NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis (NORMIMS study): a randomised, placebo-controlled trial

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Summary

Background Treatment of relapsing-remitting multiple sclerosis with interferon beta is only partly effective, and new more effective and safe strategies are needed. Our aim was to assess the efficacy of oral methylprednisolone as an add-on therapy to subcutaneous interferon beta-1a to reduce the yearly relapse rate in patients with relapsing-remitting multiple sclerosis.

Methods NORMIMS (NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta-1a for treatment of relapsing-remitting Multiple Sclerosis) was a randomised, placebo-controlled trial done in 29 neurology departments in Denmark, Norway, Sweden, and Finland. We enrolled outpatients with relapsing-remitting multiple sclerosis who had had at least one relapse within the previous 12 months despite subcutaneous interferon beta-1a treatment (44 μg three times per week). We randomly allocated patients by computer to add-on therapy of either 200 mg methylprednisolone or matching placebo, both given orally on 5 consecutive days every 4 weeks for at least 96 weeks. The primary outcome measure was mean yearly relapse rate. Primary analyses were by intention to treat. This trial is registered, number ISRCTN16202527.

Findings 66 patients were assigned to interferon beta and oral methylprednisolone and 64 were assigned to interferon beta and placebo. A high proportion of patients withdrew from the study before week 96 (26% [17 of 66] on methylprednisolone vs 17% [11 of 64] on placebo). The mean yearly relapse rate was 0·22 for methylprednisolone compared with 0·59 for placebo (62% reduction, 95% CI 39–77%; p<0·0001). Sleep disturbance and neurological and psychiatric symptoms were the most frequent adverse events recorded in the methylprednisolone group. Bone mineral density had not changed after 96 weeks.

Interpretation Oral methylprednisolone given in pulses every 4 weeks as an add-on therapy to subcutaneous interferon beta-1a in patients with relapsing-remitting multiple sclerosis leads to a signifi cant reduction in relapse rate. However, because of the small number of patients and the high dropout rate, these fi ndings need to be corroborated in larger cohorts.

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Introduction

Interferon beta is an effective and safe treatment for relapsing-remitting multiple sclerosis.[1,2] Similar to other treatments for this disorder, interferon beta is only partly effective, and second-line therapies with enhanced effectiveness are associated with potentially serious adverse events.[3–6] Thus, new safe and effective regimens are needed.

The findings of previous studies suggest that methylprednisolone might be beneficial in patients with clinically isolated syndromes or relapsing-remitting multiple sclerosis.[7,8] However, the production of neutralising antibodies against interferon beta is a major obstacle in high-dose interferon beta therapy,[9] despite an improvement in the formulation of subcutaneous interferon beta-1a.[10] Methylprednisolone as an add-on therapy to interferon beta-1b has been shown to reduce the production of neutralising antibodies to interferon beta.[11] Because methylprednisolone might enhance the therapeutic effect of interferon beta and reduce the concentrations of neutralising antibodies, we tested the efficacy and safety of oral methylprednisolone given every 4 weeks as an add-on therapy to subcutaneous interferon beta-1a in patients with relapsing-remitting multiple sclerosis who had had at least one relapse during the previous 12 months while taking interferon beta.

Methods

Patients

The NORMIMS (NORdic trial of oral Methylprednisolone as add-on therapy to Interferon beta for the treatment of relapsing remitting Multiple Sclerosis) study was a multicentre, randomised, double-blind, parallel-group, from outpatient clinics at 29 neurology departments in Denmark, Norway, Sweden, and Finland. Recruitment started in August, 2003, and the last patient visit was on December 10, 2007. Eligible patients had multiple sclerosis according to the McDonald criteria[12] and clinically defi nite relapsing-remitting multiple sclerosis as defi ned by the Poser criteria.[13] Further inclusion criteria were: age 18–55 years; baseline expanded disability status scale (EDSS)[14] score of 5·5 points or less; treatment with subcutaneous interferon beta-1a for at least the previous 12 months and at a dose of 44 μg three times a week for at least the 3 months immediately before entering the study; and recent clinical activity, defi ned as at least one relapse during the previous 12 months, while on interferon beta. We also required patients to be prepared and able to follow the study protocol for the whole study period. Women of childbearing age had to use adequate methods of contraception during the study period and have a negative pregnancy test at screening.

Patients were excluded if they had been treated previously with lymphoid irradiation, mitoxantrone, cyclophosphamide, or long-term systemic glucocorticoids. Other excluded drugs and regimens were: azathioprine or other immunosuppressive drugs; ciclosporin, glatiramer acetate, or intravenous immunoglobulin within 6 months; change of interferon beta preparation or dose within 3 months; or treatment with corticosteroids or adrenocorticotropic hormone within 8 weeks. Further exclusion criteria were: relapse within 30 days of randomisation, epilepsy that was not controlled by antiepileptic drugs, and being a women of childbearing age who did not use appropriate birth control or was pregnant or breastfeeding. Also, we excluded patients if they had converted to secondary-progressive multiple sclerosis, had a history of peptic ulcer or current symptoms of dyspepsia, diabetes mellitus, alcohol or drug abuse, major depression, cardiac or renal insufficiency, or other serious medical disorders, or had any medical illness that needed treatment with systemic corticosteroids. Finally, we excluded patients who had had a previous severe reaction to corticosteroids, had increased circulating concentrations of the liver enzymes aspartate aminotransferase or alanine aminotransferase (>2·5 times the normal upper limit), leucopenia (<2500 leucocytes per μL), or thrombo cytopenia (<100 000 thrombocytes per μL).

The NORMIMS study protocol was approved in 2002 and 2003 by independent ethics committees and regulatory authorities in Denmark, Norway, Sweden, and Finland. The study was undertaken in accordance with the Declaration of Helsinki, the European Medicines Agency note for guidance on good clinical practice, and the laws and regulations for clinical research in the participating countries. All patients provided written informed consent before any study procedure was undertaken.

Randomisation and masking

We randomly assigned patients to treatment with either oral methylprednisolone or placebo. The randomisation list was generated by computer (SAS PROC PLAN version 8.1; SAS, NC, USA) in 16 blocks of 20, by an independent contract research organisation (Smerud Medical Research International AS, Oslo, Norway) by operators who were not otherwise involved with the implementation of the study. The randomisation number was sent to the investigator with an order form for the study drug. Methylprednisolone and placebo were supplied in packs of 60 tablets. Study medication was packed at the central pharmacy for Copenhagen County (Herlev, Denmark) by people who had no further role in the study. Thereafter, the study drug was sent to the investigator who was responsible for the conduct of the study at the study site and was usually one of treating physicians. The randomisation code was not known by Merck Serono, the investigator, or the patient.
To maintain treatment blinding, we used the two-physician principle: a treating neurologist was responsible for overall care of the patient, including assessment and management of adverse events, and analysis of laboratory test results; and an evaluating neurologist assessed patients at scheduled visits and at unscheduled relapse examinations, but was not otherwise involved in patient care. Both the treating and evaluating physicians were unaware of treatment allocation.

Procedures

Oral methylprednisolone (100 mg) and placebo tablets were formulated to look, smell, and taste identical. Two tablets were taken after the morning meal for 5 days

consecutively every 4 weeks for at least 96 weeks, in combination with subcutaneous interferon beta-1a (44 µg three times a week). The drug accountability log was kept by the study nurse and monitored by a clinical research associate from the independent contract research organisation.

At baseline, we collected demographic data, took a medical history, assessed inclusion and exclusion criteria, asked about concomitant treatments, and took readings of vital signs. We did a clinical neurological examination that included EDSS and multiple sclerosis functional composite (MSFC) scores;[15] MSFC scores were calculated from the paced auditory serial addition test, the nine-hole peg test, and the timed 25-foot walk test. We also did an electrocardiogram, a pregnancy test, laboratory tests (haematology, blood chemistry, thyroid-stimulating hormone, binding and neutralising antibodies, and standard urinalysis), measurements of bone density in the lumbar spine, and MRI. When all laboratory tests and MRI findings had been analysed, the patient was randomly allocated to a treatment arm, and the study medicine was dispensed.
The treating physician examined the patient every 12 weeks and recorded adverse events, concomitant medication, and the results of laboratory tests on their clinical record forms. The evaluating neurologist did neurological examinations, including EDSS score evaluation, at 24-week intervals and MSFC score evaluation at weeks 48 and 96. In the case of a suspected relapse, patients were examined within 7 days from onset of symptoms. The study was terminated when the last enrolled patient had completed 96 weeks of follow-up.
We measured neutralising antibody concentrations at baseline and weeks 24, 48, 72, and 96 with an antiviral neutralisation bioassay (Biomonitor, Copenhagen, Denmark).[16] We defined a sample as positive for neutralising antibodies if it had a neutralising capacity of at least 20%, because this value was previously shown as the lowest concentration of neutralising antibodies to have clinical importance.[17] We used the "anytime positive, always positive" (ie, based on one positive sample) principle to classify patients as positive for neutralising antibodies.[18]

We did brain MRI scans at baseline and week 96 according to a standard procedure and used the same MRI scanners at each visit, operating at 1·0 or 1·5 T. Gadolinium contrast was not used. For lesion assessment, we obtained 3 mm axial images (fi eld of view 250 mm; matrix 256×256) with a proton-density and T2-weighted turbo-spin-echo sequence (50 slices) and a fl uid-attenuated inversion recovery (FLAIR) sequence (36–50 slices). To analyse brain atrophy, we acquired a three-dimensional T1-weighted gradient-echo sequence (128–170 slices of 1·0–1·3 mm; field of view 250 mm; matrix 256×256). All two-dimensional images from both sessions were coregistered and resliced to the T2-weighted image of a random session (baseline or follow-up) so as not to introduce systematic differences due to the reslicing, with the Statistical Parametric Mapping 2 (SPM2) toolbox.
A trained technician manually delineated the lesions seen on the FLAIR images with in-house developed software, and these lesions were checked and corrected by a physician with experience of this procedure; the technician and physician were blinded to treatment allocation and the order of the images. We used the delineated lesions to calculate lesion volumes and the number of new or enlarging lesions. On follow-up images, we defi ned a lesion as new if it did not overlap with a lesion seen on the baseline images by more than 20% for small lesions (volume less than that of a sphere of 5 mm diameter) or 50% for larger lesions (volume greater than that of a sphere of 5 mm diameter). We judged a lesion to be enlarged if its volume had increased by 50% for small lesions or by 20% for large lesions compared with overlapping lesions on baseline images.

We estimated brain parenchymal volumes and brain parenchymal fractions on magnetisation-prepared rapid gradient-echo (MPRAGE) images with the Oxford Centre for Functional MRI of the Brain (FMRIB) Automated Segmentation Tool (FAST),[19] which is part of the FMRIB software library (FSL) software library version 3.3.11.[20] We used structural image evaluation, using normalisation, of atrophy (SIENA version 2.4; Oxford, UK),[21] which is also part of FSL, to estimate the percentage change in brain volume between baseline and week 96. For patients who withdrew from the study prematurely, we did a brain MRI at 8 weeks after the last dose of study drug.

The primary outcome measure was mean number of documented relapses per patient per year (mean yearly relapse rate) during weeks 0–96. This endpoint was recorded in the original protocol, but was changed in a later version of the protocol to "mean number of documented relapses per patient per year at 48 and 96 weeks". However, to avoid having more than one primary endpoint, the original primary outcome measure was re-established before the end of the study when all data in the database were still masked. Relapses were defi ned, according to Schumacher and colleagues,[22] as the appearance of new, or worsening of old, neurological symptoms, without fever, that persisted for more than 48 h, and were preceded by more than 30 days with a stable or improving condition. A documented (qualifying) relapse was defi ned as a relapse that caused objective changes seen on neurological examination, whereas changes in bowel and bladder function could not solely be classifi ed as documented relapses. An undocumented (non-qualifying) relapse was defi ned as a relapse that fulfi lled the defi nition of Schumacher and colleagues without new changes in the neurological examination. Secondary endpoints were mean yearly relapse rate during weeks 0–48 and weeks 49–96; time to worsening of disability assessed as an increase of 1 point or more in EDSS score and confi rmed at two consecutive visits 24 weeks apart; changes in MSFC score from baseline to week 48 and from baseline to week 96; number of active lesions (new or enlarging lesions) on T2-weighted MRI; and the presence of neutralising antibodies at any point up to week 96.

The tertiary endpoints were: total number of reported relapses; probability of remaining relapse free and other relapse-related outcomes; proportion of patients with disability progression, total volume of lesions on T2-weighted MRI; and change in normalised brain parenchymal volume.

For safety comparisons, we recorded adverse events,

withdrawals due to adverse events, serious adverse events, bone-density measurements, and laboratory test results.

Statistical analysis

On the basis of data from the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study,[2] the yearly relapse rate in the interferon beta-1a plus placebo group was estimated as 0·8 and the relative reduction in relapses as 30% in the interferon beta-1a plus methylprednisolone group. We calculated that a sample size of 130 patients in each group would be needed to reach a power of 80%. We anticipated a dropout rate of 15%; hence, a cohort of 300 patients was planned for the trial. However, enrolment was discontinued prematurely after 130 patients had been randomised, owing to slow recruitment.

All statistical analyses were approved by the NORMIMS study steering committee before unmasking. The primary analyses were intention to treat, which included all randomised patients, whereas patients who completed 96 weeks of treatment and assessments without any major protocol deviations were included in the per-protocol analyses.

We assessed baseline comparability with a two-way analysis-of-variance model and categorical variables with χ^2 tests. We analysed the primary endpoint (mean yearly relapse rate) with a Poisson regression model; to estimate the effect of baseline variables on the primary outcome we used multiple Poisson regression analysis. If the EDSS score was missing for a visit, we deemed disability as not increased for that visit compared with the previous visit. The probability of remaining relapse free and the increase in disability measured with the EDSS were estimated by Kaplan–Meier survival analysis, and we assessed the differences in the survival curves with the log-rank test. We analysed the MSFC with the t distribution at every visit to the evaluating neurologist. MSFC scores were standardised to the mean baseline MSFC value for the intention-to-treat population.[23] We used Poisson regression to evaluate the number of active lesions on MRI. The occurrence of neutralising antibodies was analysed with logistic regression and proportional odds models, both with and without adjustment for baseline status. For sensitivity analyses of the primary outcome measure, we used the Poisson regression model for multiple imputations of relapses for early dropouts. We used 200 imputations for every missing observation and combined the results in accordance with standard methods.[24] All statistical tests were two-sided (α=0·05). All models were checked for assumption violations. Poisson models were tested for overdispersion and underdispersion and, if necessary, adjusted with quasi-likelihood estimates.[25] We did all calculations with SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

This trial is registered, number ISRCTN16202527.

Role of the funding source

Data management and analyses were done by an independent contract research organisation (Smerud Medical Research International AS, Oslo, Norway). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

130 patients were randomly assigned to add-on therapy: 66 to oral methylprednisolone and 64 to placebo (figure 1). Table 1 shows baseline demographics and clinical characteristics.

The number of scheduled visits was similar between treatment groups (380 in the methylprednisolone group vs 382 in the placebo group), whereas more unscheduled visits were made for suspected relapses by patients in the placebo group (n=79) than by patients in the methylprednisolone group (n=51). 75 patients completed follow-up and 55 patients discontinued study medication prematurely, but 27 of the patients who withdrew did so after week 96; therefore, 102 patients completed 96 weeks or longer of follow-up (figure 1). The longest follow-up was 126 weeks.

Adherence, as measured according to the entries in the drug accountability log, was similar between groups (mean 88% [SD 39] in the methylprednisolone group and 86% [28] in the placebo group).

Table 2 shows the distribution of documented relapses in the two treatment groups up to week 96. In the intention-to-treat population, there were 23 relapses in the methylprednisolone group and 66 relapses in the placebo group. Total treatment duration was 103·6 years for patients randomly assigned to methylprednisolone and 112·0 years for those assigned to placebo, giving a mean yearly relapse rate of 0·22 (95% CI 0·15–0·33) on methylprednisolone and 0·59 (0·46–0·75) with placebo (relative reduction in relapse rate 62%, 95% CI 39–77%; p<0·0001). Only minor differences in mean yearly relapse rate were recorded between treatment groups during weeks 0–48 (relative reduction 63%, 32–80%; p=0·002) and during weeks 48–96 (relative reduction 62%, 19–82%; p=0·013). In the per-protocol population, four relapses occurred during 49·8 patient-years in the methylprednisolone group and 29 relapses during 69·3 patient-years in the placebo group (yearly relapse rate 0·08 vs 0·42; relative reduction in relapse rate 81%, 45–93%; p=0·002).

Because many patients withdrew from the study, we did sensitivity analyses to assess the effect of early withdrawals on the measurement of relapse activity. We imputed recorded relapses for the remainder of the study (from withdrawal to 96 weeks) and calculated the estimated relapse ratio. Assuming a yearly relapse rate of 0·59 (which is the mean yearly relapse rate for the placebo group) for all patients who withdrew, the difference between treatment groups was significant (estimated relapse rate ratio 0·49, 95% CI 0·31–0·76; p=0·002). If we assume a yearly relapse rate of 1·2 (twice the mean yearly relapse rate for the placebo group), the estimated relapse rate ratio was 0·61 (0·40–0·91; p=0·017). Finally, assuming a yearly relapse rate of 1·2 for patients who withdrew because of adverse events and 0·6 for patients who withdrew for other reasons, the estimated relapse ratio was 0·58 (0·37–0·90; p=0·015). 35 reported relapses (documented and undocumented) in 103·6 patient-years occurred in the methyl prednisolone

group and 92 relapses occurred in 112·0 patient-years in the placebo group (yearly relapse rate 0·34 vs 0·82; between-group difference 0·41, 95% CI 0·28–0·61; p<0·0001) in the intention-to-treat population. 21 relapses in the methylprednisolone group and 70 relapses in the placebo group were treated with glucocorticoids. Mean time to first recorded relapse was 30·8 (SD 23·5) weeks in the methylprednisolone group compared with 34·9 (26·2) weeks in the placebo group. By Kaplan–Meier estimate, the probability of remaining relapse free throughout the trial was 76% in the methylprednisolone group compared with 34% in the placebo group (between-group absolute difference 42% [95% CI 26–58%]; log-rank p<0·0001). We also did a sensitivity analysis of the relapse-free patients that assumed the best scenario (no relapses in the dropouts) and the worst scenario (all dropouts had a relapse). For the best scenario, the estimated odds ratio would be 0·15 (95% CI 0·06–0·36; p<0·0001); for the worst scenario, the estimated odds ratio would be 0·48 (0·22–1·05; p=0·064).

To account for any interaction between baseline variables and treatment outcome, the yearly relapse rate was analysed according to EDSS score (0–2·5 points [eg, no or negligible disability] vs 3·0–5·5 points [eg, some disability]), number of relapses in the 12 months before randomisation (one vs two or more), ascertained from documentation or patient recollection, age (older or younger than the median age of 38·7 years for the intention-to-treat population), sex, and country. A significant interaction was noted between treatment effect and baseline EDSS score (p=0·007), implying that no treatment effect was seen for patients with a baseline EDSS of 3 points or more. However, the overall treatment effect adjusted for baseline EDSS was significant (relapse rate ratio 0·33, 95% CI 0·19–0·56; p<0·0001). This interaction effect could be accounted for by differences in withdrawals: more patients with low baseline EDSS scores withdrew in the methylprednisolone group (n=20) compared with patients in the placebo group (n=7). No other significant interactions were reported.

Figure 2 shows the Kaplan–Meier estimates of an increase in disability by 1 point or more on the EDSS, confirmed at 24 weeks. The difference between groups was not statistically significant (p=0·29), with an estimated probability of progression at 96 weeks of 16% (95% CI 6–26%) in the methylprednisolone group and 25% (13–36%) in the placebo group (36% reduction [95% CI –37 to 70%]).

Table 3 shows the MSFC score and its subscales and change from baseline to weeks 48 and 96. MSFC score was calculated from the results of the paced auditory serial addition test, the nine-hole peg test, and the timed 25-foot walk test. Scores were standardised to the baseline MSFC score for the intention-to-treat population.[23] The difference between treatments in MSFC score from baseline to week 48 was –0·11 (95% CI –0·26 to 0·05; p=0·17), and –0·05 (–0·22 to 0·11; p=0·52) from baseline to week 96.

MRI at baseline and at study termination (after 96 weeks or after discontinuation of study drug) was done in 54 patients in the methylprednisolone group and 56 patients in the placebo group. 34 of 55 patients who withdrew underwent MRI after discontinuation of the study drug. In the methylprednisolone group, 253 active lesions were recorded in 92·8 patient-years, whereas 369 active lesions in 104·4 patient-years were noted in the placebo group.

The mean number of new or enlarging lesions per patient per year was 2·7 (95% CI 2·0–3·8) in the methylprednisolone group and 3·5 (2·7–4·7) in the placebo group (23% reduction; relative rate ratio 0·77, 95% CI 0·50–1·19; p=0·24). Table 4 shows the changes in T2-lesion volume and normalised brain parenchymal volume from baseline.

Neutralising antibodies were detected at least once in 12 of 47 (26%) patients in the methylprednisolone group and in 16 of 46 (35%) patients in the placebo group. Some blood samples contained toxic substances (eg, bacterial endotoxins) or endogenous antiviral activity that prevented measurement of neutralising antibodies. Nine (23%) of 39 patients in the methylprednisolone group and 13 (30%) of 43 patients in the placebo group were positive for neutralising antibodies at 96 weeks. Table 5 shows the yearly relapse rate and number of new or enlarging T2 lesions seen on MRI in patients grouped according to neutralising antibody status.
Because an unexpectedly high number of patients discontinued study medication, additional analyses were done to assess whether withdrawal of the study drug in these patients had affected the assessment of treatment efficacy. Of 18 patients who discontinued methylprednisolone but completed follow-up at 96 weeks, 15 continued with interferon beta-1a as the only immunomodulatory drug, two were treated with mitoxantrone, and one received glatiramer acetate. Of the nine patients in the placebo group who discontinued placebo but completed follow-up at 96 weeks, five continued with interferon beta-1a as the only immunomodulatory drug, two were treated with mitoxantrone, and two received natalizumab. Mean time in the trial after treatment termination was 53·4 weeks (SD 37·3) in the methylprednisolone group and 29·4 weeks (25·7) in the placebo group. Post-hoc analysis showed no difference between the treatment groups for mean time to sustained increase in disability or number of patients with a sustained increase in disability in the patients who discontinued.

Table 6 shows adverse events according to treatment group. More adverse events were recorded in the methylprednisolone group than in the placebo group: 18 patients (27%) assigned to methylprednisolone and two (3%) assigned to placebo withdrew from the study because of adverse events. Most adverse events in both groups were deemed by the investigators as possibly or probably related to the treatment. In particular, psychiatric symptoms, mainly insomnia and restlessness, and gastrointestinal symptoms, particularly dyspepsia, were reported more frequently by the methylprednisolone group than they were by the placebo group. Neurological symptoms were also reported more frequently by the methylprednisolone group than by the placebo group; changes in taste (dysgeusia and ageusia) were the most common. Osteoporosis was recorded as an adverse event in three patients in each group. Measurements of bone mineral density of the lumbar spine showed small changes from baseline at week 96: a mean reduction of 2·8% (SD 6·3%) in the

methylprednisolone group, whereas in the placebo group the decline was 0·6% (5·9%). More abnormalities in the results of laboratory tests were recorded in the methylprednisolone group than in the placebo group, but few of the abnormalities were judged as clinically significant by the investigators: in the methylprednisolone group, five patients had increased liver enzymes, one had leucopenia, and one had an increased white blood cell count.
Serious adverse events were reported by ten patients (11 events). In the methylprednisolone group, one person was admitted to hospital owing to urosepsis and another was admitted because of a peritoneal infection; both events were deemed treatment related. One patient was admitted to hospital for arthroscopy of the knee, which was unrelated to the study drug; one had severely raised concentrations of liver enzymes ascribed to the interferon beta treatment; and another had recurrence of a cancer in the parotid gland, which was unrelated to the study drug. In the placebo group, one patient had two serious adverse events—a deep vein thrombosis in the right lower limb and an extrauterine pregnancy; both adverse events were deemed unrelated to the study drug. Another patient was admitted to hospital with dystonia that started before the first dose of study drug and was therefore regarded as unrelated to treatment. One patient was admitted to hospital for a cholecystectomy, another was admitted with pyelonephritis, and another with severe migraines, which were deemed as unrelated to the treatment drug by the investigator. One patient in the placebo group died during the trial after admission to hospital with signs of pneumonia; this was not deemed related to the treatment by the investigator and a post-mortem examination was not done.

Discussion

The findings of the NORMIMS study showed that add-on therapy of oral methylprednisolone for 96 weeks in patients with relapsing-remitting multiple sclerosis reduced the yearly relapse rate compared with that of patients on placebo. Unfortunately, the enrolment of patients had to be terminated prematurely because of slow recruitment; therefore, we believe the study was underpowered to show the predicted 30% reduction in relapse rate. However, our findings showed that methylprednisolone as an add-on therapy had a positive effect on the primary outcome measure was owing to a higher than expected reduction in relapse rate.
There was no difference in the main secondary MRI outcome—new or enlarging T2 lesions—in the methylprednisolone group compared with the placebo group. The difference between the effect on relapse-related outcomes and on new or enlarging T2 lesions is intriguing, and we cannot provide a clear explanation. However, the converging evidence of a treatment effect of methylprednisolone was encouraging, and all secondary and tertiary efficacy measures were in favour of methylprednisolone, although the change in T2-weighted lesion volume was the only MRI measure that reached statistical significance.
Differences in baseline characteristics were minor, and multiple regression analysis that included the baseline variables showed only an interaction between EDSS and treatment response, which could not explain the difference in treatment effect between methylprednisolone and placebo.

As is reported in other studies of effective drugs for multiple sclerosis, more unscheduled visits for suspected relapses were reported in the placebo group than in the methylprednisolone group. Although this difference was expected, we cannot exclude the possibility that the higher number of unscheduled visits from patients taking placebo might have introduced a slight bias, because unscheduled visits could increase the chance of documenting a relapse.

Our study was hampered by an unexpectedly high number of patients who discontinued their assigned medication or withdrew. We did analyses to see if treatment with another drug after discontinuation of the assigned regimen in patients who continued follow-up could have introduced bias that might have affected the results. Patients who discontinued their assigned study drug received mitoxantrone, glatiramer acetate, or natalizumab, or some continued treatment with interferon beta only. Mitoxantrone[4] and natalizumab[6] are thought of as more effective second-line therapies than is interferon beta;[2] however, most patients who stopped methylprednisolone treatment continued on interferon beta-1a only. Hence, we do not think that any differences in disease-modifying therapy after discontinuation of study drug could have contributed to the recorded difference in therapeutic effect between the two treatment groups.

The most frequent reasons for premature withdrawal from the study were adverse events in the methylprednisolone group and lack of efficacy in the placebo group. Because the patients who withdrew did not continue follow-up, we cannot control for any bias. However, the findings of the sensitivity analyses showed that rejection of the primary null hypothesis is robust to deviations from the assumption that data are missing at random (MAR) in the primary analysis.[24]
Baseline characteristics, discontinuation of study drug, or study withdrawal did not seem to account for the recorded difference in treatment effect between methylprednisolone and placebo. However, we cannot exclude the possibility that unknown factors with regard to the patients who either discontinued the study drugs or left the study could have affected our results.
We chose a monthly regimen of methylprednisolone in our study because the genomic and non-genomic effects of a 5-day administration of a glucocorticoid in a month are short lived,[26] and the effect on gadolinium-enhancing lesions is significant at 1 month, but not at 2 months, after high-dose intravenous methylprednisolone.[27,28] The monthly dose of methylprednisolone was similar to that used in a randomised placebo-controlled trial of pulsed methylprednisolone therapy.[8] Oral methylprednisolone is equivalent to the same dose given intravenously,[29] and one 200 mg dose fully saturates the glucocorticoid cytosolic receptors.[30]

Glucocorticoids have many effects on the immune system.[31] Their effects on the blood–brain barrier can be seen as attenuation of gadolinium enhancement and correlate with macrophage infiltration into the multiple sclerosis lesions in the brain.[32,33] Glucocorticoids interact negatively with transcription factors that have a role in T-cell activation and can induce apoptosis of activated T cells[34,35] and diminish the expression of CD26 on CD4+ T cells.[36] High doses of methylprednisolone induce

expression of transforming growth factor beta, which inhibits production of proinfl ammatory cytokines by effector T cells.[37,38] Also, the decline in IgG synthesis seen after treatment with high doses of oral methylprednisolone could be implicated in the clinical response.[39]

An additive or synergistic effect of glucocorticoids and interferon beta could be mediated by the ability of glucocorticoids to increase the sensitivity of T cells to interferon beta and upregulate interferon receptors. These effects have anti-infl ammatory potential, mediated by increased production of interleukin 10 and suppressed secretion of interferon gamma by T cells.[40]

The results of the NORMIMS study are in agreement with those of previous trials that show a detrimental effect of neutralising antibodies on the therapeutic efficacy of interferon beta,[17] despite a study duration of nearly 2 years and our use of the "anytime positive, always positive" method, which underestimates the effects of neutralising antibodies.[18] Furthermore, our fi ndings confi rmed previous work that showed that methylprednisolone does not reduce the concentrations of already induced neutralising antibodies.[41]

A randomised, single-blind, phase II trial compared intravenous cyclic methylprednisolone (1 g daily for 5 days and a prednisolone taper, administered every 4 months for 3 years and then every 6 months for 2 years) with no other treatment apart from management of acute relapses with methylprednisolone.[8] Patients who received cyclic methylprednisolone showed a 32% reduction in the probability of a sustained increase in EDSS score. Changes in the volume of T1 black holes and in brain parenchymal volume also favoured pulsed treatment with methylprednisolone.[8] No differences were recorded between the two groups in yearly relapse rate (0·6 in both groups), but less frequent administration of methyl-prednisolone than in NORMIMS might have contributed to the absence of an effect of methylprednisolone on relapses.

In the Optic Neuritis Study,[7] one course of intravenous methylprednisolone (1 g daily for 3 days with an oral taper) compared with placebo reduced the risk for developing defi nite multiple sclerosis at 2 years (odds ratio 0·43). However, at 5 years the effect had disappeared, which could be why this finding of the Optic Neuritis Study has been widely ignored. In fact, in the Controlled High-risk Avonex Multiple Sclerosis study (CHAMPS),[42] 37% of patients in the optic neuritis cohort developed defi nite multiple sclerosis within 2 years on interferon beta-1a therapy, and the 95% CI included the optic neuritis study estimate of 28%.[43] However, these study populations might not have been comparable, because cerebral MRI changes were required for inclusion in the CHAMPS study, whereas 52% of patients in the optic neuritis study had no brain lesions on MRI, and these patients had a particularly low risk for developing clinically defi nite multiple sclerosis.

A regimen of high-dose intravenous methylpredni-solone (500 mg daily for 3 consecutive days with an oral taper) was compared with a low-dose regimen (10 mg daily for 3 consecutive days with an oral taper given every other month for up to 2 years) in 108 patients with secondary-progressive multiple sclerosis.[44] No difference was recorded between the two doses with respect to the primary outcome measure—proportion of patients with sustained progression (low dose 54% vs high dose 39%; p=0·18). However, a Kaplan–Meier analysis of time to sustained progression was in favour of high-dose methylprednisolone (p=0·04).

The SENTINEL (safety and efficacy of natalizumab in combination with interferon beta-1a in patients with relapsing-remitting multiple sclerosis) study was a large, randomised, double-blind, placebo-controlled study of natalizumab as an add-on therapy to intramuscular interferon beta-1a versus placebo in patients who had breakthrough disease on interferon beta therapy.[45] The characteristics of the patients in the SENTINEL study were similar to those of our population with regard to age, EDSS score, relapse activity, and duration of interferon beta therapy, whereas the proportion of men was lower and the mean time since onset slightly longer (table 7). In the natalizumab arm, the relapse rate reduction was 54% and the decline in the probability of sustained EDSS progression was 24% compared with placebo. These efficacy measures are not very different from those reported in our study.

In the Avonex Combination Therapy (ACT) study,[46,47] bimonthly intravenous methylprednisolone (1000 mg daily for 3 consecutive days; n=66) was compared with methotrexate (20 mg daily; n=76), the combination of the two drugs (n=74), and placebo (n=70) as an add-on therapy to intramuscular interferon beta-1a (30 μg per week for 12 months) in patients with relapsing-remitting multiple sclerosis who had had a relapse during the previous year while on intramuscular interferon beta-1a or who had gadolinium-enhancing lesions seen on baseline MRI of the brain. Similar to the NORMIMS study, the ACT trial was stopped early because of slow recruitment: the original plan was to enrol 900 patients, with follow-up of 24 months, and relapse rate as the primary outcome;[46] however, the trial was discontinued after 313 patients were enrolled, the study time was reduced to 12 months, and the primary endpoint was changed to the number of new or enlarging T2 lesions on brain MRI. In the 12-month study, 23 out of 78 patients (29%) in the placebo group and 23 out of 74 patients (31%) in the methylprednisolone group discontinued the study or study medication. The ACT study used a 2×2 factorial design, which makes direct comparison of the treatment effect of methylprednisolone versus placebo with the effect in our study difficult. Several of the ACT outcome measures favoured methylprednisolone, as they seem to do in our study, although the diff erences were not signifi cant: relapse rate ratio 0·70, 95% CI 0·42–1·17 (p=0·17); odds ratio of change in EDSS score 0·76, 0·47–1·22 (p=0·25); ratio of probability of progression 0·62, 0·26–1·48 (p=0·24); and odds ratio of new or enlarging T2 lesions 0·74, 0·47–1·15 (p=0·18). Furthermore, the ACT study was underpowered to show effects on clinical endpoints, with relative reductions of about 30%. Compared with our study, the most notable differences in the ACT trial were shorter study duration, reduced frequency of methylprednisolone administration, and no blinding of the intravenous methylprednisolone treatment.[46,47] To ascertain whether the frequency of methylprednisolone administration aff ects relapse rate

will require a large dose-comparison study. By comparison with our study population, patients in the ACT trial were older, had longer duration of disease, and had lower relapse activity in the 12 months before inclusion (table 7).

The methylprednisolone in combination with interferon beta-1a (MECOMBIN) study is a multicentre, double-blind, randomised, parallel-group trial of 341 patients with relapsing-remitting multiple sclerosis who are treatment naive; the findings of this trial are as yet unpublished but have been presented as an abstract at the 2009 American Academy of Neurology annual meeting.[48] Patients were randomly assigned to either methylprednisolone (500 mg per day for 3 consecutive days every month for 3–4 years; n=172) or placebo (n=169) as add-on treatment to intramuscular interferon beta-1a. The yearly recorded relapse rate was 0·205 in the methylprednisolone group and 0·333 in the placebo group (relative reduction 38%; p<0·01). Time to sustained progression did not differ between treatment groups (hazard ratio 0·8; p=0·33). Mean MSFC score rose by 0·06 in the methylprednisolone group, but decreased by 0·14 in the placebo group (p<0·05). Median change in T2-lesion volume was –69 mm^3 in the methylprednisolone group and 71 mm^3 in the placebo group (p<0·02).

In conclusion, the addition of monthly oral methylprednisolone pulses to subcutaneous interferon beta-1a treatment was safe, and although many patients in the treatment arm dropped out, most patients tolerated methylprednisolone as an add-on to interferon beta-1a. The addition of methylprednisolone significantly reduced the relapse rate and might also benefit disease progression and disease activity seen on MRI. Our findings are important because oral methylprednisolone is inexpensive and easily administered in patients with breakthrough disease who are on interferon beta therapy. Owing to the limited number of patients and the high proportion of patients who discontinued therapy in the NORMIMS trial, the findings should be corroborated in larger trials. Furthermore, the results of the large MECOMBIN study need to be scrutinised before any final conclusions can be made with regard to the effect of methylprednisolone as an add-on therapy to interferon beta. On the basis of the results of the NORMIMS study, cyclic oral methylprednisolone as an add-on therapy to interferon beta could be an important alternative to more expensive and potentially more harmful therapies for patients with relapsing-remitting multiple sclerosis whose disease is insufficiently controlled by first-line therapies.

Contributors

Implementation and data analysis of the NORMIMS study was supervised by a steering committee comprising PSS (principal investigator), SIM, AS, IE, JLF, AGB, KMM, and MSW. MRI assessments were done under the supervision of LVS. Data analyses, which were prespecified by the NORMIMS steering committee, were done by ICO, who is an employee of the independent contract research organisation Smerud Medical Research International AS, Oslo, Norway. PSS wrote the first draft of the manuscript. All authors contributed to study design, interpretation of data, and revision of the manuscript and have read and approved the final version.

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Conflicts of interest

PSS has received honoraria for lectures, advisory councils, and trial steering committees, and travel expenses for attending meetings. The Department of Neurology, Rigshospitalet, has received unrestricted research grants or compensation for participation in industry-sponsored clinical trials in the past year from Biogen Idec, Bayer Schering, Merck Serono, TEVA, Sanofi –Aventis, BioMS, and Genmab. SIM has received travel expenses for attending meetings. The Department of Neurology, University Hospital of North Norway, has received compensation for participation in industry-sponsored clinical trials in the past year from Merck Serono and Bayer Schering. IE has received honoraria for lectures and travel grants for attending meetings from Biogen Idec, Bayer Schering, Merck Serono, and Sanofi –Aventis. JLF has received honoraria for lecturing, membership of advisory councils, and trial steering committees, and travel expenses for attending meetings. The Department of Neurology, Glostrup University Hospital, has received unrestricted research grants or compensation for participation in industry-sponsored clinical trials in the past year from Biogen Idec, Bayer Schering, Merck Serono, TEVA, Sanofi –Aventis, and GlaxoSmithKline. AGB has received travel expenses for attending meetings by Biogen and MerckSerono and has received compensation for participating in clinical trials from Merck Serono. KMM has received honoraria for lecturing, membership of advisory councils, and participation as principal investigator, investigator, or member of trial steering committees, and travel expenses for attending meetings, and the Department of Neurology, Haukeland University Hospital, has received unrestricted research grants or compensation for participation in pharmaceutical company sponsored clinical trials in the past year from Bayer Schering, Biogen Idec, GlaxoSmithKline, Merck Serono, and Sanofi –Aventis. MSW has received honoraria for lectures, advisory councils, and data safety monitoring boards, and travel expenses for attending meetings from Biogen Idec, Bayer Schering Pharma, Genentech, Merck Serono, Sanofi –Aventis, and TEVA. The Department of Neurology, Lund University Hospital, has received compensation for participation in industry-sponsored clinical trials in the past year from Biogen Idec and BioMS. AS, LVS, and ICO have no conflicts of interest. The reader centre based at the Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre, is analysing MRI from clinical trials sponsored by Biogen Idec and Merck Serono.

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	Methylprednisolone (n=66)	Placebo (n=64)
Age (years)	37·8 (7·4) [39·2]	39·5 (7·8) [38·5]
Men	29 (44%)	21 (33%)
Time since onset of symptoms (years)	6·9 (5·1) [5·3]	8·5 (5·9) [7·0]
EDSS score	2·5 (1·3) [2·5]	2·9 (1·4) [3·0]
Number of relapses within previous year	1·6 (0·9) [1·0]	1·5 (1·0) [1·0]
Relapses in previous year		
1	41 (62%)	45 (70%)
2	15 (23%)	13 (20%)
≥3	10 (15%)	6 (9%)
Duration of interferon beta-1a treatment (years)	2·8 (1·8) [2·3]	3·4 (2·1) [2·8]
T2 lesion volume (mm^3)	7671·9 (8705·3) [3888·0]*	11507·7 (14538·0) [6054·0]†
Brain parenchymal volume (cm^3)	1184·1 (127·5) [1189·0]‡	1166·1 (142·4) [1140·5]§
Number positive for neutralising antibodies	12/47 (26%)	16/46 (35%)

Data are mean (SD), [median], or number of patients (%). EDSS=expanded disability status scale. *n=56. †n=54. ‡=55. §n=52.

Table 1: **Baseline demographics and clinical characteristics**

	Methylprednisolone (n=66)	Placebo (n=64)
0	52	23
1	7	24
2	5	11
3	2	5
4	0	0
5	0	1

Data are number of patients, ranged by number of relapses.

Table 2: **Distribution of documented relapses between 0 and 96 weeks**

	Methylprednisolone (n=49)	Placebo (n=53)
MSFC		
Baseline	–0·02 (0·70)	0·02 (0·64)
Week 48	0·12 (0·39)	0·01 (0·42)
Week 96	0·12 (0·52)	0·06 (0·33)
Paced auditory serial addition test		
Baseline	0·02 (0·97)	–0·03 (1·04)
Week 48	–0·06 (0·87)	0·15 (0·63)
Week 96	0·29 (0·77)	0·24 (0·68)
Nine-hole peg test		
Baseline	–0·02 (0·97)	0·02 (1·04)
Week 48	0·26 (0·43)	0·01 (0·62)
Week 96	0·07 (0·54)	–0·05 (0·61)
25-foot timed walking		
Baseline	–0·06 (1·2)	0·06 (0·74)
Week 48	0·15 (0·92)	–0·13 (0·55)
Week 96	–0·01 (1·26)	–0·03 (0·79)

Data are mean (SD). MSFC=multiple sclerosis functional composite.

Table 3: **MSFC and subscales. Baseline values and change from baseline to week 48 and to week 96**

	Methylprednisolone (n=54)	Placebo (n=56)	Difference (95% CI)	p
T2-lesion volume (mm^3)	–136·6 (1468·1)	464·7 (1628·0)	601·3 (14·7 to 1188·0)	0·045
Normalised brain parenchymal volume (%)	–1·33 (1·23%)	–1·60 (1·22%)	0·27 (–0·19 to 0·74)	0·25

Data are mean (SD), mean change from baseline (%), or difference (95% CI).

Table 4: **Change from baseline in T2-lesion volume and normalised brain parenchymal volume**

	Neutralising antibodies		Yearly rate ratio	p
	Negative	Positive		
Yearly relapse rate				
Methylprednisolone	0·24 (0·16–0·38)	0·16 (0·06–0·42)	1·55 (0·15–4·56)	0·43
Placebo	0·52 (0·38–0·70)	0·88 (0·58–1·33)	0·59 (0·35–0·98)	0·04
New or enlarging T2 lesions				
Methylprednisolone	2·28 (1·57–3·33)	4·03 (2·27–7·16)	0·57 (0·30–1·08)	0·08
Placebo	2·66 (1·90–3·72)	5·86 (3·66–9·37)	0·45 (0·26–0·78)	0·005

Data are mean (95% CI).

Table 5: **Yearly relapse rate and number of new or enlarging T2 lesions on MRI in patients grouped according to neutralising antibody status**

	Methylprednisolone (n=66)	Placebo (n=64)
Influenza-like symptoms	3	2
Muscle tenderness	8	4
Fever	2	4
Fatigue	4	2
Irritation or pain at injection site	2	3
Psychiatric symptoms	17	7
Infections	32	25
Gastrointestinal symptoms	14	10
Headache	5	6
Pain	9	8
Neurological symptoms*	18	12
Endocrine disturbance	8	6
Cardiovascular symptoms	6	5
Skin symptoms	8	8
Autonomic disturbance	4	..
Sleep disturbance	17	5
Osteoporosis or osteopenia	3	3
Respiratory disturbance	4	1
Laboratory test result abnormalities	11	2
Other	15	8

Data are number of events. *Most commonly dysgeusia and ageusia.

Table 6: **Adverse events according to treatment group**

	NORMIMS (n=66)	ACT (n=74)	SENTINEL (n=589)
Baseline demographics			
Age (years)	37·8	42·9	38·8
Proportion men	44%	28%	25%
Time since onset of symptoms (years)	5·3*	10·7	7·0*
EDSS score	2·5	2·8	2·4
Relapses during previous 12 months	1·6	1·3	1·4
Duration of interferon beta-1a treatment (years)	2·8	2·8	2·8
Efficacy measures			
Reduction in relapse rate	62% (p<0·0001)	30%	55% (p<0·001)
Reduction in progression rate	38% (p=0·29)	..	24% (p=0·02)
Reduction in new or enlarging T2 lesions	23% (p=0·24)	..	83% (p<0·001)

Data are mean, unless otherwise indicated. ..=not done. *Median.

Table 7: **Comparison of methylprednisolone add-on groups in NORMIMS and ACT trials and the natalizumab add-on group in the SENTINEL trial**

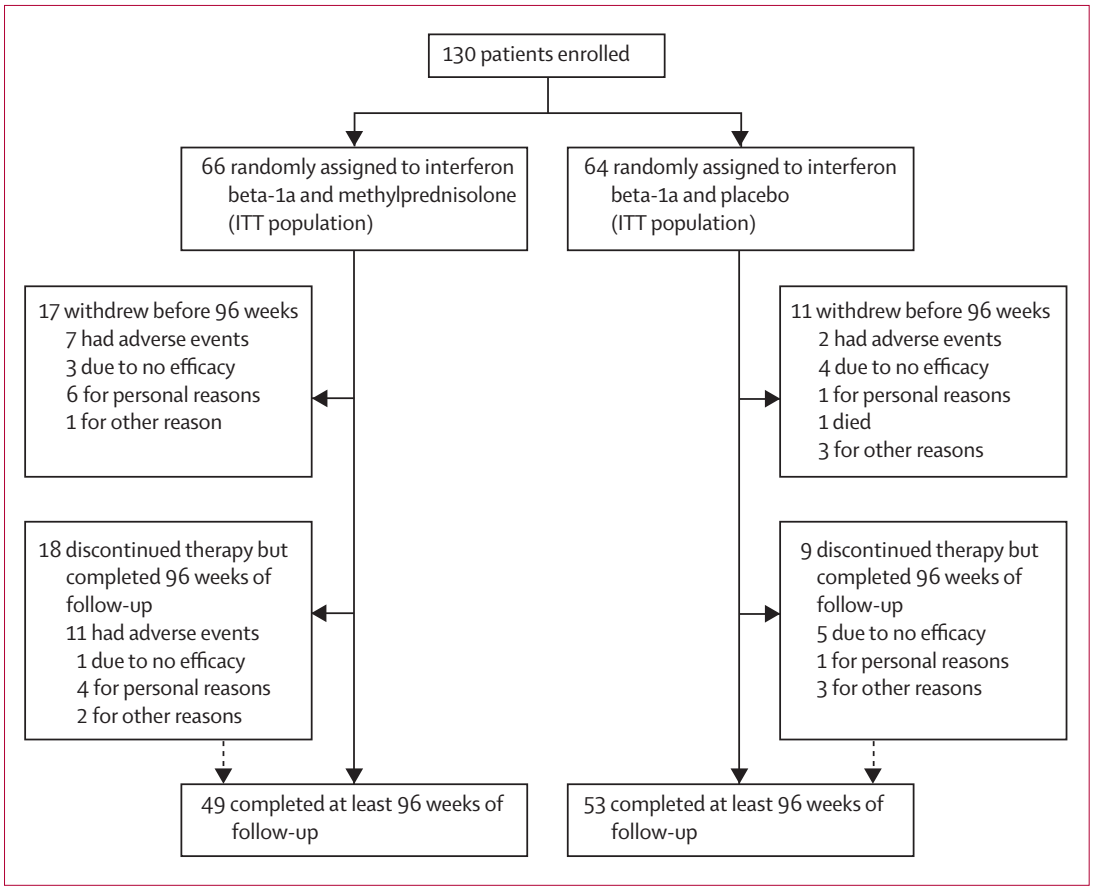

***Figure 1*: Trial profile**
ITT=intention to treat.

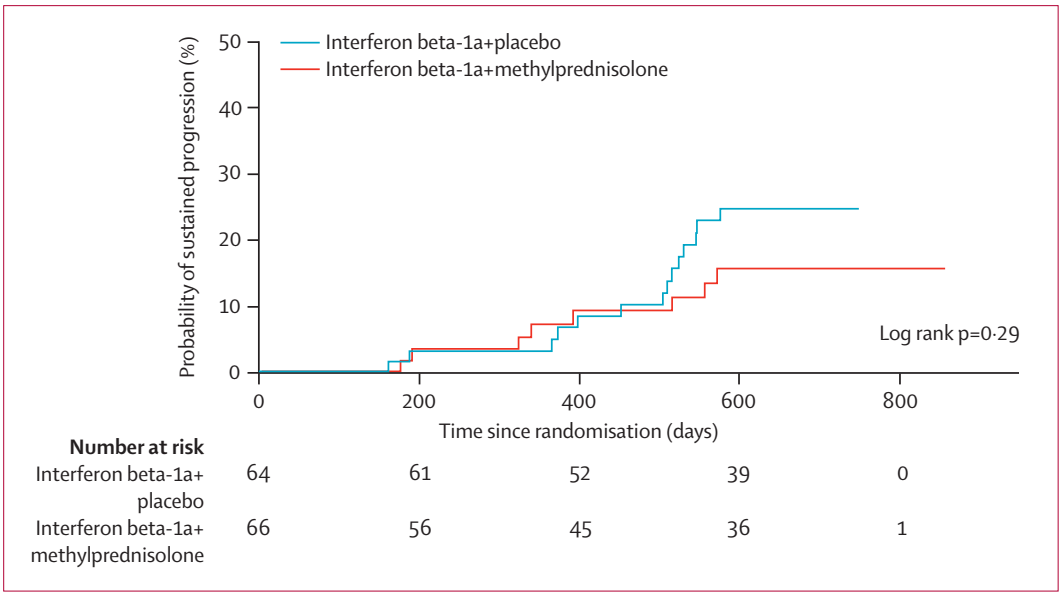

***Figure 2*: Kaplan–Meier plots of time to sustained progression of disability**