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Quality of Life and Utility Measurement in a Large Clinical Trial Sample of Patients with Mild to Moderate Alzheimer's Disease: Determinants and Level of Changes Observed

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ABSTRACT

Objective: To evaluate the performance (in terms of responsiveness to change, associations with other criterion standards, and indicators of Alzheimer's disease [AD] severity) of a quality-of-life measure (Quality of Life in Alzheimer's Disease [QOL-AD]) and a health utility measure (Health Utilities Index Mark 3 [HUI-3]) from two recently completed clinical trials of a new drug for AD. **Methods:** Change from baseline scores was calculated, and treatment effects were analyzed using mixed models for repeated measures. Three separate models were then estimated to examine the association between the quality-of-life/utility end points and the clinical and other health outcome end points measured during the trials, including cognition, function, behavior, and dependence. **Results:** The performance of the two measures differed. Subject-assessed QOL-AD was found to be weakly associated with clinical measures of cognition, and with caregiver reports of function, behavior, and dependence, and showed little movement over time and did not appear to differ by baseline AD severity. Proxy-assessed QOL-AD scores were consistently lower than subject-assessed scores, and the level of decline in QOL-AD was greater using proxy-assessed QOL-AD. Proxy-assessed HUI-3 scores were more strongly associated with clinical measures of cognition, function, behavior, and dependence than the subject- and proxy-assessed QOL-AD scores. Larger proportionate changes over 78 weeks were observed with HUI-3 scores and greater separation in HUI-3 scores by baseline severity. **Conclusions:** Subject-assessed QOL-AD is less likely than proxy-assessed QOL-AD to respond to changes in clinical measures used to track progression in clinical trials of subjects with mild to moderate AD. Proxy-assessed HUI-3 assessments were more in line with other outcome assessments and could therefore be better outcome measures to evaluate clinical progression in mild to moderate AD.

Keywords: Alzheimer's disease, Health Utility Index (HUI), patient-reported outcomes, Quality of Life in Alzheimer's Disease (QOL-AD).

Introduction

Quality-of-life (QOL) assessment is increasingly important in the regulatory assessment of new drugs [1,2]. Equally, utility is important as part of health technology assessments surrounding funding decisions [3]. There has been much debate about how best to measure health-related QOL and utility in Alzheimer's disease (AD) because of challenges of changing cognitive performance and patient insight over the course of a study and concerns about bias among family caregivers who provide proxy assessments [4]. There have been a number of reviews on QOL assessment in AD [5,6]. The Quality of Life in Alzheimer's Disease (QOL-AD) is one of the most frequently used QOL measures in AD and offers both patient-assessed and proxy-assessed options [7].

The QOL-AD has been widely used in cross-sectional [8–15] and longitudinal observation studies [16–18], in a clinical trial examining long-term follow-up strategies for patients with AD [19], and in a 6-month study examining the efficacy of Ginko Biloba [20]. These studies have already provided useful information about determinants of QOL-AD scores assessed by the patient and the proxy: in general, depression, anxiety, insight, and use of antidementia treatment have been shown to be associated with patient-assessed QOL-AD while proxy-assessed QOL-AD is determined by many factors including patient impaired function, neuropsychiatric symptoms, cognition, dependency, and caregiver characteristics. On the basis of these findings, researchers have argued that the patient and proxy ratings should be considered complementary and not combined in a composite score. A European consensus panel recommended the QOL-AD as a measure of choice for evaluating psychosocial interventions research in dementia care, having reviewed the literature on a number of QOL outcome measures [21].

Recent long-term observational studies have shown that larger mean changes might be expected in the proxy-assessed

Conflict of interest: Loretto Lacey and Chris Leibman were full-time employees of Janssen Alzheimer Immunotherapy Research & Development, LLC, at the time the work was conducted. Joel Bobula, Katja Rüdell, and Jose Alvir are employees of Pfizer, Inc.

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QOL-AD than in the patient-assessed QOL-AD. In a 2-year follow-up study, patient-assessed QOL-AD scores did not change significantly but proxy-assessed QOL-AD scores did change significantly [17]. In a 3-year follow-up observational study, there was a significant decline in mean scores for proxy-assessed QOL-AD at 12 and 36 months, but vast individual differences in QOL-AD scores [16]. The authors noted that "the wide variation in changes from baseline may affect the validity of using QoL measures as efficacy parameters because improvements in QoL cannot with certainty be appraised as an effect of the intervention."

Shearer et al. [22] reviewed the literature on the use of the Health Utility Index Mark 3 (HUI-3) in AD and concluded that the "validity of the HUI3 for caregiver reports was supported in two studies [23,24] although the validity of the HUI3 for use in AD patients (i.e., patient completed) has been queried due to poor correlations with patient self-assessments of functional status" [23]. For self-completion by patients with mild dementia and for proxy completion, the reliability of the HUI-3, using test-retest reliability (intraclass correlation coefficients), has been reported to be 0.70 or more [23].

Two recently completed randomized clinical trials of bapineuzumab, despite failing to show significant efficacy on the primary outcomes of cognition and function [25], provide a rich data set to investigate the performance of the subject- and proxy-assessed QOL-AD as well as the performance of the proxy-assessed HUI-3 as a measure of utility and its interrelationships with multiple symptoms, including measures of cognition, function, behavior, and dependence. The primary objective of Study ELN115727-301 and Study ELN115727-302 (hereafter referred to as Study 301 and Study 302, respectively) was to demonstrate the safety and efficacy of multiple doses of intravenously administered bapineuzumab in patients with mild to moderate AD compared with placebo (Study 301: NCT00667810 and Study 302: NCT00676143).

This article presents a comprehensive evaluation of the performance of subject- and proxy-assessed QOL-AD and the proxy-based HUI-3 based on pooled data from these two placebo-controlled randomized clinical trials investigating the efficacy of bapineuzumab. These analyses could inform decisions about the usefulness of QOL-AD and HUI-3 in future clinical trials in those with mild to moderate AD. Moreover, the multitude of other instruments and indicators of health status in this trial allows for a better understanding of the determinants of QOL. This may help other evaluations of interventions to improve both patient- and proxy-assessed QOL in patients with mild to moderate AD.

Methods

Study Design

Study 301 and Study 302 were multicenter, randomized, double-blind, placebo-controlled, parallel-group outpatient studies in male and female subjects aged 50 years to younger than 89 years with mild to moderate AD (Study 301: ClinicalTrials.gov identifier NCT00667810 and Study 302: ClinicalTrials.gov identifier NCT00676143). Study 302 was conducted at 170 sites in the United States from December 2007 through April 2012 and included participants who were carriers of the apolipoprotein E (*APOE*) $\varepsilon 4$ allele, a genetic risk factor for AD. Study 301 was conducted at 218 sites in the United States (195 sites), Canada (17), Germany (4), and Austria (2) from December 2007 through June 2012 and included participants who were noncarriers [26]. Bapineuzumab or placebo was administered via an intravenous infusion every 13 weeks for a total of six infusions over the course of the 78-week study. Informed consent was obtained from all participants, or, if not capable of providing informed consent, from their legally acceptable representative. The studies were conducted according to the Declaration of Helsinki and were approved by independent review boards.

Full inclusion and exclusion criteria are described elsewhere (Study 301: NCT00667810 and Study 302: NCT00676143). Briefly, subjects were enrolled in the study if they were aged 50 years to younger than 89; had a diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria and a screening visit brain magnetic resonance imaging scan consistent with a diagnosis of AD; a Mini-Mental State Examination (MMSE) score of 16 to 26 inclusive; a Rosen Modified Hachinski Ischemic score [27] of 4 or less; and lived at home or independently in a community dwelling and had a caregiver who consented to participate in the study, could accompany the subject on all clinic visits, and was a reliable informant in the opinion of the investigator. Subjects were excluded if they had clinically significant neurological disease other than AD; a major psychiatric disorder; history of stroke or seizures; a brain magnetic resonance imaging scan indicative of significant non-AD abnormality; or history or evidence of any clinically significant autoimmune disease or chronic illness that was likely to result in deterioration affecting the subject's safety during the study.

The QOL-AD and HUI-3 [28] were administered at baseline, week 26, week 52, and week 78. Both caregivers and patients completed the QOL-AD, but only the caregivers completed the self-administered proxy version of the HUI-3. The QOL-AD is a 13-item questionnaire designed to provide both a subject report and a caregiver report of the subject's QOL. Points are assigned to each item as follows: poor = 1, fair = 2, good = 3, and excellent = 4. The total score is the sum of all the 13 items and the total range of possible scores is 13 to 52 (higher scores indicate better QOL). The proxy version of HUI-3 is a generic, preference-weighted, health status assessment system completed by the caregiver. The proxy version encompasses 16 questions (one additional item than the self-reported version to identify the relationship of the respondent) that are used to obtain data about patients so that their health status can be described using HUI-3 health states, and ultimately a preference-based utility score for their health. Possible HUI-3 utility values can range from −0.36 (worse than death) to 1 (perfect health), with 0 representing death.

At baseline, week 26, week 52, and week 78, cognitive function was assessed using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (AQDAS-COG; range 0–70) [29], functional ability was assessed with the Disability Assessment for Dementia (DAD; range 0%–100%) [30], and neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI; range 0–144) [31]. Patient dependence on others was assessed using the dependence scale (DS; range 0–15) [32]. Global disability was assessed using the Clinical Dementia Rating Scale-Sum of Boxes [33]. MMSE (0–30) [34] assessments were also made at baseline and at weeks 19, 32, 45, 58, and 78. To estimate MMSE levels at weeks 26 and 52, the mean of two assessments (19 and 32; 45 and 58) was calculated.

Analysis

Level of Change Analysis Using Individual Study Data

For the individual studies, change from baseline scores was calculated for the subject-assessed QOL-AD scores and the proxy-assessed QOL-AD scores at week 78 and treatment effects were analyzed using a restricted maximum likelihood–based mixed model for repeated measures, similar to that used for primary efficacy measures in both studies. Only descriptive