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Effect of intravenous methylprednisolone on the number, size and confluence of plaques in relapsing–remitting multiple sclerosis

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Abstract

The aim of the present study was to evaluate whether intravenous methylprednisolone (IVMP) pulses affect the confluence and enlargement of T2 lesions in the long term in patients with relapsing–remitting (RR) multiple sclerosis (MS). Of 88 RR MS patients, randomly assigned to regular pulses of IVMP (1 g/day for 5 days with an oral prednisone taper) or IVMP on the same dose schedule only for relapses, and followed up without other disease-modifying drug therapy for 5 years, 81 patients completed the trial as planned. Pulsed IVMP was given every 4 months for 3 years, and then every 6 months for the subsequent 2 years. Calculations were performed for number, size and lesion volume (LV) of T2- and confluent T2-lesions. At study entry, the number, size and LV of T2- and confluent T2-lesions were well matched in the two study arms. At the end of the study, patients who received IVMP pulses every 4–6 months for 5 years had significantly fewer confluent T2 lesions (105 vs. 270, $p<0.0001$), lower confluent T2-LV (5.4 ml vs. 17.4 ml, $p<0.00001$), fewer large T2 lesions (>10 mm) (165 vs. 541, $p<0.00001$), and lower T2-LV/N° T2 lesion index (0.52 vs. 1.1, $p=0.007$) when compared to patients who received IVMP only for relapses. There were more small T2 lesions (1082 vs. 288, $p<0.000001$) in the IVMP pulsed arm. Patients who received higher total doses of IVMP showed the smallest changes in confluent T2-LV during the study. This study suggests that treatment with pulses of IVMP may prevent the confluence of T2 lesions, which may in turn contribute to slower progression of disability in the long term. However, pulsed IVMP treatment did not significantly slow down accumulation of overall T2-LV and there were more smaller T2 lesions in the IVMP pulsed arm at the end of the study.

Keywords: Multiple sclerosis; Steroid therapy; T2 lesions; Confluence

1. Introduction

There is general consensus that intravenous methylprednisolone (IVMP) hastens recovery from multiple sclerosis (MS) relapses and for this reason it is considered the standard treatment for relapses in MS. It has also been suggested that cyclical pulses of IVMP as disease-modifying therapy may be relevant in both relapsing–remitting (RR) [1] and secondary-progressive [2] MS.

We previously demonstrated—in a randomized, controlled, single blind, phase II clinical trial of IVMP in RR MS patients—that prolonged treatment with pulsed IVMP slowed development of T1 black holes and delayed brain atrophy and progression of disability [1]. This study also demonstrated that pulsed IVMP therapy only partially slowed down the accumulation of disease burden (T2-lesion volume [LV]). In fact, both treatment arms showed a significant increase in T2-LV between baseline and year five, and there were no significant differences in T2-LV accumulation between the two treatment arms at the five-

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year follow-up, although there was a trend suggesting an increased accumulation of T2-lesions in the control group.

In order to conduct a thorough investigation into the effect of pulsed IVMP on the size, number and confluence of T2 lesions in the long term, we studied 81 patients who completed a randomized, controlled, single blind, phase II clinical trial of IVMP in RR MS. Therefore, the present study represents an extended analysis of the MRI measures of disease activity, derived from a previously published phase II clinical trial of IVMP in RR MS [1].

2. Materials and methods

Out of 126 consecutive unselected patients screened for the study at the Center for the Diagnosis and Therapy of Multiple Sclerosis operating in the Department of Clinical Medicine and Neurology at the University of Trieste, Trieste, Italy, 88 patients (60 women and 28 men) were enrolled according to the inclusion criteria. Patients had to have clinically definite MS [3], RR disease course [1], age 18–60 years, disease duration 1–10 years and EDSS score ≤ 5.5 [4]. All patients signed written informed consents and the trial was approved by the local Ethical Committee. The study was designed as a randomized, controlled, single blind, phase II clinical trial using simple block randomization in groups of four [1]. At the approximate time when enrollment in the study concluded, the first disease-modifying treatments were approved in Italy. Thus, the selection method resulted in 43 patients being randomly assigned to regular pulses of IVMP (1 g/day for 5 days with an oral prednisone taper), with the same treatment for relapses as required (pulsed IVMP group), and 45 patients being randomly selected to receive IVMP on the same dose schedule, but only for relapses (IVMP for relapses group). Patients were followed without other disease-modifying drug therapy for 5 years. Pulsed IVMP was given every 4 months for 3 years, and then every 6 months for the subsequent 2 years. Each IV pulse was followed by prednisone administered orally starting on day six and concluding on day nine. The prednisone dosage was tapered, beginning with 50 mg for two days followed by 25 mg for 2 days. Ranitidine, 300 mg, was to be taken each evening.

Patients had cranial MRI scans at study entry and after 5 years, and standardized clinical assessments every 4–6 months. The details of the study design and patients' clinical assessments have been described elsewhere [1].

The imaging protocol included acquisition of axial images of the brain that were acquired at a 5 mm slice thickness (24 sections) using PD/T2-weighted SE sequences (TR 2709/TE 20–80) and unenhanced T1-weighted CSE sequences (TR 600/TE 27). A detailed description of the image acquisition protocol at baseline and at the end of the study has been provided elsewhere [1].

T2- and T1-LVs were calculated using a highly reproducible semiautomated local thresholding technique for lesion segmentation. The details of this method were extensively described previously [1,5,6]. Evaluation of brain atrophy was performed on a T1-weighted SE sequence measuring the BPV. An interactive home-developed program which incorporates semiautomated and automated segmentation processes was employed for the measurements [1,5].

In this analysis, calculations for number, size and LV of T2- and confluent T2-lesions were performed. The same two investigators (R.DM. and D.N.) who carried out the quantitative MRI analysis in the original trial [1] performed the calculations for number, size and LV of T2- and confluent T2-lesions at baseline and at the five-year follow-up in this study, after the MRI analysis for the original trial [1] was completed. When there was a discrepancy, a third senior investigator (M.Z.) reviewed the films and a final consensus was reached. All three investigators were blinded to patients' clinical and MRI characteristics.

A new lesion on T2-weighted images was defined as a rounded or oval lesion arising from an area of previously normal appearing brain tissue (NABT) and/or showing an identifiable increase in size from a lesion that had previously appeared stable. If a single T2 lesion actually extended over several slices it was counted only once and contoured on the representative slice where the largest area of the lesion was visible. The nominal diameter of a lesion was then calculated similarly to that previously described [7]. The purpose of calculating a nominal diameter was to help understand the comparisons of lesion sizes. Depending on their size, the lesions were classified in three subgroups: 1 = <5 mm, 2 = 6–10 mm and 3 = >10 mm. Calculation of the number of T2 lesions was based on manual tracing on the films, whereas classification of the lesion area and the size of T2 lesions was performed on computer-displayed images using the contouring-thresholding technique [5].

Confluent T2 lesions were defined as single T2 lesions with an oval shape, larger than 20 mm, typically located in the periventricular region and/or on the edges of the anterior and posterior horns of the ventricle bodies, and usually exhibiting a finger-like spread of two or more T2 lesions in the white matter (Fig. 1a and b) and/or in an area of white abnormalities (Fig. 1c and d) interconnected at the periphery by at least one or more margins. Calculation of confluent T2-LV was performed on computer-displayed images, keeping the marked hardcopies as a reference, and using a highly reproducible semiautomatic local thresholding technique for lesion segmentation [6]. To determine the reproducibility of the method, we used the same 10 MS patients who had been used for reproducibility measurements of T2-LV in the original trial [1]. Intra- and inter-rater variability was defined as the variability between mean estimates of confluent T2-LV determined five times by a single observer who repeatedly evaluated the same scan acquired from the same subject. The mean coefficient of variation (COV) for confluent T2-LV in this group was 3.2% (95% CI 2.6 to 5.2%) for inter-observer reproducibility and 2.8% (95% 1.9 to 4.1%) for intra-observer reproducibility The total analysis time for determining the confluent T2-LV by a trained operator was approximately 20 min per subject.