SHORT REPORT

A pilot study of oral calcitriol (1,25-dihydroxyvitamin D_3) for relapsing–remitting multiple sclerosis

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Background: Epidemiological and ecological studies suggest links between vitamin D deficiency and increased multiple sclerosis (MS) prevalence.
Objective: To evaluate the safety and tolerability of oral calcitriol therapy in an open label pilot study.
Methods: 15 ambulatory patients with relapsing–remitting MS and at least one clinical relapse within the previous 12 months received oral calcitriol (target dose: 2.5 μg/d) for 48 weeks. Dietary calcium was restricted to 800 mg/d. Patients were monitored using frequent clinical and laboratory examinations, the expanded disability status scale (EDSS), and brain magnetic resonance imaging (MRI).
Results: Two patients withdrew because of symptomatic hypercalcaemia (serum calcium >3.35 mmol/l in each case) resulting from persistent dietary indiscretion. Two diet compliant patients required temporary dose adjustments for mild asymptomatic hypercalcaemia. Diet compliant patients experienced mild adverse effects. The on-study exacerbation rate (27%) was less than baseline. Four patients experienced five clinical relapses but only one patient worsened by >1 EDSS point. Brain MRI revealed enhancing lesions in five patients at baseline (33%) and in four (29%) at both 24 and 48 weeks.
Conclusions: Oral calcitriol is safe and well tolerated for up to one year by diet compliant relapsing–remitting MS patients. Further study of vitamin D related mechanisms is warranted in MS.

Multiple sclerosis (MS) is a putative autoimmune disorder for which unidentified environmental exposures influence disease emergence. The worldwide prevalence of MS increases with geographical latitude (greater prevalence with increasing distance from the equator) and this gradient persists in some regions even after controlling for influences such as migration patterns.[1–3] Epidemiological and ecological studies show an inverse association between solar radiation exposure and MS prevalence or mortality.[4–6]

Vitamin D represents one potential link to explain these findings. Vitamin D is generated in the dermal skin layer after exposure to sufficient ultraviolet (UV) radiation.[7] Most UV irradiation occurs near the equator. During winter months at latitudes >45°, even prolonged sunlight exposure is inadequate to support vitamin D synthesis, and the general population is at risk for deficiency in those regions.[7 8] Vitamin D deficiency often coexists with established MS and oral supplementation may be associated with a lower risk of the disease.[9–11] Together with a recent observational study involving type 1 diabetes, these findings suggest that vitamin D status may influence susceptibility to certain immune mediated diseases.[12]

Vitamin D metabolites could also be useful for the treatment of established MS.[13] The metabolically active form of vitamin D, calcitriol (1,25-dihydroxyvitamin D_3), has potent immunological properties.[14] In murine experimental allergic encephalomyelitis, calcitriol pretreatment prevents disease expression, and therapy after disease induction prolongs survival.[15 16] Calcitriol is used to treat human psoriasis.[17] We developed this protocol to evaluate the safety and tolerability of supraphysiological doses of oral calcitriol in patients with recently active MS and to obtain preliminary evidence for therapeutic efficacy.

METHODS

Between March 1999 and March 2001, we enrolled 15 patients with clinically definite relapsing–remitting MS into this 48 week open label study. Inclusion criteria were: age 18 to 65 years; at least one clinical exacerbation in the previous 12 months; expanded disability status scale (EDSS) score 0 to 5.0; contraindication to or patient desire against treatment with β-interferons and glatiramer acetate. Exclusion criteria were: progressive MS; use of β-interferon, glatiramer acetate, corticosteroid or immunosuppressive therapy within the previous eight weeks; use of digitalis or vitamin D supplementation; any condition predisposing to hypercalcaemia; nephrolithiasis or renal insufficiency; pregnancy or unwillingness to use contraception; and unwillingness to restrict dietary calcium.

Enrolled patients completed baseline brain magnetic resonance imaging (MRI) with gadolinium, a complete blood count, electrolyte, calcium, and phosphate levels, and hepatic and renal function studies (fig 1). Treatment was initiated with oral calcitriol 0.5 μg/d and the daily calcium intake limited to 800 mg. The calcitriol dose was increased in 0.5 μg/d increments every two weeks (if serum calcium and the calcium–phosphorus product remained normal) to the target dose of 2.5 μg/d. Participants were educated regarding hypercalcaemic symptoms and received written dietary guidelines. Serum calcium and creatinine levels and urine calcium and phosphate levels were assessed frequently (fig 1).

Participants had clinic visits at eight week intervals for monitoring of adverse effects and disease activity (EDSS and evaluation of relapse occurrence). We assessed compliance by monitoring serum calcium levels. Relapses were treated with corticosteroids at the discretion of the neurologist. Brain MRI with gadolinium was carried out at 24 and 48 weeks (and at least 30 days after corticosteroid therapy) and the number of scans with gadolinium enhancing lesions was compared with the number at baseline (pretreatment).

Safety, EDSS, and MRI data were summarised descriptively. The two sided paired *t* test ($\alpha = 0.05$) was used to compare serum calcium and other laboratory variables with baseline values.

Abbreviations: EDSS, expanded disability status scale; MS, multiple sclerosis

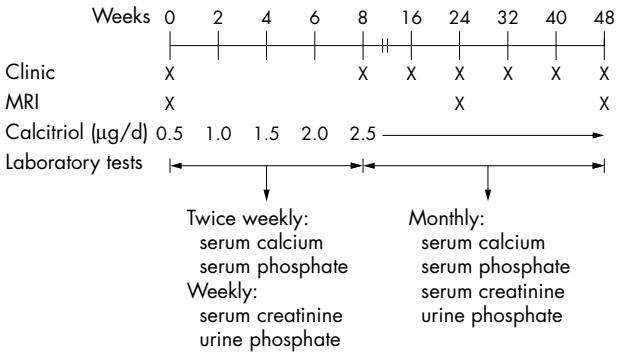

Figure 1 Study flow diagram.

RESULTS

Nineteen patients were screened to obtain 15 enrolees (12 women). Four patients were excluded owing to baseline hypercalcaemia (n = 1) or election to begin available immunomodulatory drugs (n = 3). At study onset, mean age was 36.1 years (range 22 to 44) and mean disease duration was 6.3 years (range 1 to 13). Mean enrolment EDSS was 1.9 (median 2.0; range 0 to 4.0). One patient had two attacks during the preceding year and the remainder had one attack.

Safety/tolerability outcomes

All patients achieved the target calcitriol dose and there were no events of hypercalcaemia during the dose escalation phase. Adverse effects included headache (n = 3), constipation (n = 3), dizziness (n = 1), and paraesthesiae (n = 1). There were no instances of urinary dysfunction or symptomatic nephrolithiasis.

Thirteen patients completed the study and 11 were able maintain the target calcitriol dose of 2.5 µg/d. Two patients had mild, asymptomatic hypercalcaemia (levels of 2.74 and 2.69 mmol/l; normal 2.12 to 2.62 mmol/l) which required temporary dose adjustment to 1.5 µg/d and 2.0 µg/d. After two to three weeks, both patients re-established the target dose without adverse effects.

Two patients withdrew because of symptomatic hypercalcaemia (serum calcium 3.45 and 3.35 mmol/l, respectively); headache and abdominal pain resolved after calcium levels normalised. Persistent dietary indiscretion was associated with both instances. One patient regularly used a mineral supplement providing >600 mg/d of calcium and the other did not follow dietary restrictions.

Laboratory results are summarised in table 1. Maximum serum calcium levels were reached in all patients at the target dose of 2.5 µg/d (mean (SD) time to maximum calcium level, 34.4 (7.5) weeks; range 24 to 48). All patients appeared compliant based upon serum calcium data.

MRI and clinical outcomes

At baseline, five of 15 scans (33%) showed at least one gadolinium enhancing lesion (median 0; range 0 to 3 lesions). Each of the 24 and 48 week brain MRI studies showed enhancing lesions in four of 14 patients (29%) (median 0; range 0 to 4 and 0 to 9 lesions, respectively). Three patients with enhancing lesions at baseline continued to show at least one gadolinium enhanced lesion on one or both scans during calcitriol treatment. Of the 10 patients with no enhancing lesions at baseline, three had a single enhancing lesion on one of the two studies done during calcitriol treatment; the others had negative scans for the entire study. New T2 weighted lesions were detected in six of 14 scans (43%) at the 24 week study and in four of 14 (29%) at the 48 week study.

Table 1 Laboratory values

Week	Serum calcium (mmol/l)	Serum phosphate (mmol/l)	Serum creatinine (µmol/l)
Baseline	2.28 (0.07)	1.10 (0.13)	67.7 (12.5)
24	2.45 (0.12)**	1.19 (0.17)	67.5 (23.1)
48	2.38 (0.09)*	1.08 (0.13)	72.8 (18.7)

Values are mean (SD).
*p = 0.011 and **p<0.001 for serum calcium levels compared with baseline. Serum phosphate and creatinine levels were not significantly different from baseline values.

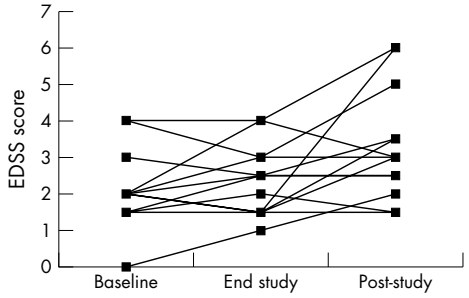

Figure 2 Line plot of expanded disability status scale (EDSS) scores at baseline, at study completion, and at final post-study follow up.

Four patients (27%) experienced a total of five clinical relapses during the 48 week study and one attack was treated with corticosteroids. Three of the relapses occurred in two patients who had concurrently active MRI scans showing gadolinium enhancing lesions.

Four patients (27%) worsened by at least one EDSS point (three patients worsened by one point and one patient by two points) during the study, when comparing baseline with week 48 EDSS scores. The mean EDSS at the end of the study was 2.2 and the median EDSS change was 0 points (range −1.0 to +2.0).

After calcitriol was discontinued, 14 patients were evaluated in routine clinical follow up for 12 months or until they started another disease modifying agent. Nine exacerbations occurred in seven patients during mean follow up of 10 months (range 6 to 12 months). Mean EDSS score increased to 3.1 (range 1.5 to 6.0) and eight of 14 patients worsened by at least one point (fig 2). Three patients eventually started β-interferon treatment. Post-trial MRI studies were not routinely done.

DISCUSSION

Calcitriol doses of up to 2.5 µg/d are safe and generally well tolerated for up to one year in diet compliant MS patients. Although this study was not designed to evaluate efficacy, the results suggest that disease aggravation is unlikely.

There may be multiple opportunities for vitamin D related intervention for demyelinating disease. Although calcitriol levels are normally tightly regulated, supraphysiological doses could provide immunological benefits for people with established MS, similar in concept to benefits observed in experimental allergic encephalomyelitis. On the other hand, 25-hydroxyvitamin D_3 levels vary with seasonal and sunlight exposure (and may correlate with gadolinium enhancing lesion frequency)[18 19]; therefore, dietary vitamin D supplementation may play a role in disease prevention for those at higher risk for MS (with a family history of the disease) or very early treatment (after development of a clinically isolated syndrome). Supplementation with vitamin D (1000 IU/d) plus calcium (800 mg/d) resulted in alteration of the

cytokine profiles in MS patients.[20] Whether supplementing dietary vitamin D (perhaps at higher doses than recommended to date)[21] to ensure subsequent paracrine or autocrine formation of physiological levels of calcitriol is sufficient to affect established MS also warrants investigation.

The calcitriol dose used in this pilot study is substantial and may not be sustainable. Further investigations are needed to determine the optimal dose using safety, efficacy, and immunological criteria. Studies are warranted to compare calcitriol with analogues having a less hypercalcaemic effect (alfacalcidol has been safely administered to MS patients for six months[22]), or dietary supplementation of vitamin D, along with investigations designed to test vitamin D related mechanistic hypotheses.

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