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www.bioinformation.net **Hypothesis**

Short term response is predictive of long term response to acetylcholinesterase inhibitors in Alzheimer's disease: A starting point to explore Bayesian approximation in clinical practice

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Abstract:
This study was aimed at identifying, in 203 patients with Alzheimer's disease followed during long-term treatment with Acetylcholinesterase inhibitors (ChEIs), the predictive factors of the clinical response among cognition (MMSE), functioning (BADL and IADL) measures and age and gender at the baseline (T0). The ANCOVA test showed a significant association between MMSE scores at time T0 and T3, and the variation T9 to T0, T15 to T0 and T21 to T0 of the MMSE scores, using also gender, age and drug as covariates. The significance was higher for the patients affected by mild dementia. Regarding functional activities, a significant relationship was detected, by the ANCOVA test, only between the scores at T3 and the variation T15 to T0 for BADL, and the variation T9 to T0, T15 to T0 for IADL, respectively. Our results confirm, in a real world setting, that ChEIs provide long-term cognitive benefit, which is correlated to, and predictable by, the short-term response (within the third month) as well as the cognitive status (evaluated by means of the MMSE) at the beginning of the treatment. These factors should be the basis of any cost/effectiveness algorithm in health economic decision models.

Keywords: acetylcholinesterase inhibitors; Alzheimer's disease; dementia; mini mental state examination; Bayesian approximation; decision making

Background:
Alzheimer's disease (AD) is a progressive disease of the brain. It is a common type of dementia in the elderly, which can have devastating outcomes on the diagnosed patient, on the caregivers and family, and on society at large. Although the amyloid β-mediated neurotoxicity is considered the pivotal pathophysiological factor, an inflammatory response has been hypothesized, and some processes involved in the physiologic modulation of the immune response are emerging as potential biological prognostic factors. **[1]**

Acetylcholinesterase inhibitors (ChEIs) have proved to be an effective treatment in mild to moderate AD, by enhancing cholinergic neurotransmission. **[2]** Despite the large amount of literature demonstrating the efficacy and safety of ChEIs therapy in AD, clear evidence is lacking about patterns and predictors of the clinical response, which is a topic of crucial interest, clinically and from an economical point of view. In fact, the non-response represents a potential waste of the limited funds available to health management systems. Baseline measures, such as degree of cognitive impairment, rate of disease progression, older age, smoking habit, and the presence of concurrent vascular risk factors, are able to affect the clinical response. Some of these parameters (age, cerebrovascular disease, as well as hippocampal atrophy) may act through structural mechanisms, smoking through chemical ones. **[3]** The presence of subcortical vascular lesions has been reported not to significantly affect the response to ChEIs. **[4]**

Another question at issue is the reproducibility, in a "real world" setting, of the results achieved in controlled clinical trials, where the selection of AD patients, based on very restrictive criteria, makes the cohorts more homogeneous and generally younger with respect to everyday clinical practice. **[5]** Recently, the Italian Ministry of Health-sponsored "Cronos Project" (conceived to administer ChEIs free of charge to all mild to moderate AD subjects) seems to confirm that also non selected AD patients with mild to moderate dementia, living at home, benefit from ChEIs treatment. **[6, 7]**

Taken together, these observations show the need of a novel approximation approach for posterior expectations of real valued functions, given observed data, which may allow clinical practitioners to obtain a clearer view of the expected net benefit of a treatment. Therefore, encouraging clinical data collection from "real world" patients out of randomized clinical trials will give biostatisticians the information they need to build up an algorithm minded to give the most

certainty in the cost/effectiveness decision-making process. This is of pivotal importance in AD, a disease that drains millions of dollars in health costs worldwide every year.

Description:

We administered ChEIs to a cohort of 203 naïve patients (91 males and 112 females), mean age: 72.4 ± 8.9 years, referred to our Alzheimer's Evaluation Unit from October 2000 to December 2002, and eligible for the "Cronos Project" - diagnosis of probable AD according NINCDS ADRDA criteria **[8]**, MMSE score: 14 to 24, onset of cognitive disorders between 40 and 90 years of age, absence of comorbid diseases (asthma, cardiac rhythm disturbances, gastroduodenal ulcer, hepatic or renal failure), able to contraindicate the ChEIs therapy- were enrolled. Based on our data, we tried to identify, in a "real world" setting, the predictive factors of the clinical response among cognition (MMSE) **[9]** and functioning (BADL and IADL) **[10]** measures and age and gender at the baseline.

We excluded from the study all subjects (63), enrolled in the "Cronos Project" over the same period, but previously treated with ChEIs. The patients were commenced on either Donepezil (136 subjects, 67 percent), or Rivastigmine (52, 25 percent) or Galantamine (15, 8 percent). They could be also treated with antipsychotics or other drugs acting on the nervous system, if needed to control behavioral and psychological symptoms.

According to the study protocol, periodic clinical and multi-dimensional assessments were performed at the baseline (T0) and after months 1 (T1), 3 (T3), 9 (T9), 15 (T15), 21 (T21) and 30 (T30), on the patients not withdrawn; efficacy on the cognitive and functional aspects was evaluated respectively by MMSE, and by BADL and IADL. In the patients lost at the follow-up, the specific reasons for withdrawal were different (lack of tolerability or compliance, deaths) and found out only when reported to the physicians by the caregivers.

In order to avoid an artificial categorization of the patients, no MMSE cut-off score was set for defining the clinical response, which was evaluated based on the time course change of the MMSE and BADL-IADL scores with respect to the baseline.

The time course variation of the cognitive and functional performances of our patients during the ChEIs treatment was assessed (by means of the ANOVA for repeated measures) for MMSE scores, and for BADL and IADL scores respectively, at T0, T3, T9, T15 and T21. Data were analyzed according to previously published methods. **[6]**

The MMSE and BADL-IADL scores (means ± standard deviations, median values) of the patients from the baseline to T30 are shown in figure 1. As expected, the sample size waned during time until T30.

		T0	T1	T3	T9	T15	T21	T30
	N° (%)	203 (100)	200 (98)	175 (86)	101 (47)	92 (43)	70 (33)	30 (14)
MMSE (total sample)	*Mean*	19.12	19.74	19.44	19.47	17.71	17.38	17.92
	S. D.	4.42	4.91	4.69	4.78	5.28	5.01	5.26
	Median	19	20.4	20	20.8	18.9	18.4	18
MMSE (subgroup with MMSE > 18 at T0)	*Mean*	22.30	23.02	22.37	21.41	19.52	18.46	19.14
	S. D.	2.69	2.78	2.99	3.44	3.84	4.43	4.46
	Median	22	23.3	22.7	22.1	19.7	18.7	19.7
MMSE (subgroup with MMSE ≤ 18 at T0)	*Mean*	14.95	15.40	15.33	15.09	12.85	12.65	11.78
	S. D.	2.20	3.58	3.35	4.50	5.60	4.82	4.98
	Median	15	15.1	15	15	13	12.9	13
BADL	*Mean*	5.07	5.10	5.00	4.95	4.77	4.36	4.11
	S. D.	1.37	1.43	1.48	1.41	1.50	1.59	1.62
	Median	6	6	6	6	5	5	5
IADL	*Mean*	3.63	3.85	3.56	3.53	3.21	2.59	2.70
	S. D.	2.42	2.33	2.23	2.51	2.50	2.68	3.01
	Median	4	4	4	4	3	2	1

Figure 1: MMSE (for the total sample and for subgroups with MMSE, respectively, > 18 or ≤ 18 at T0), BADL and IADL scores (means, standard deviations, median values) over time, at T0, T1, T3, T9, T15, T21 and T30; number (N°) and percentage (%) of patients with respect to the baseline (T0)

Compared with pre-treatment T0, average MMSE scores in all groups showed a statistically significant increase at T3 ($p<0.005$, df:2; F: 5.23) and at T9 ($p< 0.001$, df:3; F: 7.61) and a decrease afterwards, at T15 ($p< 0.001$, df:4; F: 39.27) and T21 ($p< 0.001$, df:5; F: 60.52).

The BADL scores decreased, showing, a borderline statistical significance (p: 0.049; df:2; F: 3.06) at T3, but higher ($p\leq 0.001$) from T9 onwards. Regarding the IADL scores, they reduced significantly ($p< 0.001$), in each evaluation session, from T3 to T21.

As far as the type of drug is concerned, the scarce number of patients treated with galantamine, compared to those receiving donepezil and rivastigmine, made the evaluation of this covariate unreliable. For the two subgroups, affected respectively by "mild" (MMSE > 18 at T0) and "moderate" dementia (MMSE ≤ 18 at T0), the MMSE scores at time T0 and T3 correlated significantly, by the ANCOVA test, with the variation T15 to T0 and T21-T0 ($p\leq 0.001$) only in the "mild" patients; this was not confirmed for patients with "moderate" dementia.

As regards BADL measures (the afore mentioned limits of the analysis permitting), the only statistically significant ($p\leq 0.05$) association was found, by the ANCOVA test, between the scores at T3 and the variation T15 to T0.

The correlation of IADL scores at time T0 and T3 with the variation T9 to T0 revealed a high statistical significance ($p\leq 0.001$), which became lower ($p\leq 0.05$) with the variation T15 to T0, and borderline ($p< 0.053$ for T3 and 0.04 for T0) with that one T21 to T0.

Our results confirm, in real outpatient life conditions, that ChEIs provide long-term (nine months) cognitive benefit in "mild" to "moderate" AD patients. Then, the efficacy of this treatment, demonstrated in the controlled clinical trials is reproducible in a "real world" setting, as suggested by previous authors. **[6, 7]** Although AD patients treated in the clinical practice and enrolled in our study were different (older and more likely to have comorbid disorders and to use other drugs acting on the nervous system) from those included in randomized-controlled clinical trials, they seemed to benefit from ChEIs to the same extent.

Some shortcomings should be taken into account, that are typical of the general practitioner's world, firstly the large dropout rate. Although there may be the assumption that only subjects who appeared to be responding to treatment actually continued on treatment, and those who continued on treatment showed a response, this sort of a "circularity of argument" is intrinsic to this kind of open label follow up studies. Nevertheless, the finding of a significant association between the MMSE scores at time T0 and T3 and the variation T15 to T0 and T21 to T0 seem to be clearly demonstrated by our results.

This relationship was confirmed only in presence of MMSE >18 at the baseline, suggesting that the initial cognitive status and the early response (at three months) may reliably predict the long-term one only in the "mild" AD patients. On the contrary, in the moderate and moderate severely affected AD patients, the long-term response did not seem to be clearly related to, and predictable by, the early clinical benefit. Consequently, the degree of cognitive impairment appeared the most influent factor upon the long-term response; the less cognitively compromised the patients were at the beginning of the treatment with ChEIs, the more strictly associated their long-term response was to the short-term one. These factors should be taken into account in evaluating any cost/effectiveness ratio in a decision-making setting.

The relationship between MMSE scores at baseline and the clinical improvement in "mild" patients highlights the importance of appropriate diagnostic methods to identify subjects who have the earliest clinical signs of AD, in order to begin the ChEIs therapy as soon as possible. On the other hand, the highly significant correlation between the short-term response and the long-term one, suggests that, if a cognitive improvement is not detectable within the first 2 to 3 months, the ChEIs treatment should be reconsidered. For instance, it may be reasonable to switch the non-responder to another one of the three ChEIs. In fact, a beneficial effect was demonstrated in about the half of the subjects exposed to a second ChEI **[11, 12]**, since the response to a first ChEI was not predictive of that one to another. **[11, 12]** Based on our results, it seems not useful to wait for a clinical benefit of one ChEI longer than three months; after this period, the clinician has to judge the efficacy of the therapy and eventually switch non-responders to another treatment protocol.

It has been suggested that the optimal decision is the decision that yields the highest expected net benefit, according to current information. **[13]** Thus, any new data will update our knowledge concerning the parameters of interest, then, we will be able to make a revised decision based on the new information. This will lead us to choose the treatment with the highest expected benefit.

Therefore, the expected value of sample information is the difference between the expected value of a decision made after "real world" data have been collected and expected value of a decision made now, with only information related to currently available clinical trials. It is this process of updating the probability distributions, given new data *that* makes the process inherently Bayesian. Bayesian updating could be undertaken for using Markov Chain Monte Carlo methods (example, an application in Win-BUGS: http://www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml) to allow sampling from the posterior distribution.

Health economists, modelers and statisticians should be able to apply results from medical practice in the context of the expected value gained by obtaining "real world" sample information before making a decision on any single patient, such raising the efficiency of research

investments in terms of cost/effectiveness and patient's quality of life.

References:

[01] P. Prolo, *et al., Bioinformation,* 1:363 (2007) [PMID: 17597922]
[02] J. Birks, *Cochrane Database Sys Rev*., Jan 25:CD005593 (2006) [PMID: 16437532]
[03] P. J. Connelly, *et al., J. Neurol. Neurosurg. Psychiatry,* 76:320 (2005) [PMID: 15716519]
[04] I. Blasko, *et al., Pharmacology,* 72:1 (2004) [PMID: 15292648]
[05] N. Schoenmaker & W.A. Van Gool, *Lancet Neurol.,* 3:627 (2004) [PMID: 15380160]
[06] A. Bianchetti, *et al., Aging Clin Exp Res.,* 18:158 (2006) [PMID: 16702787]
[07] G. Bellelli, *et al., Aging Clin Exp Res.,* 17:54 (2005) [PMID: 15847123]
[08] G. McKhann, *et al., Neurology,* 34:939 (1984) [PMID: 6610841]
[09] M. F. Folstein, *et al., J Psych Res.,* 12:189 (1975) [PMID: 1202204]
[10] M. P. Lawton & E. M. Brody, *Gerontologist,* 9:179 (1969) [PMID: 5769669]
[11] R. Bullock & C. Connolly, *Int J Geriatr Psychiatry,* 17:288 (2002) [PMID: 11921158]
[12] S. Auriacombe, *et al., Curr Med Res Opin.,* 18:129 (2002) [PMID: 12094822]
[13] A. Brennan & S. A. Kharroubi *J Health Econ* 26:122 (2007) [PMID: 16945438]

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