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Original Research Paper

Monthly oral methylprednisolone pulse treatment in progressive multiple sclerosis

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Abstract

Background: There is a large unmet need for treatments for patients with progressive multiple sclerosis (MS). Phase 2 studies with cerebrospinal fluid (CSF) biomarker outcomes may be well suited for the initial evaluation of efficacious treatments.

Objective: To evaluate the effect of monthly oral methylprednisolone pulse treatment on intrathecal inflammation in progressive MS.

Methods: In this open-label phase 2A study, 15 primary progressive and 15 secondary progressive MS patients received oral methylprednisolone pulse treatment for 60 weeks. Primary outcome was changes in CSF concentrations of osteopontin. Secondary outcomes were other CSF biomarkers of inflammation, axonal damage and demyelination; clinical scores; magnetic resonance imaging measures of disease activity, magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI); motor evoked potentials; and bone density scans.

Results: We found no change in the CSF concentration of osteopontin, but we observed significant improvement in clinical scores, MTR, DTI and some secondary CSF outcome measures. Adverse events were well-known side effects to methylprednisolone.

Conclusion: Monthly methylprednisolone pulse treatment was safe, but had no effect on the primary outcome. However, improvements in secondary clinical and MRI outcome measures suggest that this treatment regimen may have a beneficial effect in progressive MS.

Keywords: Progressive multiple sclerosis, methylprednisolone, clinical trial, osteopontin, magnetization transfer ratio, cerebrospinal fluid

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Introduction

While there has been substantial progress in the treatment of relapsing–remitting multiple sclerosis (MS), the treatment of progressive MS remains a challenge. It is often assumed that neuronal and axonal degeneration is more important than inflammation-induced damage in progressive MS, but pathology studies show that disease progression is associated with inflammation in grey matter (GM), normal-appearing white matter (NAWM) and meninges.[1] Furthermore, several studies, including a recent study from our group, found increased systemic immune activation in progressive MS.[2] Osteopontin and other biomarkers of inflammation are elevated in the cerebrospinal fluid (CSF) of progressive MS patients, and osteopontin levels correlate with the Expanded Disability Status Score (EDSS) and biomarkers of tissue damage at the time of sampling.[3–5] Indeed, we recently showed that osteopontin and other markers of inflammation and tissue damage decrease after treatment with natalizumab in progressive MS patients.[6]

One previous study reported a significant decrease in EDSS score in primary progressive MS (PPMS) patients treated with intravenous methylprednisolone[7] Another trial failed to meet its primary endpoint (proportion of patients with progression), but showed some effect of methylprednisolone treatment on the

time to progression in secondary progressive MS (SPMS).[8] These results led us to investigate the effect of oral methylprednisolone pulse treatment in progressive MS on the CSF concentration of osteopontin and a panel of other CSF and magnetic resonance imaging (MRI) biomarkers of disease activity in MS

Material and methods

Patients

Patients were from our centre from August 2011 to May 2012. Patients were aged 18–65 years, had an EDSS score ⩽6.5 and had progressed at least one EDSS point (0.5 if EDSS was higher than 5.5) or two functional system points in the last two years before inclusion. None of the patients received any form of immunomodulatory or immunosuppressive drugs when entering the study (see Supplementary Table 1 for detailed inclusion and exclusion criteria).

Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry (DXA) scanning at screening and week 60. Osteoporotic patients (T-score below -2.5) were not eligible for the study. Osteopenic patients (T-score between -1.0 and -2.5) could be included if treated with bisphosphonates. All patients received calcium (1000 mg daily) and vitamin D supplementation (20 µg daily), and continued to take their usual medications.

Standard protocol approval, registration and patient consents

The study was initiated and driven by the investigators, performed according to the EU directive of good clinical practice and the Declaration of Helsinki, registered at clinicaltrials.gov (NCT01305837) and approved by the Danish Health and Medicines Authority and the local ethics committee. Written informed consent was obtained from all study participants.

Study design and procedures

Patients were treated with oral methylprednisolone 500 mg (Medrol, Pfizer, Denmark) for three days every fourth week. Supplementary Figure 2 shows procedures for the study visits. Lumbar punctures were performed at baseline and week 60. The same neurologist (RR) assessed EDSS, multiple sclerosis functional composite (MSFC)[9] and multiple sclerosis impairment scale (MSIS).[10] The patients answered the short form-36 questionnaire (SF-36).[11] Motor evoked potentials (MEP) were performed at baseline, week 12 and week 60. MRI endpoints included number of gadolinium-enhancing lesions (GdEL), new and enlarging T2 lesions, percentage brain volume change (PBVC), change in T2 lesion volume, NAWM and cortical (GM) volume and change in diffusion tensor imaging (DTI)-based indices (mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD) and fractional anisotropy (FA)) and magnetization transfer ratio (MTR)[6]. MRI was performed at baseline, week 12 and week 60 to account for pseudoatrophy.

Cerebrospinal fluid analyses

CSF samples were analysed by enzyme linked immunosorbent assays (ELISA) and colorimetric assays: osteopontin, CXCL13 and MMP-9 Quantikine ELISA and nitrite/nitrate (NO_x) colorimetric assay (all R&D Systems, USA); NF-Light neurofilament (NfL) ELISA (UmanDiagnostics, Sweden); and myelin basic protein (MBP) ELISA (Beckman Coulter, USA) as described previously.[4] Samples from the same patient were analysed on the same plate.

Magnetic resonance imaging

MRI scans were performed using a 3T Siemens Trio scanner (Siemens, Germany) to acquire three-dimensional whole brain scans using T1-weighted (pre- and post-gadolinium), T2-weighted, fluid attenuated inversion recovery (FLAIR), magnetization transfer, and diffusion sequences, as previously described in detail.[6]

Motor evoked potentials

Transcranial and spinal root magnetic stimulation was performed using a Magstim 200 magnetic stimulator (Magstim Company, UK). Recordings were taken from musculus tibialis anterior bilaterally, using a Viking Select EMG apparatus (Nicolet, USA) and surface electrodes. MEP latencies were measured from the first deflection of the baseline, and central motor conduction time (CMCT) was calculated by subtracting the root latency from cortical latency of the muscle responses.

Outcomes

Primary outcome measure was the concentration of osteopontin in the CSF. Secondary outcome measures of inflammation and disease activity were: changes in CXCL13, MMP-9, NO_x, CSF cell count, IgG-index and CSF/serum albumin concentration quotient (Q_{alb}); number of GdELs, volume of T2 lesions and new or larger T2 lesions. Secondary outcome measures of

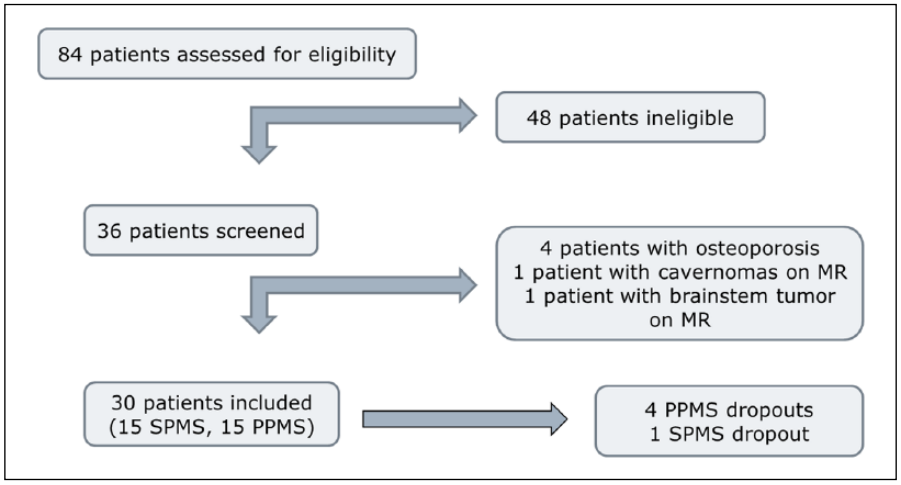

Figure 1. Flowchart of patient inclusion. Of the five patients who discontinued the study prematurely, the four PPMS patients did it due to adverse events and the SPMS patient did it due to personal reasons.

axonal damage and demyelination were: NfL and MBP in CSF, mean CMCT assessed by MEP and MRI outcomes (PBVC, MTR and DTI (FA, MD, AD and RD) diffusivity in NAWM, GM and T2 lesions). Secondary clinical outcomes were changes in EDSS, MSIS, MSFC, T25FW, 9HPT, PASAT and SF-36. Safety measures were number and type of adverse events (AE) and changes in BMD.

Power estimates and statistical analysis

We calculated sample size by projected effects on the CSF concentration of osteopontin. In a previous study we observed no significant change over one year in CSF concentrations of osteopontin in placebo-treated patients with SPMS, with a standard deviation of 29% for change.[4] Assuming similar stability for patients with PPMS and SPMS, and using a 5% significance level for paired t-test and a power of 80%, the estimated size for each subgroup (PPMS and SPMS) was nine to detect a treatment effect of an approximately 20% reduction in CSF osteopontin. A high dropout rate was expected due to methylprednisolone side effects, so we included 15 patients in each subgroup. Data were tested two-sided against the null hypothesis, with $p<0.05$ considered as significant. Statistical analyses were performed using SPSS 19 software (IBM, USA). Graphs were made using GraphPad Prism 6 (GraphPad Software Inc, USA).

Results

Eighty-four patients were assessed for eligibility. Thirty-six were screened, and 30 patients included in the study (Figure 1). Baseline characteristics are shown in Table 1. Four PPMS patients and one SPMS patient did not complete the study due to AEs or for personal reasons. Additionally one PPMS patient did not undergo lumbar puncture at week 60 because of concomitant anticoagulant treatment.

CSF outcome measures

Figure 2 summarizes the CSF outcomes. No change was found in the CSF concentration of osteopontin from baseline to week 60. There were no differences between SPMS and PPMS patients or between the sexes (data not shown). NfL decreased non-significantly, with 434 pg/ml (95% CI: 521;53 pg/ml) from 827 pg/ml (95% CI: 478;1177 pg/ml) at baseline (p=0.067). Four samples had detectable MMP-9 at baseline and MMP-9 was undetectable in all samples at week 60 (p=0.068). The IgG-index decreased, with 0.09 (95% CI: 0.02;0.15) from 0.86 (95% CI: 0.72;1.00) at baseline (p=0.009). A significant decrease in the IgG-index was also observed when patients with GdEL at baseline were excluded from the analysis (p=0.025). No changes were seen for oligoclonal bands, CXCL13, MBP, NO_x, CSF cell counts or the Q_{alb}.

Clinical outcomes, motor evoked potentials and SF-36

One patient had one relapse during the treatment period. Table 2 summarizes the changes in the clinical scores, MEP and the SF-36. The EDSS, MSIS and MSFC improved significantly from baseline to week 60. The improvement in MSFC was driven by the

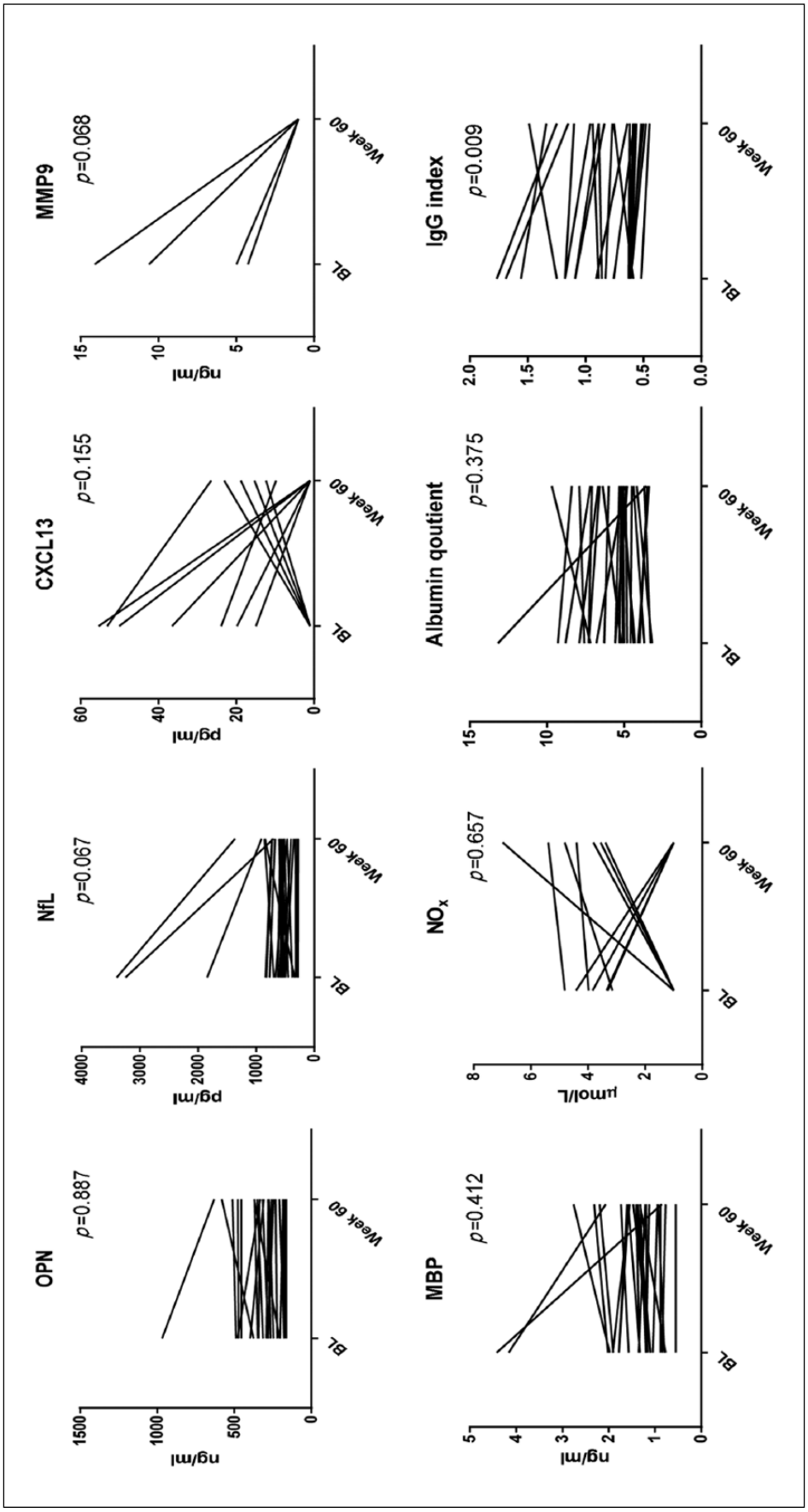

Figure 2. Change in the concentration of biomarkers of inflammation (osteopontin (OPN), CXCL13 and matrix metallorproteinase-9 (MMP9)), axonal damage (neurofilament light chain (NfL), demyelination (myelin basic protein (MBP)) and oxidative stress (NO_x) in the cerebrospinal fluid at baseline and after 60 weeks of oral methylprednisolone pulse treatment. OPN changes were analysed with the paired t-test, whereas the Wilcoxon signed rank test was used for the other biomarkers.

Table 1. Patient demographics. Values are presented as mean with interquartile ranges.

	SPMS	PPMS
Gender (women;men)	7;8	11;4
Age (years)	49 (41;52)	53 (50;57)
Disease duration (years)	12 (9;18	8 (4;16)
Duration of progressive phase (years)	4 (3;8)	8 (4;16)
EDSS progression previous two years	0.5 (0.5;1.5)	1 (0.5;1)
EDSS at baseline	5.5 (4.5;6.5)	5 (4;6)
Number of patients with relapse last year	1	0

MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale.

Table 2. Results of the clinical, neurophysiological and patient-reported outcomes: Expanded Disability Status Scale (EDSS), MS impairment scale (MSIS), MS functional composite (MSFC), including the subcomponents 9 hole peg test (9HPT), timed 25 foot walk (T25FW) and paced auditory serial addition test (PASAT). It further shows results of the short form-36 questionnaire (SF-36), including the subcomponents physical component summary (PCS) scale and mental component summary (MCS) scale, and results for motor-evoked potentials from musculus tibialis anterior bilaterally presented as mean central motor conduction time (CMCT). Change from baseline to week 60 is calculated as week 60 values minus baseline values. Values are presented as medians with interquartile ranges. Statistical analysis was by paired sample testing. Data which required non-parametric testing is marked with †.

	Baseline	Change baseline to week 60	p-value
†EDSS	5 (4.5;6.13)	−0.5 (–0.5;0.0)	0.011
MSIS	53 (39.5;63)	−7.0 (–11.5;–3.5)	0.00004
†MSFC	0.158 (–0.435;0.424)	0.166 (0.038;0.369)	0.0005
†T25FW	8.92 (6.30;12.65)	−2.27 (–4.10;–0.50)	0.001
†9HPT	25.95 (22.55;37.69)	−5.18 (–13.53;0.86)	0.004
PASAT	51 (38.5;57)	0.5 (–1.5;6.5)	0.12
SF-36	83.25 (75.85;96.39)	7.89 (–0.94;18.99)	0.009
PCS	34.29 (26.16;40.34)	4.73 (0.52;10.79)	0.0002
MCS	50.10 (43.33;61.82)	2.02 (–4.04;8.32)	0.429
CMCT (ms)	23.63 (20.50;29.65)	−0.60 (–1.55;2.83)	0.54

physical components T25FW and 9HPT. No change was seen in CMCT from baseline to week 60. The SF-36 increased significantly from baseline to week 60 due to improvement in the physical component summary scale.

MRI outcomes

Two patients had one and one patient had two GdELs at baseline. One patient had one GdEL at week 12, whereas no patients had GdELs at week 60. Nine patients had a total of eleven new lesions from baseline to week 12, and six patients had eight new lesions from week 12 to week 60 (difference in number of new lesions, p=0.083). From baseline to week 12 there were a median of 1.5 (IQR: 0;2.0) enlarging lesions, and from week 12 to week 60 there were a median of 1.5 (IQR: 1.0;2.0) enlarging lesions (p=0.954). Table 3 summarizes the other MRI outcomes. A significant decrease in PBVC was found from baseline to week 12 (and from week 12 to week 60. A significant decrease was found in lesion volume from baseline to week 60, and was mainly due to changes occurring between week 12 and week 60. Conversely, NAWM volume increased from baseline to week 12, but did not change significantly from week 12 to week 60. Cortical GM volume did not change significantly. An increase was observed in RD for GM, AD for NAWM and GM and MD for GM from baseline to week 12. This was followed by a significant decrease from week 12 to week 60 for MD in NAWM and GM, for AD in NAWM, and for RD in NAWM and GM. None of the changes in diffusivity led to significant changes in FA. Importantly MTR values increased for all measures (NAWM, lesions and GM) from baseline to week 60, and this increase was driven solely by the period from

Table 3. MRI results (atrophy, T2 lesions, magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI)). Baseline data are shown along with change from baseline to week 12, changes from week 12 to week 60, and changes from baseline to week 60. Data are shown as median with interquartile range. *p*-values are given for changes from baseline to week 12 and for changes from week 12 to week 60, respectively. Significant *p*-values are shown in **bold**. Statistical analysis was by paired sample testing. Data which required non-parametric testing (Wilcoxon signed rank) are marked with †.

		Baseline	Change baseline–week 12	*p*-value	Change week 12–week 60	*p*-value	Change baseline–week 60	*p*-value
Atrophy								
	PBVC (%)	N/A	−0.28 (−0.69;−0.02)	**0.007**	−0.46 (−0.91;−0.01)	**0.001**	−0.73 (−1.3;−0.38)	**0.000003**
	NAWM (cm^3)	693 (660;725)	4.3 (−3.9;8.1)	**0.001**	6.1 (−5.6;13.3)	0.053	7.9 (0.3;14.1)	**0.003**
	GM (cm^3)	587 (562;613)	−7.2 (−12.6;−1.1)	0.170	−7.3 (−13.9;2.2)	0.056	−6.4 (−13.7;−1.9)	**0.001**
T2 lesions								
	T2 lesion volume (mm^3)	3087 (1735;11664)	−19 (−141;61)	0.298 †	−183 (−344;16)	**0.027** †	−178 (−501;−8)	**0.009**
MTR								
	NAWM	39.2 (38.6;39.7)	−0.05 (−0.32;0.24)	0.466 †	0.4 (0.06;0.68)	**0.008**	0.33 (−0.04;0.56)	**0.009** †
	Lesions	32.5 (30.2;34.8)	0.18 (−1.02;0.78)	0.94 †	0.79 (0.25;1.42)	**0.0060**	0.84 (0.02;1.44)	**0.037**
	GM	31.6 (31.0;31.9)	0.07 (−0.38;0.53)	0.596 †	0.82 (0.23;1.22)	**0.0001**	0.86 (0.36;1.15)	**0.001** †
DTI								
	FA							
	NAWM	0.364 (0.347;0.379)	−0.002 (−0.005;0.002)	0.122 †	0.002 (−0.005;0.006)	0.627 †	−0.001 (−0.005;0.004)	0.543 †
	Lesions	0.271 (0.243;0.315)	0.004 (−0.009;0.007)	0.922 †	−0.0004 (−0.012;0.006)	0.829	−0.001 (−0.012;0.011)	0.889
	GM	0.136 (0.13;0.14)	0.0002 (−0.006;0.004)	0.871 †	−0.003 (−0.007;0.003)	0.168	−0.001 (−0.005;0.003)	0.35
	MD 10–10 (mm^2/s)							
	NAWM	7.5 (7.4;7.8)	0.032 (−0.021;0.065)	0.064 †	−0.057 (−0.132;−0.008)	**0.001**	−0.028 (−0.066;0.031)	0.339
	Lesions	11.1 (10.4;12.6)	0.016 (−0.222;0.269)	0.552 †	0.094 (−0.124;0.29)	0.775	0.163 (−0.197;0.484)	0.173
	GM	9.5 (9.0;9.6)	0.14 (0.002;0.208)	**0.004** †	−0.133 (−0.239;0.061)	**0.015**	0.039 (−0.077;0.161)	0.471
	AD 10–10 (mm^2/s)							
	NAWM	10.6 (10.6;10.9)	0.038 (−0.039;0.087)	**0.048** †	−0.057 (−0.132;−0.017)	**0.005**	−0.029 (−0.067;0.061)	0.405
	Lesions	15.4 (14.4;16.7)	0.149 (−0.144;0.328)	0.107 †	0.052 (−0.188;0.163)	0.675 †	0.118 (−0.215;0.378)	0.347
	GM	11.0 (10.6;11.2)	0.092 (0.013;0.296)	**0.004** †	−0.094 (−0.298;0.131)	0.109	0.084 (−0.081;0.22)	0.209
	RD 10–10 (mm^2/s)							
	NAWM	6.0 (5.7;6.2)	0.02 (−0.03;0.079)	0.157 †	−0.051 (−0.123;0.01)	**0.025**	−0.019 (−0.061;0.047)	0.624
	Lesions	9.6 (8.4;10.7)	0.049 (−0.225;0.249)	0.496 †	−0.007 (−0.139;0.285)	0.893 †	0.116 (−0.225;0.52)	0.255
	GM	8.7 (8.3;8.9)	0.0996 (−0.011;0.24)	**0.009** †	−0.117 (−0.248;0.064)	**0.017** †	0.047 (−0.059;0.154)	0.563

AD: axial diffusivity; FA: fractional anisotropy; GM: cortical grey matter; MD: mean diffusivity; N/A: not applicable; NAWM: normal appearing white matter; PBVC: percentage brain volume change; RD: radial diffusivity.

week 12 to week 60. A significant increase in MTR values was also observed when the patients with Gd-enhancing lesions at baseline were excluded from the analysis (all $p \leqslant 0.01$).

Adverse events and safety

A total of 125 AEs were reported (Supplementary Figure 3). Three of the AEs were considered serious (SAE): one patient was hospitalized due to a pseudo relapse, one patient had markedly elevated liver enzymes due to a cytomegalovirus infection and one patient had a deep venous thrombosis. None of the three SAEs were judged to be drug related. Ninety-seven of the 125 AEs were well-known side effects, such as insomnia, flushing, acne, metallic taste, palpitations, oedemas, down period after treatment and urinary tract infections in close temporal relation to treatment.

DXA scans showed a significant increase of the spine T-score of 0.14 (95% CI: 0.02;0.26) at week 60 from -0.93 (95% CI: -1.38;-0.47) (p=0.022). This increase was restricted to the 15 patients with osteopenia who received treatment with alendronate. No change was observed for the T-score at the hip (data not shown).

Discussion

This open-label phase 2A study used CSF and MRI biomarkers of intrathecal inflammation and tissue damage to investigate the effect of oral methylprednisolone pulse treatment in progressive MS patients. We found no change in the primary outcome measure, the CSF concentration of osteopontin, but observed significant clinical improvement and improvement in some secondary CSF and MRI outcome measures. As expected, treatment with methylprednisolone resulted in many AEs, but in spite of this, the drug seemed to be well tolerated, with no detrimental effect on bone density.

We found continuing brain volume loss beyond week 12, where we would normally expect to observe pseudoatrophy due to the anti-inflammatory effects of glucocorticoids. The mean PBVC from week 12 to week 60 was around the upper limit of normal recently reported for healthy control subjects,[12] and slightly lower than previously reported for the natural history of brain volume loss in progressive MS.[13] The observed increase in NAWM volume from baseline to week 12 is at least partly explained by a concomitant decrease in lesion volume. However, to our surprise, only T2 lesion volume, but not NAWM or GM volume, decreased significantly from week 12 to week 60. This might indicate a delayed treatment effect on inflammation. Indeed, GdELs were observed in a minority of patients at baseline and week 12, but not at week 60, and in spite of a longer period of follow-up, a trend to a lower number of new T2 lesions was observed between weeks 12 and 60 compared to baseline and week 12. This is supported by the trend towards normalization of MMP-9 concentrations in CSF, as MMP-9 has been associated with blood–brain barrier damage in MS.[14]

Patients with progressive MS have lower MTR values than healthy controls and relapsing–remitting MS patients, and MTR might be a useful biomarker of progression in MS.[15–17] We found a significant increase in MTR in NAWM, GM and lesions, which might indicate an anti-inflammatory effect, with a decrease in tissue water content or changes in myelination, although we observed no concomitant changes in the CSF concentration of MBP. This interpretation is further supported by the analysis of DTI indices, where we found decreases in MD in NAWM and GM, which is consistent with a decrease in extracellular water due to resolution of inflammatory oedema, although other effects might also contribute.

We observed clinical improvement as assessed by the EDSS, MSIS, MSFC and the SF-36 questionnaire. Since the study was uncontrolled and unblinded, these data should be interpreted with caution. Indeed, they were not associated with improvement in CMCT or in CSF concentrations of MBP or NFL. We previously reported the effects of monthly methylprednisolone pulse treatment on systemic immune cell activation, as assessed by flow cytometry after 12 weeks of treatment.[18] In an exploratory analysis we did not, however, find any correlation between clinical improvement and these immunological effects (data not shown).

Treatment possibilities for patients with progressive MS are limited.[19] Two previous studies indicated some efficacy of methylprednisolone pulse therapy in PPMS and SPMS.[7,8] In the present study we investigated the effect of methylprednisolone treatment using the same design as in our previous natalizumab study.[6] We expected to find an effect on the CSF concentration of osteopontin, but this was not the case. Plasma osteopontin concentrations may increase after methylprednisolone treatment, but we found no such increase in CSF in a previous study of patients treated with methylprednisolone for MS relapse, suggesting that glucocorticoid-induced increases in CSF osteopontin are an unlikely explanation for the lack of an effect in progressive MS.[5] Whether the concomitant

treatment with vitamin D in all patients could have an effect on the CSF concentration of osteopontin is unknown, but in supplemental analyses, we found no evidence that bisphosphonate treatment influenced our results. We did, however, observe a significant decrease in the IgG-index after treatment, and a borderline-significant reduction in CSF concentrations of MMP-9, which was not detected in CSF after treatment. We are currently investigating changes in a panel of other biomarkers of immune activation and oxidative damage in order to assess whether changes in these may explain the apparent effect of methylprednisolone pulse treatment on several of our secondary outcome measures.

In conclusion, we found no effect of monthly oral methylprednisolone pulse treatment on the CSF concentration of osteopontin in progressive MS patients, but observed effects on some secondary CSF outcome measures. Furthermore, the analysis of MRI and clinical measures suggests some beneficial effects, and future controlled trials of this treatment regimen are warranted.

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Conflict of interest

Rikke Ratzer has had travel expenses reimbursed by Merck Serono, TEVA, Biogen Idec and Sanofi-Aventis, Almiral and Genzyme. Pernille Iversen has received conference fee payment from Biogen Idec. Lars Börnsen has received support for congress participation from Novartis. Tim Dyrby has received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec. Jeppe Romme Christensen has received speaker honoraria from Genzyme and TEVA, consultant honoraria from Biogen Idec and Royalty Pharma, and has had travel expenses reimbursed by Merck Serono. Cecilie Ammitzbøll has had travel expenses reimbursed by TEVA and Biogen Idec. Camilla Gøbel Madsen has received conference fee payment from Biogen Idec. Ellen Garde has received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec. Mark Lyksborg has nothing to disclose. Birgit Andersen has nothing to disclose. Lars Hyldstrup has lectures sponsored by Novartis, Lilly, Takeda/Nycomed, Novo-Nordisk, Amgen, GlaxoSmithKline, Servier, MSD, Ferrosan, Pfizer, Pharma-Vinci A/S and Renapharma, and serves as advisory board member at Amgen. Per Soelberg Sorensen has served on scientific advisory boards for Biogen Idec, Merck Serono, Novartis, Genmab, TEVA, Elan and GSK, has been on steering committees or independent data monitoring boards in clinical trials sponsored by Merck Serono, Genmab, TEVA, GSK and Bayer Schering and he has received funding of travel for these activities; he has served as Editor-in-Chief of the *European Journal of Neurology*, and is currently editorial board member for *Multiple Sclerosis Journal, European Journal of Neurology*, and *Therapeutic Advances in Neurological Disorders* and has received speaker honoraria from Biogen Idec, Merck Serono, TEVA, Bayer Schering, Sanofi-aventis, Genzyme and Novartis; he has received payment for writing and reviewing manuscript from IBI Consulting, a division of Informa plc. His department has received research support from Biogen Idec, Bayer Schering, Merck Serono, TEVA, Baxter, Sanofi-Aventis, BioMS, Novartis, Bayer, RoFAR, Roche and Genzyme, and from the Danish Multiple Sclerosis Society, the Danish Medical Research Council and the European Union Sixth Framework Programme: Life sciences, Genomics and Biotechnology for Health. Hartwig R. Siebner has received honoraria as a speaker from Lundbeck A/S, Valby, Denmark, Biogen Idec, Denmark A/S and Genzyme, Denmark, has received honoraria as editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany, and travel support from MagVenture, Denmark. Finn Sellebjerg has served on scientific advisory boards for Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Teva; has served as consultant for Biogen Idec and Lundbeck; has received support for congress participation from Biogen Idec, Novartis, Sanofi Aventis and Teva; and has received speaker honoraria from Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi-Aventis and Schering-Plough. His laboratory has received research support from Biogen Idec and Novartis.

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