Qualitative and quantitative volumetric evaluation of the efficacy of intravenous immunoglobulin in multiple sclerosis: preliminary report

Abstract We conducted a double-blind, placebo-controlled study in 13 patients (aged 22 to 54 years) with relapsing-remitting multiple sclerosis (MS). They were randomly assigned to receive a loading dose of immunoglobulin IgG, 0.4 g/kg body weight/day for 5 consecutive days, followed by single booster doses of 0.4 g/kg/day, or placebo, once a month for 9 months. MRI was obtained before and during the 3rd and 6th months of treatment; examinations in the 9th and 12th months were planned. Qualitative and quantitative blinded assessments were performed. There were seven patients who received active treatment and six who received placebo. Statistical analysis was performed by the Wilcoxon test. A decrease in the size and number of lesions was observed on MRI in five patients (71%) in the treatment group, and in two (33%) of the placebo group at 3-month follow-up. At 6 months follow-up MRI, a decrease in the amount of lesions was observed in all patients treated with IV IgG, and in two (33%) of the placebo group; four patients (66%) receiving placebo showed an increase. Quantitative analysis showed a statistically significant decrease in the volume of lesions in treatment group at both 3 and 6 month follow-up. There was no statistically significant change in the placebo group.

Key words Multiple sclerosis · Magnetic resonance imaging · Immunoglobulin G

Introduction MRI is very sensitive in diagnosing multiple sclerosis (MS) [1,2]. Most lesions shown on MRI are asymptomatic, and serial studies have revealed new lesions to be five to ten times as frequently as clinical relapses [3–5]. Imaging provides objective assessment of the extent of disease. These attributes have led to the use of MRI for monitoring treatment efficacy in clinical trials [6–8]. MRI measurements can be qualitative or quantitative [9–11]. A method commonly used for measuring lesion volumes is an intensity-based semiautomated segmentation method developed by Wicks et al. [9]. This involves two interactive steps: the operator must choose the threshold for segmentation and conduct a manual review to correct any error in lesion detection. Our purpose of this study was to determine the efficacy of intravenous immunoglobulin G (IV IgG) treatment qualitatively and quantitatively using MRI in patients with MS.

Materials and methods We prospectively investigated 12 women and one man 22–54 years of age (mean 34.5 years) with relapsing-remitting MS. Mean disease duration was 4.5 years (range 1–15 years). A double-blind, placebo-controlled protocol specified IV administration of IgG (Gammapard S-D, Eczacibasi, Istanbul, Turkey) at a loading dose of 0.4 g/kg body weight/day or placebo, 0.9% saline, for five consecutive days. Booster doses of 0.4 g IgG/kg/day or placebo were given for five consecutive days once a month for 9 months. No patients received any other kind of medication. All patients and investigators were blinded to treatment.
MRI was performed before and after 3 and 6 months of treatment; examinations at 9 and 12 months were planned. MRI was obtained on a 1 Tesla superconductive system with standard parameters. The patients were positioned using a standardized protocol to determine the angle of section for subsequent examinations. Spin-echo proton-density (TR 2300 TE 30 ms, one excitation) and T2-weighted (TR 5400 TE 90 ms, three excitations) and T1-weighted (TR 400 TE 14-23 ms, three excitations) 5 mm images with no interslice gap were obtained in multiple planes.

Two neuroradiologists assessed the images qualitatively and quantitatively. Initially, proton-density and T2-weighted images before and after treatment were assessed qualitatively. Lesions were counted and measured individually from the hard copies by the two neuroradiologists working by consensus. The total number of lesions and the size of the each one were compared between studies. After identification of lesions, the proton-density and T2-weighted axial images were transferred to a workstation. Lesion volumes were then measured on the computer-displayed images, keeping the hard copies as a reference and using a standard semi-automated thresholding technique (Fig. 1) [12,13]. Statistical analysis of the lesion load before and after the treatment was performed by the Wilcoxon test using a standard statistical package (SPSS for Windows 8.0).

Results
On qualitative assessment, a decrease in the size and number of lesions on MRI was observed in five patients (71%) in the treatment group at 3 months, and in all seven patients (100%) at 6 months (Table 1). In the placebo group, a decrease was observed at 3 months in only two patients (33%); there was no change in 2 other patients (33%), while there was an increase in the re-