High-dose oral methylprednisolone for the treatment of multiple sclerosis relapses: cost-minimisation analysis and patient's satisfaction

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ABSTRACT

Objective To study the use of high-dose oral methylprednisolone compounded formulation and intravenous methylprednisolone for the treatment of multiple sclerosis relapses. To compare both routes of methylprednisolone administration related to cost and patient's satisfaction with the treatment.

Methods A retrospective cohort observational study was performed from January 2012 to December 2016. All multiple sclerosis relapses treated with high-dose oral methylprednisolone compounded formulation or intravenous methylprednisolone were studied. Patient's acceptance grade of the treatment was analysed with a survey based on the Treatment Satisfaction Questionnaire for Medication. A cost-minimisation analysis using real world data from our hospital was performed to compare the high-dose oral methylprednisolone formulation and intravenous administration.

Results 92 patients were included (88% had recurrent remitting multiple sclerosis). Median Expanded Disability Status Scale score was 2 (IRC: 1–3.5). 162 relapses were treated: 77 with intravenous methylprednisolone and 85 with high-dose oral methylprednisolone formulation. The most frequent prescriptions were 1000 mg intravenous methylprednisolone and 1250 mg oral methylprednisolone during 4 days. Recovery from relapse was achieved in 91% of patients in the intravenous group and 93% in the oral group. The survey revealed that 79% of patients preferred the oral route because of convenience (P<0.001) and global satisfaction (P<0.04). Real world data demonstrated savings of €61 708 (91%) using the high-dose oral methylprednisolone formulation during the study period.

Conclusions High-dose oral methylprednisolone compounded formulation was a cost-effective alternative compared with methylprednisolone intravenous administration. Moreover, patients with multiple sclerosis preferred the oral compounded formulation for the treatment of relapses.

INTRODUCTION

Multiple sclerosis (MS) is a multifocal demyelinating disease leading to progressive neurodegeneration caused by an autoimmune response in genetically predisposed individuals.[1] It 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.[2] MS has a high impact on a patient's life because it is the neurological disease that most frequently causes disability in young adults who require care and expensive treatments.[3]

Disease-modifying therapies (DMT) have decreased the risk of accumulation of new focal lesions, but when relapses occur, high-dose intravenous corticosteroids are commonly used.[4] Nowadays, high-dose intravenous steroid treatment is one of the best therapies available to induce accelerated remission from an MS attack, and to limit the residual neurological deficits.[5 6] Clinical guidelines recommend 500–1000 mg intravenous methylprednisolone (MP) for 3–5 days. Unfortunately, the intravenous administration of steroids requires that patients be admitted to hospital with the consequent personal burden and institutional costs. Moreover, intravenous therapy is associated with indirect costs such as loss of productivity and work-force-related costs, as well as increased patient discomfort.[7]

A recent Cochrane meta-analysis[8] addressed whether the efficacy of oral versus intravenous administration of steroids differed. Despite some limitations related to the number of patients and trials, and the heterogeneity of design and methodology, the analysis did not show any significant difference in clinical, radiological or pharmacological outcomes. On this basis, oral steroids seem to be an appealing treatment for acute relapses of MS. The major concerns about the studies reviewed were the time window between the onset of symptoms and the beginning of treatment (1 month), the absence of reliable randomisation methods or concealment of allocation, an inadequate blinding of participants and assessors, and finally, only one study used proper equivalence design techniques.[7]

Emmanuelle Le Page and colleagues[4] published the COPOUSEP study, a double-masked, randomised, non-inferiority study at 13 centres in France. The objective was to compare oral and intravenous MP at 1000 mg per day for 3 days, and at day 28, assessed for improvement on the Kurtzke Functional System Scale, the trial's primary endpoint. a total of 81% of the patients in the oral MP group and 80% of the patients in the intravenous group had an improvement of at least one point on the Kurtzke Functional System Scale (absolute treatment difference 0·5%, 90% CI −9·5 to 10·4), meeting the study's predetermined criterion for non-inferiority. The safety and tolerability profile of the two routes of MP administration also did not differ. Recently, Luo *et al* published another meta-analysis in which no significant differences

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were found in terms of clinical (benefits and adverse events), radiological and pharmacological outcomes in MS relapses in patients after oral or intravenous steroid treatment.[9]

In Spain, formulations of high-dose steroids for oral administration are not available. For this reason, pharmacists developed a high-dose oral MP compounded formulation for the treatment of MS relapses in our hospital. The purpose of this paper is to demonstrate with real world data that treating MS relapses with a high-dose oral MP formulation instead of intravenous MP administration may contribute to important savings in costs and logistics with a high patient satisfaction. Moreover, a comparative study of both routes of MP administration was included to confirm with real world data the non-inferiority of the high-dose oral MP formulation as it is described in the aforementioned literature.

METHODS

A retrospective cohort observational study was performed at Guadalajara Integrated Management Area in Spain from January 2012 to December 2016. This healthcare area includes one university hospital with a neurological department. Treatment of MS relapses was analysed by comparing intravenous MP administered at the day hospital with a high-dose oral MP compounded formulation self-administered by the patient at home.

All patients with MS who received at least one dose of intravenous MP at the day hospital or the high-dose oral MP compounded formulation to treat relapses were included in the study. Relapse was defined as follows: new or worsening neurological symptoms attributable to MS, lasting at least 24 hours without pirexia.

The clinical data recorded were demographics (gender, age), MS subtype, duration of MS, health state defined by the Expanded Disability Status Scale (EDSS), use of DMTs, first or second line DMTs, intravenous MP dose (mg), oral MP dose (mg), side effects, treatment duration (days) and recovery from relapse. Recovery from relapse was defined as no visit to the emergency department because of neurological symptoms for 1 month after receiving MP treatment (oral or intravenous). All data were collected from electronic clinical history and pharmaceutical records.

Treatment of relapses consisted of 1000 mg MP infusion in 100 mL saline fluid for 3–5 days at the day hospital. A high-dose oral MP compounded formulation was elaborated and dispensed by the hospital pharmacist to be self-administered by the patient at home. The oral formulation consisted of 30 mL of MP (625 or 1250 mg) for 3–5 days.

A satisfaction survey was performed to find out the patient´s acceptance grade of the treatment. The survey was designed by the hospital pharmacist based on the Treatment Satisfaction Questionnaire for Medication (TSQM).[10] The TSQM assesses the patient's treatment satisfaction for chronic diseases and is a useful tool for measuring treatment satisfaction in patients with MS.[11] Two additional questions were included to test the administration route preferred by the patients and the complete resolution of the relapse after the treatment.

Costs of relapse treatment considering the route of administration were analysed. The Hospital Analytical Account Department and Pharmacy Department provided costs. Intravenous MP administration cost was calculated considering the cost of medication and the day hospital admission rate, which included staff salary, structural and intermediate costs. The cost of the high-dose oral MP compounded formulation included MP, elaboration, packaging and pharmacy staff salary. An exhaustive study was carried out to calculate the cost of each individual relapse considering the route of administration. Total costs and average per year cost were obtained from this study. Cost calculations were annualised and reported in EUR 2016.

Cost-minimisation analysis (CMA) is a tool used in economic evaluation to compare the cost per course of treatment when alternative therapies have demonstrably equivalent clinical effectiveness. If equivalent efficacy is confirmed in our study, a CMA will be chosen to compare both therapeutic options.

Baseline characteristics were described using median and IQR (continuous data) and by percentage (categorical data). Mean and SD were used in the case of normal distribution (continuous data). To compare qualitative variables, the χ^2 test (or Fisher's exact test if the expected counts were below five) was used. A t-test or ANOVA (Mann–Whitney U test or Kruskal Wallis test in the case of non-normal distribution) was used to compare quantitative variables.

The study was powered to assess non-inferiority of oral MP compared with intravenous MP with a predetermined non-inferiority margin of 15%, as in the COPOUSEP study.[4] Oral MP efficacy was judged to be non-inferior to intravenous MP when the lower limit of the 95% confidence interval (CI) of the absolute difference between the proportions of patients who had complete resolution of relapsing disease was higher than $\delta = -15\%$.

Factors associated with recovery from relapses were assessed using univariate and multivariate logistic regression models. Odds ratios (ORs) were reported with 95% CIs. In the multivariate models, the OR was adjusted for sex, age, EDSS, days of treatment, line of treatment and oral versus intravenous MP treatment. All the tests were two tailed and the statistical significance was considered if the P value was less than 0.05. All analyses were conducted with STATA V.15.0 (STATA Corp, College Station, Texas, USA). The local ethics committee approved the study. All patients provided written informed consent at enrolment.

RESULTS

During the study period, 92 patients with MS received treatment for relapses. The median age was 41 years (interquartile range (IQR): 35–46). A total of 77% of the patients were women and 88% had remitting relapsing multiple sclerosis (RRMS). Median EDSS was 2 (IQR: 1–3.5). Thirty-nine patients were treated with intravenous MP at the day hospital, 38 patients received the high-dose oral MP compounded formulation at home, and 15 patients received both treatments, intravenous and oral MP. Clinical and demographic characteristics of the patients are described in table 1. All treatment groups were similar in terms of age, gender, MS subtype, duration of MS and EDSS. No statistical significances were found between treatment groups ($P > 0.05$).

During the study period, 162 patients with MS relapses received treatment: 77 with intravenous MP at the day hospital and 85 with the high-dose oral MP compounded formulation at home. Relapses are described in table 2. It is important to note that both treatments, intravenous MP and the high-dose oral MP compounded formulation, were always administered in the morning to avoid insomnia. One patient on high-dose oral MP discontinued the treatment due to nausea and vomiting and another patient because of a psychotic attack. All patients in the intravenous MP group completed the prescribed treatment.

According to recovery from relapse, oral MP was 2% better than intravenous MP (95% CI: −6.4% to 10.4%; P=0.634).

Table 1 Clinical and demographic characteristics of the patients

	Intravenous group	Oral group	Oral and intravenous group	P value
Patients (n)	39	38	15	–
Women (%)	29 (74.4%)	25 (65.8%)	11 (73.3%)	0.689
Men (%)	10 (25.6%)	13 (34.2%)	4 (26. 7%)	
Median age, years (IQR)	42.5 (35.5–49.5)	44 (36.3–49.5)	47.5 (41.5–50.5)	0.359
MS subtype (%)				0.911
RRMS	35 (89.7%)	33 (86.8%)	13 (86.7%)	
SPMS with relapses	4 (10.3%)	5 (13.2%)	2 (13.3%)	
Duration of MS, median years (IQR)	10.5 (6.5–16.5)	9 (3.5–14.3)	13.5 (8.5–15.5)	0.267*
Median EDSS (IQR)	2 (1–3.2)	1.7 (1–2.7)	3.5 (1.3–5.2)	0.061*

Data are median (IQR) or n (%).
*Kruskal Wallis test used.
EDSS, Expanded Disability Status Scale; IQR, interquartile range; MS, multiple sclerosis; RRMS, remitting relapsing multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

The non-inferiority of oral MP was confirmed with these data (the lower limit of the 95% CI was higher than δ=−15% considered in methods).

A multivariate adjustment was made using logistic regression (table 3). This analysis included the recovery from relapses as a dependent variable, and as independent variables: route of MP administration (oral vs intravenous), EDSS, gender, age, days of MP treatment, DMT line of treatment (first vs second line). Route of administration of MP did not predict the recovery from relapses.

During the study period, the adverse effects of MP were registered. There were no statistical differences between treatment groups considering the route of MP administration, except for mood changes (more frequent in the intravenous MP group). Data are included in table 4.

The satisfaction survey was answered by 79 patients (86%). The TSQM (version 1.4) comprises 14 items across four domains focusing on effectiveness (three items), side effects (five items), convenience (three items) and global satisfaction (three items). The results from TSQM are presented in table 5. With the exception of item 4 (presence of side effects: yes or no), all items have five or seven responses, scored from one (least satisfied) to five or seven (most satisfied). Item scores are summed to give four domain scores. Domains are scaled to a maximum score of 100 according to Vermersch *et al*.[11] Item 4 was not included in the scoring, and was answered by 29 patients in group 1 and 26 patients in group 2.

The satisfaction survey showed that 79% of patients preferred oral MP administration to intravenous MP for the treatment of MS relapses. The main problem for the majority of patients was the bitter flavour of the oral MP compounded formulation.

Total cost of relapses was calculated considering real world data of the Guadalajara Integrated Management Area. The Hospital Analytical Account Department provided the cost of intravenous MP infusion at the day hospital. This cost included staff salary, structural and intermediate costs. From 2012 to 2016, the day hospital admittance rates were: €206, €210, €198, €203 and €240 respectively. Direct acquisition cost of a 1000 mg MP vial (€10.74) and 100 mL saline fluid (€0.60) were included with no variation during the study period. The daily intravenous MP administration cost was €217, €221, €209 and €251 from 2012 to 2016.

The cost of the high-dose oral MP compounded formulation was calculated considering MP acquisition cost, elaboration, packaging and pharmacy staff salary. The daily costs of 625 mg MP oral formulation were: €8.77, €9.31, €9.35, €9.28 and €9.33 from 2012 to 2016, respectively. The daily costs of the 1250 mg MP oral formulation were: €17.89, €18.43, €18.47, €18.40 and €18.44 during the study period.

To study the cost of both MP routes of administration, individual costs were calculated for each relapse, taking into account dosage, treatment duration and the above-mentioned costs. For each year, the average cost of relapses was calculated by dividing

Table 2 Relapses in patients treated with intravenous or the high-dose oral MP compounded formulation

	Group 1 (intravenous MP)	Group 2 (high-dose oral MP)	P value
Relapses (n)	77	85	–
Recovery from relapse (%)	70 (91)	79 (93)	0.774
Relapses without DMTs (%)	12 (16)	38 (44)	0.053*
Relapses with first-line DMTs (%)	47 (61)	22 (26)	
Relapses with second-line DMTs (%)	18 (23)	25 (30)	
Relapses (n) (MP dose)	77 (1000 mg)	9 (625 mg) 76 (1250 mg)	–
Median treatment duration days (IQR)	4 (3–5)	4 (3–5)	0.597

*Linear by linear association.
High-dose oral MP: high-dose oral metilprednisolone compounded formulation. First-line DMTs: interferon, glatiramer acetate, teriflunomide and dimethylfumarate; second-line DMTs: natalizumab and fingolimod.
DMT, disease-modifying therapy; IQR, interquartile range; MP, metilprednisolone.

Table 3 Multivariate analysis

Dependent variable: recovery from relapses			
	Sig.	OR	95% CI for OR
Oral MP vs intravenous MP	0.827	0.872	0.255 to 2.978
EDSS	0.255	1.251	0.851 to 1.838
Gender (male)	0.844	1.148	0.29 to 4.544
Age (years)	0.986	1.001	0.936 to 1.07
Days of MP treatment	0.111	0.594	0.313 to 1.127
Line of treatment (first–second)	0.777	1.133	0.477 to 2.692
Constant	0.035	51.89	

First-line DMTs: interferon, glatiramer acetate, teriflunomide and dimethylfumarate; second-line DMTs: natalizumab and fingolimod.
95% CI, 95% confidence interval; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MP, methylprednisolone; OR, odds ratio; Sig., significance.

Table 4 Adverse effects of methylprednisolone

Adverse effects (%)	Group 1 (intravenous MP), %	Group 2 (high-dose oral MP), %	P
Digestive disturbances	10	5	0.388
Nausea and vomiting	12	6	0.417
Skin rash	17	6	0.085
Swelling of extremities	14	12	0.648
Headache	12	7	0.578
Insomnia	13	7	0.417
Weight gain	9	5	0.552
Mood changes	23	8	0.001
Others	6	11	0.411

MP, methylprednisolone.

the cost of all relapses by the number of relapses for both routes of administration, intravenous and oral. Data are included in figure 1.

As equivalent efficacy had been confirmed for both treatments with real world data in our study, a CMA was done. During the study period, the total cost of 77 relapses treated with intravenous MP was €67 587 while the total cost of 85 relapses treated with the high-dose oral MP formulation was €6149. This result showed that use of the high-dose MP compounded formulation was 91% (P<0.001) cheaper than intravenous MP for the treatment of MS relapses.

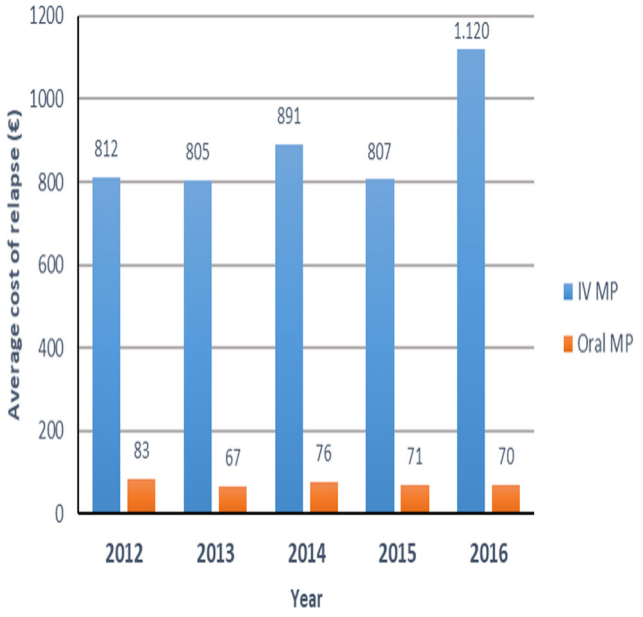

Figure 1 Average cost of methylprednisolone (MP) relapse (€).

DISCUSSION

The majority of the study population consisted of young women with RRMS. Related to disability grade, most patients had a mild EDSS and were treated with DMT mainly in the intravenous MP group. This is similar to recent data published in Spain by Oreja-Guevara and Kobelt *et al*: a larger proportion of patients with RRMS in the early stages of the disease with less disability. The availability of DMT has led to changes in patient management and to focus on earlier and better diagnosis and adjustments in the diagnostic criteria.[12] Nearly half of the relapses in the high-dose oral MP group did not have DMT because it was the debut of MS.

In the present study, with respect to the outcome of complete resolution of relapse, there were no differences between the high-dose oral MP group and the intravenous MP group. The statistical analysis showed that oral MP was non-inferior to intravenous MP. This is similar to data published in previous studies.[4 8 9 13–17]

The most frequent dose of oral MP was 1250 mg, which is equivalent to 1000 mg of intravenous MP because oral MP[14] biodisponibility is 80%. In the study by Le Page and colleagues, 10 tablets were needed to reach the cumulative daily dosage of 1000 mg of MP. In our study, patients received 625–1250 mg of MP in a 30 mL oral compounded formulation. We consider that this formulation is easier and more convenient for the patients than 10 tablets. One of the major advantages of oral administration is the shortening of the time interval between onset of relapse and treatment.

Although one important limitation of our study is the absence of MRI data to support the clinical findings, previous studies have consistently shown the effects of high-dose steroids on clinical and MRI measures.[14 17]

The main innovation of this paper is the patient´s satisfaction study with the route of MP administration. For this purpose, we designed a satisfaction survey based on the TSQM. The TSQM showed that the effectiveness of intravenous MP or the high-dose oral MP formulation was similar for patients, but convenience and global satisfaction were better in the oral MP group with statistical significance. The satisfaction survey showed a high grade of acceptance of the oral MP compounded formulation compared with the intravenous MP infusion. The explanation for this is that the oral MP formulation allows a more convenient patient self-administration treatment instead of going to hospital for 3–5 days to receive an MP infusion. Moreover, the oral formulation avoided contact with needles, which was a problem for some patients. The side effects reported by patients were similar in both the oral and the intravenous MP treatment groups: digestive disturbances, nausea and vomiting, skin rash, swelling of extremities, headache and insomnia. Only mood changes were more frequent in the intravenous MP group.

The main inconvenience for the oral compounded formulation was its bitter flavour. A possible solution would be to develop high-dose MP gelatine capsules at the pharmacy laboratory. These gelatine capsules would mask the MP's bitter flavour. The hospital pharmacy could elaborate MP gelatine capsules in advance for the emergency department. This would allow them to start treating MS relapses without delay and patients would continue relapse treatment at home.

Related to the CMA, our data suggested that the use of the high-dose oral MP compounded formulation has allowed important cost savings in the treatment of MS relapses compared with intravenous MP administration with high patient satisfaction in our health integrated management area. In one study from Canada,[18] the estimated mean cost of a MS relapse is

Table 5 TSQM (version 1.4) results

	Group 1 (intravenous MP)	Group 2 (high-dose oral MP)	P value
Effectiveness	82.6 (19.3)	81.6 (24.2)	0.829
Adverse reactions	48.3 (20.4)	60.0 (23.3)	0.052
Convenience	63.0 (18.7)	91.3 (11.2)	<0.001
Global satisfaction	76.1 (18.6)	84.3 (20.3)	0.04

Data presented as mean (SD).
TSQM, Treatment Satisfaction Questionnaire for Medication.

€4203, which is in line with a European[19] multicentre study. Recently Oreja-Guevara[12] *et al* estimated the average cost of a relapse for patients with an EDSS between 0 and 6 at €2044 in Spain. However, this cost includes steroid treatment and additional costs (informal care, long-term sick leave, short-term employment absence, tests, consultations).

Despite accumulating evidence for the equal effects of intravenous and oral high-dose steroids, oral administration has not entered clinical practice, except in a few countries, and is mostly not considered as a treatment scheme for relapses in clinical trials, perhaps because in most countries formulations of high-dose steroids for oral administration are not available.[7]

To our knowledge, this is the first study that has evaluated patients' satisfaction with the route of administration of corticosteroids for the treatment of relapses of MS. Based on the TSQM questionnaire, we have found that convenience and global satisfaction were better in the oral MP group.

In our experience, the high-dose oral MP compounded formulation has been a cost-effective alternative to intravenous MP for the treatment of MS relapses with relevant advantages for both patients and the community. The choice of oral rather than intravenous steroid therapy results in savings to the healthcare system. Oral delivery is simpler and less invasive, more convenient for the patient and allows obvious savings in costs and logistics. The hospital pharmacy may contribute to helping the healthcare system to optimise costs in the management of MS relapse treatment.

What this paper adds

What is already known on this subject

- Multiple sclerosis (MS) relapses are usually treated with intravenous steroids, although high-dose oral steroids have similar effects.
- Most countries do not have high-dose oral methylprednisolone (MP) formulations available.

What this study adds

- Patients with MS prefer high-dose oral MP to intravenous MP administration for the treatment of MS relapses.
- Real world data demonstrated savings of 91% using a high-dose oral MP formulation.
- The high-dose oral MP formulation elaborated by the hospital pharmacy is a cost-effective alternative to intravenous MP and may contribute to important cost savings for the healthcare system.

Contributors AMH-H was responsible for the planning and design of the study. AMH-H, EM-A and MB-C were responsible for data collection. AMH-H and AA-N were responsible for collecting patient's satisfaction survey. MT was responsible for statistical analysis. AMH-H wrote the first draft. BE-I, AY-I and MT provided critical revision; all authors read and approved the final manuscript.

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