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Simvastatin improves final visual outcome in acute optic neuritis: a randomized study

Anna Tsakiri[1], Klaus Kallenbach[1], Dan Fuglø[2], Benedikte Wanscher[3], Henrik Larsson[2] and Jette Frederiksen[1]

Abstract

Background: In recent years, small-scale clinical trials have indicated that statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors exert pleiotropic immunomodulatory effects, with potential therapeutic implications in multiple sclerosis (MS).

Objective: To investigate whether simvastatin treatment (80 mg daily for 6 months) in patients with optic neuritis (ON) had a beneficial effect on visual outcome and on brain MRI.

Methods: Sixty-four patients with acute ON were randomized to simvastatin treatment ($n = 32$) or placebo ($n = 32$) for 6 months. None of the patients had been on immunosuppressive therapy for 6 months prior to inclusion or treated with steroids from symptom onset. Contrast sensitivity (Arden plates), visual acuity, colour perception, visual evoked potentials (VEP) – latency and amplitude, Visual Analogue Scale (VAS) score, and gadolinium enhancing and T2 lesions on brain MRI were evaluated at screening visit, day 14 (except brain MRI), day 90 and day 180.

Results: Simvastatin had a beneficial effect on VEP in both latency ($p = 0.01$) and amplitude ($p = 0.01$), a borderline effect on the Arden score ($p = 0.06$) and VAS ($p = 0.04$), and no effect on brain MRI or on relapse rate between the groups.

Conclusion: This study provides Class I evidence that simvastatin 80 mg daily is well tolerated and possibly effective in patients with acute ON.

Keywords

disease modifying therapies, multiple sclerosis

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Introduction

Optic neuritis (ON) represents an inflammatory and demyelinating condition of the optic nerve. It is one of the clinically isolated syndromes (CIS) suggestive of multiple sclerosis (MS), and approximately 30% of patients presenting with acute optic neuritis will develop MS within 5 years.[1–3] There is no known cure for ON. Much of the current understanding of the treatment comes from the Optic Neuritis Treatment Trial (ONTT).[4] In recent years, small-scale clinical trials have indicated that statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors exert pleiotropic immunomodulatory effects, with potential therapeutic implications in MS.[5–10] The mechanism by which statins may play a role in autoimmunity involves the inhibition of HMGCoA reductase. Besides the biosynthesis of cholesterol, this enzyme regulates the biosynthesis of isoprenoids, which results in a decrease of autoimmune responses.[11,12] The use of statins in the treatment of hypercholesterolaemia for the past 20 years has shown them to be very well-tolerated agents with few side effects.[13] In two small open-label studies a beneficial effect was observed regarding brain MRI lesions.[8,10] These results need to be reproduced in larger placebo-controlled studies.

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It is, however, not known whether simvastatin treatment as a single treatment initiated during the acute phase of ON may improve outcome or hasten recovery. We aimed to investigate whether simvastatin treatment initiated within 4 weeks after onset of ON had a beneficial effect on visual outcome after 6 months and on MRI disease activity assessed by the development of new enhancing lesions on MRI.

Methods

Patients

The patients were referred to the Optic Neuritis Clinic, Glostrup University Hospital, Denmark, from September 2006 to December 2008 by ophthalmologists and neurologists in Sealand and the county of Funen, which includes approximately 2.9 of 5.3 million inhabitants in Denmark. None of the patients received corticosteroids for ON, either at the referring centre or at the central trial site. Inclusion criteria were a clinical diagnosis of ON, age between 18 and 59 years, symptom duration of <4 weeks, and reduced contrast sensitivity, defined as a score of ≥78 on Arden gratings. The exclusion criteria were previous ON in the same eye, pregnancy and breastfeeding, immunosuppressive or steroid treatment within 6 months and 1 month, respectively, prior to inclusion, liver and kidney insufficiency, myopathy, hypothyroidism, diabetes, alcoholism, concomitant administration of fibrates, treatment with statins, and concomitant participation in other trials. The patients were estimated to be physically and mentally able to participate in a trial of 6 months' duration and they gave written informed consent before entering the study. According to the protocol, patients who experienced a relapse during the follow-up were treated with methylprednisolone for 2 weeks, and patients converting to Clinically Definite MS (CDMS) during the follow-up, if accepted, were treated with interferon-β concomitantly with the trial medication.

Standard protocol approvals, registrations and patient consents

The study was designed as a one-centre, parallel trial and was randomized, double-blind and placebo-controlled, evaluating the clinical efficacy of simvastatin treatment in patients with ON. The trial was conducted according to Good Clinical Practice (GCP) guidelines suggested by the International Committee on Harmonization. The trial was approved by the regional scientific ethics committee on human experimentation for any experiments using human subjects, and the Danish Medicines Agency. The trial was registered in the international database ClinicalTrials.gov with identifier NCT00261326. Written informed consent was obtained from all patients participating in the study.

Treatment assignment

The 64 patients were randomized in blocks of eight by a computerized random numbers system, which included two treatments: simvastatin (Alpharma Aps) 80 mg (two 40 mg tablets daily) ($n = 32$) or placebo (two tablets) ($n = 32$). The randomization and the coding of the treatment were prepared at the Central Pharmacy of Copenhagen University Hospital, Herlev. The sealed envelopes containing the randomization code were kept at the study site for safety reasons. The participants, who met all the inclusion and none of the exclusion criteria, were enrolled consecutively in the trial by the treating physician. At day 0 the treating physician delivered a sealed plastic tub with the randomization number to the patient. The treatment was initiated the same day in the evening, within 28 days from onset of symptoms and 7 days from the screening visit. Compliance was estimated by calculating the number of tablets remaining at the end of the trial.

Procedures

A general physical and neurological examination was performed in the Clinic of ON, Glostrup Hospital at screening visit and patients were scored on the Kurtzke Expanded Disability Status Scale (EDSS).[14] Blood tests included, among others, sedimentation rate, cobalamine, antinuclear antibody and treponemal antigen screening to exclude patients with other systemic diseases. Liver enzymes, creatinine kinase (CK), total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)-cholesterols, triglycerides and homocysteine were included to monitor side effects of simvastatin. To ensure blinding, the total cholesterol, LDL and HDL-cholesterol, triglyceride and homocysteine blood test results were seen and, if necessary, monitored by another physician in the neurological department, who was blinded to treatment allocation. Lumbar puncture was performed (day 0 prior to trial treatment) in 63 patients, and cell count, protein, glucose, IgG index and oligoclonal bands were measured in the cerebrospinal fluid (CSF).

Contrast sensitivity (CS) was assessed by Arden grating with a maximum score of 150. A score ≥78 was considered abnormal, based on gender- and age-matched normal material performed in our clinic. Visual acuity (VA) was assessed by the Snellen chart. When VA was <0.1, arbitrary scores were assigned for patients' ability to count fingers (0.02) or to register movement or presence of light (0.01). Colour vision

was assessed by Lanthony's desaturated 15-hue test[15] and by Velhagen pseudochromatic plates.[16] The patients assigned the severity of visual impairment to a 10-cm long VAS, where 0 cm was normal eyesight and 10 cm indicated blindness.

VEP was examined by checkerboard pattern reversal stimulation.[17] In the absence of a reproducible signal, latency was assigned an arbitrary value of 250 ms. Latency above 102 ms and amplitude below 5.0 μV were considered abnormal. Both the visual assessments and VEP analyses were undertaken by technicians blinded to the patients' treatment allocation.

Structural MRI was performed in the Unit of Functional Imaging, Glostrup Hospital on a Philips Achieva 3.0T whole body MRI scanner (Philips Healthcare, Best, The Netherlands). Numbers of T2 and Gd^+ enhanced T1 lesions were counted by a radiologist blinded to treatment allocation, and patients were classified according to McDonald criteria.

Follow-up

Patients were re-examined for all the mentioned tests on days 14 (except brain MRI), 90 and 180. Adverse events, changes in concomitant medication and relapses were confirmed and registered. Adverse events were classified according to Body System Classification.

Primary research question

Has simvastatin (80 mg daily for 6 months) improved contrast sensitivity assessed by Arden plates in patients aged 18 to 59 with acute ON after a 6-month treatment period?

Statistics

Sample size calculations were based on our previous trials including patients with ON. The sample size was calculated to reveal a true difference of 17 points on Arden gratings between treatment groups with a power of 80%, assuming a two-sided test at the 0.05 level. Based on findings in previous studies, this corresponds to a 50% reduction in the proportion of patients with abnormal contrast sensitivity after 6 months' follow-up. The statistical analysis of the experimental data was pre-specified in the trial protocol and was carried out by the study statistician (Statcon APS Denmark) by PROC MIXED in SAS 9.2 (SAS Institute Inc., Cary, North Carolina). It was based on the intention-to-treat principle, with all available follow-up data included, regardless of whether or not the patient had completed all the scheduled tablet treatment. The analysis was a mixed model including baseline as covariate and time, treatment and the interaction between these two. In case the data were not liable to be normally distributed, the two treated groups were compared with a non-parametric test at each time point. For the non-parametric test, a Wilcoxon Rank Sum test, with an approximate *t*-test and a Media Two Sample test, was carried out. For variables for which the normal approximation could be assumed, a repeated measures analysis (ANOVA) was carried out. No corrections were used for multiplicity issues, but the results were viewed in the light of the possibility that multiplicity issues might be present.

Results

A total of 169 patients with possible ON were referred to our department in the recruiting period. ON was confirmed in 144 patients, of whom 109 were eligible to participate in the trial, and 64 of them gave written informed consent after receiving detailed information. None of the randomized codes were broken until the statistical analysis of the data. Two patients in the simvastatin and three in the placebo group discontinued the study (Figure 1).

MRI at day 0 was performed in 62 patients (31 in the simvastatin and 31 in the placebo group) and at day 180 in 55 patients (27 in simvastatin and 28 in placebo). Claustrophobia was the reason why two patients did not participate in MRI scans at day 0.

Baseline results

Baseline characteristics are summarized in Table 1. Ten patients (31.3%) in the simvastatin group and 17 (56.7%) in the placebo group had a score of 5 in the optic function in Kurtzke's EDSS at baseline. The difference was reflected in the total EDSS score: the patients in the simvastatin group had a median EDSS score of 2.5, and in the placebo group the median score was 5. Thus, the median EDSS score was predominantly determined by the optic function, since very few patients had previous neurological symptoms, and the symptoms were very mild, with no great influence on the EDSS score in the rest of the functional systems. The baseline difference regarding the visual outcome (Table 2) was not significantly different between groups, and it was taken into account by the statistical model used. Abnormal VEP latency was registered in 95% of the patients.

Treatment effect on primary outcome

The primary outcome measure, contrast sensitivity assessed by Arden grating, was slightly lower in the simvastatin group ($p = 0.0572$) (Figure 2). The mean values

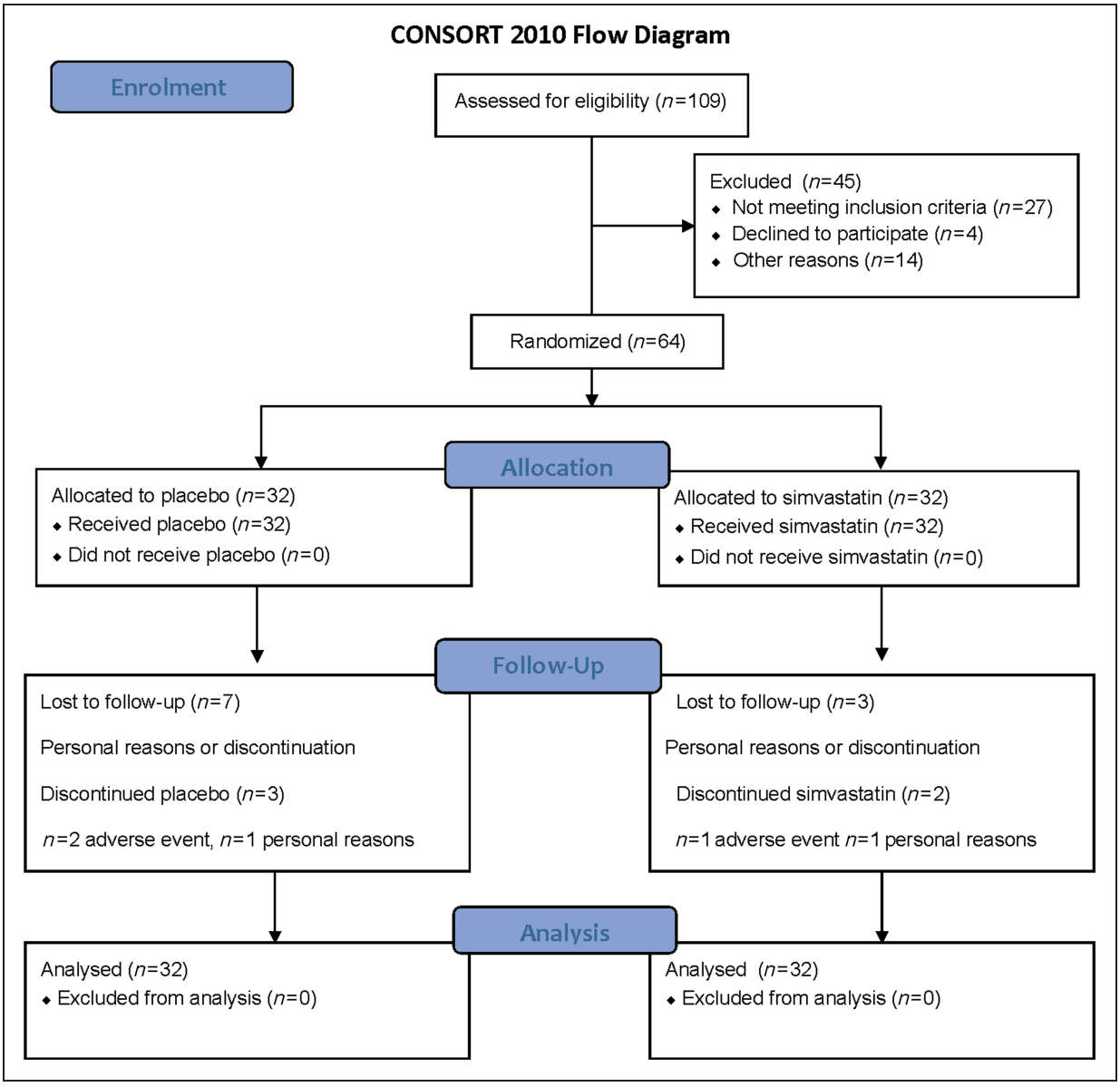

Figure 1. Flow chart for patients.

of the visual outcome during the treatment are shown in Table 2.

Treatment effect on the secondary outcome

There was no statistically significant difference between groups in VA and colour perception. Colour perception by Velhagen pseudoisochromatic was slightly better in the simvastatin group ($p = 0.0531$). There was a significant effect on the secondary effect variables VEP latency ($p = 0.0132$) and VEP amplitude ($P = 0.0103$) for simvastatin (Fig. 2). Ten patients in the simvastatin group and 14 in the placebo group had VEP latency = 250 ms and VEP amplitude = 0 μV at baseline. The corresponding mean latency at day 14 was 184 ms and 199 ms and amplitude 3.6 μV and 2.3 μV respectively ($n = 4$ and $n = 11$ [latency = 250 and amplitude = 0] respectively). At day 90 the corresponding mean values were 172 ms and 182 ms and 7.2 μV and 4.8 μV respectively ($n = 3$ and $n = 6$ respectively). At day 180 the corresponding mean values were 154 ms and 172 ms and 8.3 μV and 4.8 μV respectively ($n = 3$ and $n = 5$ respectively). At day 14 two new cases in the placebo group and none in the simvastatin group were found with latency = 250 and amplitude = 0.

Also, self-evaluated visual function assessed by VAS was better in the simvastatin group ($p = 0.0391$). A strong significant effect of time was seen in both groups regarding all the parameters mentioned above ($p < 0.0001$) (Table 2).

Table 1. Baseline characteristics of patients

Baseline characteristics	Simvastatin $n=32$	Placebo $n=32$	Total $n=64$
Age, years, mean (min;max)	35 (18;47)	33 (21;50)	
Gender, female, N (%)	24 (37.5)	16 (25.0)	40 (62.5)
EDSS, median (Q1;Q3)	2.5 (2;5)	5 (2;5)	
N (%) of patients with monosymptomatic ON	30 (93.8)	30 (93.8)	60 (93.8)
Duration of ON symptoms at day 0: days, mean (min;max)	12 (7;26)	15 (5;28)	13.5 (3;28)
N (%) of patients with previous neurological symptoms suggestive for MS	5 (15.6)	3 (9.4)	7 (12.5)
• *N* (%) of patients with previous ON	3 (9.4)	1 (3.1)	4 (6.2)
• *N* (%) of patients with other neurological symptoms	2 (6.2)	1 (6.2)	3 (6.2)
Detected oligoclonal bands in the CSF, *N* (%)	23 (36.5)	21 (33.5)	44 (70)
Dissemination in space (three of four McDonald criteria, brain MRI)	3 (9.4)	2 (6.2)	5 (7.8)

CSF: cerebrospinal fluid, EDSS: Expanded Disability Status Scale, ON: optic neuritis, N=Number of patients, (%)= Percentage of patients

The total number of Gd^+ lesions on brain MRI at screening visit was four in the simvastatin group and three in the placebo group; on day 90, four and two and on day 180, two and one respectively. The total number of T2 lesions on brain MRI at the screening visit was 153 in the simvastatin group and 140 in the placebo group; on day 90, 137 and 139 and on day 180, 135 and 146 respectively. Overall no statistical difference was observed between the groups ($p > 0.05$).

Follow-up characteristics

Five patients in the trial experienced relapse during the follow-up and were treated with medrol. Seven patients (11%) were diagnosed with CDMS at the end of the trial. Of these, four in the simvastatin group and two in the placebo group initiated interferon-β concomitant to the trial treatment. Sixteen patients (25%) were diagnosed with MS according to McDonald criteria at the end of the trial (Table 1).

Safety and compliance

The high-dose simvastatin was tolerated very well; adverse events were few and mild and were not different from the placebo group (Table 3), which was favourable to ensuring blindness for both the assessing physician and the patients. The levels of liver enzymes and CK were not significantly different between the groups. Total cholesterol ($p = 0.0005$) and LDL-cholesterol ($p < 0.0001$) were reduced while HDL-cholesterol ($p = 0.0049$) was elevated in the simvastatin group at day 180. The adverse events are listed in Table 3.

Two patients in each group had experienced a serious adverse event (SAE) (Table 3). A high level of CK was discovered by routine blood test (day 14) in one patient treated with simvastatin; it had probably been caused by hard exercise during the week prior to CK elevation. The patient chose to discontinue the treatment and the CK was normalized within a week. One patient presented with an ovarian cyst during treatment with simvastatin, but did not discontinue the treatment. In the placebo group, one patient experienced syncope and one presented with depression. Both discontinued the trial treatment.

The compliance assessed using tablet returns was >95% in both groups. According to the measurements of LDL-cholesterol levels in the simvastatin group, all the patients, except those two who had discontinued the treatment due to adverse events or for personal reasons, had significantly reduced LDL-cholesterol levels on day 180 compared with day 0.

Discussion

The study was designed as a single-centre, randomized, double-blind, placebo-controlled trial, evaluating the clinical efficacy of simvastatin treatment in patients with ON. The daily dose of 80 mg simvastatin (the highest Food and Drug Administration (FDA)-approved dose) was chosen on the basis of promising clinical results and good tolerability of statins.[10,18,19]

The primary efficacy outcome of our study was to find out whether the visual function measured by the Arden contrast sensitivity plates was improved by simvastatin treatment after 180 days. We found that simvastatin tended to improve the primary outcome ($p = 0.0572$). From the secondary outcome measures, significant improvement in the simvastatin group was observed regarding VEP latency ($p = 0.013$) and VEP amplitude ($p = 0.0103$). Self-evaluation with VAS was also improved in the simvastatin group, contributing to the beneficial effect of simvastatin ($p = 0.0391$). Previous studies regarding treatment of ON patients

Table 2. Visual outcome during the follow-up

	Placebo					Simvastatin					
Outcome measures	Min	Max	Mean	*N*	95% CI	Min	Max	Mean	*N*	95% CI	*p* value
Arden contrast sensitivity											
Baseline	79	150	139	32	132;147	92	150	133	32	125;141	0.2147
Day 14	61	150	120	32	110;131	49	150	109	32	98;119	
Day 90	62	150	97	28	87;106	50	150	87	30	79;94	
Day 180	51	150	93	31	82;103	45	150	84	29	76;92	
Visual acuity											
Baseline	0	1	0.3	32	0.1;0.4	0	1	0.4	32	0.3;0.6	0.1067
Day 14	0	1	0.5	32	0.4;0.7	0.01	1	0.7	32	0.5;0.8	
Day 90	0	1	0.7	28	0.6;0.8	0.02	1	0.9	30	0.8;0.9	
Day 180	0	1	0.8	31	0.7;0.9	0.01	1	0.9	29	0.8;1	
Lanthony desaturation D-15 test											
Baseline	2	105	75	32	61;89	0	105	57	32	41;74	0.0779
Day 14	0	105	45	32	28;61	0	105	33	32	18;47	
Day 90	0	105	28	30	15;40	0	105	24	30	10;37	
Day 180	0	105	28	29	15;41	0	105	20	29	7;33	
Velhagen pseudoisochromatic test											
Baseline	0	21	14	32	12;17	0	21	12	32	9;15	0.2367
Day 14	0	21	10	32	6;13	0	21	7	32	4;10	
Day 90	0	21	7	30	4;10	0	21	4	30	2;6	
Day 180	0	21	7	29	4;9	0	21	3	29	1;6	
Visual analog scale											
Baseline	1.6	10	7	32	6.1;7.9	0.3	10	6.2	31	5.0;7.4	0.4361
Day 14	0	10	4.5	30	3.4;5.6	0	7.9	3.4	31	2.4;4.4	
Day 90	0.2	10	2.7	28	1.6;3;7	0	7.6	1.9	29	1.1;2.7	
Day 180	0	10	2.4	31	1;43.4	0	7.3	1.7	29	0.8;2.5	
VEP latency, ms											
Baseline	100	250	182	32	159;205	92	250	167	32	144;189	0.3465
Day 14	93	250	170	32	149;191	89	250	144	32	128;160	
Day 90	93	250	158	27	127;180	88	250	138	30	122;153	
Day 180	92	250	155	30	135;174	89	250	133	29	117;150	
VEP amplitude, μV											
Baseline	0	21.1	4.17	32	2.22;6.11	0	20.7	5.54	32	3.39;7.69	0.1367
Day 14	0	20	5.36	32	3.29;7.43	0	31.2	8.12	32	5.54;10.7	
Day 90	0	80.6	7.25	27	4.98;9.53	0	31.5	9.91	30	7.18;12.6	
Day 180	0	23.4	7.15	30	4.90;9.41	0	21.6	9.56	29	7.26;11.8	

CI: confidence interval.

were not able to demonstrate efficacy on the visual outcome.[20–22]

The high dose of simvastatin was very well tolerated, with only one discontinuation of the treatment due to side effects. Only five patients experienced relapse during the follow-up period in this trial. Compared with the earlier trials of our group,[20,21] the number of patients with MS included in this study was very low, and consequently the development of relapses was also low, due to the improved criteria for the diagnosis and early treatment of MS.[23] Increased VEP latency, presumed to reflect the degree of optic nerve fibre demyelination, occurs at an early stage in acute ON and undergoes a progressive shortening for at least 2 years. Although ion channel reorganization may play a part, the most likely explanation would seem to be an ongoing process of remyelination.[24] Increased latency is detected in 57–94% of patients with MS without a history of ON, most likely reflecting clinically silent demyelination of the optic pathways,[25] and in 30–40% of

Table 3. Adverse events

	Simvastatin			Placebo		
Number of exposed subjects	$N = 32$			$N = 32$		
Adverse events by Body System Classification	N	(%)	E	N	(%)	E
Serious adverse events	2	(6.2%)	2	2	(6.3%)	2
Cardiovascular symptoms	2	(6.2%)	2	1	(3.1%)	1
Fatigue	2	(6.2%)	2	1	(3.1%)	1
Flu-like symptoms	1	(3.1%)	1	0	(0.0%)	0
Gastrointestinal symptoms	8	(25.%)	10	5	(15.6%)	7
Headache	0	(0.0%)	0	4	(12.5%)	4
Infection	5	(15.6%)	7	3	(9.4%)	4
Laboratory disturbances	2	(6.2%)	3	0	(0.0%)	0
Musculoskeletal disorders	3	(9.4%)	3	5	(15.6%)	6
Neurological symptoms	6	(18.7%)	6	4	(12.5%)	4
Other	1	(3.1%)	1	0	(0.0%)	0
Psychiatric symptoms	1	(3.1%)	1	3	(9.4%)	3
Renal and urinary disorders	1	(3.1%)	1	0	(0.0%)	0
Reproductive system	2	(6.2%)	2	1	(3.1%)	1
Skin symptoms	0	(0.0%)	0	4	(12.5%)	4
Adverse events total	36	–	41	33	–	37
Adverse events by intensity						
Mild	18	(84.6%)	33	15	(68.6%)	24
Moderate	5	(15.4%)	6	5	(25.7%)	9
Severe	0	(0.0%)	0	2	(5.7%)	2

E: the total number of adverse events that occurred during the trial, N: number of patients who experienced an adverse event

patients with ON an increased latency is detected in the unaffected eye.[26] An increased latency persists even in cases in which VA recovers.[27–29]

VEP amplitude may be very much attenuated during the early stages of ON, but usually recovers over the ensuing weeks, roughly in parallel with the improvement of VA. Two trials in MS aiming at functional repair have used VEP as a secondary outcome measure, and, along with other measures, failed to prove efficacy of intravenous immunoglobulins for chronic visual impairment[30] or visual outcome after acute ON.[21] A meta-analysis of 12 randomized, controlled trials of corticosteroid treatment in patients with ON and MS confirmed that, although high-dose intravenous corticosteroids were effective in improving short-term visual recovery, there was no statistically significant benefit on long-term outcome.[31] In our study corticosteroids were given only to patients who experienced a relapse (except for ON) during the treatment period. The serious side effects of high-dose corticosteroids outweigh their short-term beneficial effect, and therefore corticosteroids are not a standard treatment for ON in our clinic. Methylprednisolone is not standard therapy for acute optic neuritis in Denmark, based on our finding that it has no effect on the visual function in the long term (8 weeks from start of treatment).[32] We are aware that it is standard treatment in some other countries. As far we know, no reports exist yet regarding comparison between methylprednisolone and statins in MS relapse.

Concern was expressed that statins block the anti-inflammatory effect of interferon (IFN)-beta in combination therapy[33] and for this reason an interim analysis was performed of the Simvastatin as an Add-on Treatment to Interferon-Beta-1a for the Treatment of Relapsing-Remitting Multiple Sclerosis (SIMCOMBIN) trial. It was found that simvastatin does not block the anti-inflammatory effect of IFN-beta when these drugs are taken together by patients with MS. There was no significant difference in the time to first relapse between the two treatments, and no difference in the annualized relapse rate.[34]

Our study, as the first clinical trial, shows an improvement of VEP regarding both the latency and the amplitude in patients with acute ON treated with simvastatin, and the findings point towards efficacy of simvastatin, supporting current data from a double-blind placebo-controlled study investigating simvastatin add-on interferon treatment in patients with Relapsing

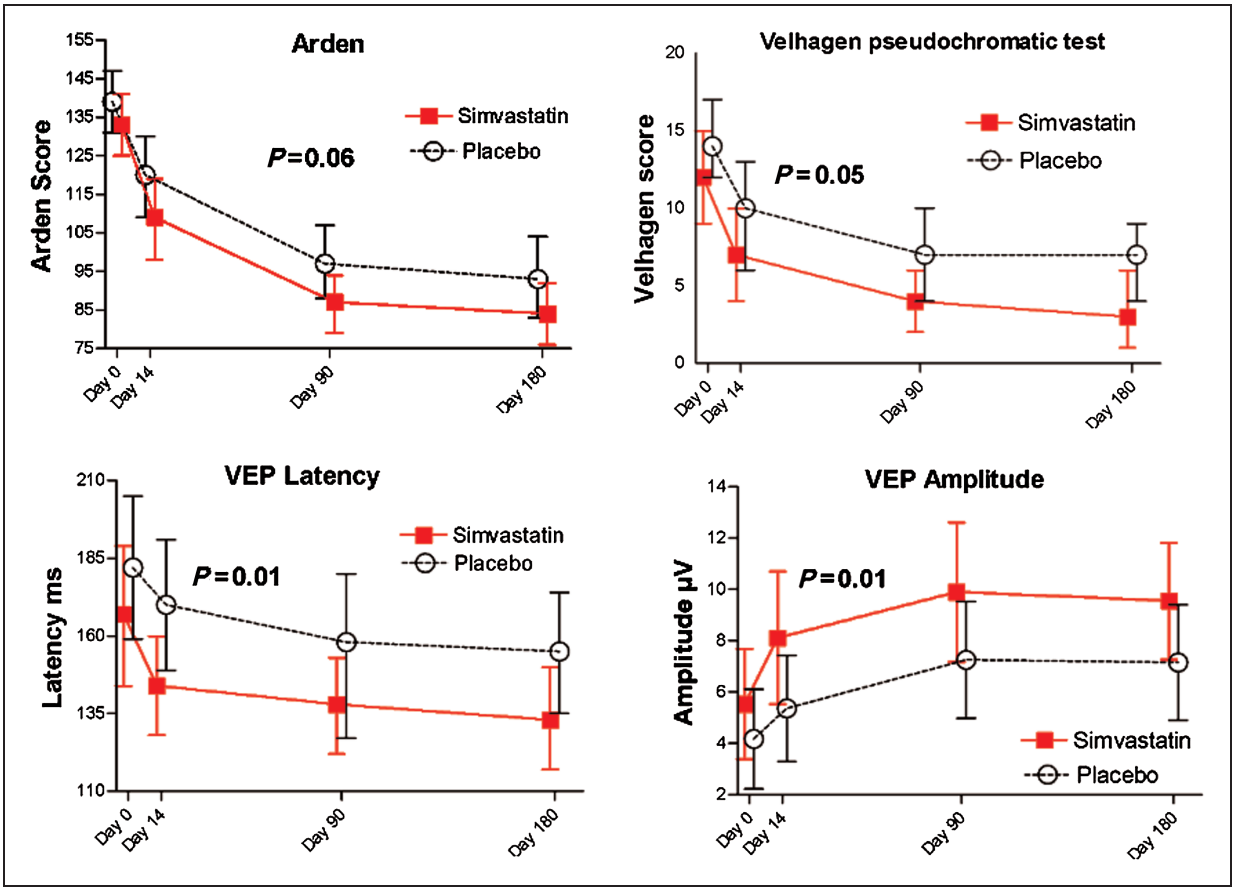

Figure 2. Mean and 95% CI of the Arden score (primary outcome), Velhagen colour test, VEP latency and VEP amplitude (secondary outcomes) in the simvastatin group and the placebo group during the follow-up.
CI: confidence interval, VEP: visual evoked potential.

Remitting Multiple Sclerosis (RRMS).[35] The beneficial effect of simvastatin on VEP might be due to promotion of the remyelination of the optic nerve and axon repair, according to earlier reports regarding the beneficial effect of statins in remyelination and repair. Thus, in previous studies using an experimental autoimmune encephalomyelitis (EAE) model induced by immunization with myelin basic protein (MBP) in rats as well as in different EAE models in mice, an improved clinical outcome and delayed manifestation of the disease were observed under statin treatment.[36–38] In addition, the anti-inflammatory and neuroprotective effects of statins in EAE were reported to be due to the ability of statins to alter the level of isoprenoids in situ, and thus Rho family functions in glial cells. Furthermore, simvastatin inhibited the formation of new inflammatory lesions in the CNS in both MS and EAE, in association with sparing of Oligodendrocytes (OLGS) and enhanced myelin repair by progenitor cells.[10,38,39]

A beneficial effect of simvastatin on the number of Gd^+ lesions (mean at baseline = 2.31) was reported in a trial performed on patients with RRMS and with no control group.[10] We found no difference between groups regarding new enhancing lesions on MRI, probably due to the low number of Gd^+ lesions at baseline (mean = 0.15). The total number of T2 lesions on brain MRI was reduced by 12% during the follow-up in the simvastatin group and was increased by 4% in the placebo group. The difference was not statistically significant, though it supports the beneficial effect of simvastatin.

At the end of the trial, 36% of ON patients (11% CDMS and 25% based on McDonald criteria, i.e. CSF and MRI findings) were diagnosed with MS. No differences in the conversion to MS were observed between groups. The high percentage of MS conversion in our study was probably due to the better MRI images (a 3.0 T scanner was used) and was in accordance with previous published data regarding high-field imaging.[40] These results support the need for early identification and treatment of MS.

In conclusion, simvastatin 80 mg daily for 6 months was very well tolerated and had a very good safety profile. The results point towards a beneficial effect of

simvastatin favouring the long-term visual outcome, though these results should be viewed with caution due to the size of the trial and because the treatment showed efficacy only in some of the secondary outcome measurements.

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Conflict of interest statement

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