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Randomized trial of daily high-dose vitamin D_3 in patients with RRMS receiving subcutaneous interferon β-1a

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Abstract

Objective

In the phase II, randomized, double-blind, placebo-controlled Supplementation of Vigantol Oil versus Placebo Add-on in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS) Receiving Rebif Treatment (SOLAR) study (NCT01285401), we assessed the efficacy and safety of add-on vitamin D_3 in patients with RRMS.

Methods

Eligible patients with RRMS treated with SC interferon-β-1a (IFN-β-1a) 44 μg 3 times weekly and serum 25(OH)D levels <150 nmol/L were included. From February 15, 2011, to May 11, 2015, 229 patients were included and randomized 1:1 to receive SC IFN-β-1a plus placebo (n = 116) or SC IFN-β-1a plus oral high-dose vitamin D_3 14,007 IU/d (n = 113). The revised primary outcome was the proportion of patients with no evidence of disease activity (NEDA-3) at week 48.

Results

At 48 weeks, 36.3% of patients who received high-dose vitamin D_3 had NEDA-3, without a statistically significant difference in NEDA-3 status between groups (placebo 35.3%; odds ratio 0.93; 95% confidence interval [CI] 0.53–1.63; $p = 0.80$). Compared with placebo, the high-dose vitamin D_3 group had better MRI outcomes for combined unique active lesions (incidence rate ratio 0.68; 95% CI 0.52–0.89; $p = 0.0045$) and change from baseline in total volume of T2 lesions (difference in mean ranks: −0.074; $p = 0.035$).

Conclusions

SOLAR did not establish a benefit for high-dose vitamin D_3 as add-on to IFN-β-1a, based on the primary outcome of NEDA-3, but findings from exploratory outcomes suggest protective effects on development of new MRI lesions in patients with RRMS.

Clinicaltrials.gov identifier

NCT01285401.

Classification of evidence

This study provides Class II evidence that for patients with RRMS treated with SC IFN-β-1a, 48 weeks of cholecalciferol supplementation did not promote NEDA-3 status.

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Glossary

AE = adverse event; **ANCOVA** = analysis of covariance; **ARR** = annualized relapse rate; **CI** = confidence interval; **CUA** = combined unique active; **DMT** = disease-modifying treatment; **EDSS** = Expanded Disability Status Scale; **HR** = hazard ratio; **IEC** = independent ethics committees; **IFN-β-1a** = interferon-β-1a; **ITT** = intention-to-treat; **MS** = multiple sclerosis; **NEDA-3** = no evidence of disease activity; **OR** = odds ratio; **PBVC** = percent brain volume change; **RRMS** = relapsing-remitting multiple sclerosis; **SAE** = serious adverse event; **SC** = subcutaneous; **SOLAR** = Supplementation of Vigantol Oil versus Placebo Add-on in Patients with Relapsing-Remitting MS Receiving Rebif Treatment; **TEAE** = treatment-emergent adverse event; **TESAE** = treatment-emergent serious adverse event.

The potential role of vitamin D in multiple sclerosis (MS) has received increasing interest, with suggestions that individuals with relatively low serum 25(OH)D levels (<100 nmol/L) have a higher risk of developing MS, as well as relapses, disability progression, and lesions, especially in early MS.[1–6] Increasing serum levels have been associated with preservation of normalized gray matter volume in patients with clinically isolated syndrome.[7] Experimental studies show a profound anti-inflammatory effect of high doses of vitamin D and its active metabolite.[8]

Preliminary single-arm, open-label studies, with within-patient analyses compared with baseline values, have subsequently reported that vitamin D supplementation with or without calcium reduced relapse rates[3] and the number of gadolinium-enhancing lesions.[9] Randomized, controlled trials of vitamin D as add-on to disease-modifying treatment (DMT) have suggested a biological effect on the MS disease process, in terms of fewer new T2 lesions and a lower number of T1 gadolinium-enhancing lesions,[10] although no benefits were observed for annualized relapse rate (ARR) or Expanded Disability Status Scale (EDSS) score.[10–12] However, the studies were limited by low to moderate doses of vitamin D and small, heterogeneous patient populations that resulted in inadequate statistical power. Furthermore, the recommended serum 25(OH)D levels associated with a lower incidence of MS (≥100 nmol/L)[13] are arbitrary, and may not provide sufficient benefit at the immunologic level.[14] A linear inverse correlation between 25(OH)D and relapse risk was also found up to the highest physiologic levels.[15] Thus, we conducted the Supplementation of Vigantol Oil versus Placebo Add-on in Patients with Relapsing-Remitting MS (RRMS) Receiving Rebif Treatment (SOLAR) study to further elucidate the efficacy and safety of high-dose vitamin D_3 supplementation in patients with RRMS already on interferon-β-1a (IFN-β-1a).

Methods

Classification of evidence

This study seeks to address the following research question, with the associated level of evidence: Does 48 weeks of supplementation with high-dose vitamin D_3 improve no evidence of disease activity (NEDA-3) status in patients with RRMS treated with subcutaneous (SC) IFN-β-1a (Class II)?

Standard protocol approvals, registrations, and patient consents

The responsible independent ethics committees (IEC) reviewed and approved the study protocol and associated documents prior to patient recruitment and relevant safety data during the study. The trial started at a site after the sponsor obtained written confirmation of favorable opinion/approval from the IEC. All patients provided written informed consent for participation in the study and the study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation/Good Clinical Practice, and applicable regulatory requirements. The study was registered at ClinicalTrials.gov (NCT01285401).

Study design

SOLAR was a placebo-controlled, randomized, double-blind, multicenter study, performed at 40 sites in Denmark, Estonia, Finland, Germany, Italy, Latvia, Lithuania, the Netherlands, Norway, Portugal, and Switzerland.

Patients

Patients eligible for inclusion were aged 18–55 years with adequate renal and hepatic function, relapsing-remitting MS (RRMS) (according to the revised 2005 McDonald criteria),[4] brain or spinal MRI with findings typical of an early stage of MS, first clinical event occurring within 5 years prior to screening, EDSS score ≤4.0 at screening, evidence of some disease activity by means of either one relapse or MRI (at least one gadolinium-enhancing lesion) within the last 18 months before screening, and receiving no or low vitamin D supplementation (≤1,000 IU [25 μg] daily).

Patients were already receiving treatment with SC IFN-β-1a 44 μg 3 times weekly (TIW) for 3–18 months before baseline. A minimum of 3 months' treatment with IFN-β-1a was chosen to allow the treatment to achieve its maximal therapeutic effect.[16] Patient selection criteria are described in detail in the e-Methods (doi.org/10.5061/dryad.c81sr72).

Randomization and masking

Patients were randomized (1:1) to high-dose vitamin D_3 (Vigantol; Merck KGaA, Darmstadt, Germany) 6,670 IU/d (167 μg/d) orally for 4 weeks, followed by 14,007 IU/d (350 μg/d) for 44 weeks, or matching placebo in addition to ongoing treatment with SC IFN-β-1a (Rebif; Merck KGaA, Darmstadt, Germany) 44 μg TIW. IFN-β-1a was

formulated as a liquid for SC injection using prefilled syringes, pens, and cartridges. High-dose vitamin D_3 was dispensed at each study visit for the whole period up to the next study visit, and was self-administered by the patients orally. We selected the higher dose of vitamin D_3 based on previous clinical experience suggesting that 7,000–14,000 IU vitamin D_3 is needed to achieve sufficient 25(OH)D serum levels.[9,14,17–19] A dose of 14,007 IU/d vitamin D_3, corresponding to 350 μg/d, will increase 25(OH)D serum levels by 245 nmol/L,[20] based on a 0.70 nmol increase for each additional 1 μg vitamin D_3 input, allowing a sufficient increase in 25(OH)D levels (>150 nmol/L) while remaining below levels leading to hypercalcemia (500 nmol/L).[21] As over-the-counter vitamin formulations often contain ≤25 μg vitamin D, we permitted patients to take up to 1,000 IU/d (25 μg/d) additional vitamin D supplementation.

Randomization was performed via interactive voice recognition software, and stratified by body mass index (<25 or ≥25 kg/m^2), sex, and number of relapses in the last 2 years (1 or >1). Patients, investigators, and the sponsor were blinded to treatment allocation. Neurologic evaluation was blinded by means of the 2-physician concept. The treating physician was responsible for the management and treatment of patients but was blinded to the same level as patients. The evaluating physician performed all standardized neurologic, disability, functional, and safety assessments and was blinded to treatment decision taken by the treating physician. MRI evaluations were blinded by means of a centralized MRI analysis procedure.

Procedures

We screened patients within a period of 14 days prior to study day 1, during which baseline assessments were performed for safety variables, MRI, and neurologic evaluation. During the treatment period, there were visits at weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96, and a final safety follow-up visit 12 weeks after the final dose (table e-1, doi.org/10.5061/dryad.c81sr72).

We evaluated clinical assessments, including EDSS score and relapse, at each visit and whenever a relapse occurred. Relapse was defined as a neurologic abnormality separated by at least 30 days from the onset of a preceding attack, and lasting more than 24 hours, with an absence of fever or known infection, and objective neurologic impairment correlating with the reported symptoms. We collected blood samples to evaluate the serum levels of vitamin D metabolites: 25(OH)D and $1,25(OH)_2D_3$ at screening, study day 1 and weeks 48 and 96 using the DiaSorin immunoassay method.

We performed MRI assessments at study day 1 and weeks 48 and 96. MRI scans included T2- and T1-weighted images (3 mm slice thickness and ~1-mm in-plane resolution) before and after administration of IV gadolinium and MRI assessments are described in detail in the e-Methods (doi.org/10.5061/dryad.c81sr72).

A patient diary, which was reviewed and compared with drug accountability results, was used to assess compliance with study treatments.

Outcomes

The primary outcome was the proportion of patients with NEDA-3, defined as no relapses, EDSS progression, or combined unique active (CUA) lesions (new gadolinium-enhancing or new/enlarging T2 lesions) at week 48. During the study, we changed the primary outcome from the original outcome: total volume of T2 lesions at week 48 and the proportion of relapse-free patients at week 96 and the planned study duration was reduced from 96 to 48 weeks.[22] This change was made due to difficulties in recruitment and withdrawal from the study after the introduction of first-line oral DMTs to the market, which provided alternatives to SC IFN-β-1a. Inclusion started in 2011 and, at the end of the anticipated inclusion period in 2013, 232 of 348 participants required for the original primary outcome were included. Due to these difficulties in recruitment, an alternative primary outcome decided by the steering committee and sponsor, which was compatible with the study design and schedule of assessments, was required to reduce the sample size by 33% to 232 patients.

When the primary outcome was changed, 106 of 232 (45.6%) randomized patients had attended the week 48 visit and were followed to 96 weeks as originally planned. No interim analysis of the study data was performed during the process of changing the primary outcome to NEDA-3 at week 48.

Secondary outcomes at week 48 included ARR, EDSS, time to first relapse and confirmed EDSS progression, number of CUA lesions per patient per scan, number of new T1-hypointense lesions, change from baseline in the total volume of T2 lesions, and percent brain volume change (PBVC).

Safety information was collected and assessed throughout the study, including physical examinations and vital signs, occurrence of adverse events (AEs), serious AEs (SAEs), and laboratory abnormalities. Severity was graded according to NIH and National Cancer Institute Common Terminology Criteria for AEs version 4.0.

Statistical analysis

In the Rebif vs Glatiramer Acetate in Relapsing MS Disease (REGARD) study, the proportion of relapse-free patients after 2 years of treatment with SC IFN-β-1a alone was 53%.[23] Disease activity–free status was not included as an endpoint in that study, but it appeared reasonable to assume that the proportion of disease activity–free patients was 50% for patients treated with SC IFN-β-1a and placebo add-on. Sample size calculations were performed to enable identification of an increase of 20 percentage points in the proportion of disease activity–free patients in the group with cholecalciferol oil as add-on to SC IFN-β-1a. We selected the arbitrary difference of 20% based on the acceptance of clinical relevance for add-on treatments by the scientific community. Based on these assumptions, a 2-sided test with 80% power at 5% significance ($\alpha = 0.05$) required an estimated sample size needed for analysis of the primary outcome of 230 patients (115 per

treatment arm), assuming a dropout rate of 10% of patients up to week 48. The study analysis populations are described in detail in the e-Methods, doi.org/10.5061/dryad.c81sr72.

Analysis of NEDA-3 status at week 48 was estimated in the intention-to-treat (ITT) population using a logistic regression model with time of exposure to trial medication and the stratification variables as covariates; treatment effect is presented as odds ratio (OR) and 95% confidence intervals (CIs). After database lock, the EDSS scoring from study sites was reviewed and discrepancies were identified. The modified or confirmed value of EDSS scoring was used for a recalculation of the NEDA-3 status at week 48. All secondary outcomes were considered as exploratory. Dichotomous variables were analyzed using logistic regression models adjusted for time of exposure to trial medication and stratification variables, and presented as ORs and 95% CIs. ARR was analyzed using a Poisson regression model corrected for overdispersion and adjusted for time of exposure to trial medication, as defined in the statistical analysis plan finalized before database lock. Time-to-event variables were analyzed using Cox proportional hazard models, adjusted for time of exposure to trial medication and stratification variables, and presented as hazard ratios (HRs) and 95% CIs. Time-to-event variables were displayed using Kaplan-Meier plots and were right-censored for premature withdrawal or week 48, whichever came first. Cumulative MRI lesion counts (T1 and CUA lesions) were analyzed using generalized linear models for negative binomially distributed count data (negative binomial regression) and analysis of covariance (ANCOVA) on the ranks, adjusting for time of exposure to trial medication, using presence of T1 gadolinium-enhancing lesions at baseline and the stratification variables as covariates.

Change from baseline in total volume of T2 lesions was analyzed using ANCOVA on the ranks, adjusted for time of exposure to trial medication and stratification variables. PBVC was analyzed using ANCOVA on the ranks, adjusted for the time of exposure to trial medication, baseline normalized brain volume, and stratification variables.

Safety analysis was performed on the safety population, as previously described in the protocol.

Statistical analyses were performed by biostatisticians of Pharma Consulting Group, using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Primary research question

Does high-dose vitamin D_3 supplementation provide additional efficacy in patients with RRMS treated with SC IFN-β-1a?

Data availability

Merck will share patient-level, study-level data after de-identification, as well as redacted study protocols and clinical study reports from clinical trials in patients. These data will be shared with qualified scientific and medical researchers, upon researcher's request, as necessary for conducting legitimate research. Such requests must be submitted in writing to the company's data-sharing portal and will be internally reviewed regarding criteria for researcher qualifications and legitimacy of the research purpose.

Results

Patient disposition and characteristics

Between February 15, 2011, and May 11, 2015 (database lock), 260 patients were screened and 232 randomized to treatment. Three patients never received study treatment, and 229 patients were included in the ITT population: SC IFN-β-1a plus placebo, n = 116; SC IFN-β-1a plus high-dose vitamin D_3, n = 113 (figure 1). A total of 46 of 232 patients (19.8%) prematurely withdrew from the study: 17 patients (14.8%) in the high-dose vitamin D_3 group and 29 (24.8%) in the placebo group. A greater proportion of patients in the placebo arm withdrew from the study due to withdrawal of consent or EDSS progression (figure 1 and table e-2, doi.org/10.5061/dryad.c81sr72).

Patient baseline characteristics were generally similar in both treatment groups (table 1). However, mean time since diagnosis was higher in the placebo group (14.8 months) than the high-dose vitamin D_3 group (10.4 months). Median (Q1–Q3) serum 25(OH)D levels at baseline were similar between treatments (figure e-1, doi.org/10.5061/dryad.c81sr72).

Over the study, mean (SD) compliance was high for both SC IFN-β-1a (high-dose vitamin D_3 99.02% [5.58], placebo 97.89% [7.72]) and trial medication (high-dose vitamin D_3 95.92% [13.01], placebo 90.61% [20.51]). In addition, extra vitamin D up to a maximum of 1,000 IU/d as a concomitant medication was taken by 20 patients (17.7%) in the high-dose vitamin D_3 group and 19 patients (16.4%) in the placebo group.

Primary outcome at week 48

Overall, 36% of patients in the high-dose vitamin D_3 group had NEDA-3 at 48 weeks. However, there was no statistically significant difference between treatment groups (table 2).

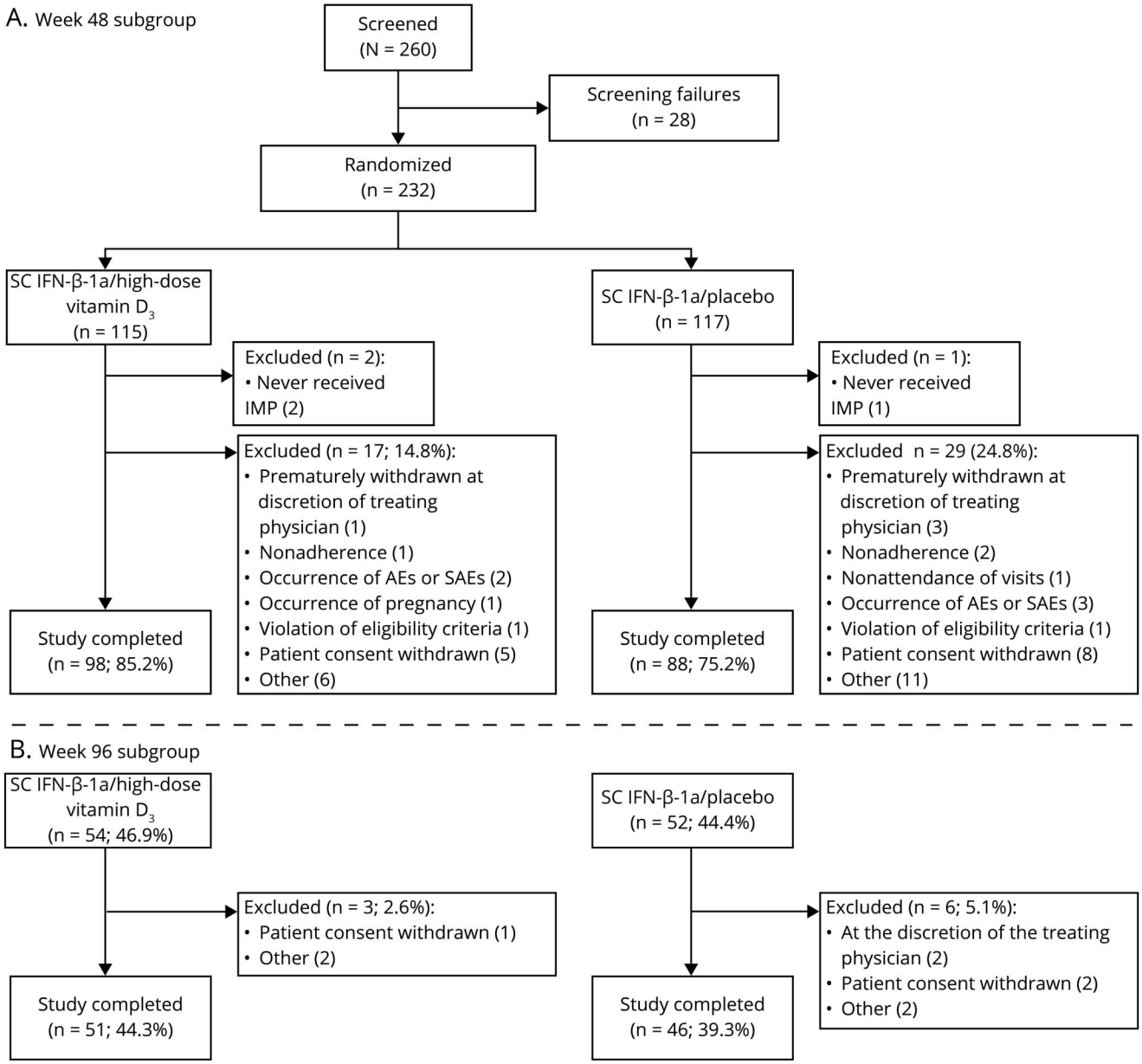
25(OH)D levels at week 48

No increase in median (Q1–Q3) 25(OH)D levels was observed in the placebo group at week 48, whereas an approximately 4-fold increase in 25(OH)D levels was observed in the high-dose vitamin D_3 group (figure e-1, doi.org/10.5061/dryad.c81sr72).

MRI findings at week 48

High-dose vitamin D_3 was associated with a 32% reduction in the number of CUA lesions vs placebo at week 48 (incidence rate ratio 0.68; 95% CI 0.52–0.89; $p = 0.0045$; table 2). In the ITT population, there was no difference between

Figure 1 Disposition of all randomized patients



(A) Week 48 subgroup. (B) Week 96 subgroup. AE = adverse event; IFN-β-1a = interferon-β-1a; IMP = investigational medicinal product; SAE = serious adverse event.

treatments for the proportion of patients free from new T1-hypointense lesions at week 48 (table 2). Compared with placebo, high-dose vitamin D_3 was associated with a reduced mean percentage change from baseline in total volume of T2 lesions at week 48 (3.57% vs 6.07%; table 2). However, one patient in the high-dose vitamin D_3 group had an unusually high increase in the total volume of T2 lesions at week 48 (change from baseline of 7,725 mm^3). Therefore, numerical mean absolute change from baseline total T2 volume appeared larger in the high-dose vitamin D_3 group vs the placebo group (130.38 vs 95.75 mm^3, respectively), despite proportional change and ANCOVA of absolute change suggesting a protective effect of high-dose vitamin D_3 on T2 volume increase (difference in mean ranks −0.074; $p = 0.035$). There was no difference between treatment arms for PBVC at week 48 ($p = 0.72$; table 2).

Clinical findings at week 48

The proportion of patients relapse-free at week 48 was similar in the high-dose vitamin D_3 and placebo groups (78.8% vs 75.0%, respectively). There were no differences between high-dose vitamin D_3 and placebo for time to confirmed EDSS progression at week 48 (HR 2.00; 95% CI 0.60–6.66; $p = 0.26$; figure 2A) and time to first relapse at week 48 (HR 0.77; 95% CI 0.45–1.32; $p = 0.34$; figure 2B). The 31% lower point estimate of ARR in the high-dose

Table 1 Patient characteristics at baseline

	IFN-β-1a + high-dose vitamin D_3 (n = 113)	IFN-β-1a + placebo (n = 116)
Age, y		
Mean (SD)	34.1 (8.0)	33.5 (9.3)
Median (Q1–Q3)	33.0 (28.0–41.0)	32.0 (26.0–40.5)
Sex, n (%)		
Female	76 (67.3)	79 (68.1)
Male	37 (32.7)	37 (31.9)
Race, n (%)		
African descent	0	1 (0.9)
Asian or Pacific Islander	0	0
Caucasian	109 (96.5)	114 (98.3)
Mixed/multiracial	2 (1.8)	1 (0.9)
Other	2 (1.8)	0
BMI, kg/m^2		
Mean (SD)	25.63 (5.67)	25.54 (5.23)
Median (Q1–Q3)	24.22 (21.97–27.97)	23.78 (21.90–27.78)
Time since MS diagnosis, mo		
Mean (SD)	10.39 (8.09)	14.80 (16.96)
Median (Q1–Q3)	8.19 (6.08–11.51)	9.83 (6.64–13.25)
No. of MS attacks in last 2 years		
Mean (SD)	1.81 (0.87)	1.71 (0.80)
Median (Q1–Q3)	2.00 (1.00–2.00)	2.00 (1.00–2.00)
Time since last MS attack, mo		
Mean (SD)	7.36 (3.76)	8.02 (3.75)
Median (Q1–Q3)	6.81 (4.96–9.57)	7.94 (5.26–10.98)
Time since start of IFN-β-1a treatment, mo		
Mean (SD)	6.51 (2.85)	6.41 (2.86)
Median (Q1–Q3)	5.82 (4.44–7.56)	5.79 (4.41–8.09)
No. of T1 Gd+ lesions		
Mean (SD)	0.1 (0.6)	0.2 (1.0)
Median (Q1–Q3)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Patients without T1 Gd+ lesions, n (%)	107 (93.0)	104 (92.9)
Total volume of T1-hypointense lesions, mm^3		
Mean (SD)	857.9 (1,147.1)	922.0 (1878.9)
Median (Q1–Q3)	317.0 (83.0–1,292.0)	239.0 (69.0–1,122.0)
Total volume of T2 lesions, mm^3		
Mean (SD)	3,186.1 (3,177.1)	2,692.4 (3,016.5)
Median (Q1–Q3)	2,380.5 (881.5–4,430.5)	1,418.0 (592.0–4,183.0)
Normalized brain volume, cm^3		
Mean (SD)	1,482.5 (74.1)	1,474.6 (66.9)
Median (Q1–Q3)	1,489.0 (1,432.0–1,534.0)	1,477.5 (1,426.5–1,529.5)

Abbreviations: BMI = body mass index; Gd+ = gadolinium-enhancing; IFN = interferon; MS = multiple sclerosis; Q1 = quartile 1; Q3 = quartile 3.

vitamin D_3 group was not different from the placebo group (table 2). There was no difference in risk of EDSS progression (table 2).

Safety findings at week 48

In the ITT population, treatment-emergent AEs (TEAEs) were reported by 87.6% and 80.2% of patients in the high-dose vitamin D_3 and placebo groups, respectively. The most common TEAEs were headache (18.3% of all patients), nasopharyngitis (15.3%), influenza (14.0%), and influenza-like illness (10.9%). The majority of TEAEs were unrelated to treatment, and those possibly or probably related to treatment were reported at comparable frequency between groups (table 3). Most TEAEs were of mild to moderate intensity for both treatments (table 3).

The incidence of severe TEAEs (12 events in total) was low and similar between both treatments (table 3). Severe TEAEs in the high-dose vitamin D_3 group were limb abscess, breast cancer, cardiac failure, hypertension, bladder dysfunction (2 events in one patient), irregular menstruation, and blood creatine phosphokinase increase. In the placebo group, severe TEAEs consisted of migraine, headache, and injection site induration.

The incidence of treatment-emergent SAEs (TESAEs) was 18.2% with high-dose vitamin D_3 and 8.6% with placebo (table 3). TESAEs with high-dose vitamin D_3 were abscess limb, appendicitis, cellulitis, pneumonia, pyelonephritis, breast cancer, ovarian cancer, depression, syncope, cardiac failure, hypertension, abdominal pain, menorrhagia, uterine polyp, and overdose; TESAEs with placebo were eye infection, headache, hemorrhoids, and overdose. TEAEs of special interest for vitamin D occurred rarely and were of mild to moderate intensity only. TESAE of a potential overdose of investigational medicinal product was reported in both groups (n = 14), and was

Table 2 Primary and secondary efficacy outcomes at week 48 (intention-to-treat population)

Efficacy outcome	IFN-β-1a + high-dose vitamin D_3 (n = 113)	IFN-β-1a + placebo (n = 116)	Treatment difference	*p* Value
Primary outcome				
Patients with NEDA-3, n (%)	41 (36.3)	41 (35.3)	OR 0.93 (0.53–1.63)	0.80[a]
Clinical outcomes				
ARR			IRR 0.69 (0.41–1.16)	0.17[b]
Mean (SD)	0.28 (0.59)	0.41 (0.83)		
Median (Q1–Q3)	0.00 (0.00–0.00)	0.00 (0.00–0.49)		
Patients who were relapse-free, n (%)	89 (78.8)	87 (75.0)	OR 1.26 (0.67–2.35)	0.47[a]
Patients who were free from EDSS progression, n (%)	80 (70.8)	88 (75.9)	OR 0.77 (0.43–1.39)	0.39[a]
Radiologic outcomes				
No. of CUA lesions per patient			IRR 0.68 (0.52–0.89)	0.0045[c]
Mean (SD)	1.09 (3.84)	1.49 (4.31)		
Median (Q1–Q3)	0.0 (0.0–1.0)	0.0 (0.0–1.0)		
Patients free from new T1-hypointense lesions, n (%)	89 (78.8)	74 (63.8)	OR 1.51 (0.70–3.29)	0.30[a]
Change from baseline in total volume of T2 lesions				0.035[d]
Mean (SD)	130.38 (830.82)	95.75 (401.87)		
Median (Q1–Q3)	0.0 (0.0–20.0)	0.0 (0.0–84.5)		
Percentage change from baseline in total volume of T2 lesions				
Mean (SD)	3.57 (20.80)	6.07 (16.53)		
Median (Q1–Q3)	0.0 (0.0–0.4)	0.0 (0.0–4.7)		
Percentage brain volume change				0.72[d]
Mean (SD)	−0.64 (1.09)	−0.80 (1.01)		
Median (Q1–Q3)	−0.62 (−1.26 to −0.10)	−0.64 (−1.25 to −0.21)		

Abbreviations: ARR = annualized relapse rate; CUA = combined unique active (either gadolinium-enhancing or new T2 lesions without enhancement); EDSS = Expanded Disability Status Scale; IFN = interferon; IRR = incidence rate ratio; ITT = intention to treat; NEDA = no evidence of disease activity; OR = odds ratio; Q1 = quartile 1; Q3 = quartile 3.
The treatment difference column presents ratio (95% confidence interval) or the difference in mean ranks.
[a] Logistic regression model and 2-sided tests, adjusted for treatment and stratification variables.
[b] Generalized linear model with Poisson distribution and 2-sided tests, corrected for overdispersion.
[c] Generalized linear model for negative binomially distributed count data and 2-sided tests, adjusted for treatment, T1 gadolinium-enhancing lesions at baseline, and stratification variables.
[d] Analysis of covariance on the ranks and 2-sided tests, adjusted for treatment, baseline value, and stratification variables. The mean T2 volume increase in the cholecalciferol group at week 48 compared to baseline is affected by a patient with an unusually high increase in T2 lesion volume.

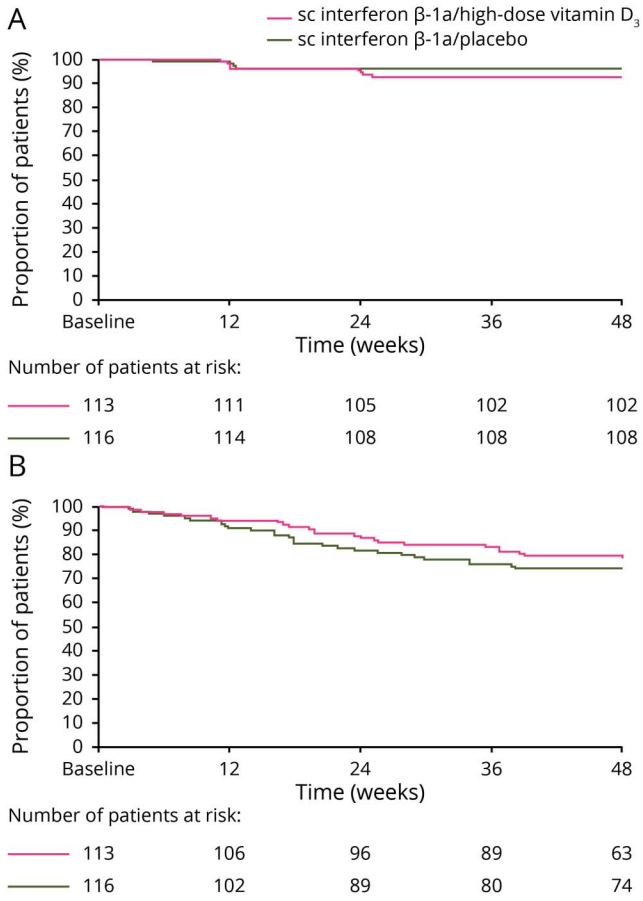
related to an initial batch of bottles with droppers providing slightly bigger volumes, which implied a potentially higher dose of vitamin D_3. At the time that this issue was identified, the first patients were in the titration period. All patients were asymptomatic with no signs of hypercalcemia or hypercalciuria.

Discussion

To date, SOLAR is the largest randomized, placebo-controlled study to evaluate high-dose vitamin D_3 as add-on to DMT, providing Class II evidence regarding the potential benefits of vitamin D_3 supplementation in patients with MS.

The primary outcome of the SOLAR study was originally a composite endpoint, which was planned to be analyzed according to a hierarchical model on the mean number of active T2 lesions at week 48 and the proportion of relapse-free patients at week 96. However, due to difficulties in recruitment of sufficient patient numbers initiating interferon treatment, the primary outcome was changed during the study to another composite endpoint, reflecting the same idea, based on the

Figure 2 Kaplan-Meier plots



Kaplan-Meier plots of (A) time to first confirmed Expanded Disability Status Scale progression up to week 48 and (B) time to first documented relapse up to week 48.

proportion of patients with NEDA-3. The difficulty in patient recruitment was multifactorial. First, SOLAR coincided with the introduction of new oral MS drugs to the market, thereby increasing the competition for patient recruitment. Second, with increasing interest in the potential role of vitamin D in the disease course of MS, patients who believed in the benefit of vitamin D were not prepared to risk randomization to the placebo arm when vitamin D supplements are easily accessible on the market. The inclusion criterion that patients had a 3- to 18-month pretreatment period was selected to exclude subresponders to IFN-β-1a and include those with good compliance with DMT with a minimum time on treatment, which would allow the expression of the full treatment effect of IFN-β-1a previously demonstrated in the short-term IMPROVE trial.[16] Although the option to extend or discard the pretreatment period may have increased the number of patients available for recruitment, the risk of including patients with low compliance or subresponders to IFN-β-1a would have confounded the analysis. Instead, power calculations suggested that the new composite primary outcome would allow the study duration to be shortened to 48 weeks and, based on previous experience and literature on the assessment of NEDA-3,[24] the required sample size to be reduced by 33% to 232 patients. However, in retrospect, this endpoint may have been too ambitious. In addition, we note that the add-on design could have masked a small effect of vitamin D_3, as previously noted in relation to MRI measurements.[25]

Overall, 36% of patients in the high-dose vitamin D_3 group had NEDA-3 at 48 weeks. SOLAR was powered on the assumption of a 20% additional treatment effect of high-dose vitamin D_3 supplementation. This value was purposely chosen to identify a clinically relevant effect for the NEDA-3 outcome and was based on the general treatment expectations of an add-on treatment, which would be considered as additional clinically relevant benefit.[23] This study cannot confirm that high-dose vitamin D_3 might have an additional clinically relevant treatment benefit to SC IFN-β-1a on the NEDA-3 outcome. However, secondary MRI endpoints suggest the presence of an additional treatment effect, which may have been less pronounced than the predefined 20% threshold of clinical relevance. Although the dropout rate was higher than the 10% originally estimated, the lack of difference in the primary outcome does not seem to be related to lack of statistical power as the results in the 2 arms were similar. Indeed, there is conflicting evidence for the effect of 25(OH)D levels on clinical and MRI outcomes in patients receiving DMT. A recent study showed that increasing levels of 25(OH)D were inversely associated with MRI disease activity in untreated patients with MS, but not in patients receiving IFN-β.[25] Other prospective studies have suggested that higher levels of 25(OH)D were associated with a reduced hazard of relapse in patients largely treated with DMTs,[15] and with longer time to relapse or gadolinium-enhancing lesions with IFN but not glatiramer acetate.[26]

The entry criteria for SOLAR were specifically selected to include patients at a relatively early stage of the disease with a sufficient degree of disease activity at baseline. It remains uncertain as to whether the challenges that affected the SOLAR study influenced the findings. During the process of changing the primary outcome to NEDA-3, no interim analysis of the data was performed, to avoid incurring a statistical penalty. It can be assumed that the low clinical disease activity, lower than expected treatment effect with high-dose vitamin D_3 supplementation, and the short duration of the follow-up period might represent the main reasons for which no statistically significant difference in clinical outcomes could be identified between the 2 treatment groups. Most likely the same factors would have also negatively affected the study with the original larger sample size. Future clinical trials may further elucidate the benefit of high-dose vitamin D_3 supplementation on a background of DMT.[27,28]

Although the secondary outcomes in SOLAR were considered exploratory, our findings suggest an effect of high-dose vitamin D_3 supplementation on MRI lesion activity

Table 3 Adverse events

	IFN-β-1a + high-dose vitamin D_3 (n = 113)		IFN-β-1a + placebo (n = 116)	
	Patients, n (%)	No. of events	n (%)	No. of events
Any TEAE	99 (87.6)	601	93 (80.2)	507
Mild	90 (90.9)	414	87 (93.5)	398
Moderate	63 (63.6)	179	52 (55.9)	105
Severe	7 (7.1)	8	4 (4.3)	4
Any TEAE leading to discontinuation of study treatment	4 (4.0)	4	7 (7.5)	12
Any TEAE by relationship to study treatment				
Unrelated	92 (92.9)	472	91 (97.8)	448
Unlikely	35 (35.4)	103	18 (19.4)	34
Possible	12 (12.1)	17	14 (15.1)	19
Probable	9 (9.1)	9	6 (6.5)	6
Any TESAE	18 (18.2)	23	8 (8.6)	9
Hypercalciuria				
Mild	1 (0.9)	1	2 (1.7)	2
Moderate	1 (0.9)	1	1 (0.9)	1
Severe	0	0	0	0
Vitamin B_{12} decreased				
Mild	1 (0.9)	1	1 (0.9)	2
Moderate	1 (0.9)	1	0	0
Severe	0	0	0	0
Urine calcium				
Mild	0	0	1 (0.9)	1
Moderate	0	0	1 (0.9)	1
Severe	0	0	0	0
Hypercalcemia (all grades)	0	0	0	0

Abbreviations: IFN = interferon; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

and, therefore, support the biological effect of vitamin D on the disease process of MS suggested by earlier studies and suggest a potential benefit over a longer outcome period than the one covered by SOLAR. A prospective cohort study that included 1,482 patients receiving IFN-β-1b found an inverse correlation between serum 25(OH)D levels and the cumulative number of new active lesions; a 50.0-nmol/L increase in serum 25(OH)D levels was associated with a 31% lower rate of new lesions.[2] In a prospective, single-arm, open-label study that included patients receiving IFN-β or glatiramer acetate, progressively increasing doses of vitamin D were associated with a decreased number of gadolinium-enhancing lesions.[9] In a randomized, double-blind, controlled trial, patients in the IFN-β-1b plus cholecalciferol group had fewer T1-enhancing lesions and a numerically lower number of new T2 lesions than those without cholecalciferol supplementation.[10] ARR was a secondary outcome in SOLAR, and no difference was observed between high-dose vitamin D_3 and placebo. Evidence to date for the effect of vitamin D_3 levels and supplementation on relapses remains inconclusive. In 2 studies that included patients receiving IFN-β-1b, there were no differences in ARR between vitamin D_3 supplementation and placebo, although these trials were limited by a lack of statistical power to address relapses[10] or a prestudy ARR that was lower than in populations typically included in clinical trials.[11] As the data from our study support evidence of a treatment effect of high-dose vitamin D_3 on the biology of MS, a longer follow-up than 48 weeks may reveal whether these effects provide benefits on relapses. However, when

interpreting the results of the secondary outcomes, the exploratory nature and use of multiple statistical testing should be considered. In particular, CUA is the most sensitive marker of inflammation and has good statistical power—hence its central role in MRI analysis.[29] Other lesional markers (black holes and T2 lesion volume) have the same numerical trend, but do not reach significance, and the proportion of patients free from black holes and brain atrophy are more difficult targets of neurodegeneration, which seem hardly affected. In addition, the lack of measurement of the formation of neutralizing antibodies to interferon represents a possible limitation of the study design.

There were no unexpected safety issues identified with high-dose vitamin D_3 and it was well-tolerated, supporting findings from previous studies with high-dose vitamin D_3.[18,30] TEAEs were similar to those known for SC IFN-β-1a.[31] As such, the risk–benefit profile of high-dose vitamin D_3 supplementation is good, as any benefits are not ameliorated by an increase in AEs.

We found that high-dose vitamin D_3 supplementation in patients with RRMS in addition to SC IFN-β-1a does not provide an additional treatment effect of at least 20% improvement in NEDA-3 status after 48 weeks of treatment compared with placebo. Whether high-dose vitamin D_3 supplements would have met the originally anticipated assumptions in the 96-week trial design remains unanswered. Findings from exploratory outcomes suggest potential benefits on MRI outcomes. In order to be able to show potential efficacy of vitamin D_3 supplementation on NEDA-3, future studies may need to enroll a population with more active disease or a larger sample size for populations with low disease activity.

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Continued

Appendix *(continued)*

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