MEDIA RELEASE

World first clinical trial finds Vitamin D supplements do not prevent the development of MS

27 October 2022: Vitamin D supplements do not prevent the development of Multiple Sclerosis.

That's the finding from PrevANZ, a ground-breaking clinical trial funded by MS Australia to determine if oral vitamin D supplements can delay the onset of MS.

The results of the trial will be presented for the first time at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Amsterdam today (*see page 3 for detailed findings*).

There has long been interest in the possible benefits of vitamin D supplements for those living with MS and whether they can be used to prevent the development of MS.

That's because the risk of developing MS can vary depending on latitude, with those living furthest from the equator more likely to be affected by the disease.

In Australia, those living in the north of the country are less likely to develop MS than those in the south.

It has long been hypothesised that this is brought on by a lack of sunlight, which could potentially lower vitamin D levels.

To test this hypothesis, MS Australia, with support from MS Western Australia, established the world's first clinical trial involving 204 people from Australia and New Zealand.

A small, highly dedicated team worked for eight years on this study, to establish the potential benefit of oral vitamin D supplementation to prevent new MS disease activity in people who had just had their first attack of MS.

Each person taking part in the trial was then randomised to one of three different daily doses of vitamin D (1000 IU (international units), 5000 IU or 10000 IU), or a placebo (no vitamin D).

Vitamin D was used as a standalone therapy - the participants were not on other disease-modifying drugs for their MS.

Professor Helmut Butzkueven, Chair of the PrevANZ Steering Committee said the participants were then followed for 48 weeks to determine whether they went on to develop MS.

"We showed conclusively that doses of up to 10,000 international units per day did not reduce MS activity compared to those who did not take vitamin D," Professor Butzkueven said.

Professor Bruce Taylor, also from the PrevANZ Steering Committee, understands this might be seen as a disappointing result, but says it is a very important one.

"We are now eagerly awaiting the results of D-LAY MS, a French study with very similar design.

"On behalf of the entire study team, we wish to thank all the study participants and investigators for their participation and dedication over so many years", Professor Taylor said.

MS Australia's Head of Research, Dr Julia Morahan said that given that vitamin D is readily available, there had been insufficient commercial interest in conducting this important research.

"To ensure this vital work was undertaken, MS Australia sponsored this trial with the first participant enrolled in 2013.

"We are very proud to have funded and facilitated this world first clinical trial, and so grateful to the participants who took part in the trial and the wider Australian MS community for supporting us to address this important question for people living with MS," Dr Morahan said.

Further research is now underway to understand more about the effects of vitamin D on the immune system and nervous system in this group. More work is needed to uncover the mechanisms underpinning the role of latitude and sunshine in the risk of developing MS.

Refer to detailed findings on page 3 - PREVANZ: A phase 2b placebo-controlled double-blind dose-ranging study of vitamin D to prevent progression to definite multiple sclerosis after a high risk clinically isolated syndrome

About MS

MS is the most common acquired chronic neurological disease affecting young adults, often diagnosed between the ages of 20 to 40 and, in Australia, affects three times more women than men. As yet, there is no cure. There is no known single cause of MS, but many genetic and environmental factors have been shown to contribute to its development.

In MS, the body's own immune system mistakenly attacks and damages the fatty material – called myelin – around the nerves. Myelin is important for protecting and insulating nerves so that the electrical messages that the brain sends to the rest of the body, travel quickly and efficiently.

As the myelin breaks down during an MS attack – a process called demyelination – patches of nerves become exposed and then scarred, which renders the nerves unable to communicate messages properly and at risk of subsequent degeneration. This means that the brain cannot "talk" to other parts of the body, resulting in a range of symptoms that can include a loss of motor function (e.g., walking and hand and arm function, loss of sensation, pain, vision changes and changes to thinking and memory).

About MS Australia

MS Australia is Australia's national multiple sclerosis (MS) not-for-profit organisation that empowers researchers to identify ways to treat, prevent and cure MS, seeks sustained and systemic policy change via advocacy, and acts as the national champion for Australia's community of people affected by MS.

MS Australia represents and collaborates with its state and territory MS Member Organisations, people with MS, their carers, families and friends and various national and international bodies to:

- Fund, coordinate, educate and advocate for MS research as part of the worldwide effort to solve MS
- Provide the latest evidence-based information and resources
- Help meet the needs of people affected by MS

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PREVANZ: A phase 2b placebo-controlled double-blind dose-ranging study of vitamin D to prevent progression to definite multiple sclerosis after a high risk clinically isolated syndrome

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Introduction

Low vitamin D status as measured by serum 25(OH)D levels and low sunlight exposure are known environmental risk factors for the development of multiple sclerosis (MS). Add-on Vitamin D supplementation trials in established MS have been inconclusive. The effects of vitamin D supplementation to prevent MS development in high-risk clinically isolated syndrome (CIS) are unknown.

Objective

To determine whether vitamin D supplementation in patients with CIS and positive MRI (modified from Paty's criteria) delays time to new disease activity (clinical relapse or new MRI Brain Flair/T2 lesion).

Trial Design

In this double-blind trial, eligible participants were randomised 1:1:1:1 to placebo, 1000, 5000, or 10000 IU of oral vitamin D_3 daily within each study site (n=23, in Australia and New Zealand) and followed for up to 48 weeks. Brain MRI scans were performed at baseline, 24 and 48 weeks.

Patient Eligibility

Aged 18 -59 with a new onset of first ever clinical episode of central nervous system demyelination (optic neuritis, transverse myelitis brainstem syndrome, other) as determined by a study neurologist, and who had an abnormal MRI with at least 2 CNS lesions suggestive of demyelination meeting the Paty criteria A or B (lesions must be ovoid and greater than 2 mm). During the study, with the evolution of MS criteria (McDonald 2017), we amended the admission criteria to allow one lesion in either the spinal cord or the optic nerve to count as one CNS lesion. Participants must also have been willing to forgo DMT therapy during the trial and not to take supplemental vitamin D or use a sunbed during the trial period. Exclusion criteria included progressive onset MS, other causes (DM)of CNS demyelination/inflammation (NMOSD, MOG associated, ADEM), history of hypercalcaemia or hyperparathyroidism.

Statistical Analysis

The main objectives of the study were assessed using interval-censored survival analysis. The event of interest was either a clinical relapse or new MRI brain lesion. Primary intention to treat (ITT) analysis compared the four randomised treatment arms with the primary outcome without adjustment for other factors. Participants who had taken at least seven doses of study medication qualified for the ITT analysis; other cases were omitted.

Survival analyses were conducted using as endpoints *either* clinical *or* radiological relapse (new MRI lesion).

The primary analysis was then adjusted for sex, age and study site.

Baseline Cohort Characteristics

Between April 2013 and Dec 2020, we enrolled 204 participants. 199 continued on study drug for 7 days or more and were included in the primary analysis.

	Placebo	1000 IU	5000 IU	10000 IU	Overall
N	50	49	51	49	199
F/M	38/12	33/16	37/14	34/15	142/57
Age Mean (SD)	35.9 (9.8)	38.3 (10.3)	36.6 (10.6)	37.3 (10.6)	37.0 (10.3)
25(OH)D level nmol/l Mean (SD)	71.2 (39.8)	65.8 (23.3)	69.0 (28.0)	69.9 (21.0)	69 (29)

25(OH)D_3 serum levels by cohort

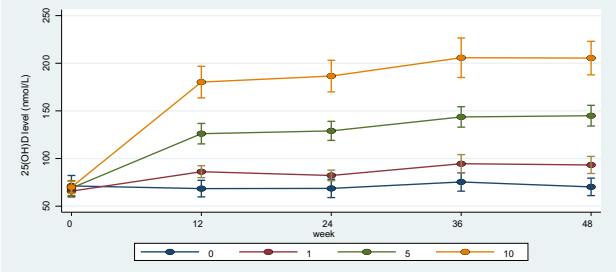

Figure 1: Serum 25(OH)D_3 level achieved during the study by dosing group : Mean and 95% CI. "0" is placebo, 1, 5 and 10 = 1000, 5000 and 10,000 IU D_3 supplementation /day.

Results: Primary Outcome

Unadjusted Hazard Ratios for time to recurrent disease activity

Placebo : 1.00 (Reference)
1000 IU : 0.87 (95% CI 0.50-1.50)
5000 IU : 1.37 (95% CI 0.82-2.29)
10000 IU : 1.28 (95% CI 0.76-2.14) p=0.28

Hazard Ratios adjusted for age, sex and site

Placebo : 1.00 (Reference)
1000 IU : 0.81 (95% CI 0.46-1.42)
5000 IU : 1.38 (95% CI 0.81-2.29)
10000 IU : 1.29 (95% CI 0.75-2.22) p=0.44

Results : Recurrent Disease Activity Timelines

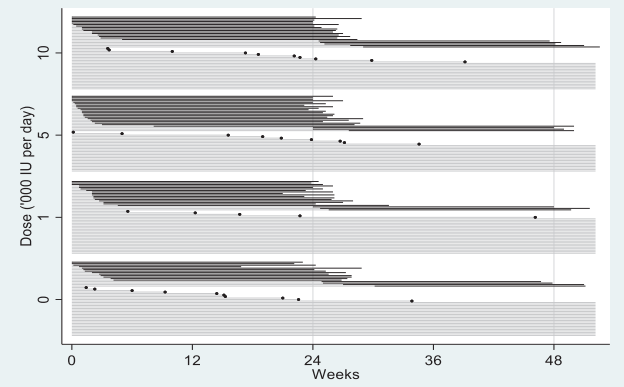

Figure 2 Outcomes for all participants by assigned treatment
MRI-conversions plotted above clinical conversions and censored patients, and then plotted in order of failure time. Grey lines show time on study. Short grey lines ending in a black dot show relapses. Vertical lines at week 24 and 48 show MRI schedule.

Results: Safety

Vitamin D_3 supplementation was well tolerated with 13 Serious Adverse Events (SAEs) recorded, all resulting in hospitalisations. None of these were thought to be related to the study medication. There were no deaths recorded. There were no difference in SAE incidence between treatment groups. One patient discontinued study medication due to asymptomatic hypercalcemia (AE) at week 8.

Conclusion

In the PREVANZ CIS monotherapy study, doses up to 10000 IU/day of oral vitamin D_3 did not reduce the rate of recurrent disease activity compared to placebo. However, only few patients were vitamin D deficient (<50nmol/L) at baseline.

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