 points or more at 6 months compared with their baseline score. As the ADAS-cog is often

used as the primary outcome in clinical trials, we describe its changes item by item (table 2). Mean scores of most items significantly increased except for spoken language ability, comprehension, word recall task and commands items.

Figures 2A and B show loss of independence for each item of the ADL and IADL. We can see that the percentage of patients reporting a loss of autonomy at 6 months increased significantly for most items of these two scales except for the transfer item of the ADL and for the housekeeping and medication items of the IADL. Figure 2C describes the percentage of patients presenting each item of the NPI. There was no significant increase in the frequency of the 12 behavioural disturbances assessed by the NPI after 6 months of follow-up.

Concerning hospital admissions, 71 patients (14.06% of the 505 patients for whom data was available) were hospitalised at least once, and among them 10 (1.98%) were hospitalised twice and 2 (0.40%) reported 3 admissions. During the 6 months, 28 patients (on 476, 5.9%) were institutionalised (with or without stopping the follow-up) and we didn't notice any initiation of

Table 4
Change in the score on each item of the ADAS-cog after 18 months of follow-up (n = 310)

Items	Baseline Mean ± SD	18 months Mean ± SD	Change Mean ± SD	P Wilcoxon
1- Spoken language ability (/5)	0.21 ± 0.61	0.39 ± 0.82	0.17 ± 0.78	<0.0001
2- Comprehension (/5)	0.29 ± 0.62	0.47 ± 0.89	0.18 ± 0.94	0.0006
3- Word finding difficulty (/5)	0.69 ± 0.92	1.00 ± 1.16	0.31 ± 1.13	<0.0001
4- Word recall task (/10)	6.13 ± 1.33	6.55 ± 1.16	0.41 ± 1.32	<0.0001
5- Naming objects and fingers (/5)	0.67 ± 0.79	0.87 ± 1.09	0.20 ± 0.88	<0.0001
6- Orientation (/8)	2.37 ± 1.78	3.41 ± 1.88	1.04 ± 1.69	<0.0001
7- Commands (/5)	0.68 ± 0.82	0.99 ± 1.08	0.32 ± 1.09	<0.0001
8- Ideational praxis (/5)	0.35 ± 0.72	0.70 ± 1.11	0.35 ± 0.91	<0.0001
9- Constructional praxis (/5)	1.00 ± 0.84	1.28 ± 1.09	0.28 ± 0.86	<0.0001
10- Word recognition task (/12)	2.85 ± 1.33	3.25 ± 1.69	0.40 ± 1.62	<0.0001
11- Remembering test instructions (/5)	0.43 ± 1.01	0.81 ± 1.49	0.39 ± 1.35	<0.0001

Table 5

Change at 6 months of the patients treated for 4 months at baseline, with a stable dose during the 6 months of follow-up and with a MMSE score ≥ 16 at baseline (n=209)

Parameters	n	Baseline Mean ± SD	6 months Mean ± SD	Change Mean ± SD	P Wilcoxon
MMSE (/30)	209	21.67 ± 2.96	20.83 ± 4.22	-0.85 ± 2.91	0.0003
ADAS-cog (/70)	205	15.26 ± 5.69	16.83 ± 7.20	1.57 ± 4.65	<0.0001
CDR sum of boxes (/18)	206	5.62 ± 2.77	6.22 ± 3.19	0.60 ± 1.66	<0.0001
ADL (/6)	208	5.62 ± 0.66	5.37 ± 0.94	-0.25 ± 0.65	<0.0001
IADL (/5)	201	2.83 ± 1.39	2.60 ± 1.47	-0.23 ± 0.87	0.0002
NPI (freq x grav) (/144)	203	12.78 ± 12.23	15.10 ± 15.77	2.32 ± 13.42	0.0196
NPI (freq) (/48)	203	7.55 ± 6.12	8.30 ± 7.32	0.75 ± 5.62	0.0565
Zarit (/88)	169	20.95 ± 13.76	22.53 ± 16.20	1.58 ± 10.40	0.2736
MNA (/30)	164	24.70 ± 2.92	24.27 ± 2.88	-0.44 ± 2.26	0.0213
Weight (kg)	207	64.97 ± 13.40	64.79 ± 13.55	-0.19 ± 3.09	0.6171

memantine treatment.

Evolution at 18 months

Among the 611 patients initially selected, 35 (5.73%) patients died, 33 (5.40%) were lost to follow-up, 31 (5.08%) were institutionalised and had to discontinue follow-up, 39 (6.38%) withdrew their consent and 32 (5.24%) dropped out for various other reasons (move to another district, caregiver's health problem) (figure 1). A total of 170 patients (27.82%) dropped out during follow-up.

After 18 months of follow-up, looking at the mean differences between final and baseline scores (table 3), we observed a statistically significant change in MMSE, ADAS-cog, CDR-SB, ADL, IADL, MNA and Zarit scores. These differences reflected a worsening in patients' status and also in caregiver burden. NPI score and mean weight did not significantly change during the 18 months. The mean change on the ADAS-cog was about +4 points at 18 months and looking at change on this scale item by item, it appeared that

mean scores of each item increased significantly (table 4). Concerning change in the MMSE, 142 patients (39.78%) reported a loss of 3 points or more compared with their baseline score.

As shown in figures 3A and 3B, there was a significant increase in the percentage of patients reporting a loss of autonomy on each of the items of the ADL and of the IADL. Concerning behavioural disturbances (figure 3C), the prevalence of apathy, disinhibition and aberrant motor behaviour increased but not that of the other disturbances.

We also observed that 72 patients (19.78%) reported 1 hospital admission during follow-up, 19 (5.22%) reported 2 admissions and 7 (1.92%) reported 3 or 4 admissions. Thus almost 27% of the patients followed for 18 months were hospitalised at least once. Moreover, during follow-up, 71 patients (on 454, 15.6%) were institutionalised. Lastly, we observed that memantine treatment was initiated in only 3 patients.

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Table 6

Change at 18 months of the patients treated for 4 months at baseline, with a stable dose during the 18 months of follow-up and with a MMSE score ≥ 16 at baseline (n=135)

Parameters	n	Baseline Mean ± SD	18 months Mean ± SD	Change Mean ± SD	P Wilcoxon
MMSE (/30)	134	21.55 ± 2.99	19.49 ± 4.75	-2.06 ± 3.50	<0.0001
ADAS-cog (/70)	124	14.47 ± 4.65	17.42 ± 7.01	2.96 ± 5.50	<0.0001
CDR sum of boxes (/18)	131	5.40 ± 2.67	7.57 ± 3.72	2.17 ± 2.83	<0.0001
ADL (/6)	134	5.70 ± 0.57	5.07 ± 1.25	-0.63 ± 0.99	<0.0001
IADL (/5)	128	2.96 ± 1.37	2.02 ± 1.43	-0.95 ± 1.23	<0.0001
NPI (freq x grav) (/144)	130	11.77 ± 11.74	13.67 ± 13.90	1.90 ± 12.65	0.2758
NPI (freq) (/48)	130	6.74 ± 5.61	7.34 ± 7.12	0.60 ± 6.30	0.8171
Zarit (/88)	110	18.36 ± 11.23	22.26 ± 11.54	3.90 ± 11.44	0.0021
MNA (/30)	100	24.60 ± 2.76	23.88 ± 2.84	-0.72 ± 2.95	0.0251
Weight (kg)	132	63.57 ± 13.02	63.53 ± 12.84	-0.04 ± 4.73	0.7809

Evolution at 6 and 18 months in a subpopulation of patients treated by AChEIs for at least 4 months at baseline, who took these drugs at a stable dose during 6 or 18 months and with a MMSE ≥ 16 at baseline

Among the patients included, 294 were treated by AChEI for at least 4 months and had a MMSE score ≥ 16. After 6 months, 209 of them were assessed and it appears that the change was significant in most parameters except for Zarit score and weight (table 5).

Looking at the progression at 18 months of the 135 patients of this subpopulation, we noticed a significant change in MMSE, ADAS-cog, CDR sum of boxes, ADL, IADL, Zarit and MNA scores. Mean NPI score and weight didn't show any statistical change (table 6).

Discussion

Evolution at 6 and 18 months of patients treated by AChEIs

AChEI treatment is known to have a symptomatic effect on AD and their use can be considered as beneficial if treated patients are stable or report a slowing in disease progression (20). It has already been demonstrated that AChEIs have a beneficial impact on the progression of AD in the general population (5, 6). The use of such specific treatments in addition to an appropriate follow-up care plan modifies the rate of progression of AD (21). The REAL.FR observational study provides important data on the evolution of patients followed and treated in current conditions after 6 and 18 months. Such information is very useful for most of the clinical trials that are now in process using an add-on design, as they can be considered as a basis to set up or to interpret results from these clinical trials.

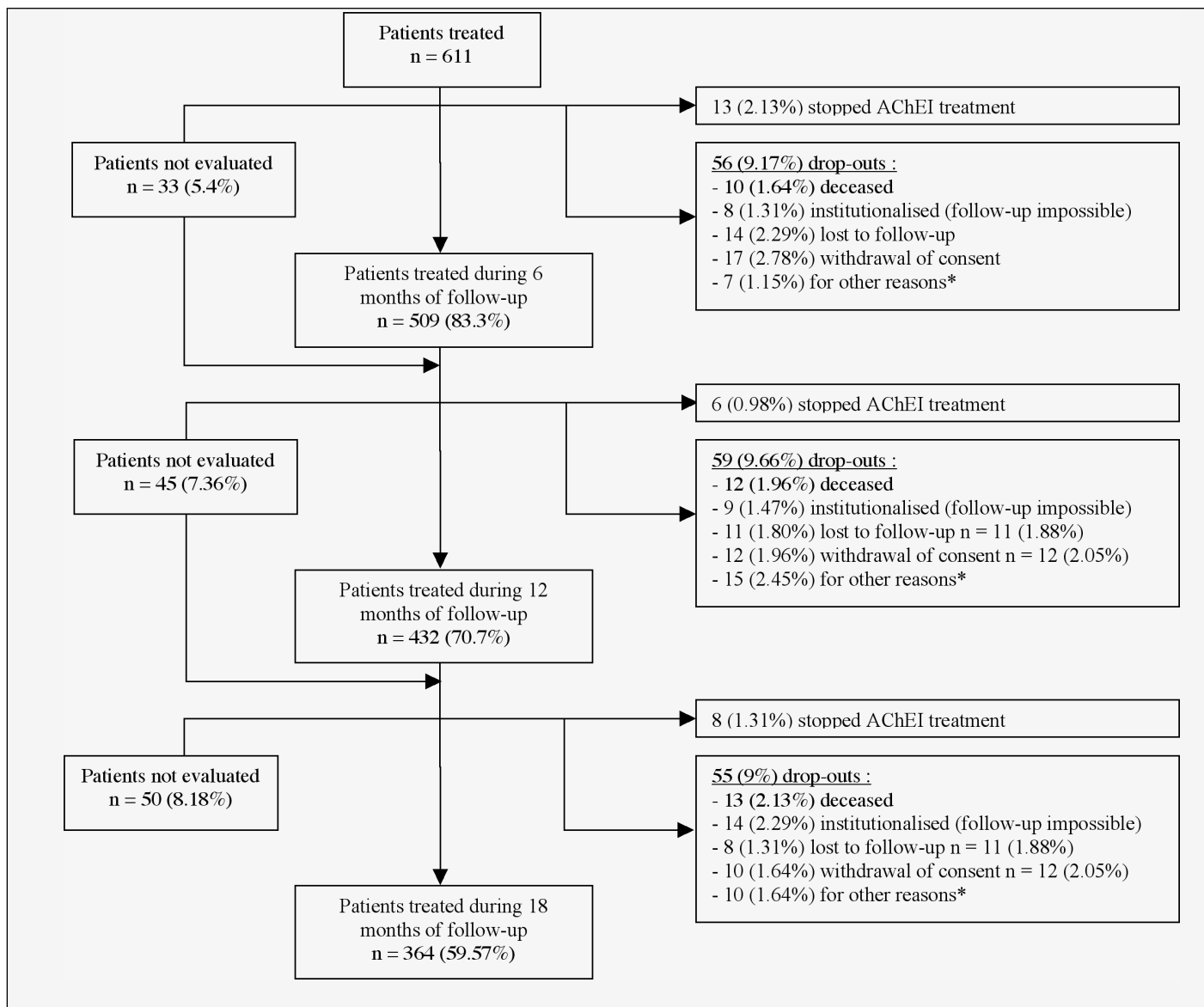
After both 6 and 18 months, it appears that changes in cognitive, functional, nutritional and general status are statistically significant. This indicates that even if all the

patients included in this work are treated by AChEIs, AD still progresses whatever the duration of the follow-up. Interestingly, after 6 or 18 months there was no significant weight loss in spite of the use of AChEIs, which appears to confirm the long-term observations already made in this cohort (5, 22). There were few changes in neuropsychiatric symptoms with only 3 disturbances being more prevalent at 18 months: disinhibition, apathy and aberrant motor behaviour.

Looking closely at the results after 6 months of follow-up, it seems that even if the change in MMSE, ADAS-cog, ADL, IADL and MNA scores is statistically significant, it is not really clinically relevant with some items of ADL, IADL or ADAS-cog that do not reflect a worsening. Change on ADAS-cog is small (+1.58 points) which would not be sufficiently large to reveal the effect of new drugs on add-on therapy. Moreover, we must take into consideration some possibility of improvement in the control group due to a placebo effect in both patient and family. Without any major change the symptomatic effect of a new drug will not be easy to demonstrate.

In this context, a follow-up of 18 months appears to be recommended (7, 23). Looking at our results after 18 months and comparing them with those of previous studies, it seems that the progression of the disease is slowed in REAL.FR: mean loss on MMSE score was about -3 points over 18 months, whereas it has been reported in a meta-analysis by Han et al. (24) that in non-treated patients the annual rate of change in the MMSE score was -3.3 points. In the same way, the mean difference in ADAS-cog score was about 4 points and an analysis by Stern et al (25) estimated that the annual change in the ADAS-cog was approximately 9-11 points per year. These observations pinpoint progression in the natural history of AD. But, in spite of this relative slowing in disease progression, these results also confirm that an 18-month follow-up seems to be long enough to assess changes in cognitive function. The mean change of the ADAS-cog is sufficient to reveal the impact of new drugs: +4.02 ± 6.83 points with all the items of

Figure 1
Overview of the 18-month follow-up



* : move to another district, caregiver's health problem, inclusion in a therapeutic protocol; Patients not evaluated at a visit were reassessed at one of the following visits

the ADAS-cog showing a significant decline, which was not the case at 6 months, and in addition 47.8% of patients had a loss of at least 3 points on the MMSE.

It seems reasonable to assess the effects of disease-modifying drugs in 18-month therapeutic trials because this is still sufficient to observe an impact of the drug and the drop-out rate of 28% is acceptable. This drop-out rate can be expected to be lower in a placebo group due to placebo effect. Rate of hospitalisation and institutionalisation can also be good endpoints to assess a clinically relevant effect of such a drug by reducing the high rate of admissions, respectively 27% and 16%.

Evolution at 6 and 18 months in a subpopulation of patients treated by AChEIs for at least 4 months at baseline, who took these drugs at a stable dose during 6 or 18 months and with a MMSE \geq 16 at baseline

These subpopulations of patients better correspond to the inclusion criteria of disease modifying trials. Looking at the results at 6 months, these patients report significant changes that are not very different from those observed at 6 months in the complete population. Except the mean NPI score that significantly increases in the subpopulation ($p=0.0196$) whereas it was not the case in the complete population ($p=0.4435$), the differences observed between the mean changes obtained in the

Figure 2

Percentage of patients after 6 months of follow-up reporting loss of complete independence on each item of the ADL and IADL scales (2A and 2B) and significant presence of each item of the NPI (score frequency x gravity ≥ 4) (2C).

○ Baseline n 6 months

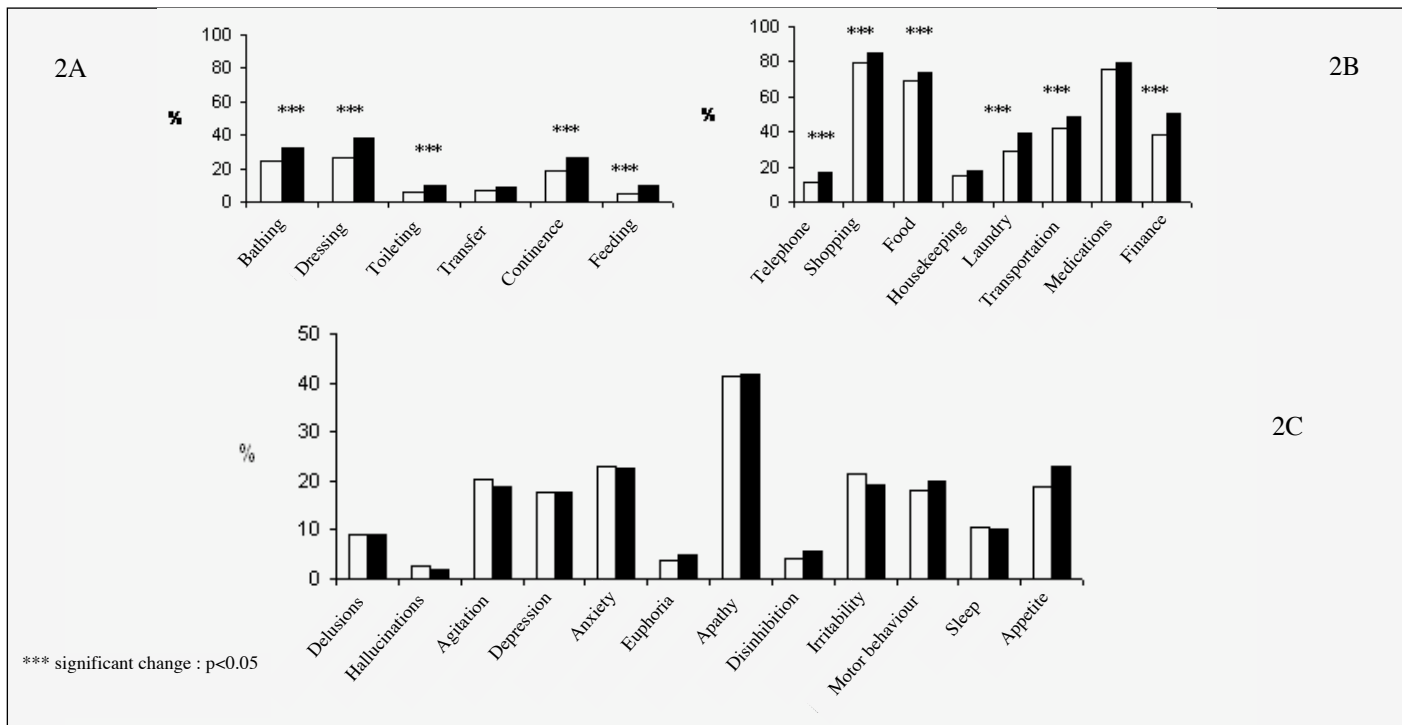
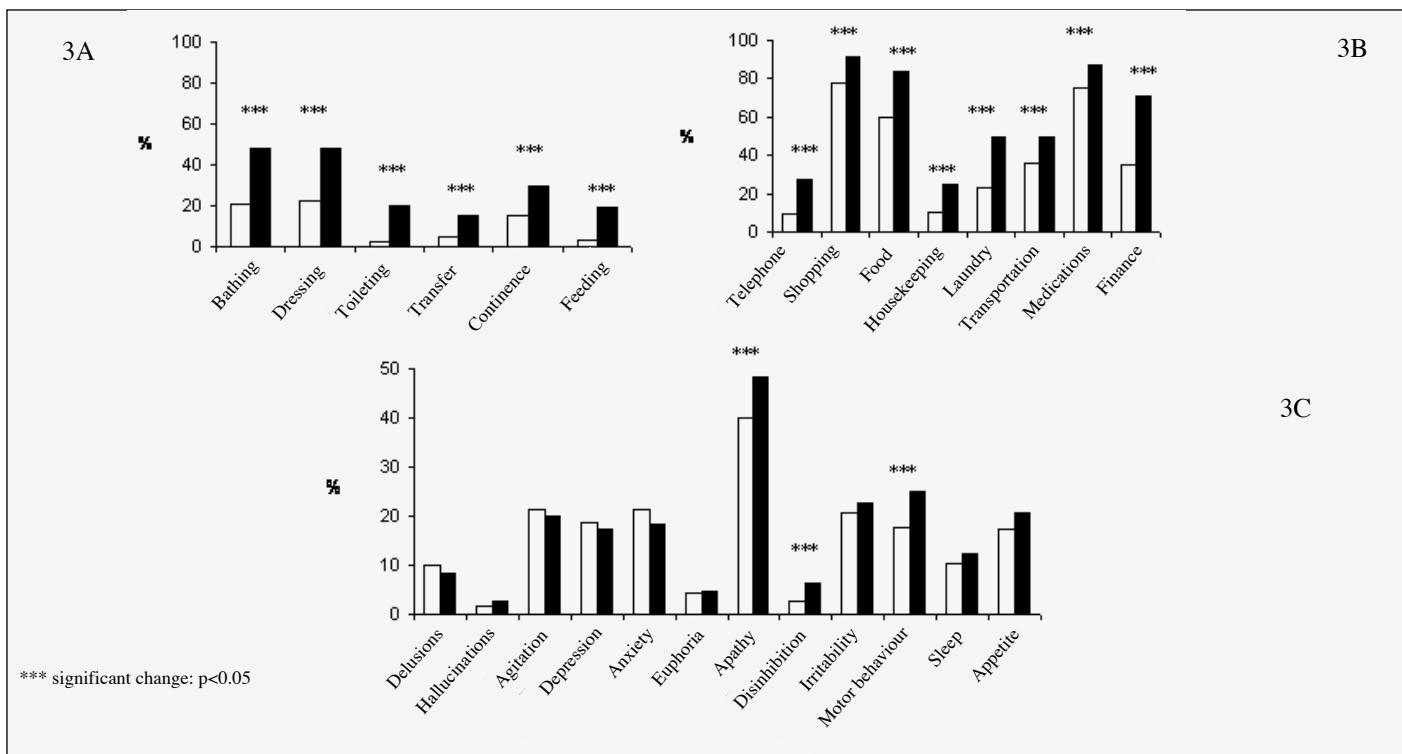


Figure 3

Percentage of patients after 18 months of follow-up reporting a loss of complete independence on each item of the ADL and IADL scales (3A and 3B) and significant presence of each item of the NPI (score frequency x gravity ≥ 4) (3C).

○ Baseline n 18 months



complete population or in the subpopulation are small and not clinically relevant. So, in the same way as we observed in the complete population of patients treated, progression at 6 months appeared to be mild.

After 18 months, we notice that parameters showing a significant change are the same than those observed in the complete population: MMSE, ADAS-cog, CDR sum of boxes, ADL, IADL, Zarit and MNA. The mean change is not different for these parameters except for ADAS-cog score with a mean change of 3 points in the subpopulation vs 4 points in the complete population indicating that cognitive decline appears to be milder at 18 months in patients of the subpopulation. This observation could be the reflect of a long term benefit of AChEI treatment on cognitive decline. But the difference observed for the ADAS-cog and the differences observed in the other parameters at 6 and 18 months could also be due to the small number of patients in the subpopulation.

In spite of these differences, results obtained in the subgroup of patients tend to confirm that, as we observe in the complete population, 6 months of follow-up aren't enough to demonstrate the impact of new drugs whereas the evolution over 18 months will allow to see the effect of disease modifying drugs.

In conclusion, observational data of the natural history of AD in patients under AChEI treatment today, with the improvement of standard care to AD patients, leaves little room to demonstrate the effect of a new treatment at 6 months. However, 18-month trials appear to have the potential to demonstrate clearly the effect of a new drug on functional scales and ADAS-cog changes, on patients who have a loss of at least 3 points on the MMSE or on the hospitalisation or institutionalisation rate.

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References

1. Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. 2000. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 54: 2269-2276.
2. Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stahelin HB, Hartman R, Gharabawi M. 1999. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ* 318(7184): 633-638.
3. Cummings JL, Donohue JA, Brooks RL. 2000. The relationship between donepezil and behavioral disturbances in patients with Alzheimer's disease. *Am J Geriatr Psychiatry* 8(2): 134-140.
4. Winblad B, Poritis N. 1993. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry* 14(2): 135-146.
5. Gillette-Guyonnet S, Andrieu S, Cortes F, Nourhashemi F, Cantet C, Ousset PJ et al. 2006. Outcome of Alzheimer's disease: potential impact of cholinesterase inhibitors. *J Gerontol A Biol Sci Med Sci* 61: 516-520.
6. Lopez OL, Becker JT, Saxton J, Sweet RA, Klunk W, Dekosky ST. 2005. Alteration of a clinically meaningful outcome in the natural history of Alzheimer's disease by cholinesterase inhibition. *J Am Geriatr Soc* 53(1): 83-87.
7. Vellas B, Andrieu S, Sampaio C, Wilcock G; European Task Force Consensus. 2007. Disease-modifying trials in Alzheimer's disease: a European task force consensus. *Lancet Neurol* 6(1): 56-62.
8. Gillette-Guyonnet S, Nourhashemi F, Andrieu S, Cantet C, Micas M, Ousset PJ, Vellas B. 2003. The REAL.FR research program on Alzheimer's disease and its management: methods and preliminary results. *J Nutr Health Aging* 7(2): 91-96.
9. Folstein MF, Folstein SE, McHugh PR. 1975. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189-198.
10. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34(7): 939-944.
11. American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders (4th ed) (DSM-IV). Washington, DC: APA.
12. Rosen WG, Mohs RC, Davis KL. 1984. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 141(11): 1356-1364.
13. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. 1963. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA* 185: 914-919.
14. Lawton MP, Brody EM. 1969. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 9(3): 179-186.
15. Cummings JL. 1997. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* 48(5 Suppl 6): S10-S16.
16. Aalten P, de Vugt M.E, Jaspers N, Jolles J, Verhey FR. (2005). The course of neuropsychiatric symptoms in dementia. Part I: findings from the two-year longitudinal Maasbed study. *Int J Geriatr Psychiatry* 20: 523-530.
17. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. 1982. A new clinical scale for the staging of dementia. *Br J Psychiatry* 140: 566-572.
18. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bannahum D, Lauque S, Albaredo JL. 1999. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 15(2): 116-122.
19. Zarit SH, Reeve KE, Bach-Peterson J. 1980. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* 20(6): 649-655.
20. Geldmacher DS, Frölich L, Doody RS, Erkinjuntti T, Vellas B, Jones RW, Banerjee S, Lin P, Sano M. 2006. Realistic expectations for treatment success in Alzheimer's disease. *J Nutr Health Aging* 10(5): 417-429.
21. Cortes F, Gillette-Guyonnet S, Nourhashemi F, Andrieu S, Cantet C, Vellas B. 2005. Recent data on the natural history of Alzheimer's disease: results from the REAL.FR Study. *J Nutr Health Aging* 9: 86-93.
22. Gillette-Guyonnet S, Cortes F, Cantet C, Vellas B. 2005. Long-term cholinergic treatment is not associated with greater risk of weight loss during Alzheimer's disease: data from the French REAL.FR cohort. *J Nutr Health Aging* 2005; 9: 69-73.
23. Sampaio C. 2006. Alzheimer disease: disease modifying trials; where are we? Where do we need to go? A reflective paper. *J Nutr Health Aging* 10(2): 113-115.
24. Han L, Cole M, Bellavance F, McCusker J, Primeau F. 2000. Tracking cognitive decline in Alzheimer's disease using the mini-mental state examination: a meta-analysis. *Int Psychogeriatr* 12(2): 231-247.
25. Stern RG, Mohs RC, Davidson M, Schmeidler J, Silverman J, Kramer-Ginsberg E, Searcey T, Bierer L, Davis KL. 1994. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. *Am J Psychiatry* 151(3): 390-396.