Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial

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Summary

Background Acute demyelinating optic neuritis, a common feature of multiple sclerosis, can damage vision through neurodegeneration in the optic nerve and in its fibres in the retina. Inhibition of voltage-gated sodium channels is neuroprotective in preclinical models. In this study we aimed to establish whether sodium-channel inhibition with phenytoin is neuroprotective in patient with acute optic neuritis.

Methods We did a randomised, placebo-controlled, double-blind phase 2 trial at two UK academic hospitals in London and Sheffield. Patients with acute optic neuritis aged 18–60 years, presenting within 2 weeks of onset, with visual acuity of 6/9 or worse, were randomly assigned (1:1) by minimisation via a web-based service to oral phenytoin (maintenance dose 4 mg/kg per day if randomised before or on July 16, 2013, and 6 mg/kg per day if randomised on or after July 17, 2013) or placebo for 3 months, stratified by time from onset, centre, previous multiple sclerosis diagnosis, use of disease-modifying treatment, and use of corticosteroids for acute optic neuritis. Participants and treating and assessing physicians were masked to group assignment. The primary outcome was retinal nerve fibre layer (RNFL) thickness in the affected eye at 6 months, adjusted for fellow-eye RNFL thickness at baseline, analysed in a modified intention-to-treat population of all randomised participants who were followed up at 6 months. Safety was analysed in the entire population, including those who were lost to follow-up. The trial is registered with ClinicalTrials.gov, number NCT 01451593.

Findings We recruited 86 participants between Feb 3, 2012, and May 22, 2014 (42 assigned to phenytoin and 44 to placebo). 29 were assigned to phenytoin 4 mg/kg and 13 to phenytoin 6 mg/kg. Five participants were lost to follow-up, so the primary analysis included 81 participants (39 assigned to phenytoin and 42 to placebo). Mean 6-month RNFL thickness in the affected eye at 6 months was 81·46 μm (SD 16·27) in the phenytoin group (a mean decrease of 16·69 μm [SD 13·73] from baseline) versus 74·29 μm (15·14) in the placebo group (a mean decrease of 23·79 μm [13·97] since baseline; adjusted 6-month difference of 7·15 μm [95% CI 1·08–13·22]; p=0·021), corresponding to a 30% reduction in the extent of RNFL loss with phenytoin compared with placebo. Treatment was well tolerated, with five (12%) of 42 patients having a serious adverse event in the phenytoin group (only one, severe rash, was attributable to phenytoin) compared with two (5%) of 44 in the placebo group.

Interpretation These findings support the concept of neuroprotection with phenytoin in patients with acute optic neuritis at concentrations at which it blocks voltage-gated sodium channels selectively. Further investigation in larger clinical trials in optic neuritis and in relapsing multiple sclerosis is warranted.

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Introduction

Multiple sclerosis is an inflammatory demyelinating disorder of the CNS in which disability arises largely from neuroaxonal loss, which occurs in relapses and progressive phases of the disease.[1] Corticosteroids hasten recovery from relapses without improving the final prognosis for recovery,[2–4] and immunomodulation has so far had limited effects on progressive disability.[5] Hence, neuroprotection for these two processes contributing to disability remains a key unmet need in multiple sclerosis.

Different mechanisms are likely to contribute to neurodegeneration in relapses and in progressive disease. In acute relapses, evidence is growing of a cascade arising from neuronal energy failure, leading in turn to reduced activity of the membrane sodium-potassium ATPase, accumulation of sodium ions entering mainly via $Na_v1·6$ channels, reverse operation of the membrane sodium-calcium exchanger, and finally toxic accumulation of calcium ions.[6] $Na_v1·6$ channels are also likely to play an important role in microglial activation and subsequent immune attack.[7] Consistent with this mechanism, voltage-gated sodium-channel inhibitors are neuroprotective in several preclinical models of neuroinflammation,[8–10] suggesting that they might also be neuroprotective in multiple sclerosis.

Phenytoin is a selective sodium-channel inhibitor used as an anticonvulsant in the treatment of epilepsy and is

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Research in context

Evidence before the study

We searched PubMed, Medline, Embase, and the Cochrane Database of Systematic Reviews, without language or date restrictions, using the terms "optic neuritis" OR "multiple sclerosis", "sodium channels" OR "phenytoin", and "clinical trials" AND "neuroprotection". The date of our last search was Sept 28, 2015. We found several preclinical studies showing neuroprotection with partial sodium-channel blockade in experimental models of inflammatory demyelination, but this strategy had not been tested previously in a clinical trial in acute optic neuritis. Sodium-channel inhibition with lamotrigine was tested in a phase 2 trial in patients with secondary progressive multiple sclerosis, which was negative for its primary endpoint, the rate of cerebral atrophy over 2 years. Interpretation of outcome was hampered by partially reversible, possibly osmotic treatment effects on cerebral volume, and by poor adherence to treatment. One retrospective study compared difference in multiple sclerosis severity scale in 51 patients exposed to carbamazepine for symptomatic therapy with 349 patients who were not exposed, and found no significant difference in outcome. A protocol has been released for a Cochrane review of sodium-channel blockade in patients with multiple sclerosis that has not yet been completed. We found three previous randomised controlled trials of neuroprotection in patients with acute optic neuritis, all with a smaller sample size (30–54 patients) than in our study. Memantine, assessed in one of the trials, reduced atrophy of the retinal nerve fibre layer (RNFL) but did not improve visual outcome. Erythropoietin, assessed in two of the trials, reduced RNFL atrophy in one trial but not in the other, and did not significantly improve visual outcome in either trial. Interpretation of these trials is difficult because they measured outcome as the change from baseline in RNFL thickness within the affected eye only, and did not take into account the swelling of the RNFL in that eye at baseline. Additionally, optic nerve measurements were only obtained in one trial, and none reported macular volumes.

Added value of this study

This clinical trial addresses the limitations of previous studies and provides coherent evidence that sodium-channel inhibition with phenytoin is neuroprotective in patients with acute optic neuritis. Unlike the lamotrigine trial, sodium-channel inhibition was tested in an acute inflammatory lesion (in the optic nerve), which is closer to the experimental models on which the intervention was based. Treatment was better tolerated in our much less disabled population than in the lamotrigine trial, and the confounding effects of osmotic, treatment-related tissue volume changes were avoided by timing the final readout 3 months after stopping treatment. Unlike the previous trials in acute optic neuritis, the primary analysis avoided the problem of swelling of the affected-eye RNFL at baseline by using the baseline measurement in the unaffected eye to adjust the final affected-eye RNFL thickness. Additionally, measurements of the RNFL, macula, and optic nerve gave a consistent picture of the effects of treatment on the entire layer comprising the retinal ganglion cells and their axons.

Implications of all available evidence

Our findings suggest that the key goal of protection against neuroaxonal loss can be achieved using partial sodium-channel inhibition after development of acute optic neuritis. Because the pathological abnormalities in the optic nerve resemble those of plaques elsewhere in the CNS in multiple sclerosis, sodium-channel inhibition might be neuroprotective in relapses affecting other sites in the brain and spinal cord, and could begin to address a major unmet need to preserve tissue and thereby to prevent disability. These observations need to be reproduced in phase 3 trials of sodium-channel inhibitors in patients with optic neuritis and other relapses of multiple sclerosis.

neuroprotective at therapeutic concentrations in experimental models.[8,9,11] It can be loaded rapidly to achieve therapeutic serum concentrations within days. This property is important because results of experimental studies suggest that neuroprotection for relapses should be started as early as possible during the phase of acute inflammatory injury[10] (an inflammatory penumbra that corresponds to about the first 2 weeks of a clinical episode), and then potentially sustained until beyond the period of active inflammation, which can be detected for a median of 2 months after symptom onset.[12]

The anterior visual system has many advantages for testing neuroprotection in multiple sclerosis:[13] acute demyelinating optic neuritis is a common and often presenting manifestation of multiple sclerosis; the inflammatory optic nerve lesion is similar to plaques found elsewhere in the CNS; and the visual system can be studied using clinical, electrophysiological, and imaging techniques. Additionally, the optic nerve lesion leads to retrograde degeneration of the retinal nerve fibre layer (RNFL),[14] a relatively pure compartment of unmyelinated axons whose thickness can be measured sensitively and non-invasively using optical coherence tomography (OCT). Therefore, the RNFL thickness provides a plausible biomarker of axonal loss. Reduction of RNFL thickness is also associated with visual loss in patients with acute optic neuritis and with greater general disability in patients with multiple sclerosis, suggesting that it might provide information about treatment response that is clinically relevant.[14]

From these considerations, we aimed to establish whether early and sustained sodium-channel inhibition with phenytoin is neuroprotective in patients with acute optic neuritis.

Methods

Study design and participants

We did a randomised, parallel-group, double-blind, placebo-controlled phase 2 trial. Patients who presented to one of two trial centres in London and Sheffield, UK, or were referred there from a UK network of patient identification centres, were eligible if they were aged 18–60 years, had a clinical diagnosis of unilateral acute demyelinating optic neuritis (confirmed by a neuro-ophthalmologist, and with no alternative pathological abnormalities on OCT at presentation), visual acuity of 6/9 or worse, and an interval of 14 days or less between onset of vision loss and randomisation. Patients with a previous diagnosis of relapsing multiple sclerosis were eligible within 10 years of disease onset and with an Expanded Disability Status Scale score of 3 or less. Concurrent treatment with glatiramer acetate or interferon beta was permitted and corticosteroids for acute optic neuritis could be given at the treating physician's discretion (all participants were offered equivalent regimens of methylprednisolone, either 1 g intravenously daily for 3 days, or 500 mg orally daily for 5 days).[15] Patients were excluded if they had any of the following criteria: previous history of acute optic neuritis in either eye; comorbid ocular disease; clinical or biochemical hepatic, renal, or cardiac dysfunction (including abnormal electrocardiogram); contra-inications to phenytoin (including pregnancy); disabling temperature-dependent multiple sclerosis symptoms; use of sodium-channel or calcium-channel inhibitors in the 2 weeks preceding recruitment; corticosteroids (except for treatment of this episode of acute optic neuritis) or other immune therapies in the 2 months preceding recruitment; or seropositivity for aquaporin-4 antibodies, tested using a cell-based assay (Euroimmun UK, London, UK).

All participants gave written informed consent before entry. The study was approved by the London-South East UK Research and Ethics Committee on Nov 15, 2011. The study was overseen by a data monitoring and ethics committee independent of the study group. The full protocol is available online.

Randomisation and masking

Participants were randomly assigned (1:1) to phenytoin or placebo via an online randomisation service (Sealed Envelope, London, UK) by minimisation at 0·75 probability, with time from onset (≤7 days *vs* >7 days), centre (London *vs* Sheffield), previous multiple sclerosis diagnosis (yes *vs* no), use of disease-modifying treatment (yes *vs* no), and use of corticosteroids for acute optic neuritis (yes *vs* no) as binary minimisation variables. The minimising allocation to phenytoin versus placebo was assigned with 0·75 probability to reduce predictability. Participants were allocated a randomisation code by the treating physician, which was matched to a confidential treatment list by the study pharmacist to assign participants either to phenytoin or placebo (which were identical in appearance). Only the pharmacist was aware of treatment allocation. Treating and assessing physicians and participants were masked to treatment allocation.

Procedures

Participants were loaded orally with a total dose of 15 mg per kg of bodyweight divided into three equal doses (each rounded up to the nearest 50 mg) for a period of 3 days to achieve serum concentrations that are therapeutic for epilepsy, and as noted earlier, are neuroprotective in experimental models. A daily maintenance dose of 4 mg per kg of bodyweight (rounded up to the nearest 50 mg, to a maximum of 350 mg) was given for 3 months, and was increased to 6 mg per kg of bodyweight from July 17, 2013, at the recommendation of the data monitoring and ethics committee to achieve higher serum drug concentrations, because concentrations with the lower dose were thought to be subtherapeutic; the protocol was amended accordingly. Participants were assessed by a treating physician at 1 and 3 months from baseline to assess safety and adherence, and blood samples were obtained to measure phenytoin concentration.

High resolution spectral domain OCT images (Spectralis, software version 5.4B, Heidelberg Engineering, Heidelberg, Germany) were acquired at baseline and 6 months using identical protocols at both sites. Appropriate quality assurance was undertaken to ensure comparability, with acceptable inter-rater co-efficients of variation for measurements of the RNFL (0·51%) and macular volume (0·45%). RNFL measurements used a 3·45 mm diameter circle scan. A fast macular volume scan (20×20° field, 25 horizontal B scans, ART 9) was also done. Scans were excluded if they had a signal strength of less than 25 dB or violated international consensus quality control criteria.[16]

MRIs were obtained on two 3T scanners (Philips Achieva [London site] and Philips Ingenia [Sheffield site]; Philips Healthcare Systems, Best, Netherlands) with identical scanning protocols at both sites at baseline and 6 months. Each optic nerve was imaged separately and for all acquisitions the imaging plane for the optic nerves was set orthogonal to the longitudinal axis of the nerve. The following sequences were undertaken: a multidynamic, fat-suppressed, heavily T2-weighted, multislice, single-shot, two-dimensional (2D) turbo spin echo (TSE);[17] a conventional fat-suppressed, T2-weighted 2D-TSE; and a T1-weighted fluid attenuated inversion recovery 2D-TSE. Lesion length and position were measured by three independent assessors (RR, AT, and MCY), who were masked to treatment allocation and participant identity, using a combination of the conventional and multi-dynamic T2-weighted sequences, and rare discrepancies were resolved by consensus, still based on the blinded data. Mean optic nerve cross-sectional area was measured by a masked assessor using a semi-automated contouring technique on the baseline and 6-month T1-weighted

For the **trial protocol** see https://www.ucl.ac.uk/ion/queen-square-multiple-sclerosis-centre/trial-protocol-neuroprotection-with-phenytoin-in-optic-neuritis

images. Mean lesional baseline and 6-month cross-sectional areas were calculated by registering a baseline T2 lesion mask to the 6-month T1 scan. Measurements were corrected for the corresponding baseline mean non-lesional cross-sectional area in the unaffected eye by applying the T2 lesion mask to baseline T1 images of the unaffected eye. Brain MRI was obtained at baseline for participants without a previous diagnosis of multiple sclerosis.

To assess vision, low-contrast letter scores were measured at baseline and 6 months using retro-illuminated 1·25% and 2·5% Sloan charts (Precision Vision, La Salle, IL, USA) using best refractive correction for each eye at 2 m. Best corrected high-contrast logMAR visual acuity was measured using retro-illuminated Early Treatment Diabetic Retinopathy Study charts at 4 m. When no letters could be correctly identified, a score of 1·7 was assigned by the masked researcher. Colour vision was assessed by masked researchers using the Farnsworth-Munsell 100 hue test and recorded as the total error score. This test was assessed under standard daylight conditions using daylight linear full-spectrum bulbs with a colour temperature of 6500 K in participants with a logMAR visual acuity better than 1·0.

Visual evoked potentials (VEPs) to reversal achromatic checks (subtending 15 min of arc visual angle) were recorded at both sites at baseline and 6 months according to International Federation of Neurophysiology guidelines on a Synergy system (Viasys Healthcare, Conshokocken, PA, USA) in standard background office lighting. Responses were recorded from the occipital midline (Oz) using midline frontal (Fz) as reference and midline central (Cz) as ground. Latency and amplitude of the P100 component were measured to one decimal place in the replicates. Participants with absent VEP latencies or amplitudes were assigned a value of 200 and 0, respectively.

Adverse events were recorded at all study visits, and blood samples were taken at baseline, 1-month, and 3-month study visits to measure full blood count and liver and renal function.

Outcomes

The primary endpoint was mean reduction in RNFL thickness in the affected eye at 6 months compared with RNFL thickness in the unaffected eye at baseline, measured with OCT. Secondary structural endpoints were macular volume, measured with OCT, and optic nerve cross-sectional area and lesion length, measured with MRI. Secondary electrophysiological endpoints were latency and amplitude of the VEP. Secondary clinical endpoints were monocular high-contrast and low-contrast letter visual acuities, and colour perception. Primary and secondary endpoints were measured at baseline and 6 months by trained staff masked to treatment allocation. The 3-month gap between cessation of treatment and the final assessment was designed to allow any artifactual effects of sodium-channel inhibition (eg, pseudoatrophy)[18] to reverse before the final readout.

Statistical analysis

Treatment effect was defined as the mean difference between 6-month RNFL thickness in the affected eye and baseline RNFL thickness in the unaffected eye. We chose the target sample size of 45 participants per group to give 80% power to detect a treatment effect of 50% at a 5% significance level, while allowing for a 20% combined rate of loss to follow-up and non-adherence. This calculation was based on a requirement of 35 participants per group, calculated from longitudinal OCT data for participants with acute demyelinating optic neuritis, as detailed in sample size calculations published previously.[17] This sample size calculation maximised power by assuming a phenytoin-versus-placebo comparison of 6-month RNFL thickness in the affected eye, adjusted for baseline RNFL thickness in the fellow eye. The fellow eye was chosen because acute swelling in the affected eye makes this eye a poor predictor of follow-up thickness, and makes change in the affected eye uninterpretable. Healthy individuals have very similar RNFL thicknesses in both eyes, so the baseline fellow-eye RNFL thickness provides a reliable estimate of affected-eye RNFL thickness before development of acute optic neuritis. Henderson and colleagues[19] reported a significant positive correlation (r=0·63; p=0·007) between the baseline RNFL in the fellow eye and the 6-month RNFL in the affected eye.

Accordingly, we used an ANCOVA analysis method, using multiple linear regression of the 6-month RNFL of the affected eye on a trial arm indicator with the following prespecified covariates: baseline RNFL thickness in the fellow eye, centre (binary), days between onset and baseline assessment, and whether the participant was prescribed corticosteroids at the time of baseline assessment (no *vs* 1–5 days before assessment *vs* 6–30 days before assessment). We did not use two planned binary covariates—previous multiple sclerosis (yes [n=4] *vs* no [n=82]) and prescribed disease-modifying treatment (yes [n=1] *vs* no [n=85])—because the prespecified minimum number of patients was ten for the smallest category. We analysed secondary outcomes similarly, using the corresponding baseline fellow-eye value of the outcome and the same prespecified covariates. An exception was lesion length, for which the baseline fellow-eye value was not specified as a covariate; also, for imaging outcomes only, centre was not used as a covariate because only three participants underwent MRI at one of the sites (Sheffield).

The primary endpoint was analysed in a modified intention-to-treat population of all randomised participants for whom we had baseline and 6-month data.

We analysed primary and secondary outcomes in both the modified intention-to-treat population and the per-protocol population; adverse events were analysed in all randomised patients including those lost to follow-up. Secondary per-protocol analyses excluded participants

with a subsequent episode of optic neuritis, and included all participants assigned to placebo, but only participants assigned to phenytoin who were adherent to treatment (defined as having phenytoin present in their blood at 1 month); however, this per-protocol comparison has the potential for bias since no placebo subset corresponded to the adherent phenytoin subset.

When regression residuals showed signs of non-normality or heteroscedasticity, we checked p values using a permutation test, but none of the reported p values required correction. Statistical significance, where referred to, indicates a p value of less than 0·05, and all p values refer to two-tailed tests. We did the analyses using Stata, version 13.1.

This trial is registered with ClinicalTrials.gov, number NCT 01451593.

Role of the funding source

Neither the funders of the study, nor the sponsor (University College London), had a role in 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

Participants were recruited between Feb 3, 2012, and May 22, 2014, and we did the final assessments in December, 2014. None of the eligible participants had antibodies to aquaporin-4; exclusions for other reasons are detailed in figure 1. 86 participants (70 from the London centre and 16 from the Sheffield centre) were randomly assigned to receive phenytoin (n=42) or placebo (n=44; figure 1). 58 participants were randomised before July 17, 2013, 29 of whom were assigned to the lower daily maintenance dose of phenytoin (4 mg per kg of bodyweight), and 28 were randomised after this date, 13 of whom were assigned to the higher daily maintenance dose (6 mg per kg of bodyweight).

The two groups had similar baseline characteristics (table 1). 28 (33%) of 86 participants either had a previous diagnosis of multiple sclerosis or were diagnosed with multiple sclerosis on presentation, and 64 (74%) had one or more brain lesions on MRI.

Five participants were lost to follow-up, leaving 81 who attended for assessment of the primary outcome at baseline and 6 months (39 in the phenytoin group and 42 in the placebo group). Of the 39 participants in the phenytoin group, ten (26%) were withdrawn from treatment because of skin rash after a mean of 18·4 days (SD 14·98) from starting treatment, but continued to be followed up. The remaining 29 patients in the phenytoin group were adherent to treatment (mean serum phenytoin concentration 8·57 mg/L [SD 5·40]). The combined overall proportion of patients who were lost to follow-up, withdrawn from treatment, or did not adhere to treatment was 19% (16 of 86 patients). All participants who were adherent and attended the 6-month visit were included in the per-protocol analyses (29 patients in the phenytoin group and 42 patients in the placebo group).

RNFL thickness remained stable in the unaffected eye between baseline and 6 months (p=0·8353; table 2). 6-month RNFL thickness in the affected eye was significantly correlated with baseline RNFL thickness in the unaffected eye (r=0·50, p<0·0001), but not with baseline RNFL thickness in the affected eye (r=0·13, p=0·253).

In patients with both baseline and 6-month data (the modified intention-to-treat population), mean RNFL thickness in the affected eye decreased after 6 months compared with the baseline unaffected eye by 23·79 µm (SD 13·97) in the placebo group, and by 16·69 µm (13·73) in the phenytoin group, and the mean 6-month RNFL thickness in the affected eye in the phenytoin group was higher than in the placebo group (figure 2; table 3). In the modified intention-to-treat population, the adjusted mean difference in 6-month RNFL in the affected eye (phenytoin group minus placebo group) was 7·15 µm (95% CI 1·08–13·22; p=0·021; table 3), corresponding to a 30% reduction in the extent of RNFL loss with phenytoin compared with placebo. The corresponding adjusted difference in the per-protocol population was similar, at 7·40 µm (0·76–14·04; p=0·029).

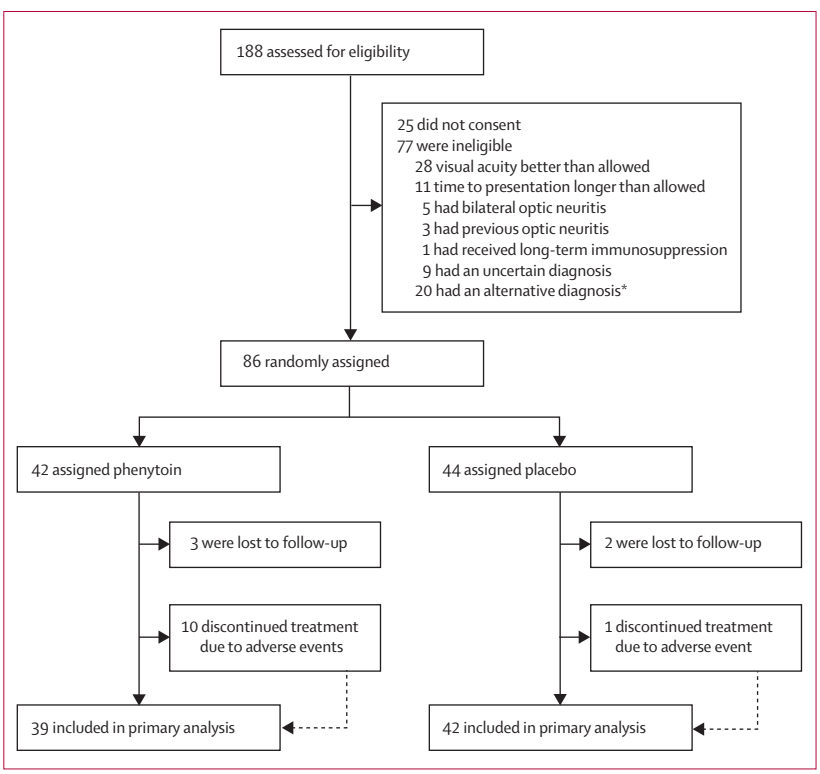

***Figure 1*: Trial profile**

*Alternative diagnoses were functional visual loss (n=4), sarcoidosis (n=3), migraine with aura (n=2), posterior scleritis (n=2), Leber's hereditary optic neuropathy (n=2), compressive optic nerve lesions (n=2), uveitis (n=1), toxic optic neuropathy (n=1), neuroretinitis (n=1), central serous retinopathy (n=1), and optic nerve drusen (n=1).

Macular volume remained stable in the unaffected eye, with insignificant change between baseline and 6 months (p=0·8137; table 2). In patients with both baseline and 6-month data, the mean macular volume in the affected eye decreased after 6 months compared with the baseline unaffected eye, by 0·59 mm³ (SD 0·34) in the placebo group and 0·39 mm³ (0·29) in the phenytoin group, and the mean 6-month macular volume in the affected eye in the phenytoin group was higher than in the placebo group (figure 2; table 3). In the modified intention-to-treat population, the adjusted mean difference in 6-month macular volume in the affected eye (phenytoin group minus placebo group) was 0·20 mm³ (95% CI 0·06–0·34; p=0·005), corresponding to a 34% reduction in the extent of macular volume loss with phenytoin compared with placebo. The corresponding adjusted difference in the per-protocol population was again similar, at 0·21 mm³ (0·05–0·36; p=0·010).

In the modified intention-to-treat population, no significant difference was noted in optic nerve lesion length between the treatment groups at 6 months (mean adjusted difference –2·45 mm, 95% CI –6·97 to 2·08; p=0·285). Similarly, lesional optic nerve cross-sectional area did not differ significantly between groups, although a nominal difference was noted (0·40 mm², 95% CI –0·02 to 0·83; p=0·061). The corresponding adjusted difference in cross-sectional area in the per-protocol population was 0·47 mm² (–0·04 to 0·97; p=0·070).

At baseline, 20 affected eyes of patients in each group had their absent VEP latencies and amplitudes assigned a value of 200 and 0, respectively (although the baseline VEP of the affected eye was not used in analyses). No baseline unaffected eyes had absent VEP latencies or amplitudes. At 6 months, three participants, all in the active group, had their absent VEP latencies and amplitudes assigned a value of 200 and 0, respectively. Although the 200 value is arbitrary, it is higher than the highest measured value in the study—188. Therefore, we thought that inclusion of these values at 6 months would be conservative; exclusion of them would have reduced the mean latency of the active group. No significant differences in visual function, VEP latency, or VEP amplitude at 6 months were noted in either the modified intention-to-treat population (table 3) or the per-protocol population (data not shown).

A higher but non-significant proportion of participants in the phenytoin group discontinued the study drug as a result of an adverse event (in all cases this was a maculopapular rash typical of a drug reaction). With the exception of a severe rash in one participant, serious

	Phenytoin (n=42)	Placebo (n=44)
Age, years	33 (8·2)	35 (9·1)
Women	31 (74%)	32 (73%)
Days from onset to randomisation	8·2 (3·1)	8·1 (3·3)
Prescribed corticosteroids	35 (83%)	33 (75%)
Clinical diagnosis		
Previous diagnosis of multiple sclerosis	1 (2%)	3 (7%)
Multiple sclerosis diagnosed at screening*	13 (31%)	11 (25%)
Clinically isolated syndrome	28 (67%)	30 (68%)
One or more hyperintense MRI brain lesion	32 (76%)	32 (73%)
RNFL thickness, µm	130·62 (46·4)	125·20 (43·4)
Macular volume, mm³	8·71 (0·46)	8·63 (0·43)
LogMAR visual acuity	1·11 (0·54)	1·07 (0·60)
Low-contrast letter score (1·25%)	0·07 (0·46)	0·45 (3·02)
Low-contrast letter score (2·5%)	0·21 (1·24)	0·77 (3·83)
FM 100-hue total error score	1066 (764·6)	1139 (775·5)
VEP latency, ms†	167·9 (35·2)	167·6 (35·8)
VEP amplitude, µV†	2·8 (3·8)	3·0 (3·8)
Optic nerve cross-sectional area, mm²	7·60 (1·55)	7·48 (1·43)
Lesion length, mm	17·2 (8·1)	18·0 (7·1)

Data are mean (SD) or number (%). RNFL=retinal nerve fibre layer. FM=Farnsworth-Munsell. VEP=visual evoked potential. *Multiple sclerosis diagnosed using the 2010 McDonald criteria.[20] †20 patients in each group had no VEP response in the affected eye, but the baseline VEP of the affected eye was not used in analyses.

***Table 1*: Baseline demographic and clinical characteristics of all randomly assigned patients, and structural and electrophysiological characteristics of the affected eye**

	Phenytoin				Placebo			
	Baseline		6 months		Baseline		6 months	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
RNFL thickness, µm	42	98·02 (11·08)	39	98·69 (11·62)	44	98·36 (10·99)	41	97·37 (13·18)
Macular volume, mm³	42	8·67 (0·41)	39	8·66 (0·40)	44	8·67 (0·39)	40	8·63 (0·43)
Optic nerve cross-sectional area, mm²	35	5·51 (0·90)	30	5·15 (0·82)	35	5·32 (0·73)	29	5·41 (0·72)
VEP latency, ms	39	104·0 (6·3)	35	108·3 (19·8)	43	104·8 (5·9)	40	106·1 (6·2)
VEP amplitude, µV	39	10·2 (5·0)	35	9·5 (5·0)	43	10·8 (5·9)	40	9·8 (6·1)
LogMAR visual acuity	42	0·03 (0·10)	39	–0·05 (0·13)	44	–0·08 (0·08)	42	–0·08 (0·10)
Low-contrast letter score (1·25%)	42	26·33 (9·90)	39	27·79 (10·47)	44	29·48 (10·35)	42	27·76 (9·75)
Low-contrast letter score (2·5%)	42	32·86 (9·55)	39	33·62 (9·65)	44	34·52 (9·96)	42	34·14 (10·77)
FM 100-hue total error score	42	88·19 (49·20)	39	84·62 (54·56)	43	90·88 (56·49)	44	95·33 (106·56)

Data are mean (SD). RNFL=retinal nerve fibre layer. FM=Farnsworth-Munsell. VEP=visual evoked potential.

***Table 2*: Baseline and 6-month outcome measures in the unaffected eye, by treatment group**

adverse events were not attributable to phenytoin (table 4). In a post-hoc analysis, we found that 50 (63%) of 80 participants guessed their treatment allocation, significantly more than should have guessed due to chance alone (p=0·033), as a result of all the patients with skin rashes guessing correctly that they were in the phenytoin group. When these patients were excluded, the number of patients who correctly guessed which treatment group they were in was not significant (40 [58%] of 69 patients; p=0·228).

No impairment of vision or other neurological function was noted with initial loading or after withdrawal of phenytoin. None of the participants developed steroid-dependent visual failure, evidence of neuromyelitis optica, or evidence of other causes of optic neuritis, during follow-up. Demyelinating relapses occurred in seven (17%) of 42 participants in the phenytoin group, and nine (20%) 44 in the placebo group. Of these participants, six had another episode of acute optic neuritis (four in the placebo group and two in the phenytoin group), three of whom (one in the phenytoin group and two in the placebo group) were affected in their contralateral eye. These participants were excluded from the per-protocol analysis. In total, 13 participants had a multiple sclerosis-defining relapse during the study (six in the phenytoin group and seven in the placebo group). We did not record any abnormalities of blood count and liver function in any patients. Similar proportions of participants in the phenytoin and placebo groups had adverse events (table 4).

We undertook several exploratory analyses. When comparing data for the ten participants in the phenytoin group who discontinued treatment because of skin rash with the placebo group, the adjusted mean difference in RNFL thickness in the affected eye was 8·29 µm (95% CI −1·96 to 18·52; p=0·1106), similar to the 7·15 µm difference observed in the modified intention-to-treat population. The between-group difference in the reduction of RNFL thickness in the 20 participants who

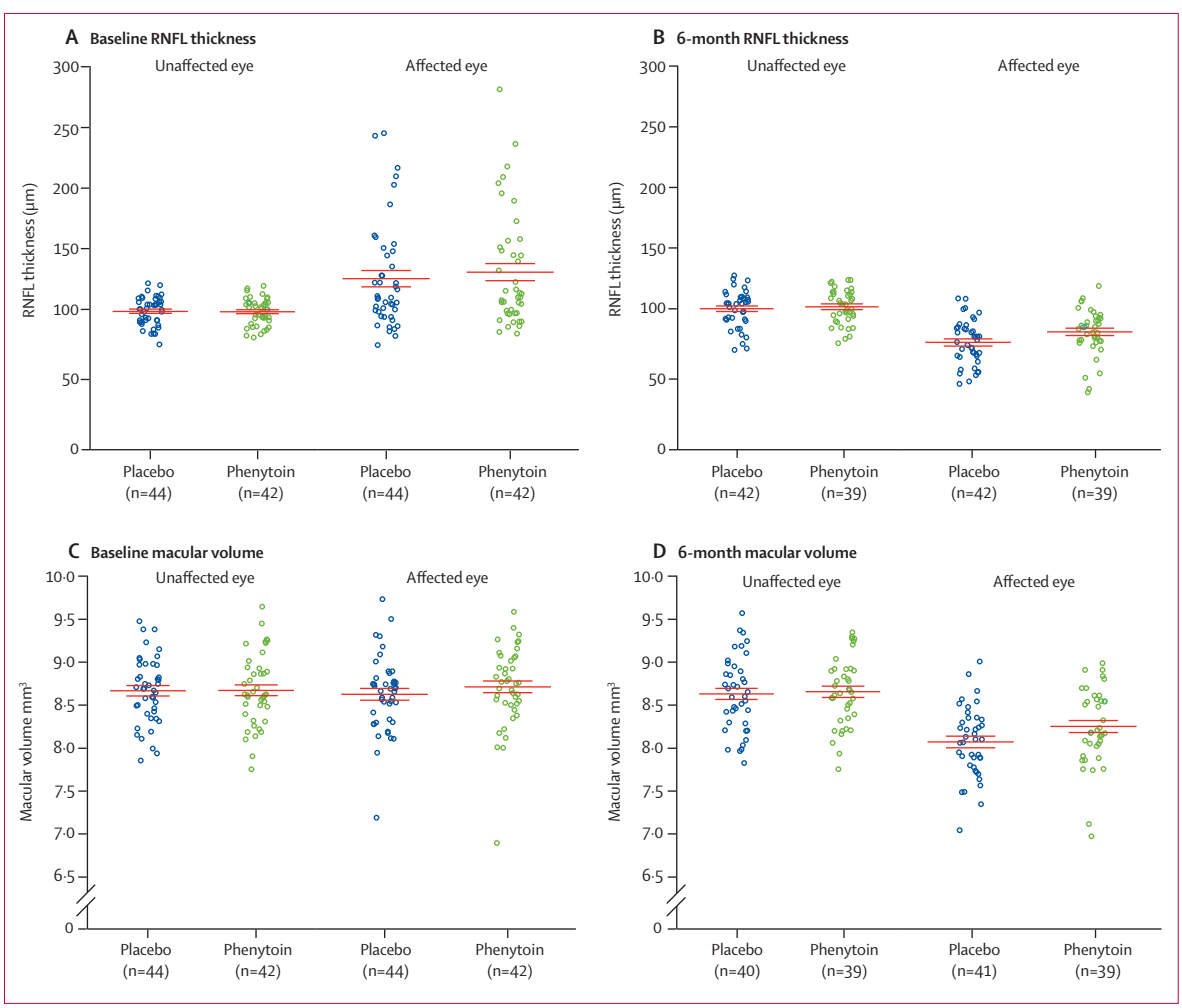

***Figure 2*: RNFL thickness and macular volume, by trial group**
RNFL thickness in the unaffected and affected eyes at baseline (A) and at 6 months (B); macular volume in the unaffected and affected eyes at baseline (C) and at 6 months (D). Circles show individual patient data; horizontal bars show SEs around unadjusted group means.

	Baseline				6 months					
	Phenytoin		Placebo		Phenytoin		Placebo		Adjusted* 6-month difference† (95% CI)	p value
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)		
RNFL thickness, µm	42	130·62 (46·4)	44	125·20 (43·4)	39	81·46 (16·27)	42	74·29 (15·14)	7·15 (1·08 to 13·22)	0·021
Macular volume, mm³	42	8·71 (0·46)	44	8·63 (0·43)	39	8·25 (0·45)	41	8·07 (0·42)	0·20 (0·06 to 0·34)	0·005
Optic nerve cross-sectional area, mm²	34	7·60 (1·55)	39	7·48 (1·43)	31	4·58 (0·88)	34	4·48 (1·01)	0·40 (–0·02 to 0·83)	0·061
Lesion length, mm	39	17·2 (8·1)	42	18·0 (7·1)	34	15·15 (7·62)	36	17·17 (10·11)	–2·45 (–6·97 to 2·08)	0·285
VEP latency, ms‡	39	167·9 (35·2)	43	167·6 (35·8)	35	133·0 (24·8)	40	127·4 (19·3)	5·71 (–4·56 to 15·99)	0·271
VEP amplitude, µV ‡	39	2·7 (3·8)	43	3·0 (3·8)	35	7·1 (4·6)	40	7·3 (4·6)	–0·18 (–1·83 to 1·46)	0·827
LogMAR visual acuity	42	1·08 (0·56)	44	1·04 (0·62)	39	0·09 (0·40)	42	0·04 (0·18)	0·02 (–0·11 to 0·16)	0·728
Low-contrast letter score (1·25%)	42	0·07 (0·46)	44	0·45 (3·02)	39	13·38 (12·14)	42	12·33 (12·13)	1·19 (–4·16 to 6·53)	0·660
Low-contrast letter score (2·5%)	42	0·21 (1·24)	44	0·77 (3·83)	39	19·69 (13·80)	42	17·55 (14·19)	2·07 (–4·10 to 8·25)	0·506
FM 100-hue total error score	42	1066 (764·6)	43	1139 (775·5)	39	181·28 (223·79)	42	195·24 (212·61)	–18·46 (–116·44 to 79·51)	0·708

RNFL=retinal nerve fibre layer. FM=Farnsworth-Munsell. VEP=visual evoked potential. *Prespecified adjustment for baseline unaffected value, centre, days between onset and baseline, and days between steroid use and baseline; centre was dropped for optic nerve area, and centre and baseline unaffected value were dropped for lesion length. †Phenytoin minus placebo. ‡The 6-month comparison includes three participants assigned to phenytoin (and none assigned to placebo) with vision too poor to obtain a VEP response, for which amplitudes of 0 µV and latencies of 200 ms were used; the baseline summaries include 20 patients assigned to phenytoin and 20 assigned to placebo with vision too poor to obtain a VEP response, for which these imputations were also used (all the unaffected eye VEPs were recordable); excluding the three participants who had vision too poor at 6 months gives a 6-month difference of –0·22 (95% CI –8·02 to 7·57), p=0·955 (for VEP latency), and 0·36 (–1·22 to 1·94), p=0·647 (for VEP amplitude).

***Table 3*: Baseline and 6-month primary and secondary outcomes in the affected eye by treatment group, and adjusted 6-month differences**

	Phenytoin (n=42)	Placebo (n=44)
≥1 adverse event	34 (81%)	40 (91%)
≥1 adverse event leading to discontinuation of study drug	10 (24%)	3 (7%)*
≥1 serious adverse event	5 (12%)	2 (5%)
Breast malignancy	1	0
Dilated superior ophthalmic vein seen on MRI†	1	0
Appendicitis	2	0
Cellulitis	0	1
Severe rash	1	0
Congenital malformation‡	0	1
Any event leading to death	0	0
Adverse events per participant	3·17 (0–10)	3·64 (0–14)

Data are number of patients (%) and mean number of events (range). *Two of these three patients were subsequently lost to follow-up and were not included in the primary analysis. †Requiring catheter angiogram. ‡Microtia following unplanned conception after randomisation.

***Table 4*: Adverse events and serious adverse events**

had a normal brain MRI brain scan at baseline was 4·34 µm (–8·30 to 16·99; p=0·496), and was 7·90 µm (95% CI 0·82 to 14·97; p=0·029) in the 61 participants who had an abnormal brain MRI brain scan at baseline. The difference between the abnormal and normal brain MRI scan groups was not significant (p=0·629); however, the study was not powered to explore such subgroup analyses. No significant associations were noted in the phenytoin group between 1-month phenytoin concentrations and any of the primary or secondary outcomes (data not shown); although a non-significant positive correlation was noted between 1-month phenytoin concentration and optic nerve cross-sectional area (r=0·39, p=0·063). No significant correlations were noted between any of the primary or secondary outcome measurements and the time from onset of visual loss to initiation of treatment (data not shown).

Discussion

In this phase 2 clinical trial, use of phenytoin was associated with a significant reduction in the loss of RNFL thickness and macular volume after acute optic neuritis compared with placebo. Loss of optic nerve cross-sectional area was also reduced with phenytoin, but not significantly so. These results are consistent with the suggestion that phenytoin protects the ganglion cells (which make up about 34% of macular volume) and their axons in the RNFL and the optic nerve via partial inhibition of voltage-gated sodium channels in an episode of inflammatory demyelination.

By contrast with the beneficial effects of treatment on structural outcomes, we noted no significant treatment effects on visual outcomes or on the VEP. Although we cannot exclude the possibility that phenytoin did protect neurons and their axons but they nevertheless remained non-functional, the findings are perhaps more consistent with the floor effect we noted on high-contrast visual acuity and VEP amplitude, which recovered well in both the phenytoin and placebo groups, and with the fact that the trial was not powered to detect treatment effects for these endpoints or on low-contrast acuity or colour vision. Additionally, we relied on central and whole-field VEPs to measure optic nerve function, whereas more sensitive determination of treatment effects might be possible using multifocal VEPs in future trial designs.

Translation of tissue protection into improved visual function is also limited by redundancy in the anterior

visual system[21] and neuroplasticity in higher visual areas, so that better neuroprotection than reported in this study might be needed for significantly improved clinical outcomes to be reported in reasonably sized trials. To achieve this goal, trials might consider investigating the following: inhibitors of sodium channels with greater potency and specificity than phenytoin; higher drug concentrations than were assessed in our trial (mean phenytoin concentrations in our trial were possibly subtherapeutic); and an earlier window of treatment in the evolution of relapse than was assessed in our trial and in previous studies. The last two suggestions are consistent with the absence of correlation between structural outcomes and the concentration of phenytoin and time to initiation of treatment in our present study. Conversely, our results do not place a lower limit on the duration for which treatment is needed for successful neuroprotection. Participants in our trial received treatment for 3 months, which is beyond the interval when gadolinium enhancement indicates inflammation in the optic nerve,[12] yet results of our exploratory analysis showed a greater, albeit non-significant, between-group difference in 6-month RNFL thickness in the affected eye when only data from the ten participants who withdrew after receiving phenytoin for a mean of 18·4 days was used.

Regarding potential sources of bias, the clinical, structural, and electrophysiological characteristics of the placebo and phenytoin groups at baseline were generally similar, typical of patients with acute optic neuritis, and the loss of RNFL thickness in the placebo group after 6 months was consistent with previous natural history studies of acute optic neuritis.[19,22] Care was taken to exclude patients with atypical acute optic neuritis, and none of the participants developed features of disorders such as neuromyelitis optica (for which antibodies were also tested at presentation) or chronic relapsing inflammatory optic neuropathy. Since the study started, further immunological subtypes of optic neuritis have been suggested (eg, those with antibodies to myelin oligodendrocyte glycoprotein[23]) and appropriate testing of these subtypes for any differences in their response to neuroprotective therapies will be important to include in future studies. In the present study, 41 (48%) of 86 participants had (or developed during the study) clinically definite multiple sclerosis, and 58 (67%) had a clinically isolated syndrome at baseline. In keeping with a demyelinating cause, about three-quarters of participants had brain lesions on MRI at baseline.[24] Those with and without brain lesions could not be distinguished on clinical grounds or with other measurements at baseline or at 6 months, suggesting that the study involved a largely homogeneous acute optic neuritis population. Additionally, we noted no statistically significant difference in the primary endpoint between the groups with and without brain lesions.

Baseline low-contrast letter acuity in the affected eye, a predictor of RNFL thickness at 6 months,[19] was noted to be a little worse in the phenytoin group than in the placebo group. This finding would bias the phenytoin group towards a lower 6-month RNFL thickness. The opposite finding, of a higher 6-month RNFL thickness in the phenytoin group compared with placebo, is therefore all the more consistent with a neuroprotective treatment effect.

As expected, the RNFL swelled in the affected eye at baseline, supporting the use of the RNFL in the unaffected fellow eye at baseline for comparisons of change in the affected eye at follow-up. This method is prone to error if the fellow eye is not actually healthy (eg, because of previous and possibly subclinical episodes of acute optic neuritis), but this error is unlikely to have affected our study because none of the participants had presented with visual symptoms previously, and measurements of the fellow eye revealed no clinically significant subclinical abnormalities. Future trial designs could avoid this issue by using OCT segmentation methods to compare the retinal ganglion cell layer at baseline and follow-up in the affected eye alone, since this structure does not swell acutely in acute optic neuritis.[25]

Corticosteroid treatment at presentation is unlikely to have affected the main neuroprotective findings because care was taken to adjust the analysis for the use and timing of corticosteroids. Also, measurements of the RNFL and macular volume remained stable in the fellow eye in both the phenytoin and placebo groups, and results of previous studies have shown that corticosteroids do not prevent atrophy of the RNFL[26] or optic nerve,[27] or visual recovery after optic neuritis.[2]

Treatment with phenytoin was generally well tolerated and was not associated with abnormalities in the blood count or liver function. We did not note any acute deterioration of vision that might be attributed to conduction block from inhibition of sodium currents, or any rebound deterioration upon withdrawal of treatment—effects that had previously been thought to potentially limit the use of drugs acting on this target in demyelinating disorders. Only one participant had a severe adverse reaction—a skin rash—attributable to phenytoin, but a further nine participants developed minor, self-limiting skin rashes and were withdrawn from treatment by the investigators according to protocol. As noted in the Results section, masking of participants to treatment allocation failed in some cases as a result of skin rashes. Although this unmasking might have had an effect on patient-based clinical assessment, it should not have affected the primary outcome.

As a result of patient withdrawal from treatment, ten (26%) of the 39 participants assigned to phenytoin available at follow-up were classified as non-adherent. Although this non-adherence might have affected the power of the modified intention-to-treat analysis, the robustness of the results is supported by the agreement between the modified intention-to-treat and per-protocol analyses, and the consistency of treatment effects in the macula, RNFL,

and optic nerve. Although more values were missing in the optic nerve analysis than in the macula and RNFL analyses, they were missing as a result of MRI acquisition problems, which could plausibly be regarded as missing at random and is unlikely to cause bias.

Our results support the utility of OCT for measuring outcome in future trials of neuroprotection in patients with acute optic neuritis, and add to the evidence showing the usefulness of OCT from previous small trials of other agents.[28–30] By comparison with OCT, MRI of the optic nerve is limited by the effects of myelin and other supporting tissue, and has a lower resolution. OCT is also easier to use and costs less than MRI.

In previous trials, memantine reduced the loss of the RNFL,[28] whereas erythropoietin was effective in one trial,[29] but not in another.[30] Our study addressed limitations of these studies by correcting measurements in the affected eye for baseline measurements in the unaffected eye, and reporting macular volume data as well as detailed MRI data.

At the average concentration achieved in this trial, phenytoin is an almost pure activity-dependent inhibitor of voltage-gated sodium channels.[31] Therefore, it is plausible that other sodium-channel inhibitors could also be neuroprotective in patients with acute optic neuritis and in other types of relapse in multiple sclerosis in view of the similarities between acute optic neuritis and other types of relapse. In turn, the present trial design should enable proof of concept of neuroprotection after relapse for treatments with other modes of action. Implications for treating progressive multiple sclerosis are hard to define because of possible differences in pathophysiological abnormalities: microglial activation is likely to remain important in progressive disease, whereas sodium-channel expression might change.[32] Previously, we reported a trial of neuroprotection using lamotrigine to inhibit sodium channels in secondary progressive multiple sclerosis.[18] Treatment did not affect the rate of cerebral atrophy, although interpretation was hampered by a high rate of non-adherence, and positive treatment signals were reported, including significant slowing of the rate of deterioration of the timed walk and lowering of serum neurofilament concentrations in the adherent group of participants between baseline and the end of the trial.[33]

In conclusion, the results of this clinical trial support the concept of neuroprotection using phenytoin to inhibit voltage-gated sodium channels in patients with acute optic neuritis. These results should encourage larger, phase 3 trials of sodium-channel inhibitors in optic neuritis and other relapses of multiple sclerosis. Future studies should also establish more precisely the optimal therapeutic window for neuroprotection in relapses.

Contributors

RK was the principal investigator and RS the project manager. DRA, KS, GG, DHM, and RK contributed to the concept and design of the study. DRA did the statistical plan and statistical analysis. RR, SJH, AT, and BS recruited and followed up the participants. SM and DP did the 6-month masked vision and optical coherence tomography measurements. RR, SJH, AT, MCY, NH, CAMGW-K, and DHM were responsible for MRI acquisition and analysis, and RR, PM, PGS, and MK were responsible for visual evoked potential acquisition and analysis. RR, DRA, and RK wrote the first draft, and all the authors contributed to and approved the final version.

Declaration of interests

RR, RS, DRA, DHM and RK report grants from the US National Multiple Sclerosis Society and grants from the Multiple Sclerosis Society of Great Britain and Northern Ireland, during the conduct of the study. AT has received personal fees from Biomedia, EXCEMED (formerly SSIF), and Bayer, and meeting expenses from Biogen Idec. DP has received personal fees from Teva pharmaceuticals. DRA has received personal fees from Merck & Co, Inc. MK has received grants and personal fees from Pfizer, and personal fees from GlaxoSmithKline, Merck, Nanomerics and Calchan. CAMGW-K has done clinical trials work for Biogen Idec and Novartis. KS has done clinical trials work for Roche, Teva, and Novartis, and has received personal fees from Biogen, Teva, and Novartis. GG has reported clinical trial steering committees with AbbVie, Biogen, Novartis, Teva, and Roche, and has received personal fees from Biogen, GlaxoSmithKline, Merck-Serono, Novartis, Genzyme-Sanofi, and Synthon BV. DHM received grants from UCL/UCLH Biomedical Research Centre, during the conduct of the study; has received grants from Biogen, GlaxoSmithKline, the National Institute for Health Research, Novartis, and Apitope; has board membership with Biogen Idec, GlaxoSmithKline, Bayer Schering Pharma, and Mitsubishi Pharma Europe; has been a consultant for Merck and Chugai; and has received personal fees from McAlpine's Multiple Sclerosis, 4th edition. RK has clinical trial steering committees with Biogen; has received personal fees and travel support from Biogen and Genzyme, grants from Novartis and Teva, and personal fees from Roche and KaroBio; and has a patent pending. All other authors declare no competing interests.

Data monitoring and ethics committee

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