Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial

Emmanuelle Le Page, David Veillard, David A Laplaud, Stéphanie Hamonic, Rasha Wardi, Christine Lebrun, Fabien Zagnoli, Sandrine Wiertlewski, Véronique Deburghgraeve, Marc Coustans, Gilles Edan, for the COPOUSEP investigators and the West Network for Excellence in Neuroscience*

Summary

Background **High doses of intravenous methylprednisolone are recommended to treat relapses in patients with multiple sclerosis, but can be inconvenient and expensive. We aimed to assess whether oral administration of high-dose methylprednisolone was non-inferior to intravenous administration.**

Methods **We did this multicentre, double-blind, randomised, controlled, non-inferiority trial at 13 centres for multiple sclerosis in France. We enrolled patients aged 18–55 years with relapsing-remitting multiple sclerosis who reported a relapse within the previous 15 days that caused an increase of at least one point in one or more scores on the Kurtzke Functional System Scale. With use of a computer-generated randomisation list and in blocks of four, we randomly assigned (1:1) patients to either oral or intravenous methylprednisolone, 1000 mg, once a day for 3 days. Patients, treating physicians and nurses, and data and outcome assessors were all masked to treatment allocation, which was achieved with the use of saline solution and placebo capsules. The primary endpoint was the proportion of patients who had improved by day 28 (decrease of at least one point in most affected score on Kurtzke Functional System Scale), without need for retreatment with corticosteroids, in the per-protocol population. The trial was powered to assess non-inferiority of oral compared with intravenous methylprednisolone with a predetermined non-inferiority margin of 15%. This trial is registered with ClinicalTrials.gov, number NCT00984984.**

Findings **Between Jan 29, 2008, and June 14, 2013, we screened 200 patients and enrolled 199. We randomly assigned 100 patients to oral methylprednisolone and 99 patients to intravenous methylprednisolone with a mean time from relapse onset to treatment of 7·0 days (SD 3·6) and 7·4 days (3·9), respectively. In the per-protocol population, 66 (81%) of 82 patients in the oral group and 72 (80%) of 90 patients in the intravenous group achieved the primary endpoint (absolute treatment difference 0·5%, 90% CI −9·5 to 10·4). Rates of adverse events were similar, but insomnia was more frequently reported in the oral group (77 [77%]) than in the intravenous group (63 [64%]).**

Interpretation **Oral administration of high-dose methylprednisolone for 3 days was not inferior to intravenous administration for improvement of disability scores 1 month after treatment and had a similar safety profile. This finding could have implications for access to treatment, patient comfort, and cost, but indication should always be properly considered by clinicians.**

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Clinical Neuroscience Centre, CIC-P 1414 INSERM (E Le Page MD, V Deburghgraeve MD, Prof G Edan MD) **and Epidemiology and Public Health Department** (D Veillard MD, S Hamonic MSc), **Rennes University Hospital, Rennes, France; UMR1064, INSERM, and CIC015, INSERM, Nantes, France** (Prof D A Laplaud MD); **Neurology Department, Saint Brieuc Hospital, Saint-Brieuc, France** (R Wardi MD); **Neurology Department, Nice University Hospital, Nice, France** (C Lebrun MD); **Neurology Department, Military Hospital, Brest, France** (F Zagnoli MD); **Neurology Department, Nantes University Hospital, Nantes, France** (S Wiertlewski MD); **and Neurology Department, Quimper Hospital, Quimper, France** (M Coustans MD)

Correspondence to: Prof Gilles Edan, Service de Neurologie, CHU Pontchaillou, Rennes 35033, France **gilles.edan@chu-rennes.fr**

See **Online** for appendix

Introduction

Multiple sclerosis is the neurological disease that most frequently causes disability in young adults. Multiple sclerosis is characterised by an inflammatory process that is initially focal or multifocal and associated with relapses, and which then becomes diffuse and chronic and is associated with a gradual worsening.[1] Disease-modifying therapies have decreased the risk of accumulation of new focal lesions, but when relapses occur, high-dose intravenous corticosteroids, which have proven effectiveness in randomised controlled trials,[2–9] are commonly used. However, questions remain as to whether treatment could be given in a simpler and less invasive way (ie, orally). Little evidence has been shown for use of high-dose oral steroids in multiple sclerosis.[10,11]

The authors of a Cochrane review[12] did a meta-analysis of five randomised trials from the past 20 years[13–17] including 215 patients that compared oral and intravenous steroids for the treatment of relapses. The authors concluded that the analysis did not show any significant differences in clinical, radiological, or pharmacological outcomes for oral or intravenous administration. However, they did point out major limitations, including methodological weaknesses and insufficient statistical power, underscoring the need for larger scale trials with sufficient power to compare the two regimens. Because infusions of corticosteroids are widely used to treat relapses of multiple sclerosis, it is important to clarify whether oral corticosteroids can be used with the same safety and efficacy. We therefore undertook the French

Research in context

Evidence before this study

On Sept 15, 2005, before this study, we searched PubMed using the following MeSH terms: "multiple sclerosis", "relapses", "corticosteroids", "methylprednisolone", "high-dose", "oral", "intravenous", and "clinical trials". We identified two randomised controlled trials (Alam and colleagues, 1993, and Barnes and colleagues, 1997) comparing efficacy, but not tolerability, of oral versus intravenous high-dose methylprednisolone, in 25 and 80 patients, respectively. When we did another search and review in December, 2014, we identified three additional randomised controlled studies showing no difference between oral and intravenous high-dose methylprednisolone on MRI and clinical parameters in 48 and 40 patients (Ramo-Tello and colleagues, 2014, and Martinelli and colleagues, 2009), and on pharmacokinetic parameters in 16 patients (Morrow and colleagues, 2004). The data of these five randomised trials[13–17] were included in a 2012 Cochrane review and meta-analysis by Burton and colleagues addressing the question of oral versus intravenous methylprednisolone, which found no difference in relapse recovery between oral and intravenous methylprednisolone, but also underlined insufficient power in these studies and several other limitations.

Added value of this study

Our study was the first adequately powered, randomised, double-blind, non-inferiority trial to compare a similar dosage of oral versus intravenous methylprednisolone, given early after onset of relapse of multiple sclerosis (1 week). We took into account the weaknesses of previous trials to design the study, using a methodology that corresponds to Burton and colleagues's recommendations in the Cochrane review, to resolve the question of oral corticosteroids to treat multiple sclerosis relapses. We showed oral methylprednisolone was non-inferior to intravenous administration in reduction of disability after relapses at 28 days.

Implications of all the available evidence

These results provide strong arguments for the possibility of improving management of multiple sclerosis relapses. Oral delivery is simpler and less invasive, more convenient for a quick primary and community care response, and allows obvious savings in cost and logistics.

Corticothérapie Orale dans les Poussées de Sclérose en Plaques (COPOUSEP) non-inferiority trial to assess the effect of oral versus intravenous administration of high-dose methylprednisolone, given soon after relapse onset, on recovery from multiple sclerosis relapses.

Methods

Study design and participants

In this multicentre, randomised, double-blind, non-inferiority trial, we enrolled patients at 13 multiple sclerosis centres within hospitals in France. Eligible patients were aged 18–55 years with relapsing-remitting multiple sclerosis[18] fulfilling the 2005 McDonald criteria[19] and with an Expanded Disability Status Scale (EDSS) score of five or lower before the relapse that led to inclusion. Pre-relapse data were available in patients' files and the neurologist had to report it in the case report form at the screening visit. Because consensus is yet to be declared on the criteria for decisions about whether or not to treat relapses with corticosteroids, we defined the relapse of inclusion as follows: new or worsening neurological symptoms attributable to multiple sclerosis, lasting at least 24 h without pyrexia, responsible for an increase of at least one point in one or more scores on the Kurtzke Functional System Scale (FSS[20]; congruent with potential subjective complaints), and resulting in a score of two or higher on the most affected scale (≥3 on the sensory scale). So we did not miss the window of opportunity for successful treatment with corticosteroids, the first dose of methylprednisolone had to be given no more than 15 days after onset of a relapse, which was preceded by a period of stability of at least 1 month. Disease-modifying therapy was permissible, except for natalizumab, mitoxantrone, and cyclophosphamide. Key exclusion criteria were medical disorders that could interfere with participation in the study (diabetes, infection that was not controlled with an appropriate antibiotic therapy, psychiatric disorder, or pregnancy). Further exclusion criteria are listed in the protocol (appendix). Each patient could only be included once in the trial. The study was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice[21] and the principles of the Declaration of Helsinki.[22] Local ethics committees approved the protocol. All patients provided written informed consent at enrolment.

Randomisation and masking

We allocated patients to the oral or intravenous group using a computer-generated randomisation list in a one to one ratio with blocks of four. The randomisation list was centralised by the pharmacist of the principal investigation centre (Rennes University Hospital), who assigned the next number available on the list to each newly enrolled patient and informed the local centre's pharmacist of the treatment group allocation. All treatment boxes contained three bags of sterile saline (0·9% NaCl), plus either three bottles of methylprednisolone 1000 mg and 30 placebo capsules for the intravenous group or 30 capsules of methylprednisolone 100 mg for the oral group (so that all patients received an infusion and took ten capsules each day for 3 days). A nurse, separate from the one who gave the study drug, opened the box and prepared the infusion. Patients, treating neurologists, investigators assessing outcomes, nurses administering medication,

and personnel analysing the data were masked to treatment allocation. Because both intravenous and oral methylprednisolone can induce a metallic taste that could prevent the masking of patients and treating clinicians or nurses to treatment assignment, the nurse administering the drugs made sure that patients swallowed capsules just as the infusion started, ensuring any taste would occur at the same time.

Procedures

The matching capsules of placebo and methylprednisolone 100 mg were manufactured at the pharmacy of Rennes University Hospital. Each batch was checked by the pharmacist against the specifications of the European Pharmacopoeia (uniformity of mass and uniformity of content, using UV spectrophotometry to verify the uniformity of content).

Individual patients were assessed by the same treating neurologist throughout the study. The treating neurologist assessed the EDSS and FSS on day 1 just before the start of treatment; at days 3, 8, 28, and 180; and at any unscheduled visit when additional worsening before day 28 or a fresh relapse after day 28 was suspected. An additional worsening before day 28 (by at least one point on one or more FSS scores) warranted treatment with the allocated study drug for a further 2 days (given in the same procedure). At each scheduled visit, the treating neurologist had to determine whether a patient's recovery was complete and, if so, to indicate the date.

To assess safety, patients completed self-report questionnaires 24 h, 48 h, 72 h, 8 days, and 28 days after the start of treatment (available in appendix). They were asked to go through a list of symptoms commonly attributed to corticosteroid infusions and indicate which ones, if any, they experienced after being given the study treatment (metallic taste, hot flashes, headache, insomnia, agitation, anxiety, euphoria, gastric pain, nausea, vomiting, diarrhoea, palpitations, and chest pain). Additionally, up to the end of follow-up, treating neurologists reported any other unexpected or serious treatment-emergent adverse events, which were explored if necessary (physical examination, vital signs, and electrocardiograph; appendix). Patients with a history of digestive problems were given gastroprotective drugs and patients were given potassium supplementation if they had hypokalaemia or were on a concomitant treatment that could induce hypokalaemia. A specific drug (zolpidem 10 mg) for insomnia was systematically prescribed.

Outcomes

The primary endpoint was the proportion of patients in the per-protocol population who received 3 days of treatment (with no retreatment) who had improved by at least one point on the most affected FSS score by day 28. Secondary endpoints, measured over the 6 months after start of treatment of relapse that led to inclusion were a change in the overall EDSS score, the proportion of patients who improved by at least one EDSS point, the proportion of patients who recovered fully from the relapse, the time to total recovery, the proportion of relapse-free patients (no new relapse requiring corticosteroids), and the proportion of patients starting a disease-modifying therapy or switching to a different one. Quality of life was recorded and will be reported in a later report. These secondary outcomes included all patients in the per-protocol population, irrespective of whether they received retreatment with corticosteroids within 28 days.

Statistical analysis

The intention-to-treat and safety populations were defined as all randomly assigned patients who received at least one dose of any study medication. The study team monitored and classified protocol deviations, which were then validated by the data monitoring committee before database lock and before unblinding. The per-protocol population was composed of patients in the intention-to-treat population who had no major protocol deviations.

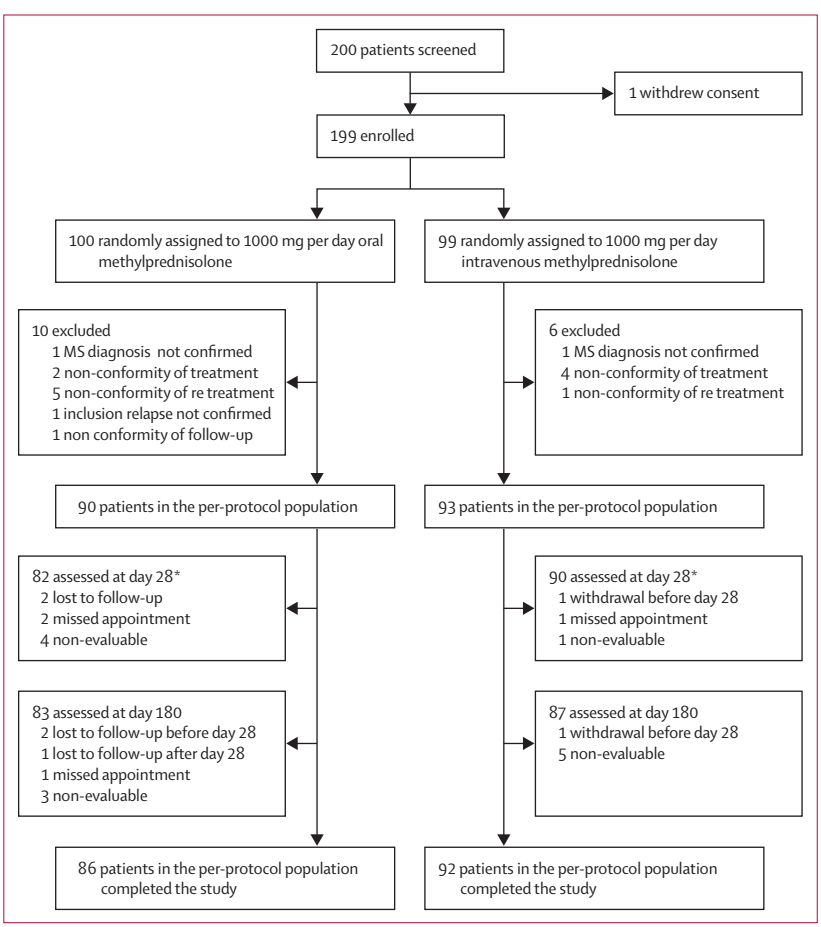

Figure 1: **Trial profile**
All randomly assigned patients were included in the intention-to-treat population. Non-conformity of treatment and retreatment was defined as changes in dose, duration, interruption, or retreatment with corticosteroids not according to the protocol considerations. No patients with missing data for the primary endpoint at day 28 were retreated with additional methylprednisolone before day 28. MS=multiple sclerosis.

	Oral methylprednisolone group (n=100)	Intravenous methylprednisolone group (n=99)
Median age (years)	35·0 (18·2-62·6)	34·7 (18·3–58·7)
Women	74 (74%)	74 (75%)
Time from MS onset to randomisation		
Median time (years)	6·2 (3·4–11·9)	5·7 (3·0–10·7)
0–2 years	18 (18%)	20 (20%)
2–5 years	19 (19%)	22 (22%)
>5 years	63 (63%)	56 (57%)
Median residual EDSS score before inclusion relapse	1·0 (0–2·0)	1·5 (1·0–2·0)
Relapses in the previous year		
Median number	0 (0–1)	0 (0–1)
0	60 (60%)	60 (61%)
1	29 (29%)	31 (31%)
2	7 (7%)	8 (8%)
≥3	4 (4%)	0
Baseline relapse		
Median time from relapse onset (days)	6·5 (4·0–9·5)	7·0 (4·0–10·0)
Most affected functional system		
Pyramidal	25 (25%)	33 (33%)
Sensory*	33 (33%)	26 (26%)
Cerebellar	10 (10%)	14 (14%)
Visual	13 (13%)	13 (13%)
Brainstem	19 (19%)	12 (12%)
Bowel and bladder	0	1 (1%)
Score of the most affected functional system		
Pyramidal	3·0 (2·0–3·0)	3·0 (3·0–3·0)
Sensory*	3·0 (3·0–3·0)	3·0 (3·0–3·0)
Cerebellar	2·0 (2·0–3·0)	2·0 (2·0–2·0)
Visual	2·0 (2·0–4·0)	2·0 (2·0–3·0)
Brainstem	3·0 (2·0–3·0)	3·0 (2·0–3·0)
EDSS score at inclusion	3·5 (3·0–4·0)	3·5 (3·0–4·0)
Change in EDSS score due to relapse	2·0 (1·0–3·0)	2·0 (1·0–2·5)
Disease-modifying therapy at inclusion	52 (52%)	55 (55%)
Interferon-beta	27 (27%)	31 (31%)
Glatiramer acetate	20 (20%)	21 (21%)
Mycophenolate mofetil	3 (3%)	1 (1%)
Azathioprine	1 (1%)	2 (2%)
Fingolimod	1 (1%)	0

Data are median (range) or n (%), unless otherwise stated. MS=multiple sclerosis. EDSS=Expanded Disability Status Scale. *Two patients had a score of two on the sensory functional system (most affected system) but were included due to a decision from the data monitoring committee.

Table 1: **Demographic and baseline characteristics**

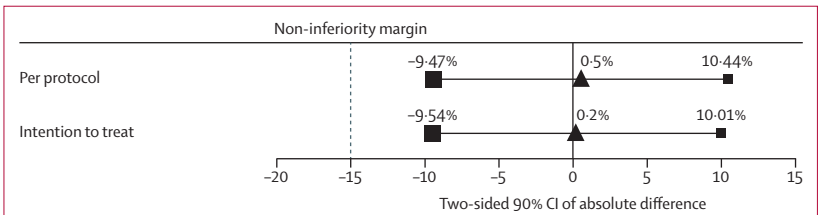

Figure 2: **Treatment differences for day 28 improvement of at least one point in the most affected functional system scale score without need for retreatment**
Difference is oral versus intravenous methylprednisolone.

Sample size was based on the primary efficacy endpoint in the per-protocol population who did not receive retreatment with corticosteroids. The predetermined non-inferiority margin δ was an absolute 15% difference (corresponding to a relative 18·75% difference) between treatment groups. Assuming a one-sided α of 0·05, a power of 80%, and an 80% proportion of patients improved at day 28 in the oral and intravenous groups (with no retreatment with methylprednisolone), 90 patients per group were needed. Assuming a 10% dropout rate, the required sample size was 200 patients.

The non-inferiority margin of 15% was set only for the primary endpoint. Oral methylprednisolone efficacy was to be judged non-inferior to intravenous methylprednisolone when the lower limit of the 90% CI (computed using Dunnett and Gent's[23,24] continuity corrected χ^2 for non-inferiority) of the absolute difference between the proportions of patients improved at day 28 was higher than –δ=–15%.

We summarised baseline clinical and demographic characteristics with descriptive statistics. For secondary outcomes, we summarised with descriptive statistics and then compared between treatment groups using the χ^2 test or Fisher's exact test (according to application conditions) for categorical variables, and the *t* test or Wilcoxon-Mann-Whitney test (according to application conditions) for continuous variables. We analysed time to total recovery with the Cox proportional hazards model, including treatment group as a factor, and provided the results as hazard ratios (HRs) with 95% CIs. We produced Kaplan-Meier plots for both time-to-event endpoints (time to first new relapse, time to total recovery). For participants who did not achieve the event, time to event was censored at the date of their last visit.

We compared numbers of relapses per patient using Poisson regression including the treatment group and follow-up duration. All the analyses of the primary and secondary endpoints were done for both the intention-to-treat population and the per-protocol population. In an amendment to the protocol made by the data monitoring committee before database lock and before unblinding, patients whose day 8, 28, and 180 visits were delayed (taking place after day 12, 45, and 270, respectively) were excluded from the day 8, 28, and 180 analyses. All patients with a recorded study end visit were deemed to have completed the study.

Adverse events were summarised per treatment group, and analysed as proportions, in terms of patients with adverse events and overall number of adverse events, using the χ^2 test for comparisons between the treatment groups. We also report presence of serious adverse events, their postulated correlation with treatment, and any resulting discontinuation.

All the analyses were done using SAS statistical software (SAS version 9.3). An independent data monitoring committee at Rennes University Hospital

reviewed study conduct and all safety data. This trial was registered with ClinicalTrials.gov, number NCT00984984.

Role of the funding source

The trial was designed independently of the sponsor and funders. Data were collected, analysed, and interpreted by the investigators, and the manuscript was edited and submitted totally independently of the sponsors and funders. SH had full access to data. ELP, DV, and GE were responsible for submission of the manuscript.

Results

Between Jan 29, 2008, and June 14, 2013, we enrolled 199 patients and randomly assigned 100 to oral methylprednisolone and 99 to intravenous methylprednisolone (figure 1). 96 (96%) patients assigned to the oral methylprednisolone group and 94 (95%) patients assigned to the intravenous methylprednisolone completed the study. 90 patients in the oral group and 93 patients in the intravenous group were included in the per-protocol population (figure 1). Protocol deviations that excluded patients from the per-protocol population were unconfirmed multiple sclerosis (n=2), unconfirmed inclusion relapse (n=1), non-conformity of treatment (different dose, duration, or interruption from the protocol; n=6), non-conformity of retreatment (retreatment with corticosteroids not following the protocol treatment scheme; n=6), and non-conformity of follow-up (incomplete data; n=1; figure 1).

Demographic and baseline characteristics were similar in the treatment groups (table 1) and representative of a relapsing-remitting multiple sclerosis population not receiving second-line disease-modifying therapy (table 1). The data monitoring committee allowed the inclusion of two patients with a score of two for the sensory system. The inclusion relapse was most frequently pyramidal or sensory, and caused an increase in the mean EDSS score of 2·1 points (SD 1·2) in the oral group and 1·9 (1·1) points in the intravenous group as compared with before the relapse. The 1000 mg of methylprednisolone was given a mean of 7·0 (SD 3·6) days after relapse onset in the oral group and 7·4 (3·9) days after relapse onset in the intravenous group (table 1). Seven (9%) of 82 patients in the oral group and 12 (13%) of the 90 patients were retreated for 2 additional days according to the protocol (p=0·31).

At day 28, 66 (81%) of 82 patients who received oral methylprednisolone improved by at least one point on the most affected FSS score without need for retreatment with corticosteroids versus 72 (80%) of 90 who received intravenous methylprednisolone. The absolute treatment difference was 0·5% (90% CI –9·5 to 10·4). The lower limit of the confidence interval for the absolute difference (–9·5) was higher than the –15% margin specified in the protocol (figure 2, table 2).

The proportion of patients whose score on the most affected FSS score improved by at least one point (irrespective of retreatment) was 72 (88%) of 82 in the

	Oral methylprednisolone group	Intravenous methylprednisolone group	Absolute difference (90% CI non-inferiority)	Difference (95% CI)	p value
Day 28					
Number assessed	82	90	..	..	..
Patients improved by at least 1 point on the most affected functional system scale without retreatment with methylprednisolone	66 (81%)	72 (80%)	0·5% (–9·5 to 10·4)	..	..
Patients retreated for 2 days	7 (8%)	12 (13%)	..	–5% (–19·7 to 10·1)	0·31
Patients improved by at least 1 point on the most affected functional system (irrespective of retreatment)	72 (88%)	84 (93%)	..	–5·5% (–20·3 to 9·5)	0·21
Patients improved by at least 1 EDSS point from baseline	63 (77%)	68 (76%)	..	1·3% (–13·7 to 16·2)	0·84
Patients fully recovered from the relapse	32 (39%)	40 (44%)	..	–5·4% (–20·2 to 9·6)	0·47
Change in EDSS score from baseline	–1·5 (1·0)	–1·3 (0·9)	..	–0·13 (–0·42 to 0·16)	0·57
Change in the most affected functional system scale from baseline	–1·7 (1·1)	–1·6 (0·8)	..	–0·05 (–0·34 to 0·24)	0·79
Day 180 (6 months)					
Number assessed	83	87	..	..	..
Patients improved by at least 1 EDSS point from baseline	65 (78%)	68 (78%)	..	0·2% (–14·9 to 15·3)	0·98
Patients fully recovered from the relapse*	59/90 (66%)	62/93 (67%)	..	–1·1% (–15·6 to 13·4)	0·87
Time to total recovery from the relapse (months)*†	1·8 (1·0–4·1)	1·3 (0·9–4·8)	..	0·97 (0·66–1·42)†	..
Change in EDSS score from baseline	–1·6 (1·0)	–1·5 (1·1)	..	–0·1 (–0·41 to 0·22)	0·69
Change in the most affected functional system scale from baseline	–2·1 (1·1)	–2·0 (1·1)	..	–0·2 (–0·49 to 0·18)	0·30
Number of relapses per patient, treated by methylprednisolone	0·4 (0·6)	0·3 (0·6)	..	0·02 (–0·15 to 0·19)	0·79
Relapse-free patients*	63/90 (70%)	67/93 (72%)	..	–2·0% (–16·6 to 12·3)	0·76

Data are n (%), mean (SD), median (IQR), and n/N (%), unless otherwise stated. HR=hazard ratio. EDSS=Expanded Disability Status Scale.*Of those to complete trial. †HR (95% CI).

Table 2: **Clinical outcomes in the per-protocol population**

oral group and 84 (93%) of 90 in the intravenous group (p=0·21). At day 28, EDSS score had improved by at least one point relative to baseline in more than three quarters of patients in both groups (table 2). The mean EDSS score improved by 1·5 (SD 1·0) for the oral group versus 1·3 (0·9) for the intravenous group. By day 28, 32 (39%) patients in the oral group and 40 (44%) patients in the intravenous group had fully recovered from the relapse (p=0·47; table 2). Results for the intention-to-treat population were similar to those in the per-protocol population (appendix).

Between day 28 and day 180, the mean number of new relapses in the per-protocol population that justified corticosteroids was 0·4 (SD 0·6) per patient in the oral group and 0·3 (0·6) per patient in the intravenous group and the proportion of patients free of relapse at this time was similar between groups (table 2). Results were similar in the intention-to-treat population (appendix).

Over the total follow-up period, in the per-protocol population, 59 (66%) of 90 patients in the oral group and 62 (67%) of 93 patients in the intravenous group recovered fully from the relapse (table 2). The median time to total recovery was 1·8 months (IQR 1·0–4·1) in the oral group and 1·3 months (0·9–4·8) in the intravenous group (HR 0·97, 95% CI 0·66–1·42; figure 3). Both the proportion of patients whose EDSS score improved by at least one point and the mean improvement EDSS score were similar between groups in both the per-protocol and the intention-to-treat population (table 2, appendix).

Because of the relapse leading up to inclusion in this trial, patients' therapeutic management could be modified during the study period. In the per-protocol population, 38 (42%) of 90 patients in the oral group and 36 (39%) of 93 patients in the intravenous group started or switched disease-modifying therapy. In the oral group, 19 (50%) of the 38 patients started or moved to a first-line therapy (interferon-beta or glatiramer acetate), and the other 19 (50%) started or moved to a second-line therapy (nine to fingolimod, six to natalizumab, three to mitoxantrone, and one to mycophenolate mofetil). In the intravenous group, 22 (61%) of the 36 patients started or moved to a first-line therapy, and the remaining 14 (39%) started or moved to a second-line therapy (five to fingolimod, four to natalizumab, four to mitoxantrone, and one to alemtuzumab). Findings were very similar in the intention-to-treat population (data not shown).

The overall incidence of treatment-emergent adverse events reported by patients until day 28 was similar in both groups, except for insomnia, which was reported by 77 (77%) of 100 patients in the oral group and 63 (64%) of 99 patients in the intravenous group (p=0·0390; table 3). Two moderate-to-severe adverse events potentially related to methylprednisolone were reported in the oral group (one case of nausea and vomiting, and one of profound depression), and ten moderate-to-severe adverse events potentially related to methylprednisolone were reported in the intravenous group (three cases of abdominal pain, one of vomiting, five of insomnia, and one of profound depression; table 3).

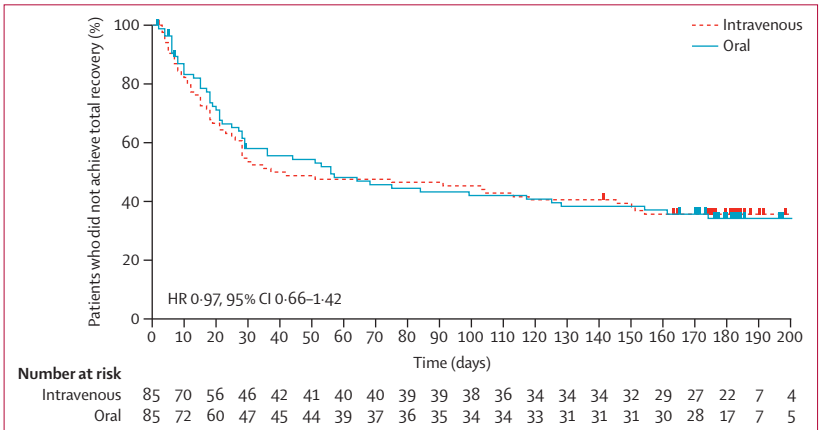

***Figure* 3: Kaplan-Meier curves for time to total recovery**
Kaplan-Meier estimates of time to total recovery in the per-protocol population. Dashes represent participants who did not achieve total recovery and were censored at the date of their last visit.

	Oral methylprednisolone (n=100)	Intravenous methylprednisolone (n=99)	p value
Patients with at least one adverse event	97 (97%)	97 (97%)	..
Metallic taste	75 (75%)	80 (81%)	0·32
Hot flashes	63 (63%)	58 (59%)	0·52
Headache	72 (72%)	63 (64%)	0·21
Insomnia	77 (77%)	63 (64%)	0·0390
Agitation	42 (42%)	29 (29%)	0·06
Anxiety	39 (39%)	37 (37%)	0·81
Euphoria	8 (8%)	11 (11%)	0·46
Epigastric pain	43 (43%)	45 (45%)	0·73
Nausea	32 (32%)	34 (34%)	0·73
Vomiting	14 (14%)	12 (12%)	0·69
Diarrhoea	23 (23%)	16 (16%)	0·22
Palpitations	36 (36%)	29 (29%)	0·31
Chest pain	18 (18%)	13 (13%)	0·34
Rash	28 (28%)	30 (30%)	0·72

Data are n (%), unless otherwise stated. Population is the intention-to-treat population.

***Table* 3: Adverse events reported at least once by patients on self-questionnaires completed each day after 1000 mg of methylprednisolone and until day 28**

Discussion

In this trial, we show that oral administration of high-dose corticosteroids was non-inferior to intravenous corticosteroids in improvement of disability scores 28 days after a relapse. In the 2012 Cochrane meta-analysis[12] for oral versus intravenous methylprednisolone, the authors underlined the insufficient power of available studies and pointed out other important methodological limitations, such as a time from onset of relapse to first dose of up to 1 month, by which time the resolution phase has already

spontaneously started.[13,14] There was also little reliable concealment of allocation or randomisation method, a failure to use bioequivalent dosing (oral regimen ten times lower than the intravenous one in the largest study[14]), and little evidence that an appropriate assessment was done. Only one study[16] used proper equivalence design techniques, but the patients and the clinical assessors of EDSS and adverse events were not masked to allocation. The authors concluded that none of the five trials showed a significant difference between the oral and intravenous administration of corticosteroids for the treatment of multiple sclerosis relapses, and recommended that future trials be done on a larger scale, and use an equivalence or non-inferiority design, as well as concealment of allocation, with definitive methods of randomisation, double blinding, and masking of interventions; clear and meaningful endpoints; and inclusion of relapses less than 1 month after onset. We designed the methods of the trial in accordance with these recommendations.

Because no consensus exists about which types of relapses justify corticosteroids, for the sake of rigour, we decided to focus on individual FSS scores rather than on the overall EDSS score (which can be stable even when a relapse has been confirmed[18,25]). To avoid mild relapses that might recover spontaneously, we established a criterion whereby the score on the functional system most affected by the exacerbation had to increase by at least one point, reaching a score of two or more, except for the sensory system, which had to reach a score of three or more (table 1). Our patients had significant relapses, mainly pyramidal or sensory, with the two relevant FSS scores reaching a median score of 3·0 (baseline) in both groups, and the EDSS increased by 2·0 points, reaching a median score of 3·5 (baseline) in the two groups. We used the same parameter to assess the primary outcome at 1 month, even though in the literature, the EDSS score is generally the primary outcome (either a variation from baseline or the percentage of patients whose score has improved by at least one point) that is compared between groups. In our study, the results did not vary much whether the measure was the most affected FSS score or the overall EDSS score. Patients with secondary progressive multiple sclerosis were not included to avoid confusion between the residual deficit from an exacerbation and underlying progressive disease.

Similar to previous trials,[15] we sought to assess the efficacy and safety of the 3 days of methylprednisolone 1000 mg that are commonly used for the treatment of multiple sclerosis relapses,[26] even if some researchers maintain that corticosteroid treatment should last for 5 days, rather than for 3 days.[13,16,27] As a result, patients could be treated for 2 extra days in the protocol, but were not included among those who reached the primary endpoint. However all the patients (treated for 3 days or 5 days) were included for secondary outcomes.

We did not compare exactly bioequivalent doses of methylprednisolone for oral and intravenous administration because all patients received 1000 mg per day (as in some other trials[13,16]), even though bioavailability is estimated to be 82% when the drug is given orally versus intravenously[17,28]—hence why some researchers have designed trials with 1250 mg[15] or 1400 mg[27] for oral doses and 1000 mg administered intravenously. We chose to use a dose that is classically recommended for multiple sclerosis relapses in the oral group, reasoning that if the hypothesis of non-inferiority were satisfied, taking ten tablets of methylprednisolone 100 mg (marketed in France for other neurological indications) would be appropriate to manage multiple sclerosis relapses in real life. In our study, the oral administration of corticosteroids was not associated with more frequent new relapses over the subsequent 6 months (figure 2), despite the absence of tapering as recommended after the ONTT study.[6–8]

We enrolled patients no later than 15 days after relapse onset so that we did not miss the hypothetical window in which oral and intravenous steroid therapy might differ in efficacy, with quite a short median time to treatment start of 7 days in both groups. Our data gave some insight into the benefits of early administration of high doses of methylprednisolone (oral or intravenous) for treating relapses. 64% (128 of 199) of the intention-to-treat population was deemed to fully recover up to 6 months, meaning that 36% (71 of 199) had persistent residual signs confirmed by the treating physician. When Lublin and colleagues[25] analysed patients from the placebo groups of two trials, 57% of the 140 patients having an EDSS increase during relapse had a residual deficit of at least 0·5 EDSS points for an average of 2 months after the relapse. However, the comparison should be cautious since the context of the study, the parameters analysed, and the period of assessment were different from ours. In our study, the median time to total recovery was 1·8 months in the oral group and 1·3 months in the intravenous group. This non-significantly quicker recovery in the intravenous group might be due to more patients (13% [12 of 90]) in the intravenous group being retreated with methylprednisolone before day 28 than in the oral group (8% [seven of 82]; figure 3).

We based our study solely on clinical parameters, and could not add an MRI assessment. In daily practice, MRI is not used for the diagnosis of relapse, with diagnosis remaining based on clinical symptoms. Nor is it used to decide whether corticosteroids should be used. A limitation of the study might be the absence of MRI, but we note that the real benefit (shortening the duration of relapse) and the usefulness of intravenous high-dose methylprednisolone for relapses was mainly documented on clinical grounds.[8] Furthermore, two randomised studies[15,16] (involving 50 patients and 40 patients, respectively) that used MRI as a surrogate outcome reported no significant difference between intravenous and oral methylprednisolone groups on MRI findings at 1 month.

In our study, the various specified adverse events were scored in self-questionnaires, which induces a greater incidence of adverse events than in spontaneous reporting. However, the tolerability was similar for both regimens, except for insomnia, which was more frequent in the oral group than in the intravenous group, even though patients could receive the corticosteroids at any time of day. This was also reported in the meta-analysis,[12] and might be due to prolonged bioavailability. We therefore recommend giving the oral treatment in the morning.

Our data support the use of oral methylprednisolone 1000 mg per day for 3 days to treat multiple sclerosis relapses. This finding could have implications for rapidity of access to treatment, patient comfort, and cost of the management of multiple sclerosis relapses. However, because oral administration is easier and cheaper, it might increase non-specialists' use of this treatment in a more liberal way, without thorough consideration of the indication.

Contributors

ELP and GE were the main investigators of this project, and participated in study design, enrolment of patients, data gathering, analysis, and interpretation, and revision of the report. DV participated in the literature search, conception, study design, statistical analysis, data interpretation, and manuscript writing. DAL participated in enrolment of patients, data interpretation, and writing the manuscript. SH was the statistician, provided data analysis, figures, and wrote the statistical section. RW, CL, FZ, SW, VD, and MC participated in enrolment of patients, data interpretation, and writing the manuscript. All authors have seen and approved the final version of the manuscript.

Declaration of interests

ELP received consultancy fees and non-personal research grants from Novartis, Biogen-Idec, Teva, and Genzyme Sanofi Aventis; DV declares grants from PHRC National–Ministry of Health, PREPS–Ministry of Health, Foundation de France, and Foundation ARSEP; DAL declares grants from Foundation ARSEP, grants and personal fees from Biogen, personal fees from TEVA Pharma, grants and personal fees from Novartis, and personal fees from Genzyme; MC reports personal fees from Biogen and personal fees from Teva Pharma, Novartis, and Genzyme; SW received personal fees from Biogen, Genzyme, and Novartis; RW received grants from Foundation ARSEP; GE reports grants and personal fees from Merck Serono, grants and personal fees from Teva Pharma, personal fees from Biogen, grants and personal fees from Novartis, personal fees from Sanofi; all outside the submitted work. SH, CL, FZ, and VD declare no competing interests.

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