Methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN study): a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial

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Summary

Background Interferon beta is commonly used to treat patients with relapsing-remitting multiple sclerosis; however, the treatment is only partially effective in reducing relapses and progression of disability. Corticosteroids are used to treat relapses in patients with multiple sclerosis. We therefore aimed to investigate the combination of cyclic methylprednisolone and interferon beta for the treatment of relapsing-remitting multiple sclerosis.

Methods In 2001, we designed a multicentre, double-blind, randomised, parallel-group trial, termed the methylprednisolone in combination with interferon beta-1a for relapsing-remitting multiple sclerosis (MECOMBIN) study. Patients were recruited between October, 2002, and March, 2005 from 50 neurology departments in eight countries. We included treatment-naive patients with relapsing-remitting multiple sclerosis who had an expanded disability status scale (EDSS) score of 4 or less. Patients all started to receive interferon beta-1a and after 3 months were randomly assigned to add-on methylprednisolone or placebo 500 mg/day orally for 3 consecutive days per month for 3–4 years. Placebo tablets were identical to methylprednisolone tablets. Treating physicians, examining physicians, and patients were masked to treatment allocation. Patients were clinically assessed every 3 months and had brain MRI at baseline and 3 years later. The primary outcome was time to onset of disability progression, according to an increase in EDSS score sustained over 6 months. All patients who received at least one dose of study drug were included in all planned analyses. This trial is registered with ClinicalTrials.gov, NCT00168766.

Findings 341 patients were randomly assigned to methylprednisolone (n=172) or placebo (n=169); 171 patients in the methylprednisolone group and 167 in the placebo group received at least one dose of study drug. 90 patients had sustained disability progression: 44 of 167 in the methylprednisolone group and 46 of 171 in the placebo group. The time to sustained progression did not differ between groups (hazard ratio 0·879, 95% CI 0·566–1·365; p=0·57). There were 1436 adverse events, 24 of which were serious, in the methylprednisolone group and 1070 events, 35 of which were serious, in the placebo group.

Interpretation Monthly pulses of methylprednisolone in combination with interferon beta-1a do not seem to affect disability progression any more than interferon beta-1a treatment alone. More research is required to assess whether this treatment regimen might benefit particular subsets of patients.

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Introduction

Since 1993, interferon beta has been commonly used in the treatment of relapsing-remitting multiple sclerosis. Treatment with interferon beta is safe but only partially effective, and hence better treatments are needed. Since the 1950s, corticosteroids have been used to treat relapses in patients with multiple sclerosis. The efficacy of both intravenous and oral high-dose regimens of corticosteroids have been reported.[1,2] Milligan and colleagues[2] reported a 73% improvement on the expanded disability status scale (EDSS) at week 4 in patients who received intravenous methylprednisolone and a 29% improvement in patients on placebo. A randomised trial reported a decrease in disease progression and brain atrophy in patients with multiple sclerosis treated with cyclic methylprednisolone intravenously compared with those treated with methylprednisolone at relapses only.[3] In addition, corticosteroids and interferon beta seem to have synergistic effects in multiple sclerosis.[4,5] We therefore decided to do a randomised clinical trial to investigate whether the combination of cyclic methylprednisolone treatment and interferon beta is more effective than interferon beta alone in suppressing disability progression in patients with relapsing-remitting multiple sclerosis.

Methods

Patients

In 2001, we designed this multicentre, randomised, placebo-controlled, parallel-group trial termed the methylprednisolone in combination with interferon beta-1a for

relapsing-remitting multiple sclerosis (MECOMBIN) trial. Patients were recruited between October, 2002, and March, 2005, from 50 centres in eight countries (Norway, Sweden, Finland, Denmark, the Netherlands, Belgium, Switzerland, and the UK). Inclusion criteria were age 18–55 years; diagnosis of relapsing-remitting multiple sclerosis according to the Poser[6] or McDonald[7] criteria; clinical disease activity, defined as at least one reported or documented relapse within the past year; and an EDSS score of 4 or less at baseline. Patients were excluded if they had other diseases for which the use of methylprednisolone was contraindicated or that would interfere with the clinical assessments, were addicted to alcohol or drugs, were pregnant or breastfeeding, had severe depression, or had had a multiple sclerosis relapse within 1 month before baseline. Women who were not postmenopausal or who had not had surgical sterilisation had to use reliable contraception.

The study was approved by the local scientific ethics committees and was overseen by a steering committee, and patients provided signed informed consent as part of the inclusion criteria.

Randomisation and masking

Patients started to received interferon beta-1a 30 µg intramuscular once weekly at baseline (month 0) and were randomly assigned to treatment after a run-in period of 3 months. The randomisation sequence was computer generated in 150 blocks of four (two methylprednisolone and two placebo) with sealed treatment randomisation codes kept at the sites and the clinical research organisation (aCROnordic, Hørsholm, Denmark). We used the two-physician principle: a treating physician took care of the patient and did a general physical examination and an examining physician assessed the patient on the EDSS[8] and the multiple sclerosis impairment scale (MSIS).[9,10] The multiple sclerosis functional composite (MSFC) assessment was done by a nurse at each site who was masked to treatment allocation. Treating physicians, examining physicians, and patients were also masked to treatment allocation. Methylprednisolone and placebo tablets were sugar coated and were identical in size and shape. Patients were instructed not to tell the examining physician about relapses, progression, or adverse events.

Procedures

Patients remained on interferon beta-1a and were randomly assigned to monthly pulses of 500 mg/day oral methylprednisolone (methylprednisolone group) or placebo (placebo group) for 3 consecutive days. After the baseline visit, patients attended a study visit every 3 months. Patients were assessed on the EDSS and MSIS every 3 months and on the MSFC and fatigue severity scale every 6 months. Patients were followed up for at least 3 years and a maximum of 4 years after randomisation (plus a possible 3-month period to confirm sustained disability).

The primary outcome was the time to sustained disability progression, defined as an increase sustained for 6 months of at least 1 point if the EDSS score was 1 or more at randomisation or at least 1·5 points if the EDSS score was 0 at randomisation.

Secondary outcomes were mean change in the MSFC score[11] from randomisation to the end of the study, annualised relapse rate from randomisation to the end of the study, and absolute change in brain parenchymal fraction[12] on MRI from baseline to month 39.

Patients who had new neurological symptoms were instructed to report by telephone to the treating physician within 3 days and to visit the study site within 10 days of onset. A reported relapse was defined as new or worsening neurological symptoms or signs in the absence of fever, persisting for more than 48 h, and with a previous stable or improving condition for more than 30 days. A relapse was defined as documented when the deterioration was equivalent to an increase of at least 1 point on the EDSS in two functional systems (the pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, or others), an increase of 2 points in one functional system, or an increase of at least 0·5 points on the EDSS. Changes in bowel and bladder or cerebral functional systems alone were not documented as a relapse. Relapses were treated with 1 g methylprednisolone intravenously daily for 3 days at the investigator's discretion.

We also did several prespecified exploratory analyses. We assessed the mean change in the MSIS and the integrated disability status scale (IDSS) score (defined as the area under the EDSS curve).[13] Fatigue was investigated by completion of the self-rated fatigue severity scale questionnaire[14] every 6 months. In further exploratory investigations, we assessed T1 and T2 lesions at baseline and month 39 on MRI.

For MRI investigations, we obtained 3 mm axial images (field of view 250 mm; matrix 256×256) by use of a T1-weighted spin-echo sequence (50 slices) before and after gadolinium contrast injection, a proton-density and T2-weighted turbo-spin-echo sequence (50 slices), and a fluid-attenuated inversion recovery sequence (34–50 slices). All 2D images from both baseline and month 39 were co-registered and re-sliced to the T2-weighted image of the baseline session by use of the Statistical Parametric Mapping 2 toolbox (SPM2; University College London, London, UK). To analyse brain atrophy, we obtained a 3D T1-weighted gradient-echo sequence (128–192 slices of 1·0–1·3 mm, field of view 250 mm, matrix 256×256).

A central reading centre (Danish Research Centre for Magnetic Resonance, Hvidovre, Denmark) did all MRI-related analyses. A trained technician manually delineated the T2 lesions on the fluid-attenuated inversion recovery images and marked gadolinium-enhancing lesions on T1 images. All lesions were checked by a physician with

experience in multiple sclerosis, and both the technician and physician were masked to treatment allocation. We used the delineated T2 lesions to calculate lesion volumes and the number of new or enlarging lesions, and the marked T1 lesions to calculate the number of enhancing lesions. On follow-up images we defined a lesion as new if it did not overlap with any lesions on the baseline images, and enlarging if the volume had increased by 50% compared with overlapping lesions on baseline images. We estimated brain parenchymal volumes and brain parenchymal fractions with automated segmentation software (FAST). We used SIENA 2.4 to estimate the percentage change in brain volume between baseline and month 39. Both programs are part of the FMRIB software library version 3.3.11 (FMRIB, Oxford, UK).

To assess treatment safety, we did an adrenocorticotropic hormone stimulation test to measure plasma cortisol and measured bone density with dual-energy x-ray absorptiometry scans of the lumbar spine at randomisation and month 39.[15] Glucocorticoid-induced bone mineral loss occurs early after treatment onset and is particularly rapid over the first 2–3 months.[16] Likewise, risk of bone fracture becomes clinically evident over the first 3–6 months. Therefore, as an amendment to the protocol, we did a masked interim analysis of dual-energy x-ray absorptiometry scans in the first 100 patients after 1 year of treatment to assess bone mineral loss. Data were analysed by two independent specialists in osteoporosis. No osteoporosis warning signal was observed at this point and the steering committee decided to let the study run to the end without changes in the protocol.

Laboratory assessments included haematology (haemoglobin, complete blood cell count, differential leucocyte count, and thrombocytes), biochemistry (sodium, potassium, creatinine, albumin, urea, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, glucose, and haemoglobin A1c), and urine analyses (haemoglobin, albumin, ketones, and glucose). Blood and urine samples were collected at baseline (month 0), randomisation (month 3), and every 3 months thereafter.

Adverse events were recorded at each visit after random allocation. Serious adverse events were defined as any adverse event that resulted in death, was life-threatening, required admission to hospital or prolonged a stay in hospital, or resulted in persistent or substantial disability.

Statistical analysis

The sample size was estimated on the basis of a previous trial of intramuscular treatment with interferon beta-1a.[17] We estimated that 37% of patients in the placebo group would experience disability progression sustained over at least 6 months within 3 years. We assumed a minimum clinically relevant difference between groups of 35% relative reduction and we expected to lose 15% of patients to follow-up. A sample size of 192 patients in each group would give a statistical power of 80%. All patients who received at least one dose of study drug were included in all planned analyses.

We analysed the primary outcome by use of Kaplan-Meier curves and a non-parametric log-rank test stratified by site, two-sided at the 5% significance level. A Cox regression model was used in the survival analyses, with EDSS score at randomisation included as a covariate. For endpoints with continuous outcome (MSFC, MRI, MSIS, fatigue severity scale, IDSS, adrenocorticotropic hormone stimulation test, and bone mineral density), analysis was the change from randomisation to 39 months; for disability progression and annualised relapse rate, analysis was of change from baseline to 39 months. If the data collected did not show a normal distribution, a non-parametric Wilcoxon analysis was done. The number of relapses and number of MRI lesions were analysed in a general linear mixed model by use of a logarithm as a link function. A statistician who was independent of the study sponsor (Christian Max Møller, aCROnordic) did all statistical analyses.

This trial is registered with ClinicalTrials.gov, NCT00168766.

Role of the funding source

The sponsor funded the study drug (methylprednisolone and placebo), the per-visit investigator fees, and the expenses related to the clinical research organisation services and per-protocol investigations (MRI and dual-energy x-ray absorptiometry). The steering committee had access to the full dataset and a statistical report by the clinical research organisation and had final

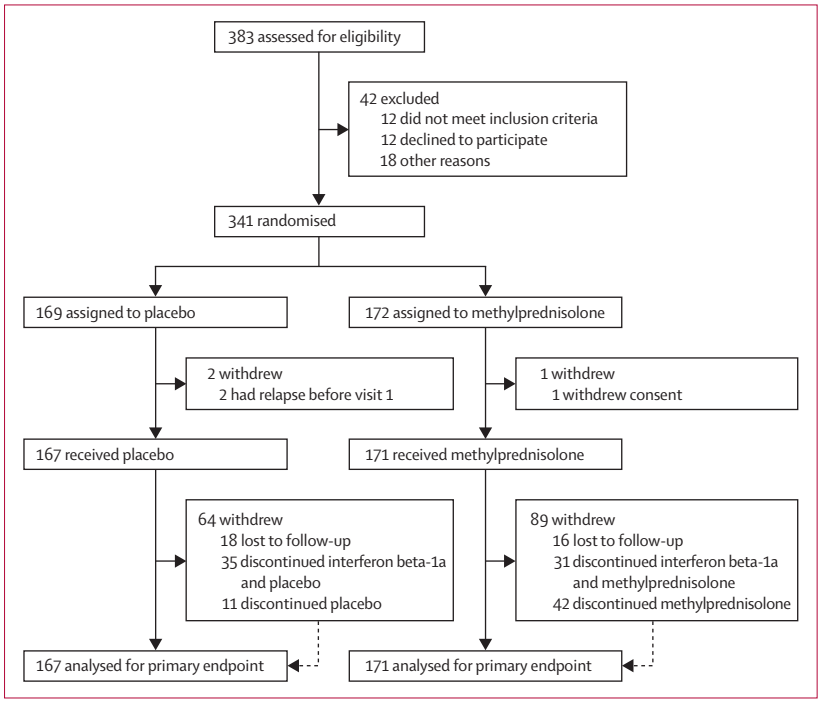

Figure 1: **Trial profile**

	Methylprednisolone group (n=171)			Placebo group (n=167)		
	Discontinued methylprednisolone	Discontinued methylprednisolone and interferon beta-1a	Lost to follow-up	Discontinued placebo	Discontinued placebo and interferon beta-1a	Lost to follow-up
Year 1	29 (17%)	15 (9%)	4 (2%)	3 (2%)	14 (8%)	5 (3%)
Year 2	5 (3%)	4 (2%)	4 (2%)	4 (2%)	10 (6%)	5 (3%)
Year 3	4 (2%)	5 (3%)	6 (4%)	4 (2%)	7 (4%)	3 (2%)
>Year 3	2 (1%)	5 (3%)	2 (1%)	0	2 (1%)	5 (3%)
Unknown	2 (1%)	2 (1%)	0	0	2 (1%)	0
Total	42 (25%)*	31 (18%)	16 (9%)	11 (7%)*	35 (21%)*	18 (11%)

Data are number (%). Because of insufficient completion of the discontinuation forms, the reasons for the discontinuations cannot be reported. *Percentage different from sum of above percantages owing to rounding.

Table 1: **Discontinuation and loss to follow-up**

	Methylprednisolone group (n=171)	Placebo group (n=167)
Men	65 (38%)	55 (33%)
White	169 (99%)	165 (99%)
Age (years)	38·2 (8·4)	37·1 (8·9)
Weight (kg)	76·8 (15·5)	73·6 (14·9)
Time from first symptom (years)	1·2 (0·1–34·1)	1·2 (0·3–28·6)
EDSS score	2 (0–6)	2 (0–7)
Timed 25-foot walk (s)*	4·8 (1·8)	5·0 (2·0)
9-hole peg test (s)*	20·5 (3·6)	20·5 (4·6)
Paced auditory serial addition test-3 score*	50·8 (8·9)	49·9 (10·9)
Multiple sclerosis impairment score*	4 (0–39)	4 (0–39)
T2 lesion volume (mm^3)	6500 (9274)	5854 (7053)
Patients with T1 gadolinium-enhancing lesions	71 (42%)	73 (44%)
Number of T1 gadolinium-enhancing lesions per person	1·5 (2·9)	1·3 (2·3)

Data are number (%), mean (SD), or median (range). *At randomisation. Some patients deteriorated over the 3-month period between baseline and randomisation, which explains why the maximum EDSS values are above the range allowed from the inclusion criteria (EDSS≤4·0). EDSS=expanded disability status scale.

Table 2: **Demographics and characteristics at baseline or randomisation**

responsibility for the decision to submit for publication. An employee of the study sponsor (BS) was involved in reviewing the statistical analysis, contributed to the writing and reviewing of the paper, and approved of the final version, but the study sponsor had no further role in the data collection, data analysis, data interpretation, or writing of the report.

Results

Recruitment for the MECOMBIN trial started in October, 2002, and ended in March, 2005. The last patient finished the study in November, 2008. We screened 383 patients, of whom 341 were randomly allocated treatment (figure 1). One patient in the methylprednisolone group and two in the placebo group withdrew before receiving treatment. 89 of 171 patients who received methylprednisolone and 64 of 167 who received placebo withdrew before the study endpoint. Of these, 16 patients in the methylprednisolone group and 18 in the placebo group were lost to follow-up. Thus, 155 patients in the methylprednisolone group and 149 in the placebo group were assessed for the full 39-month follow-up. 48 patients in the methylprednisolone group and 22 in the placebo group withdrew in year 1, 13 in the methylprednisolone group and 19 in the placebo group withdrew in year 2, and 15 in the methylprednisolone group and 14 in the placebo group withdrew in year 3 (table 1).

Demographics and characteristics at baseline or randomisation were similar between the groups (table 2). Patients were included in the trial a median of 1·2 years after symptom onset in both groups. 90 patients reached the primary outcome of disease progression sustained for at least 6 months: 44 of 171 in the methylprednisolone group and 46 of 167 in the placebo group. Time to sustained progression was not different between groups (hazard ratio 0·879, 95% CI 0·566–1·365; p=0·57; figure 2). The adjusted mean change in Z score on the MSFC was 0·031 (SE 0·057) in the methylprednisolone group and –0·139 (–0·059) in the placebo group (estimated difference 0·170, 95% CI 0·039–0·302; p=0·011; table 3), and that for the Z score on the 9-hole peg test subsection of the MSFC was 0·190 (0·065) in the methylprednisolone group and –0·135 (0·067) in the placebo group (p=0·0002). The adjusted mean change in the MSIS Z score was 1·03 (0·83) in the methylprednisolone group and 3·44 (0·85) in the placebo group (p=0·036). The adjusted mean change in the IDSS was 0·07 (SE 0·20) in the methylprednisolone group and 0·63 (0·20) in the placebo group (p=0·018; figure 3, table 3).

There were 138 documented relapses in the methylprednisolone group and 209 in the placebo group. The adjusted mean annualised documented relapse rate was 0·21 (SE 0·03) in the methylprednisolone group and 0·33 (0·04; table 3) in the placebo group (absolute reduction 0·12; relative reduction 0·38). The annualised documented relapse rate in year 1 was 0·20 in the methylprednisolone group and 0·48 in the placebo group (p<0·0001; figure 4). In a post-hoc analysis of patients who discontinued during the first year, the adjusted mean annualised documented relapse rate in year 1 was 0·24 (SE 0·07) in the methylprednisolone group and 1·29 (0·24) in the placebo group (relative reduction 0·81;

p<0·0001). In the subpopulation of patients who adhered to the study drug for the entire study, the adjusted mean annualised documented relapse rate was 0·15 (SE 0·03) in the methylprednisolone group and 0·26 (0·04) in the placebo group (relative reduction 0·42; p=0·0086).

Seven patients in the methylprednisolone group and six in the placebo group did not have gadolinium enhancement measured on baseline MRI. 40 of 71 patients in the methylprednisolone group who had at least one gadolinium-enhancing lesion at baseline and 67 of 93 patients without gadolinium enhancement completed year 1 on the study drug. In a prespecified analysis, in the subpopulation of patients who had T1-gadolinium-enhancing lesions at baseline (n=144; table 2), the adjusted mean annualised documented relapse rate at year 1 was 0·20 (SE 0·07) in the methylprednisolone group and 0·56 (0·11) in the placebo group (relative reduction 0·64; p=0·0068). In the subpopulation of patients without T1-gadolinium-enhancing lesions at baseline (n=181) the adjusted mean annualised documented relapse rate at year 1 was 0·21 (SE 0·05) in the methylprednisolone group and 0·44 (0·09) in the placebo group (relative reduction 0·51; difference between two ratios p=0·66). The adjusted mean annualised reported relapse rates were 0·41 (SE 0·04) in the methylprednisolone group and 0·60 (0·05) in the placebo group (relative reduction 0·33; p=0·001). 101 of 171 patients in the methylprednisolone group and 79 of 167 in the placebo group were relapse free at 39 months. The 25th percentile of the time to first documented relapse was 1·40 years in the methylprednisolone group and 0·68 years in the placebo group (figure 5). The mean number of relapses treated with rescue drug per relapsing patient was 0·83 (SD 1·32) in the methylprednisolone group (n=105) and 1·25 (1·43) in the placebo group (n=117; p=0·0059). The number needed to treat to avoid one documented relapse was 3·6 for year 1 and 8·0 for the entire study.

The absolute change in the brain parenchymal fraction was –0·030 in the methylprednisolone group and –0·029 in the placebo group. The adjusted mean percentage change in normalised brain parenchymal volume was –2·25% (SE 0·22) in the methylprednisolone group and –2·10% (0·22) in the placebo group (p=0·52; table 3). The median change in T2 lesion volume was –69 mm³ (range –17 461 to 21 046) in the methylprednisolone group and 71 mm³ (–6134 to 9922) in the placebo group (p=0·019). The median change in T1 lesion volume was 0 mm³ (–3144 to 17 380) in the methylprednisolone group and 88·5 mm³ (–1783 to 17 919) in the placebo group (p=0·043), and the mean number of T1-gadolinium-enhancing lesions decreased from 1·51 to 0·19 in the methylprednisolone group and from 1·32 to 0·30 in the placebo group (p=0·82). The adjusted mean number of new or enlarging T2 lesions was 5·2 (SE 0·64) in the methylprednisolone group and 8·0 (0·78) in the placebo group (relative reduction 0·35; p=0·007). The adjusted mean change in fatigue severity score was –0·08 (SE 0·11) in the methylprednisolone group and 0·18 (0·11) in the placebo group (p=0·092).

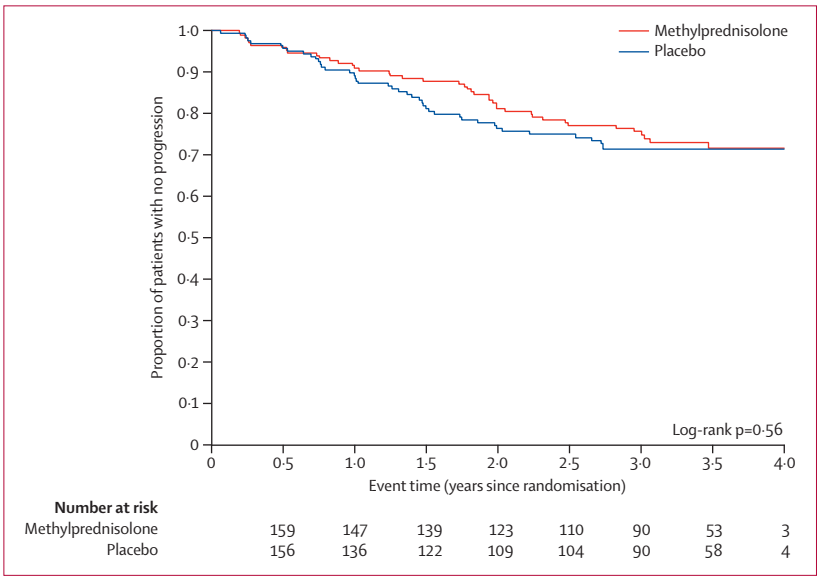

Figure 2: **Kaplan-Meier plot of the time to sustained progression of disability**
44 patients in the methylprednisolone group and 46 in the placebo group had disease progression. The 25th percentile of the time to sustained progression was 2·96 years in the methylprednisolone group and 1·99 years in the placebo group. The Cox regression estimate was –0·082 (hazard ratio 0·879, 95% CI 0·566–1·365; p=0·57).

Bone mineral density and adrenocorticotropic hormone stimulation test results were similar in both groups (bone mineral density p=0·17; adrenocorticotropic hormone p=0·19) and the number of fractures was similar in both groups (table 4). There were 1436 adverse events in the methylprednisolone group and 1070 in the placebo group. The common short-term adverse events caused by methylprednisolone were more frequent in the methylprednisolone group than in the placebo group (dysgeusia p<0·0001, insomnia p=0·00086, palpitations p=0·0665, and flushing p<0·0001; webappendix). By contrast, 78 patients in the methylprednisolone group reported flu-like symptoms compared with 96 in the placebo group (p=0·0375). There were no unusual adverse events or unexpected rates of adverse events. There were 24 serious adverse events in the methylprednisolone group and 35 in the placebo group. No deaths were reported. There were 228 infections in the methylprednisolone group and 239 in the placebo group; no opportunistic infections were reported and laboratory assessments did not differ between the groups (table 4 and webappendix).

See Online for webappendix

Discussion

In this study, cyclic methylprednisolone treatment in combination with intramuscular interferon beta-1a did not influence disease progression, as assessed by change in EDSS score over 3 years. However, there was a 38% relative reduction in relapse rate and less T2-lesion accumulation in the methylprednisolone group compared with the placebo group.

	Methylprednisolone		Placebo		Estimated difference (95% CI)	p
	n	Value	n	Value		
Progression-related outcomes						
Multiple sclerosis functional composite change in Z score	133	0·031 (0·057)	120	−0·139 (−0·059)	0·170 (0·039 to 0·302)	0·011
Timed 25-foot walk change in Z score	138	−0·211 (0·124)	120	−0·343 (0·129)	0·132 (−0·117 to 0·381)	0·30
9-hole peg test change in Z score	137	0·190 (0·065)	125	−0·135 (0·067)	0·325 (0·153 to 0·497)	0·0002
Paced auditory serial addition test change in Z score	133	0·145 (0·056)	122	0·083 (0·058)	0·062 (−0·080 to 0·205)	0·39
Multiple sclerosis impairment scale change in Z score	136	1·03 (0·83)	128	3·44 (0·85)	−2·41 (−4·68 to −0·16)	0·036
Integrated disability status score	169	0·07 (0·20)	165	0·63 (0·20)	−0·56 (−1·02 to −0·10)	0·018
Relapse-related outcomes						
Annualised documented relapse rate	171	0·21 (0·03)	167	0·33 (0·04)	HR 0·63 (0·47 to 0·84)	0·002
Annualised reported relapse rate	171	0·41 (0·04)	167	0·60 (0·05)	HR 0·67 (0·53 to 0·85)	0·001
Relapse-free patients	171	101 (59%)	167	79 (47%)	..	0·031
MRI outcomes						
Change in brain parenchymal fraction (%)	107	−3·49 (0·41)	111	−3·27 (0·42)	−0·22 (−1·02 to 0·57)	0·58
Change in normalised brain volume (%)	108	−2·25 (0·22)	112	−2·10 (0·22)	−0·15 (−0·61 to 0·31)	0·52
Change in number of gadolinium-positive lesions	108	0·00 (−19·0 to 1·0)	112	0·00 (−14·0 to 4·0)	0	0·82
Change in T1 lesion volume (mm³)	108	0·00 (−3144 to 17 380)	112	88·5 (−1783 to 17 919)	−100 (−215 to −3)*	0·043
Change in T2 lesion volume (mm³)	108	−69 (−17 461 to 21 046)	112	71 (−6134 to 9922)	−298 (−716 to −49)*	0·019
Number of new or enlarging T2 lesions	108	3 (0 to 31)	112	4 (0 to 45)	..	
Number of new or enlarging T2 lesions	108	5·2 (0·64)	112	8·0 (0·78)	HR 0·6 (0·48 to 0·88)	0·007
Patient-rated outcomes						
Change in fatigue severity score (points)	139	−0·08 (0·11)	130	0·18 (0·11)	−0·26 (−0·56 to 0·042)	0·092

Data are adjusted mean (SE), number (%), or median (range). Change values are between randomisation and 3 years for clinical outcomes and between baseline and 3 years for MRI outcomes. HR=hazard ratio. *Wilcoxon signed rank test.

Table 3: **Summary of secondary outcomes**

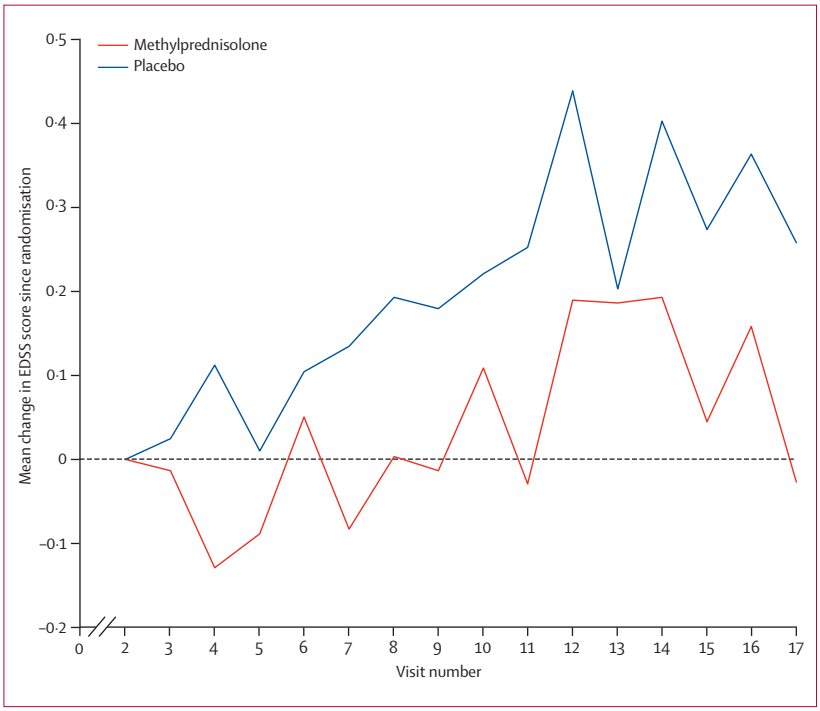

Figure 3: **Mean change in expanded disability status scale score as a function of visit number**
The area under the curve, the integrated disability status score, was 0·07 for the methylprednisolone group and 0·63 in the placebo group (p=0·018). EDSS=expanded disability status scale.

The study by Zivadinov and colleagues[3] prompted us to do the MECOMBIN study because it reported a decrease in disease progression and brain atrophy in patients with multiple sclerosis treated with cyclic methylprednisolone intravenously compared with those treated with methylprednisolone at relapses only. Several factors might explain the differences in outcomes between the study by Zivadinov and colleagues and the MECOMBIN study: the patients in our study had a shorter disease duration; we used oral monthly pulses of methylprednisolone in combination with interferon beta-1a whereas Zivadinov and colleagues used intravenous methylprednisolone with extended taper every fourth month as monotherapy; and our study was double-blind whereas in the study by Zivadinov and colleagues the investigators were masked only to the MRI results.

We were unable to detect statistically significant differences in the change in EDSS score. However, we did identify a substantial difference between the groups in the change in Z score on the MSFC in favour of methylprednisolone pulse treatment. The clinical significance of this difference is difficult to interpret. However, the clinical relevance is supported by the accumulation of neurological deficits on the MSIS. The difference in the mean MSIS change from randomisation to month 39 was 2·41 points, which corresponds to development of, for example, moderate ataxia in one

limb, severe reduction of vibration in one limb, or moderate paresis in one hand.

The large treatment effect in year 1 was mainly driven by a high relapse rate in the placebo group, which decreased over the next 2 years. This might be because of a gradual onset of the effect of interferon beta-1a and suboptimum immune modulation in the early phase of treatment.

Because of insufficient completion of the discontinuation forms, we are unable to report the reasons why patients discontinued the study. However, the high number of discontinuations in the methylprednisolone group in year 1 is most likely to be because of adverse events caused by methylprednisolone, whereas adverse events caused by interferon beta-1a or lack of efficacy are the most plausible reasons for discontinuation in the placebo group; this difference might have increased the year 1 treatment effect falsely in the subpopulation of patients who discontinued during year 1. This is what we found in the post-hoc, subgroup analyses: in the subpopulation of patients who adhered to the study drug for the entire study, the relative reduction in the adjusted mean annualised documented relapse rate between the methylprednisolone group and the placebo group was 0·42, compared with 0·38 for the entire study population. This suggests that patients who adhered to the combination treatment were less likely to relapse than those who discontinued, and that the favourable outcome for patients in the methylprednisolone group was not generated by a better outcome in patients who discontinued treatment.

This trial has several limitations. The suboptimum recruitment of patients and the lower than expected event rate in the placebo group negatively affected the statistical power of our study. Furthermore, all significant differences were from secondary and tertiary outcomes, which weakens the conclusions that can be drawn from the study.

We identified three previous trials that reported the use of cyclic corticosteroids and interferon beta in patients with multiple sclerosis. In the Nordic trial of oral methylprednisolone as add-on therapy to interferon beta-1a for treatment of relapsing-remitting multiple sclerosis (NORMIMS),[18] patients with breakthrough multiple sclerosis received subcutaneous interferon beta-1a and add-on treatment with methylprednisolone 200 mg/day or placebo for 5 days monthly for 2 years. The relative reduction in annualised relapse rate in those receiving methylprednisolone was 62% and, unlike in the MECOMBIN study, the relative reduction was similar in years 1 and 2. There were no substantial differences between the groups in terms of disability progression sustained for 3 months or changes in the MSFC. The T2 lesion volume decreased in the methylprednisolone group (–136·6 mm³) but increased in the placebo group (464·7 mm³) and the accumulation of new or enlarging T2 lesions was 23% lower in the methylprednisolone group than the placebo group. There was no effect on normalised parenchymal volume. Relapse activity despite treatment with interferon beta-1a might be due to a more aggressive disease process, which might explain the larger reduction in relapse rate in NORMIMS than in the MECOMBIN trial, in which patients were treatment naive. Also, in NORMIMS, the presence of neutralising antibodies might have reduced interferon beta efficacy. In NORMIMS, 12 of 47 patients in the methylprednisolone group and 16 of 46 in the placebo group had clinically

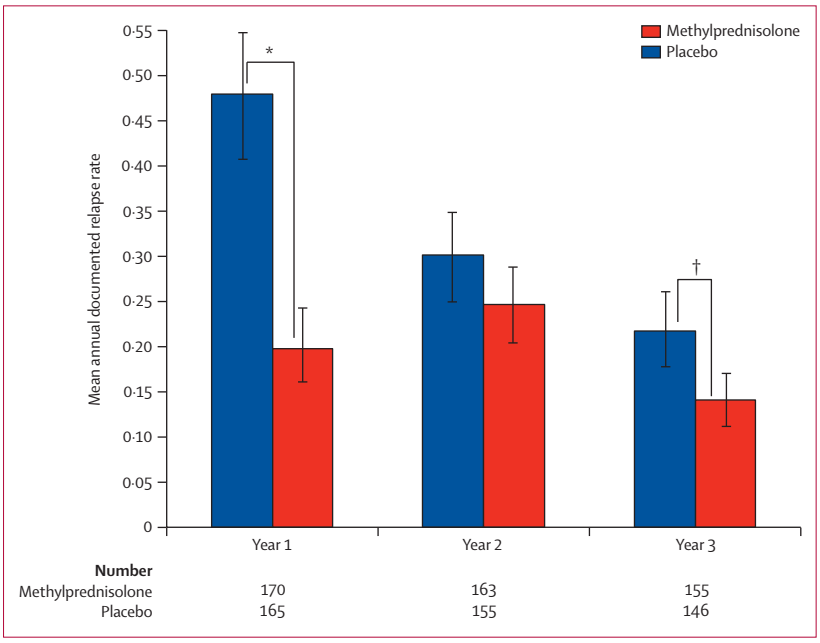

Figure 4: **Mean annualised documented relapse rate by year**
*p<0·0001. †p=0·049. Bars=SE.

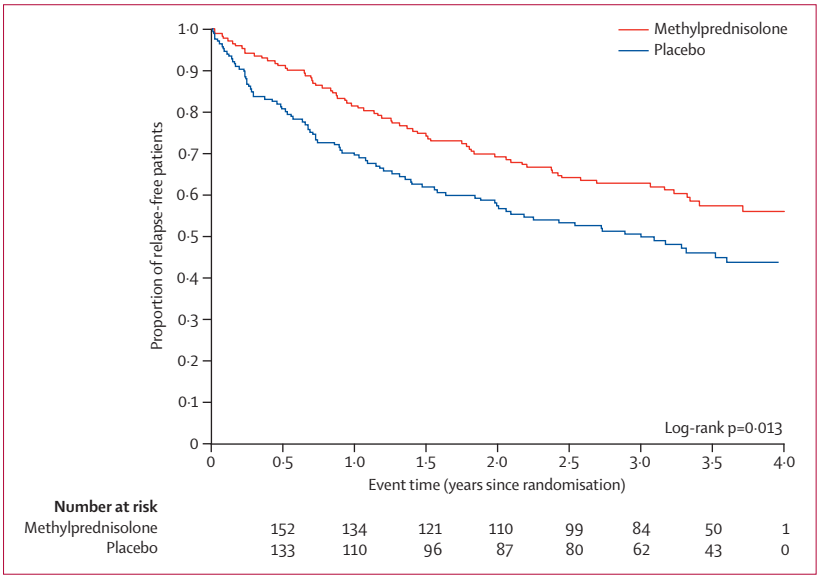

Figure 5: **Kaplan–Meier plot of the time to first documented relapse**
69 patients in the methylprednisolone group and 87 in the placebo group had at least one documented relapse. The Cox regression estimate was 0·435 (hazard ratio 0·641, 95% CI 0·456–0·902; p=0·011).

	Methylprednisolone (n=171)	Placebo (n=167)
Adverse events		
Total	1436	1070
Infections	228	239
Fractures	4	3
Serious adverse events	24	35
Patients with serious adverse events	14 (8%)	27 (16%)
Bone mineral density		
Baseline lumbar spine (g/cm²)	1·063	1·067
Month 39 lumbar spine (g/cm²)	1·036	1·035
Median change in lumbar spine	0·00%	−0·99%
Increase in plasma cortisol*		
Baseline (nmol/L)	381 (188)	402 (172)
Month 39 (nmol/L)	409 (178)	388 (183)
Patients with diabetes mellitus	2	1

Data are number (%) or mean (SD). *From baseline to 30 min after the adrenocorticotropic hormone stimulus.

Table 4: **Safety assessments**

relevant levels of neutralising antibodies, defined as a neutralising capacity of at least 20%. In patients with neutralising antibodies, the annualised documented relapse rate was 0·16 in the methylprednisolone group and 0·88 in the placebo group. Neutralising antibodies were not measured in the MECOMBIN study, but the low occurrence of neutralising antibodies in patients receiving intramuscular interferon beta-1a once weekly is well documented.[17,19,20] Thus, the proportion of patients in the placebo group who had neutralising antibodies in the MECOMBIN study is probably lower than that reported in NORMIMS. This interpretation is supported by the finding that the annualised documented relapse rate in the methylprednisolone groups of the two trials were similar (0·22 in MECOMBIN and 0·21 in NORMIMS) and the annualised documented relapse rates of the placebo groups differed (0·33 *vs* 0·56). Thus, we believe that differences in the methylprednisolone treatment regimens between NORMIMS and the MECOMBIN study are unlikely to be responsible for the difference in treatment effect.

The Avonex Combination Trial (ACT)[21] used a factorial design to test several combinations of treatment for relapsing-remitting multiple sclerosis, one of which was intravenous methylprednisolone 1000 mg daily for 3 consecutive days once every 2 months as add-on therapy to intramuscular interferon beta-1a 30 µg weekly for 12 months. The study was underpowered and negative, but clinical and MRI endpoints seemed to suggest benefit of the combination of methylprednisolone and interferon beta-1a (30% relative reduction in relapse rate).

Havrdova and colleagues[22] did a combination trial with three treatment groups: the first group received 30 µg intramuscular interferon beta-1a weekly, the second received oral azathioprine 50 mg daily in addition to interferon beta-1a, and the third received oral prednisolone 10 mg every other day in addition to interferon beta-1a and azathioprine. The primary outcome was the annualised relapse rate at year 2 and there was a borderline significant beneficial effect of the three-drug combination (p=0·06 for the comparison between the three-drug combination group and the monotherapy group). Patients in the study were not treatment naive and had had two or more relapses the past 12 months or three or more relapses in the past 24 months. Thus, the study included patients with a higher disease activity than the MECOMBIN trial. Nevertheless, baseline characteristics, including the EDSS score, disease duration, and T2 lesion volume, were similar between the two studies. Thus, differences in the outcome of the two studies can be accounted for mainly by the treatment regimens. From this review of combination trials, high-dose treatment with monthly methylprednisolone pulses seems to be the most efficacious treatment regimen.

The proportion of patients who completed treatment was 47% in the methylprednisolone groups of both NORMIMS and the MECOMBIN study, 69% in the placebo group in NORMIMS, and 62% in the MECOMBIN study. Even though 90% of patients in the MECOMBIN study and 78% in NORMIMS completed follow-up, the high discontinuation rates call for caution in the interpretation of the data. In the two studies combined, only 103 patients completed 2–3 years of monthly methylprednisolone pulses; therefore, the long-term risk of rare adverse events remains unknown.

There was no excess bone mineral loss in the methylprednisolone group compared with the placebo group and the number of fractures was similar between the two groups, suggesting that this treatment regimen does not induce clinically significant bone mineral loss. We also did not identify any cases of avascular osteonecrosis. However, avascular osteonecrosis can occur subclinically in patients with multiple sclerosis who are treated with methylprednisolone pulses.[23] The pathogenesis of this condition has not yet been identified, and patients on cyclic methylprednisolone regimens should be assessed carefully for this side-effect.

The high rate of study drug discontinuation in both the MECOMBIN study and NORMIMS[18] is evidence of the large number of adverse events caused by methylprednisolone. However, adherence to methyl-prednisolone pulse treatment might be improved by patients being aware of the potential benefits of the combination treatment.

In summary, add-on treatment with methyl-prednisolone in patients receiving interferon beta-1a does not seem to reduce disability progression any more than interferon beta-1a treatment alone but seems to reduce the risk of relapses. Although data suggest a better treatment effect in patients with T1-gadolinium-enhancing lesions at baseline than those without, our results do not allow us to discriminate responders from non-responders. So far, methylprednisolone pulse treatment of multiple sclerosis seems to be safe; however, rare but serious adverse events cannot be ruled out.

Contributors

MR and PSS conceived the trial hypothesis and wrote the protocol. MR was the coordinating investigator and chair of the steering committee, wrote amendments to the protocol, was responsible for the implementation of the protocol in Denmark, took part in creating the statistical analysis plan, and reviewed the statistical analysis. PSS was a member of the steering committee, was involved in the statistical analysis plan, and reviewed the statistical analysis. MA, EGC, PJJ, IE, EB, CSC, and KB were members of the steering committee, were responsible for the implementation of the protocol (MA in Sweden, EGC in Norway, PJJ in the Netherlands, IE in Finland, EB in Belgium, CSC in the UK, KB in Switzerland), were involved in the statistical analysis plan, and reviewed the statistical analysis. EG was responsible for the central MRI reading and for the analysis of MRI data. BS acted as contact between the steering committee and the sponsor and was involved in reviewing the statistical analysis. All authors contributed to the writing and reviewing of the submitted manuscript, and have seen and approved the final version.

Conflicts of interest

MR has received honoraria and consultancy fees from Biogen Idec, Merck Serono, Sanofi-Aventis, and Novartis, and has received travel grants from Bayer Health, Biogen Idec, Merck Serono, and Sanofi-Aventis. The University Hospital of Odense (MR) has received research support from Biogen Idec, Merck Serono, and Genzyme. PSS has received honoraria for lecturing and acting on advisory councils or trial steering committees or travel expenses for attending meetings from Biogen Idec, Bayer Schering, Merck Serono, Teva, Sanofi-Aventis, Novartis, and Genmab. The Department of Neurology, Rigshospitalet (PSS) has received unrestricted research grants or compensation for participation in clinical trials from Biogen Idec, Merck Serono, Teva, Sanofi-Aventis, BioMS, and Novartis. EGC has received travel grants and fees for lecturing from Sanofi-Aventis, Novartis, Biogen Idec, and Bayer Health. PJJ has received travel grants from Teva, Bayer Schering, and Merck Serono and lecture fees from Merck Serono. The MS4 Research Institute (PJJ) has received research grants and consultancy fees from Teva, Bayer Schering, Novartis, Allergan, Biogen Idec, and Merck Serono. IE has received travel grants and honoraria for lecturing from Bayer, Merck Serono, Sanofi-Aventis, and Biogen Idec. EB has received consultancy fees from Biogen Idec, Merck Serono, Sanofi-Aventis, Medical Device Works, and Novartis, and has received travel grants from Biogen Idec and Novartis. Erasme Hospital, Brussels (EB) has received research support from Biogen Idec. CSC has received research support from Bayer Schering, Biogen Idec, Centocor, Cephalon, GlaxoSmithKline, GW Pharma, Merck Serono, Teva, Novartis, Roche, and UCB, honoraria and consultancy fees from Almirall, Bayer Schering, Biogen Idec, Centocor, GlaxoSmithKline, GW Pharma, Merck Serono, Teva, and Novartis, and travel support from Bayer Schering, Biogen Idec, Merck Serono, and Teva. KB has received honoraria for speaker's activities (clinic for neurology Kantonsspital St Gallen) and travel grants for congresses from Bayer Schering, Biogen Idec, Merck Serono and Sanofi-Aventis. The Danish Research Centre for Magnetic Resonance in Hvidovre Hospital (EG) has received payment for reading and analysis services from Biogen Idec and Merck Serono. BS is an employee of Biogen Idec and own shares in the company. MA has no conflicts of interest.

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