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Featured Article

Demonstration of safety of intravenous immunoglobulin in geriatric patients in a long-term, placebo-controlled study of Alzheimer's disease

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Abstract

Introduction: We present safety results from a study of Gammagard Liquid intravenous immunoglobulin (IGIV) in patients with probable Alzheimer's disease.
Methods: This was a placebo-controlled double-blind study. Subjects were randomized to 400 mg/kg (n = 127), 200 mg/kg (n = 135) IGIV, or to 0.25% human albumin (n = 121) administered every 2 weeks ± 7 days for 18 months.
Results: Elevated risk ratios of IGIV versus placebo included chills (3.85) in 9.5% of IGIV-treated subjects (all doses), compared to 2.5% of placebo-treated subjects, and rash (3.08) in 15.3% of IGIV-treated subjects versus 5.0% of subjects treated with placebo. Subjects in the highest IGIV dose group had the lowest proportion of SAEs considered related to product (2 of 127 [1.6%]). Subjects treated with IGIV experienced a lower rate of respiratory and all other infections compared to placebo.
Discussion: IGIV-treated subjects did not experience higher rates of renal failure, lung injury, or thrombotic events than the placebo group. There were no unexpected safety findings. IGIV was well tolerated throughout 18 months of treatment in subjects aged 50–89 years.

Keywords: IGIV; Intravenous immunoglobulin; Adverse events; Alzheimer's disease; Safety of IGIV

1. Introduction

Intravenous immunoglobulin (IGIV) was developed over 30 years ago to serve as plasma protein replacement therapy for patients with primary immunodeficiency diseases. Since that time, IGIV has also been found to be beneficial for inflammatory and immune disorders, such as immune thrombocytopenic purpura, dermatomyositis, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, myasthenia gravis, and stiff person syndrome [1]. IGIV exerts immune modulatory and anti-

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An article focused on the primary outcome measure of this study, the efficacy of IGIV treatment in Alzheimer patients, is currently under review. The current article is unique in scope in that it focuses on safety results only.

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inflammatory effects that are potentially relevant to treating Alzheimer's disease (AD). Human sera from normal donors contain antibodies to amyloid beta (Aβ) protein [2], which were shown to be neuroprotective in vitro [3]. Antibodies purified from human IGIV products reduced amyloid levels in the central nervous system when infused in Aβ transgenic mice [4]. IGIV was therefore considered a promising agent in passive immunotherapy because it contains naturally occurring polyclonal human antibodies that bind to Aβ aggregates, foster the dissolution of Aβ fibrils, and enhance microglia-mediated phagocytosis of amyloid deposits in vitro [5–7]. Previous early-phase, investigator-initiated clinical studies suggested that IGIV might halt or reverse symptoms of dementia in subjects with mild-to-moderate AD [8–11]. For this reason, a large randomized, placebo-controlled, phase 3 study in mild-to-moderate AD was initiated to test the safety and efficacy of 18 months of IGIV treatment at 200 or 400 mg/kg/2 wks [12,13]. There were 262 subjects exposed to IGIV, and 121 subjects exposed to human albumin as a control.

IGIV has an established safety profile in children and adults. Elderly subjects are treated with IGIV for both labeled and unlabeled conditions [1,14]; however, there are limited data available from appropriately placebo-controlled, double-blinded studies on the safety of IGIV in elderly patients, with most data derived from case studies and retrospective studies [15–19]. IGIV has been associated with uncommon but serious adverse events (SAEs) for which the elderly carry an increased risk such as thrombotic events, transfusion-related lung injury (TRALI), and renal failure. Although the study described in this report did not meet its primary or secondary efficacy endpoints of reducing cognitive decline and preserving functional abilities in AD [20], a substantial body of safety data was amassed in one of the largest placebo-controlled studies of intravenous immunoglobulin conducted in a geriatric population [21,22].

2. Methods

2.1. Study design and participants

This was a phase 3, randomized, double-blind, placebo-controlled, two-dose arm study in elderly subjects with mild-to-moderate AD. Subjects were enrolled in the study at 45 centers within the Alzheimer's Disease Cooperative Study (ADCS, San Diego, CA) consortium in the United States and Canada. Approximately 385 randomized subjects were planned to be enrolled.

At screening, each subject underwent mini-mental state examination (MMSE), as well as physical, neurological, and laboratory assessments. Subjects were randomly assigned in a 1:1:1 ratio to one of three treatment arms to receive infusions every 2 weeks for 70 weeks (a total of 36 infusions) as an add-on to conventional Food and Drug Administration approved AD pharmacotherapy. The three treatment arms were: IGIV 200 mg/kg, IGIV 400 mg/kg, and albumin placebo control at either 2 mL/kg or 4 mL/kg. A concentration of 0.25% albumin was chosen to match the volume, color, and foam-forming characteristics of the IGIV.

Clinical assessments were conducted every 3 months, and magnetic resonance imaging (MRI) was done every 9 months. End-of-study assessments were performed at week 76. An independent data safety monitoring board performed safety monitoring at regular intervals throughout the study.

Eligible participants of either gender were aged 50–89 years with a diagnosis of probable AD of mild-to-moderate severity as determined by a score of 16–26 on the MMSE scale. Subjects may have been receiving stable doses of AD medication (acetylcholinesterase inhibitor and/or memantine) for at least 12 weeks before screening and required the participation of an able caregiver. The main exclusion criteria were non-Alzheimer's dementia, residence in a skilled nursing facility, clinically significant cardiovascular disease, recent central or peripheral thrombosis and/or thromboembolic disease, or active renal disease.

At the investigator's discretion, subjects may have received investigational product infusions at a clinic, home or other suitable locations. Clinical and laboratory assessments were conducted every 3 months until the end-of-study visit.

2.2. Safety outcome measures

Safety objectives included the proportion of subjects experiencing: any adverse events (AEs), product-related AEs, or serious adverse events (SAEs), the number of infusions temporally associated (defined as during or within 72 hours of completion of an infusion) with AEs or SAEs, infusions causally associated with AEs and/or SAEs, and infusions discontinued, slowed, or interrupted due to an AE. Also examined were the proportions of IGIV-treated subjects experiencing a decrease in hemoglobin ($>$1.5 g/dL) and clinically significant rash requiring systemic therapy.

2.3. Randomization and statistical analysis

Randomization was conducted using a stratified permuted block method with an allocation ratio of 1:1:1. Assignments to the three treatment groups were stratified by site, *APOE* ε4 carrier status (Y/N), and disease severity as defined by MMSE category ($\leq$20, $>$20) at screening.

The sample size was powered for efficacy analyses, which constituted the primary and secondary endpoints of the study. The safety analysis set consisted of all subjects who received study product (IGIV or albumin placebo). Descriptive statistics (counts, percentages, and relative risk) were used to summarize safety outcome measures. Relative risk confidence intervals which were calculated using the approximation proposed by Katz et al. [23].

2.4. Role of the funding source

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