Sustained efficacy and safety of idebenone in the treatment of Alzheimer’s disease: update on a 2-year double-blind multicentre study

H. Gutzmann and D. Hadler

1 Krankenhaus Hellersdorf, ö.B. Wilhelm-Griesinger-Krankenhaus, Abteilung für Gerontopsychiatrie, Berlin, and
2 Takeda Europe, Research & Development Centre GmbH, Frankfurt/Main, Federal Republic of Germany

Summary. The 2-year efficacy and safety of idebenone were studied in a prospective, randomized, double-blind multicentre study in 3 parallel groups of patients with dementia of the Alzheimer type (DAT) of mild to moderate degree. A total of 450 patients were randomized to either placebo for 12 months, followed by idebenone 90mg tid for another 12 months (n = 153) or idebenone 90mg tid for 24 months (n = 148) or 120mg tid for 24 months (n = 149). The primary outcome measure was the total score of the Alzheimer’s Disease Assessment Scale (ADAS-Total) at month 6. Secondary outcome measures were the ADAS cognitive (ADAS-Cog) and noncognitive score (ADAS-Noncog), the clinical global response (CGI-Improvement), the SKT neuropsychological test battery, and the Nurses’ Observation Scale for Geriatric Patients (NOSGER-Total and IADL subscale). Safety parameters were adverse events, vital signs, ECG and clinical laboratory parameters. During the placebo controlled period (the first year of treatment), idebenone showed statistically significant dose-dependent improvement in the primary efficacy variable ADAS-Total and in all the secondary efficacy variables. There was no evidence for a loss of efficacy during the second year of treatment, as a further improvement of most efficacy variables was found in the second year in comparison to the results at the 12 months visit. Also, a clear dose effect relationship (placebo/90mg < idebenone 90mg < idebenone 120mg) was maintained throughout the second year of treatment. This suggests that idebenone exerts its beneficial therapeutic effects on the course of the disease by slowing down its progression. Safety and tolerability of idebenone were good and similar to placebo during the first year of treatment and did not change during the second year.

Introduction

Idebenone (CV-2619) is a benzoquinone derivative that improves brain metabolism and protects the cell membranes against lipid peroxidation. It has
already been investigated in various clinical studies for its effectiveness in dementia of the Alzheimer type (DAT) (Senin et al., 1992; Weyer et al., 1997; Gutzmann et al., 1997). We report on the 2-years results of one of these studies, whose 12 months results have already been reported and reviewed elsewhere (Weyer, 1996; Gutzmann, 1997).

Material and methods

Patient population

Study participants were inpatients and outpatients of both sexes, aged between 40 and 90 years with a diagnosis of primary degenerative dementia (DSM-III-R; American Psychiatric Association, 1987) and a diagnosis of probable Alzheimer’s disease according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). Patients with a diagnosis of dementia of vascular or mixed (degenerative and vascular) origin were excluded as of a score of 5 or more on the Hachinski Ischemia Scale (Hachinski et al., 1975). The differential diagnosis was further supported by a CT- or MRI-scan without evidence of infarction or other focal lesions. Patients with a diagnosis of another type of dementia as evidenced by clinical or neurological examination or laboratory were also excluded. Mild to moderately severe degrees of dementia were defined by a score range of 10 to 24 points on the Mini Mental State Examination (MMSE; Folstein et al., 1975), a score of 9 points or above on the SKT neuropsychological test battery (Erzigkeit, 1989) and a total score of at least 20 points on the Alzheimer’s Disease Assessment Scale [ADAS; Rosen et al., 1984; a validated German version (Weyer 1993) was used]. Each outpatient had a caregiver (close relative or professional caretaker) who ensured compliance with the protocol and served as informant for the patient’s daily activities.

Written informed consent was obtained from the patient and from the caregiver who agreed to monitor the patient’s compliance during the course of the study. The study was approved by the relevant ethics committee established at the “Arztekammer Berlin” and conducted according to the provisions of the World Medical Association’s Declaration of Helsinki (Version 1989).

Study design

The study was performed according to a double-blind, randomized parallel group design in 14 study centres throughout Germany. Patients were identified at an initial screening visit. The inclusion and exclusion criteria were reexamined after a 3 to 4-week placebo wash-out phase and thereupon, after having carried out baseline measurements, eligible patients were randomly assigned to one of three treatment groups: placebo for 12 months, followed by idebenone 90mg tid for another 12 months or idebenone 90mg tid for 24 months or 120mg tid for 24 months. Assessments of efficacy and safety following baseline were scheduled after one and three months and subsequently in 3-month intervals during the entire treatment period.

Outcome measures

Instruments used by trained investigators for the evaluation of efficacy were the ADAS, the SKT, the Nurses’ Observation Scale for Geriatric Patients (NOSGER; Spiegel et al.,