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A randomized clinical trial of oral versus intravenous methylprednisolone for relapse of MS

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Abstract

Background: Steroids improve multiple sclerosis (MS) relapses but therapeutic window and dose, frequency and administration route remain uncertain.

Objective: The objective of this paper is to compare the clinical and radiologic efficacy, tolerability and safety of intravenous methylprednisolone (ivMP) vs oral methylprednisolone (oMP), at equivalent high doses, for MS relapse.

Methods: Forty-nine patients with moderate or severe relapse within the previous 15 days were randomized in a double-blind, noninferiority, multicenter trial to receive ivMP or oMP and their matching placebos. Expanded Disability Status Scale (EDSS) scores were determined at baseline and weeks 1, 4 and 12. Brain MRI were assessed at baseline and at weeks 1 and 4. Primary endpoint was a noninferiority assessment of EDSS improvement at four weeks (noninferiority margin of one point), with further key efficacy assessments of number and volume of T1 gadolinium-enhancing (Gd+), and new or enlarged T2 lesions at four weeks' post-treatment initiation. Secondary outcomes were safety and tolerability.

Results: The study achieved the main outcome of noninferiority at four weeks for improved EDSS score. No differences were found between ivMP and oMP in the number of Gd+ lesions (0 (0–1) vs 0 (0–0.5), $p = 0.630$), volume of Gd+ lesions (0 (0–88.0) vs 0 (0–32.9) mm^3, $p = 0.735$), or new or enlarged T2 lesions (0 (0–194) vs 0 (0–123), $p = 0.769$). MP was well tolerated, and no serious adverse events were reported.

Conclusions: This study provides confirmatory evidence that oMP is not inferior to ivMP in reducing EDSS, similar in MRI lesions at four weeks for MS relapses and is equally well tolerated and safe.

Trial registration: clinicaltrials.gov identifier: NCT00753792

Keywords

Methylprednisolone, multiple sclerosis, relapses

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Introduction

The main objective of therapy for multiple sclerosis (MS) is to decrease the risk of experiencing a relapse. None of the currently available treatments can completely avoid exacerbations; hence, adequate treatment of relapses remains essential in the management of MS. Administration of a short course of high-dose steroids is the mainstay therapy for this purpose. Steroids may hasten functional recovery in acute MS relapses, but they do not provide any long-term functional benefit. Therefore, the need for this treatment might be questioned. However, relapses affect the patients' psychological health, and a treatment that can shorten the

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Table 1. Definition of relapse intensity.

Available EDSS prior to relapse:

- For optic neuritis, myelitis or brainstem relapse, an increase of one point in the visual, brainstem or pyramidal functional system is required
- For uncertain location relapse: EDSS has to increase at least one point

Unavailable EDSS prior to relapse:

- For optic neuritis, myelitis or brainstem relapse, at least two points in the visual, brainstem or pyramidal functional system is required
- For uncertain location relapse: EDSS has to be of two points at least

Moderate intensity (increase 1–2.5 points on EDSS)
Severe intensity (increase ≥ 3 points on EDSS)

EDSS: Kurtzke's Expanded Disability Status Scale.

intensity and duration of the symptoms is well worthwhile.[1,2] The percentage of patients whose symptoms improve within one month following steroid treatment ranges from 34% to 91%.[3–5]

Several studies have consistently demonstrated that steroids improve clinical recovery[6,7] and reduce brain magnetic resonance imaging (MRI) activity.[8–11] The therapeutic window and the optimal choice of drug, dose, frequency, treatment duration and administration route remain uncertain.[12] Considerable variability between specialists in the prescription of this treatment has been observed in clinical practice.[13,14]

Patients tend to prefer oral administration over intravenous therapy,[15–18] because it interferes less with family and social life, is more convenient, and avoids the contact with needles. In keeping with the hypothesis investigated by other authors that oral methylprednisolone (oMP) is not inferior clinically or radiologically to intravenous methylprednisolone (ivMP), and that it is equally well tolerated and safe,[17–19] we conducted the present clinical trial for the treatment of MS relapse with the aim of providing evidence that would tilt the scale toward oral administration of steroids to spare patients from more invasive, less convenient, and more costly medical practice.[20]

Methods

Study design

This phase-IV, multicenter, double-blind, randomized clinical trial was conducted at seven MS units in Catalonia (Spain). The study was approved by local institutional review boards of participating centers. Patients were assigned to treatment only after they had given informed consent. Academic investigators (CRT, JC, MT, AR) and a statistician (FT) designed and conducted the trial, whose protocol was registered (ClinicalTrials.gov number, NCT00753792).

Two academic authors (CRT, LGL) guaranteed the veracity and completeness of the data analyses and were responsible for writing the manuscript. An independent data and safety monitoring committee was responsible for safety reviews and interim analyses based on the primary endpoint variable. An independent CRO was responsible for monitoring, storing and checking data for consistency, and then received allocation codes and performed analyses according to the approved plan.

Patients

The study included adults who met the 2005 McDonald criteria[21] for relapsing–remitting MS and experienced a recent moderate or severe relapse. Because there is no consensus definition establishing the intensity of a relapse, we applied the definition used by other authors,[22] as shown in Table 1. To be included patients had to have 1) relapsing–remitting MS; 2) age between 18 and 59 years; 3) Expanded Disability Status Scale (EDSS) score prior to relapse: 0 to 5.0; 4) a moderate or severe clinical relapse without improvement at the time of inclusion; 5) recent clinical relapse onset (<15 days) without fever; and 6) one month of clinical stability prior to relapse. The exclusion criteria were isolated clinical syndrome, primary or secondary progressive MS, use of steroids during the previous three months, use of natalizumab or immunosuppressive therapy at any time, pregnancy or breastfeeding, diseases that contraindicate treatment with corticosteroids (diabetes and gastric ulcer were not excluded), history of serious adverse reaction or hypersensitivity to drugs related to the study medication, inability to have regular MRI scans, anesthesia requirement, lactose intolerance (because the capsules were supplemented with lactose as an excipient), allergy to gadolinium contrast-based agents and known renal impairment. Current treatment with interferon and glatiramer acetate was allowed.

Written informed consent was obtained from each patient before randomization, and the ethics committees of all participating centers approved the trial protocol.

Randomization, study intervention, masking and compliance

Patients were randomly assigned to receive active ivMP at a dose of 1000 mg/24 hours for three days and an oral placebo, or active oMP at a dose of 1250 mg/24 hours (considering that MP has an oral bioavailability of 80%) for three days and an intravenous placebo. Thus, each subject received either oral or intravenous active treatment. The MP capsules used were prepared specifically for the trial. Patients took 12 nº 00 capsules containing 100 mg of MP per capsule and one capsule containing 50 mg, or 13 placebo capsules. The investigators decided which patients required gastroprotective treatment based on their clinical history. Patients with insomnia received specific treatment.

Patients were randomly assigned (1:1) to one of the two arms by the Pharmacy Department of Germans Trias i Pujol Hospital according to a list of trial codes and medication contained in sealed envelopes. To ensure that a similar number of patients were entered in each treatment group, the randomization codes (using random numbers generated centrally by computer) were provided in blocks of four. ivMP or placebo were prepared by an unblinded pharmacist.

Patients, researchers, nurses, caregivers, those assessing the outcomes and data managers were blinded to group assignment. Placebo was identical and indistinguishable from the active drug in both formats: ampoules and capsules. Treatment was administered in the emergency management out-patient clinic for three consecutive days, so the compliance deviations were recorded.

Clinical assessments and outcomes

The primary endpoint was the noninferiority assessment of the oMP arm in EDSS improvement at four weeks' post-treatment initiation evaluated by the same certified attending physician in each center, with a noninferiority margin of one EDSS point. Clinical visits for EDSS and brain MRI assessments were held at baseline and at weeks 1 and 4 after the first treatment dose. After clinical and brain MRI evaluation at baseline (days –3 to –1), treatment was started. The treating physician made an additional EDSS assessment at 12 weeks.

Secondary outcomes were safety and tolerability of both administration routes. Patients completed a specifically designed questionnaire to evaluate treatment tolerance at 24–48 and 72 hours following initiation, and at one and four weeks. Treatment-related adverse events were systematically recorded.

Brain MRI assessments

All participating centers were required to pass a dummy run before acceptance in the trial. Brain MRI studies were carried out on a 1.5-T system during a single session. The following sequences were performed without moving the patient from the trolley: 1) axial proton density- (PD) and T2-weighted turbo spin echo (repetition time (TR) 2800 msec, echo time (TE) 15/20 msec, echo train length 4–6; 2) axial T1-weighted spin echo (TR 600–650 msec, TE 10–15 msec, number of averages 2); and 3) axial post-contrast (five minutes after injection of 0.1 mmol/kg Gd). For each sequence, 44 contiguous, 3 mm-thick axial slices with a 256 × 256 matrix size and 250 field of view were obtained. The slices were positioned to run parallel to a line joining the most inferoanterior and inferoposterior portions of the corpus callosum. On follow-up scans, patients were carefully repositioned, and new and persistent T1 gadolinium-enhancing (Gd+), and new or enlarged T2 lesions were identified following published guidelines.[23]

MRI outcome variables were the number and volume of T2 and T1 Gd+ lesions at baseline, and number and volume of new or enlarged T2 lesions, and new or persistent Gd+ lesions/at one and four weeks post-treatment initiation.

Volumetric analysis

From the PD/T2-weighted and pre- and post-gadolinium T1-weighted images, an experienced rater visually assessed the presence and number of T2 and Gd+ lesions at baseline, and the new or enlarged T2 and the number of new and persistent Gd+ lesions on each follow-up MRI scan.

For calculating T2 and Gd+ lesion volumes at baseline, and Gd+ and new or enlarged T2 lesions on follow-up scans, a single rater, previously trained to ensure a high level of reproducibility, outlined the lesions on the computer image using a semiautomatic local thresholding contour technique (Dispimage, DL Plummer, University College, London, UK).[24] A computer program then summed all the individual lesion areas and a final volume was generated and stored in a specially constructed database.

Populations and statistical analysis

With 22 valid patients per group, the study had a power of 80% assuming a noninferiority margin of one point on the EDSS scale, with a standard deviation of 1.13 and a unilateral significance level of 2.5% (97.5% unilateral confidence interval (CI)).[25] The primary efficacy variable and the continuous secondary outcomes were assessed using an analysis of covariance (ANCOVA) model with the baseline measurement as covariate. A nonparametric sensitivity analysis using the Hodges-Lehmann estimator was also made for the main outcome variable and for continuous non-Gaussian variables. Fisher's exact test was used to compare categorical variables. The overall statistical analysis was conducted on the population *per protocol* (PP) and

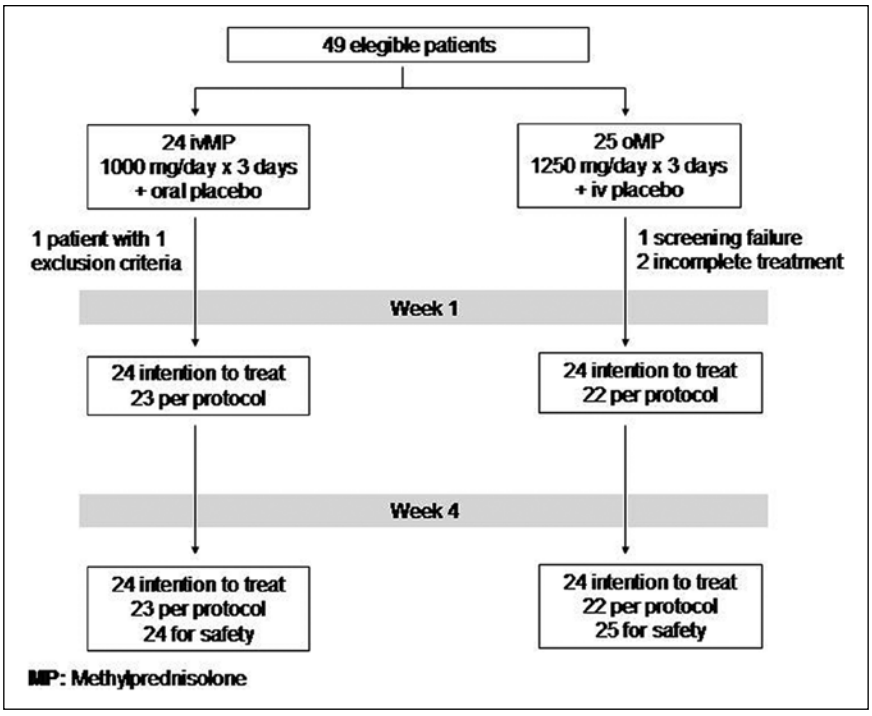

Figure 1. Flowchart.
ivMP: intravenous methylprednisolone; oMP: oral methylprednisolone.

the analysis of the primary variable was also conducted on the *intent-to- treat* (ITT) population. The analysis was performed using SAS version 9.1.3 software (SAS Institute Inc, Cary, NC, USA), and significance was established at <0.05 (two sided), except for the noninferiority analyses where the one-sided 0.025 was used.

Results

Forty-nine patients were randomized to receive either ivMP (24 patients) or oMP (25 patients) between November 2008 and January 2011. A screening failure occurred in one patient from the oMP group, and the patient was excluded from the analysis. Treatment was discontinued in two patients from the oMP group, one because of pregnancy and one because of abdominal pain. One patient from the ivMP group who had received steroid treatment during the previous three months was excluded (Figure 1).

The two treatment groups were well balanced in terms of sex, age, EDSS score prior to and on relapse and MRI findings at baseline. Twenty patients (44.4%), 10 per group, were not receiving immunomodulatory treatment (Table 2). All patients included had a moderate relapse.

Clinical outcome

The study achieved the main outcome of noninferiority at four weeks for improved EDSS score (i.e. parametric analysis, noninferiority margin of one EDSS point and use of the PP population set), ivMP group –1.13 (–1.53 to –0.73) and oMP group –1.06 –1.46 to –0.65), mean difference (95% CI): –0.07 (95% CI –0.64, 0.49); (Table 3). Sensitivity analyses using the parametric approach with the ITT population and the nonparametric approach with the PP population confirmed the results of the primary analysis (see Figure 2).

An improvement in the EDSS score was observed in both treatment groups at one and four weeks vs baseline ($p < 0.001$ for both groups at both time points). No differences were found in the EDSS between groups during the study period. An improvement in EDSS of at least one point was found in 46% of patients who received oMP and in 39% of those who received ivMP at week 1 (rapid response, $p = 0.767$), in 68% and 65% at week 4 ($p = 1.0$) and in 73% and 70% at week 12 ($p = 1.0$). Two patients in the oMP group (8.0%, 95% CI (2.2%, 25.0%)) and two patients in the ivMP group (8.3%, 95% CI (2.3%, 25.9%)) experienced a relapse between two and three months after inclusion ($p = 1.0$). No patient required hospitalization.

MRI outcome

At the baseline examination (Table 2), brain MRI parameters were similar in the two groups. Patients with more than nine T2 lesions on brain MRI were 37 (82%), 20 (87%) in the ivMP group and 17 (77%) in the oMP group. Gd+ lesions were present in 53% of patients, 13 (57%) in the ivMP group and 11 (50%) in the oMP group. A median of

Table 2. Baseline characteristics.

	ivMP *n* = 23	oMP *n* = 22	Total *n* = 45
Sex, female	19 (83%)	17 (77%)	36 (80%)
Age, years	37.7 (7.8)	39.5 (7.9)	37.7 (7.8)
Drugs			
No treatment	10 (43.4%)	10 (45.4 %)	20 (44.4%)
INF beta	10 (43.4%)	9 (40.9%)	19 (42.2%)
Glatiramer acetate	3 (13.0%)	3 (13.6%)	6 (13.3%)
EDSS on relapse	4 (2.5–4.5)	3 (2.5–4)	3.5 (2.5–4)
EDSS prior to relapse	2 (1.5–3]	2 (1.5–2.5)	2 (1.5–2.5)
Baseline MRI			
More than nine T2 lesions	20 (87%)	17 (77%)	37 (82%)
T2 lesion volume, mm^3	155 (0–984)	183 (0–535)	183 (0–725)
Patients with Gd+ lesions	13 (57%)	11 (50%)	24 (53%)
T1 Gd+ lesions, number	1 (0–5)	1 (0–4)	1 (0–5)
T1 Gd+ lesion volume, mm^3	33 (0–371)	29 (0–535)	29 (0–535)

Descriptive data are *N* (%), mean (SD) or median [25th–75th percentile]. Gd+: gadolinium-enhancing; EDSS: Kurtzke's Expanded Disability Status Scale; MRI: magnetic resonance imaging; INF: interferon; ivMP: intravenous methylprednisolone; oMP: oral methylprednisolone.

one Gd+ lesion was detected in each group. The median volume of Gd+ lesions was 33 mm^3 in the ivMP and 29 mm^3 in the oMP group. Median T2 lesion volume was 155 mm^3 in the ivMP and 183 mm^3 in the oMP group.

At one week post-treatment initiation, 10 (44%) patients receiving ivMP and six (28%) of those administered oMP showed Gd+ lesions ($p = 0.21$). Gd+ lesions had a mean reduction of 13% in the ivMP group ($p = 0.03$) and 22% in the oMP group ($p = 0.02$). This difference was 9% in favor of the oMP group. The median number of Gd+-persistent lesions and new Gd+ lesions was 0 in both groups.

At four weeks, the values of Gd+ lesions were 35% and 24% ($p = 0.52$), respectively. Gd+ lesions had a mean reduction of 22% the ivMP group ($p = 0.04$) and 26 % in the oMP group ($p = 0.04$). The median number of Gd+-persistent lesions and new Gd+ lesions was 0 in both groups.

At one week and four weeks' post-treatment initiation, the median change in the volume of Gd+ lesions and median increase in T2 lesions number was 0 in both groups, and the median change in T2 lesion volume was 0 in both groups (Table 4).

Tolerability and safety

Both oMP and ivMP were well tolerated (Table 5). All except one patient reported adverse effects, but none were classified as serious. The most common were headache, mood disorder and insomnia. Other recorded side effects included a metallic taste in mouth, nausea, stomach pain, diarrhea, rash, edema and palpitations. No statistical differences were found between the groups. One patient who received oMP abandoned the study because of abdominal pain. The levels of glucose and blood pressure and heart rate did not change significantly after receiving MP in any of the two treatment groups.

Discussion

This study provides evidence that oMP is not inferior to ivMP in reducing EDSS and MRI lesions at four weeks for MS relapses and is equally well tolerated and safe.

The definition of the noninferiority margin is a matter of debate within the scientific community. It is difficult to achieve a consensus for the most acceptable cut-off point of EDSS improvement to define the noninferiority margin. We chose a delta value of 1.0 EDSS points based on the work of Sharrack.[25] Despite the fact that the study was positive with the beforehand protocol that defined a noninferiority value of one point for EDSS, it is not possible to ensure that the study, with a more stringent value of delta less than 1.0 EDSS point, would have the same results. Therefore the noninferiority positive conclusion must be taken with caution and in context to the relevance of that margin.

Since the 1980s, there has been evidence in other autoimmune diseases such as rheumatoid arthritis[26] and asthma[27] that oral treatment with MP in megadoses is equally as effective as ivMP. In 1993, Alam et al.[28] were the first to investigate this issue in a clinical trial including MS patients. The authors compared the clinical efficacy of administration of identical doses of oMP and ivMP (500 mg/24 hours for five days) as measured by EDSS scores, and found no difference between the two groups. Since then, two additional randomized clinical trials have compared the effect of oMP and ivMP treatment on acute MS relapse[3,11] and two others have done so in optic neuritis.[29,30] Although all of these studies have certain methodological limitations, analysis of the primary outcome measure showed no statistically significant differences: All the trials suggested an improvement in EDSS score within the first five weeks associated both with ivMP and oMP treatment.

Table 3. Kurtzke's Expanded Disability Status Scale (EDSS) analysis.

		Baseline values	Visit-baseline values		
			1 week	4 weeks	28 weeks
Parametric analysis PP set	ivMP (n = 23)	3.74 (3.21 to 4.27)	–0.52 (–0.79 to –0.25)	–1.13 (–1.53 to –0.73)	–1.19 (–1.61 to –0.77)
	oMP (n = 22)	3.48 (2.93 to 4.02)	–0.60 (–0.87 to –0.32)	–1.06 (–1.46 to –0.65)	–1.14 (–1.57 to –0.71)
	Differences	—	0.08 (–0.31 to 0.47) p = 0.69	**–0.07 (–0.64 to 0.49) p = 0.795**	–0.05 (–0.65 to 0.55) p = 0.865
Parametric analysis ITT set	ivMP (n = 24)	3.67 (3.15 to 4.18)	–0.50 (–0.76 to –0.23)	–1.11 (–1.49 to –0.72)	–1.18 (–1.59 to –0.77)
	oMP (n = 24)	3.44 (2.92 to 3.95)	–0.65 (–0.92 to –0.39)	–1.11 (–1.50 to –0.72)	–1.14 (–1.55 to –0.73)
	Differences	—	0.15 (–0.22 to 0.53) p = 0.412	0.00 (–0.54 to 0.55) p = 0.988	–0.04 (–0.62 to 0.55) p = 0.904
Nonparametric analysis PP set	ivMP (n = 23)	4 (2.50 to 4.00)	–0.5 (–1.00 to 0.00)	–1 (–1.50 to –0.50)	–1 (–1.50 to -0.50)
	oMP (n = 22)	3 (2.50 to 4.00)	–0.5 (–1.00 to 0.00)	–1 (–2.00 to -0.50)	–1 (–1.50 to –0.50)
	Differences	–	0 (–0.50 to 0.50) p = 0.960	0 (–0.50 to 0.50) p = 0.954	0 (–0.50 to 0.00) p = 0.686

The protocol predefined main analysis was the parametric analysis with the PP set for assessment of noninferiority with a margin of one EDSS point at week 4 (gray-shadowed cell); the remaining strategies were predefined as sensitivity analyses. Statistics are least square means and (95% CI) for the parametric analysis and medians and (95% CI) for the nonparametric approach. Values at one week, four weeks and 28 weeks are baseline-adjusted values for the parametric analysis. CI: confidence interval; ITT: intention to treat; PP: per protocol; ivMP: intravenous methylprednisolone; oMP: oral methylprednisolone.

In one of these studies, this improvement was also proven by radiologic evaluation.[11] Furthermore, a Cochrane review found no evidence to support one regimen as superior, although the authors stated that formal conclusions about equivalence could not be made because of the limitations of the studies reviewed.[31]

In the present trial, bioequivalent doses of oMP and ivMP were given, not identical doses. The oMP dose of 1250 mg/24 hours for three days corresponds to the dose needed to achieve the same blood levels as the intravenous dose, considering that MP has an oral bioavailability of 80%.[32] The patients received 1 g MP for three days (3 g total) because our practice is to limit the treatment to the three-day course, given that side effects become increasingly likely with increasing duration of treatment, and because trials examining different doses of high-dose steroids comparing 500 mg/24 hours for five days (2500 mg total)[28] and the regimen of our study: 1 g the MP for three days (3 g total)[3] have shown good response. Following the ivMP or oMP high dose we did not use a posterior tapering oMP dose because a study, comparing data from patients who had received oral steroid tapers and patients who had not, found no significant differences between the groups in follow-up.[33] The enhancement seen at MRI at almost four weeks after stopping treatment raises the question of whether a longer course of steroids should be used. We believe, as did Miller et al.,[34] that the decision to treat should be based on clinical criteria alone, and should not be influenced by asymptomatic MRI-detected disease activity, the prognostic significance of which is uncertain. A well-designed randomized clinical trial should be conducted to answer this question.

Our trial differs from previous studies in that it is double-blind, randomized and dose-bioequivalent using the same steroid (MP), it includes definitions of relapse intensity, and the primary outcome was not only clinical efficacy but also MRI improvement. The patients included had a recent onset of clinical relapse (<15 days). This criteria prevented inclusion of patients with spontaneous recovery, which could have occurred in studies including patients with onset of relapse up to one month before. Furthermore, the patients studied were similar to those encountered in clinical practice, unlike the previous study[11] in which patients with at least one Gd+ lesion on brain MRI were included. In addition the brain MRI findings investigated were Gd+ lesions as well as number and volume of new or enlarged T2 lesions. Lastly, this randomized clinical trial also included a formal record of adverse events to assess possible differences between the two administration routes, and tolerability was measured by specific questionnaires.

This trial has replicated and extends the work of other authors who have already observed a significant clinical improvement in EDSS both in oMP- and ivMP-treated patients at four weeks. We found that the clinical benefits were not significantly greater in either of the treatment

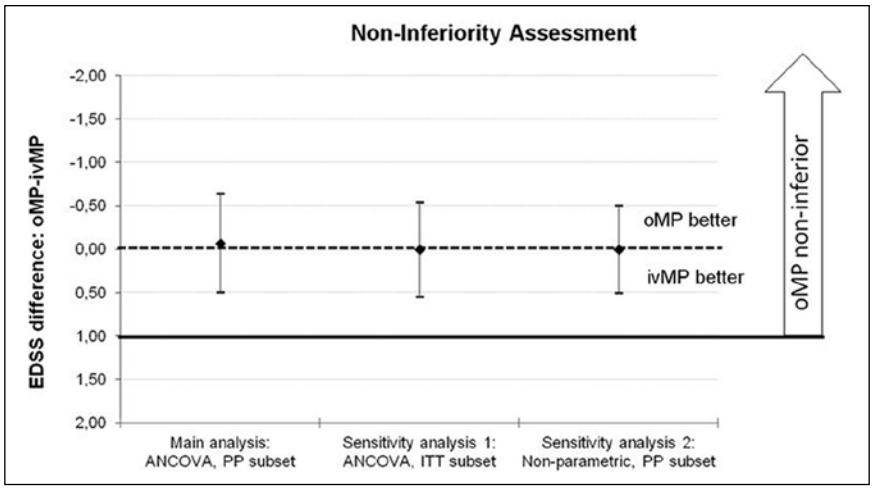

Figure 2. Sensitivity analyses using the parametric approach with the ITT population, and the nonparametric approach with the PP population.
EDSS: Expanded Disability Status Scale; ivMP: intravenous methylprednisolone; oMP: oral methylprednisolone; ANCOVA: analysis of covariance; ITT: intent-to-treat; PP: per protocol.

Table 4. MRI analysis.

	ivMP (*n* = 23) Median (95% CI)	oMP (*n* = 22) Median (95% CI)	Difference (*n* = 45) Median (95% CI)
Patients with Gd+ lesions at 1 week	**10 (44%)**	**6 (28%)**	p **= 0.21**
Patients with Gd+ lesions at 4 weeks	**8 (35%)**	**5 (24%)**	p **= 0.52**
T1Gd+ lesions at baseline MRI	**1 (0 to 5)**	**1 (0 to 4)**	**0 (–1 to 1)**
T1Gd+ PLES at 1 week	0 (0 to 3)	0 (0 to 2)	0 (0 to 0) p = 0.867
T1Gd+ PLES at 4 weeks	0 (0 to 2)	0 (0 to 0)	0 (0 to 0) p = 0.452
T1Gd+ PLES at 4 weeks vs 1 week	0 (0 to 0)	0 (0 to 0)	0 (0 to 0) p = 0.973
T1Gd+ NLES at 1 week	0 (0 to 1)	0 (0 to 0)	0 (0 to 0) p = 0.057
T1Gd+ NLES at 4 weeks vs 1 week	0 (0 to 1)	0 (0 to 0)	0 (0 to 0) p = 0.569
T1Gd+ LES volume at baseline MRI, mm³	**33 (0 to 195)**	**29 (0 to 535)**	**0 (–217 to 47)**
T1Gd+ PLES volume at 4 weeks vs baseline, mm³	0 (0 to 106)	0 (0 to 26)	0 (0 to 0) p = 0.592
T1Gd+ PLES volume at 4 weeks vs 1 week, mm³	0 (0 to 255)	0 (0 to 300)	0 (0 to 0) p = 0.775
T1Gd+ NLES volume at 1 week vs baseline, mm³	0 (0 to 17)	0 (0 to 0)	0 (0 to 0) p = 0.046
T1Gd+ NLES volume at 4 weeks vs 1 week, mm³	0 (0 to 31)	0 (0 to 0)	0 [0 to 0) p = 0.42
T2 NLES			
T2 NLES at 1 week	0 (0 to 0)	0 (0 to 0)	0 (0 to 0) p = 0.201
T2 NLES at 4 weeks	0 (0 to 0)	0 (0 to 0)	0 (0 to 0) p = 0.721
Volume of T2 LES at baseline MRI, mm³	**155 (0 to 893)**	**183 (0 to 535)**	**0 (–183 to 226)**
Volume of T2 LES at baseline vs 1 week, mm³	0 (0 to 504)	0 (0 to 266)	0 (–29 to 34) p = 0.91
Volume of T2 LES at baseline vs 4 weeks, mm³	0 (0 to 152)	0 (0 to 31)	0 (–46 to 0) p = 0.43

MRI: magnetic resonance imaging; CI: confidence interval; PLES: persistent lesions; NLES: new lesions; Gd+: gadolinium-enhancing. ivMP: intravenous methylprednisolone. oMP: oral methylprednisolone.

Table 5. Patients treated with either ivMP or oMP who experienced adverse events.

	ivMP (n = 24)	oMP (n = 25)
Headache	13 (54.2%)	18 (72%)
Anxiety	9 (37.5%)	11 (44%)
Euphoria	4 (16.7%)	10 (40%)
Depressed mood	2 (8.3%)	6 (24%)
Fatigue	4 (16.7%)	3 (12%)
Insomnia	16 (66.7%)	23 (88%)
Metallic taste	16 (66.7%)	20 (80%)
Stomach pain	6 (25%)	10 (40%)
Nausea	7 (29.2%)	6 (24%)
Diarrhea	3 (12.5%)	2 (8%)
Cutaneous rash	6 (25%)	11 (44%)
Edema	3 (12.5%)	2 (8%)
Palpitations	5 (20.8%)	9 (36%)

ivMP: intravenous methylprednisolone. oMP: oral methylprednisolone.

modalities at any time and that the responder rate was the same in the two groups. Brain MRI data showed no statistically significant differences between treatment groups in reducing the number of new or enlarged T2 or T1 Gd+ lesions at four weeks. Therefore, the response was not related to the administration route. Moreover, both oMP and ivMP were well tolerated, with a safety profile consistent with previous studies.

This trial has some limitations. First, as in previous studies, the number of patients included is relatively small. Furthermore, the clinical and radiological follow-up is relatively short and did not allow us to establish the potential reversibility of the observed effects and the long-term impact. However, our primary outcome was very specific and based on improving the symptoms of relapse and MRI parameters at short term.

Much remains to be conducted in investigating the best treatment regimen for MS relapses. In our opinion, the results of this clinical trial together with those of other trials support the use of oMP 1250 mg/24 hours for three days instead of ivMP 1000 mg/24 hours for three days for MS relapses, given the advantages of patient convenience, safety and lower cost. Capsules containing high doses of MP can be prepared in hospital or community pharmacies.

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Conflict of interest

None declared.

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