

WHAT IS CLINICALLY RELEVANT FOR DISEASE MODIFYING TRIALS IN ALZHEIMER ?

LONG-TERM CHANGES IN ADAS-COG: WHAT IS CLINICALLY RELEVANT FOR DISEASE MODIFYING TRIALS IN ALZHEIMER ?

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Abstract: With the development of long-term disease modifying trials, changes in ADAS-Cog at 18 months will rise certainly many questions. We decided to look in the Real.fr study at the links between changes in cognition, ADAS-Cog and function. A total of 346 Alzheimer's patients with ADAS-cog at entry and at 18 months. were eligible for this analysis. These patients were on average 77.44 years old and 254 (72.36%) were women. The great majority lived at home and about 93% were treated with a cholinesterase inhibitor at baseline. Thirty three patients (9%) had a gain of more than 2 points at the ADAS-cog at 18 months (Group I, improvement); 130 (38%) were considered as stable, the reference group (Group II) characterized by a stability at the ADAS-cog: decline of 2 points to gain of 2 points, 112 subjects (32%) had a moderate decline between 2 and 7 at the ADAS-cog (Group III) and finally 71 subjects (21%) had a severe impairment more than seven points at the ADAS-cog. A loss of one Basic ADL is certainly highly relevant, and such a change was found at 18 months in more than half of the subjects, which is not surprising for a long-term evolution in mild to moderate AD. An impairment of more than 7 points at the ADAS-cog was found in 21% of the subjects at 18 months and was associated with loss of basic ADL. It will be important to see if these percentages can be decreased by anti-amyloid treatments.

Introduction

We recently published an article on the relationship between 6 months changes at the ADAS-Cog and risk for death or severe dementia at two years (1). These results are useful to assess the clinical relevance of short term symptomatic treatments using drugs such as the cholinesterase inhibitors. However, long-term disease modifying trials in Alzheimer's disease are currently in process. Clinical outcome are still recommended as primary outcomes (2). The judgement criteria use to assess the evolution of cognition is in general the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) (3). Disease modifying trials are generally of 18 months duration (2). However the clinical relevance of 18 months changes on the ADAS-cog is still unknown. The aim of this article is to establish the ADAS-cog as a clinically relevant outcome for such trials, using data from the PHRC-Real.fr study, an ongoing longitudinal observational study of Alzheimer's patients

Methods

The Real.fr ("R seau sur la maladie d'Alzheimer Fran ais") is a prospective French multicenter cohort designed to study the natural history of AD and its modalities of management. The

study population included 686 older community-dwelling AD patients followed-up every six months. These patients were consecutively recruited after a consultation in one of 16 Memory clinics. The study method has been presented in full in a previous article (4). In brief, all patients met the DSM IV and NINCDS-ADRDA criteria for AD (5,6), lived in the community at the time of enrolment and were looked after by informal caregiver. The Real.fr study has been approved by an ethical review committee and patients and caregivers have signed an informed consent for participation.

At baseline screening, each patient underwent structured comprehensive investigations including the Mini-Mental State Examination (MMSE) (7) and the ADAS-cog scale (3). Disability for basic activities of daily living, including ability for bathing, dressing, toileting, transferring and eating was also assessed. Patients were followed-up every six months with the same cognitive battery. If patients did not achieve a follow-up visit, major events which occurred over the previous six months were collected, in particular hospitalisation, institutionalisation, or death.

One of the major interests from the Real-Fr study is the possibility to analyse outcomes every 6 months during a 4 years period; most of the other observational studies were done with only a yearly assessment. The 6 months assessment parts of the Real-Fr Study give to us the possibility to use our data to better

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Table 1

Follow-up Status of the Patients according to the Baseline Characteristics and the Evolution of the ADAS-cog Score at 18 months

Characteristics	Followed-up	Non followed-up	Total
Age at baseline*: mean (SD)	76.33 (6.54)	79.43 (6.68)	77.44 (6.75)
Women: n (%)	169 (75.11)	85 (67.46)	254 (72.36)
Living at home at baseline*: n (%)	223 (99.11)	120 (95.24)	343 (97.72)
Treatment with ICE at baseline: n (%)	214 (95.11)	113 (89.68)	327 (93.16)
MMS at baseline: mean (SD)	21.14 (3.76)	20.51 (3.80)	20.91 (3.78)
ADAS-cog at baseline: mean (SD)	15.35 (5.99)	16.41 (6.01)	15.73 (6.01)
Evolution of ADAS-cog score at 18 months			
- group I (gain >=3 points): n (%)	27 (12.00)	7 (5.56)	34 (9.69)
- group II (gain of 2 to decline of 2 points): n (%)	87 (38.67)	45 (35.71)	132 (37.61)
- group III (decline >=3 points): n (%)	111 (49.33)	74 (58.73)	185 (52.71)
Total	225	126	351

*: p<0.05

Table 2

Concomitant functional decline (loss of at least one B-ADL) and evolution of the ADAS-cog Score at 18 months

Evolution of the ADAS-cog score	Loss of at least one B-ADL		Total (n)
	Number	Proportion (%)	
Group I (gain >=3 points)	16	48.48	33
Group II (gain of 2 to decline of 2 points, stable)	55	42.31	130
Group III (decline 2-7 points)	52	46.43	112
Group IV (decline >7 points)	45	63.38	71
Total	168	48.55	346

p(chi-square)=0.0370

understand 18 months disease modifying trials. Moreover more than 85% of our cohort is under cholinesterase inhibitor treatment, like it is now in most add-on therapy with new anti-amyloid drugs presently under-investigation.

We considered that to be clinically relevant:

- The 18 months change in ADAS-Cog must be associated with significant change in basic activity daily living (lost of one of the 6 B-ADL, Katz scale)
- The 18 months ADAS-Cog change must be associated with more functional impairment (B-ADL) at 3 years.

An increase in the ADAS-cog score reflects a cognitive deterioration and was named "decline". On the reverse, the term "gain" was used to characterise an improvement in cognitive performances, i.e. a decrease of the score.

From the distribution of the 18-month evolution of the ADAS-cog score, 4 ordinal classes of evolution were distinguished : Group I: gain of 3 or more points (first quintile); Group II: decline of 2 points to gain of 2 points [the reference group considered as stable from a clinical perspective]; Group III: decline of 2 to 7 points; Group IV: decline of more than 7 points at 18 months (last quintile, most severe deterioration).

Functional decline was defined as clinically relevant with a

loss of at least one basic ADL at 18 months. To look at the relations between changes at the ADAS-Cog at 18 months and functional decline (B-ADL) at 3 years we used the same cohort but merged Groups III and IV.

Logistic regression models adjusted for sex, age and for the MMSE score at baseline were used to perform the analysis, providing estimation of Odds Ratio (OR) and 95% Confidence Interval.

Results

Of the 686 AD patients, 346 with ADAS-cog at entry and at 18 months. were eligible for this analysis. These patients were on average 77.44 years old and 254 (72.36%) were women (Table 1). The great majority lived at home and about 93% were treated with a cholinesterase inhibitor at baseline.

After three years of follow-up, 126 subjects were lost or refused to participate.

Thirty three patients (9%) had a gain of more than 2 points at the ADAS-cog at 18 months (Group I, improvement); 130 (38%) were considered as stable, the reference group (Group II) characterized by a stability at the ADAS-cog: decline of 2 points to gain of 2 points, 112 subjects (32%) had a moderate

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decline between 2 and 7 at the ADAS-cog (Group III) and finally 71 subjects (21%) had a severe impairment more than seven points at the ADAS-cog. (Table 2)

A concomitant functional impairment (loss of one Basic ADL) was observed in 168 patients (48%). Those with an 18 month decline of the ADAS-cog score of more than seven points (Group IV, most severe deterioration) were more likely (OR: 2.20; CI :1.19-4.05) to have a loss of at least one B-ADL (table 3). These results were significant both in bivariate and in multivariable analysis taking into account sex, age and MMSE score at baseline.

The risk of further functional decline (loss of one Basic ADL) in the next 18 months at 3 years was assessed in 221 subjects. An impairment of more than 2 points at the ADAS-Cog at 18 months was associated with an increase risk to lose one Basic ADL in the next 18 months (OR: 2.52, CI:1.39-4.56). These results were significant both in bivariate and in multivariable analysis taking into account sex, age and MMSE score at baseline (Table 4 and 5)

Table 3

Odds Ratios of concomitant functional decline (loss of at least one B-ADL) and evolution of the ADAS-cog Score at 18 months

	Odds Ratios*	95% CI	p
Evolution of the ADAS-cog score			0.0846
Group II (stable, reference group)	1	-	-
Group I (gain >=3 points)	1.18	0.54-2.59	0.6776
Group III (decline 2-7 points)	1.15	0.68-1.93	0.6034
Group IV (decline >7 points)	2.20	1.19-4.05	0.0118
Trend	1.28	1.01-1.63	0.0419

* Adjusted for sex, age, MMSE score at baseline

Table 5

Odds Ratios of further functional decline (loss of at least one B-ADL) according to the Group of Evolution of the ADAS-cog Score at 18 months

	Odds Ratios*	95% CI	p
Evolution of the ADAS-cog score			0.0054
Group II (stable, reference group)	1	-	-
Group I (gain >=3 points)	1.03	0.41-2.62	0.9428
Group III (decline >2 points)	2.52	1.39-4.56	0.0023

* Adjusted for sex, age, MMSE score at baseline

Discussion

With the development of long-term disease modifying trials, changes in ADAS-Cog at 18 months will rise certainly many questions. We decided to look in the Real.fr study at the links between changes in cognition, ADAS-Cog and function. A loss of one Basic ADL is certainly highly relevant, and such a change was found at 18 months in more than half of the subjects, which is not surprising for a long-term evolution in mild to moderate AD. An impairment of more than 7 points at the ADAS-cog was found in 21% of the subjects at 18 months and was associated with loss of basic ADL. It will be important to see if these percentages can be decreased by anti-amyloid treatments. Moreover a 2 points or more impairment in the ADAS-cog at 18 months was found in 111/221 subjects (50%) and was associated with a further decline in Basic ADL for the next 18 months up to 3 years from baseline. It will be also interesting to evaluate if with new disease modifying drugs we can significantly decrease this percentage of patient with more than 2 points impairment at the ADAS-Cog at 18 months

Very few longitudinal observational studies are available with an 18 months follow-up assessment. Most of other studies have only yearly assessments. Moreover another interesting feature of the Real.Fr study is that the large majority of the patients are on cholinesterase inhibitors treatment. Our data may help to understand the significance of findings in trials with anti-amyloid drugs currently in process. Eighteen months appears to be a good compromise to assess long-term effects for disease modifying treatment. It is long enough to see the

Table 4

Evolution of the ADAS-cog Score at 18 months and further functional decline (loss of at least one B-ADL) in the next 18 months

Evolution of the ADAS-cog score	Loss of at least one B-ADL		Total (n)
	Number	Proportion (%)	
Group I (gain >=3 points)	12	48.00	25
Group II (gain of 2 to decline of 2 points, stable)	38	44.71	85
Group III (decline >2-points)	74	66.67	111
Total	124	56.11	221

p(chi-square)=0.0062

potential effects of a drug candidate and not too long to avoid many deaths or drop out;

Our study seems to confirm the value of the ADAS-cog as a main clinical outcome in long term clinical trials in mild to moderate AD since it correlates well with functional decline on basic ADL. On the basis of these results, we propose that a reduction of the proportion of decliners (more than 7 points at the ADAS-cog) after 18 months of treatment would be a clinically relevant efficacy criteria for future trials. Moreover those with a cognitive decline of more than 2 points at the ADAS-cog at 18 months are at risk for more functional decline in the next 18 months. The effect of potentially disease-modifying drugs on this population must also be taken into consideration. In our previous article (1) we published short term change in the ADAS-Cog at 6 months and risk for death or severe dementia at 2 years. Most of these individuals were rapid decliner. It is interesting to observe that in the present study with the same population and a longer follow-up (18 and 36 months, instead of 6 and 24 months), progressive cognitive decline is also associated with functional decline.

Our study has limits that should be discussed. Firstly 126 patients were lost to follow-up or refused the follow-up screening (36%). However, the proportion of these patients was almost the same in each group of cognitive evolution.

The Real.fr study, a French cohort of AD patients, gives the opportunity to assess the evolution of the ADAS-cog score, with regular evaluations and to analyse long-term outcome in term of functional decline (8). Such data will be certainly interesting to better understand the value of ongoing trials with 18 months outcome in similar stage mild to moderate Alzheimer populations

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