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Abstract:
Three small trials suggest that intravenous immunoglobulin can affect biomarkers and symptoms of mild-to-moderate Alzheimer's disease. We tested the safety, effective dose, and infusion interval of intravenous immunoglobulin in such patients. We did a multicentre, placebo-controlled phase 2 trial at seven sites in the USA and five in Germany. Participants with probable Alzheimer's disease aged 50-85 years were randomly assigned (by a computer-generated randomisation sequence, with block sizes of eight) to infusions every 4 weeks (0·2, 0·5, or 0·8 g intravenous immunoglobulin per kg bodyweight, or placebo) or infusions every 2 weeks (0·1, 0·25, or 0·4 g/kg, or placebo). Patients, caregivers, investigators assessing outcomes, and staff at imaging facilities and the clinical research organisation were masked to treatment allocation, but dispensing pharmacists, the statistician, and the person responsible for final PET analyses were not. Treatment was masked with opaque pouches and infusion lines. The primary endpoint was median area under the curve (AUC) of plasma amyloid β (Aβ)(1-40) between the last infusion and the final visit (2 weeks or 4 weeks depending
on infusion interval) in the intention-to-treat population. The trial is registered at ClinicalTrials.gov (NCT00812565) and controlled-trials.com (ISRCTN64846759). 89 patients were assessed for eligibility, of whom 58 were enrolled and 55 included in the primary analysis. Median AUC of plasma Aβ(1-40) was not significantly different for intravenous immunoglobulin compared with placebo for five of the six intervention groups (-18·0 [range -1347·0 to 1068·5] for 0·2 g/kg, -364·3 [-5834·5 to 1953·5] for 0·5 g/kg, and -351·8 [-1084·0 to 936·5] for 0·8 g/kg every 4 weeks vs -116·3 [-1379·0 to 5266·0] for placebo; and -13·8 [-1729·0 to 307·0] for 0·1 g/kg, and -32·5 [-1102·5 to 451·5] for 0·25 g/kg every 2 weeks vs 159·5 [51·5 to 303·0] for placebo; p>0·05 for all). The difference in median AUC of plasma Aβ(1-40) between the 0·4 g/kg every 2 weeks group (47·0 [range -341·0 to 72·5]) and the placebo group was significant (p=0·0216). 25 of 42 (60%) patients in the intervention group versus nine of 14 (64%) receiving placebo had an adverse event. Four of 42 (10%) patients in the intravenous immunoglobulin group versus four of 14 (29%) receiving placebo had a serious adverse event, including one stroke in the intervention group. Intravenous immunoglobulin may have an acceptable safety profile. Our results did not accord with those from previous studies. Longer trials with greater power are needed to assess the cognitive and functional effects of intravenous immunoglobulin in patients with Alzheimer's disease.

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