D-lay MS

High-dose cholecalciferol reduces multiple sclerosis disease activity after a clinically isolated syndrome : results of a 24-month placebo-controlled randomized trial

Eric Thouvenot, David Laplaud, Christine Lebrun-Frenay, Nathalie Derache, Emmanuelle Le Page, Elisabeth Maillart, Caroline Froment-Tilikete, Giovanni Castelnovo, Olivier Casez, Marc Coustans, Anne-Marie Guennoc, Olivier Heinzlef, Laurent Magy, Chantal Nifle, Xavier Ayrignac, Agnes Fromont, Nicolas Gaillard, Nathalie Caucheteux, Ivania Patry, Jérôme De Seze, Romain Deschamps, Pierre Clavelou, Damien Biotti, Gilles Edan, William Camu, Hanane Agherbi, Dimitri Renard, Christophe Demattei, Pascale Fabbro-Peray, Thibault Mura, Manon Rival, **for the D-Lay MS Investigators**

I Introduction

Context : vitamin D (VD) deficiency is a risk factor for multiple sclerosis (MS) and is associated with the risk of disease activity and of disability.[1] VD induces pleiotropic immune regulations, decreasing differentiation of effector T and B cells, promoting regulatory subsets, modulating innate immune cells, reducing immune cell trafficking at the blood–brain barrier level and microglial and astrocytic activation, thus supporting VD therapy to reduce MS activity and progression. [2] However results from VD supplementation studies in MS are contradictory.[3-6]

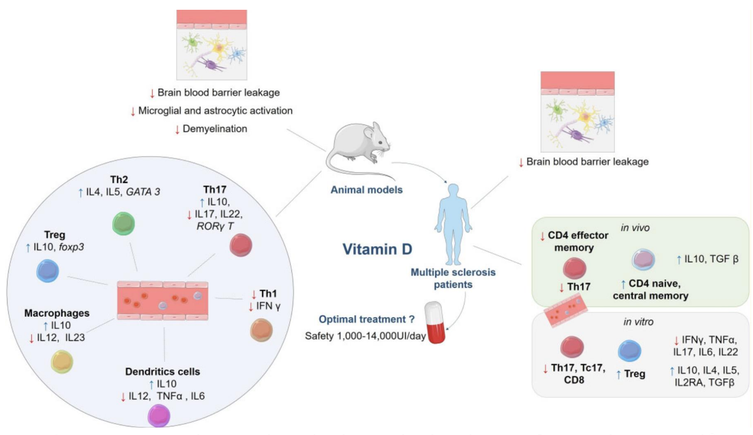

Figure 1. VD regulations described in multiple sclerosis, from *Galoppin et al.*[2]

Aims: to evaluate **efficacy of cholecalciferol** as **monotherapy** to **reduce disease activity** in patients with a **clinically isolated syndrome** (CIS) typical for MS.

II Methods

This study was a double-blind, randomized, placebo-controlled 24-month study.

The key inclusion criteria included age 18 - 55 years old, CIS < 90 days, serum 25-hydroxy vitamin D (25OHD) concentration <100 nmol/L, diagnostic MRI fulfilling the Swanton criteria or 2 lesions + oligoclonals bands (OCBs).

Patients were randomized between **oral cholecalciferol 100,000 IU or placebo every 2 weeks** (1:1 ratio), stratified by centre and presence of contrast-enhancing lesions (CELs) on diagnostic MRI

Baseline : clinical visit and reference brain and spinal cord MRI with gadolinium

Follow-up:
- Clinical visit at 3, 6, 12, 18 and 24 months
- Brain and spinal cord MRI with gadolinium at 3, 12 and 24 months

Primary outcome : **occurrence of disease activity** = **relapse** and/or new or enlarging T2 lesions (**NELs**) and/or contrast-enhancing lesions (**CELs**)

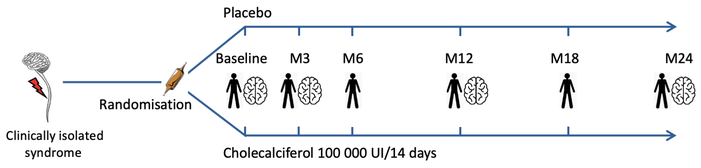

Figure 2. Study design. M: month

III Results

Population

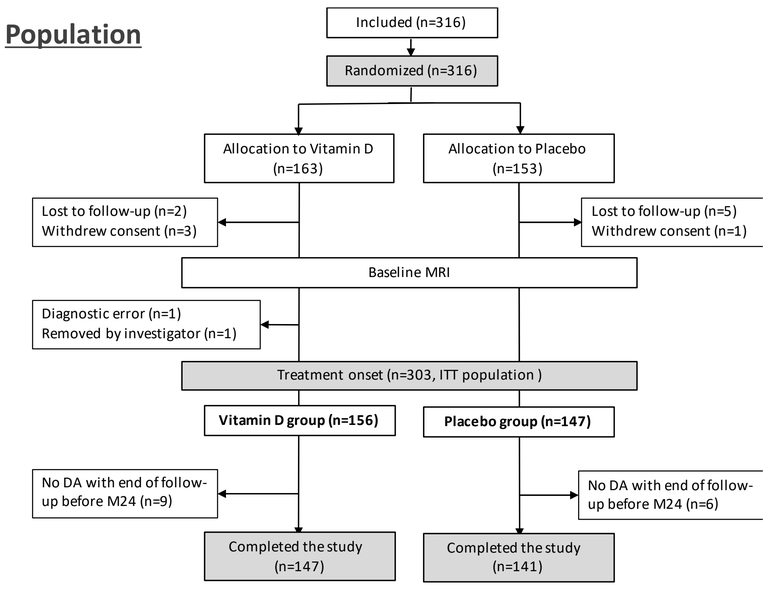

Figure 3. Flowchart. DA: disease activity

316 patients were recruited in **36 centers** in France (2012-2023). **The ITT population** included **303 patients** starting the treatment.

Characteristic	Vitamin D (n = 156)	Placebo (n = 147)
Age – yr [IQR]	35 [28-42]	34 [27-40]
Female sex – no. (%)	103/156 (66%)	108/147 (73%)
Body mass index – kg/m² [IQR][a]	24.1 [21.2-27.5]	23.5 [21.6-27.7]
Active smokers - no. (%)	57/156 (37%)	55/147 (37%)
Vitamin D levels - nmol/L [IQR]	49.5 [34.0-67.0]	42.5 [29.0-63.0]
Optic neuritis - no. (%)	55/156 (35%)	43/147 (31%)
IVMP	129/156 (83%)	128/147 (87%)
EDSS score [IQR]	1.0 [0-2.0]	1.0 [0-2.0]
Number of brain (FLAIR) lesions - no./total no. (%)		
<9	75/151 (50%)	61/143 (43%)
≥9	76/151 (50%)	82/143 (57%)
Gadolinium-enhancing lesions - no./total no. (%)		
0	74/156 (47%)	77/147 (52%)
1	67/156 (43%)	55/147 (37%)
≥2	15/156 (10%)	15/147 (10%)
T2 spinal cord lesions - no./total no. (%)		
0	68/151 (46%)	66/139 (48%)
1	44/151 (29%)	34/139 (24%)
≥2	39/151 (25%)	39/139 (28%)
Presence of CSF oligoclonal bands - no./total no. (%)	97/121 (62%)	106/119 (72%)
MS 2017 diagnostic criteria - no./total no. (%)	126/144 (88%)	121/135 (90%)
Delay between CIS and treatment – days [IQR] [b]	61 [48-80]	60 [46-83]

Table 1. Baseline characteristics. Results are shown as median [IQR] or number (%).
No.: number; CSF: cerebrospinal fluid; EDSS: Expanded Disability Status Scale; CIS: clinically isolated syndrome; DIS: dissemination in space; IVMP: high-dose intravenous methylprednisolone pulse therapy. Number of missing data per group (Vitamin D/Placebo): a 3/3, b 7/5.

Primary outcome

Disease activity (**relapse + NELs + CELs**) occurred in 94 patients (60.3%) in the VD group and 109 patients (74.1%) in the placebo group.

HR for disease activity was **0.66** [95%CI: 0.50, 0.87] in the **VD group** (**p=0.004**).

Median time to disease activity was **432** days in the **VD group** and **224** days under **placebo** (**p=0.003).**

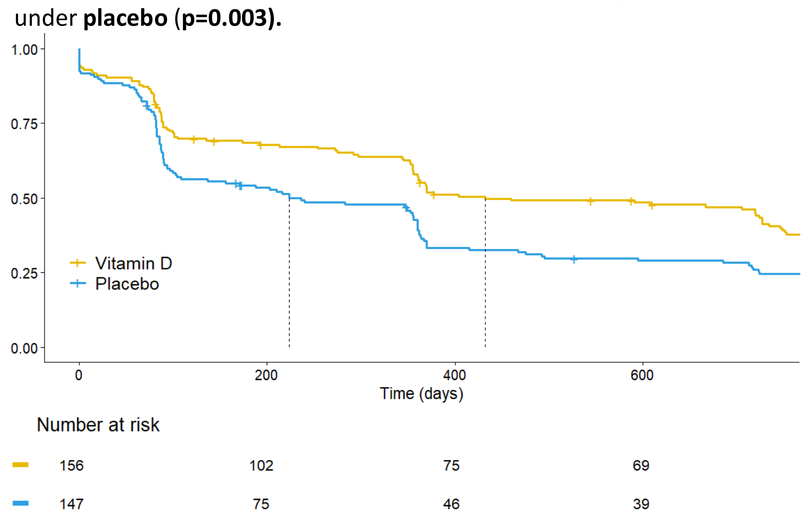

Figure 4. Kaplan Meier survival curve for disease activity during the 2 years of follow-up, VD group in yellow and placebo group in blue.

Interaction between treatment and prognostic factors

Interaction between the treatment arm and prognostic factors revealed that patients who benefited most from VD were those without spinal cord lesions at diagnosis (HR 0.23 vs. 0.85, p=0.011), severe VD deficiency (HR 0.33 vs. 0.78, p=0.03) and normal BMI at baseline (HR 0.53 vs. 0.95, p=0.048). Age, sex, CIS phenotype, methylprednisolone treatment, number of brain T2/FLAIR lesions, presence of CELs and EDSS at baseline did not influence VD effects.

Safety

Among 288 patients completed the study (95.1%), the frequency of serious adverse events (SAEs) in both groups was **comparable** (33 SAEs in 30 patients, (p=0.68)) **None** was suggestive of hypercalcemia or related to the study drug. Neither kidney failure nor moderate or severe (>2.88mM) hypercalcemia levels were reported. Mild hypercalcemia (2.6-2.88 mmol/L) was observed in 2 patients in the placebo group.

Secondary outcomes

MRI activity and occurrence of **NELs** and **CELs** on follow-up MRI scans were **significantly reduced** in the VD group. (Table 2)
The same trend of reduction was observed on relapses, although no significant. VD had no impact on disability (EDSS, PASAT), fatigue (FSMC), quality of life (EQ-5D-5L, SF-36) or depression and anxiety symptoms (HADS) during follow-up. (Table 2)

On ancillary analysis concerning 247patients with **2017McDonald criteria for RRMS** at baseline, we observed the same results. (Table 2)

				Partial adjustment	
303 patients of the ITT		Vitamin D (n event / n)	Placebo (n event / n)	HR (95%CI)	p value
Primary outcome (DA)		94 / 156	109 / 147	**0.66 (0.50-0.87)**	**0.0036**
Secondary outcomes	Relapse	28 / 156	32 / 147	0.69 (0.42-1.16)	0.160
	MRI activity	89 / 156	96 / 147	**0.71 (0.53-0.95)**	**0.022**
	CELs	29 / 156	50 / 147	**0.47 (0.30-0.75)**	**0.002**
	NELs	72 / 156	87 / 147	**0.61 (0.44-0.84)**	**0.003**
				Partial adjustment	
247 patients with RRMS (2017 McDonald criteria)		Vitamin D (n event / n)	Placebo (n event / n)	HR (95%CI)	p value
Primary outcome (DA)		79 / 126	94 / 121	**0.66 (0.49-0.89)**	**0.0073**
Secondary outcomes	Relapse	24 / 126	27 / 121	0.70 (0.40-1.21)	0.201
	MRI activity	75 / 126	84 / 121	**0.71 (0.51-0.97)**	**0.032**
	CELs	25 / 126	42 / 121	**0.49 (0.30-0.81)**	**0.006**
	NELs	59 / 126	77 / 121	**0.59 (0.42-0.83)**	**0.003**

Table 2. Efficacy measures. The partial adjustment was performed on the center and the presence of CELs on the baseline MRI scan. Bold indicates statistically significant results.
CELs: contrast-enhancing lesions; DA: disease activity; ITT: intention to be treated population; NELs: new or unequivocally enlarging T2/FLAIR lesions.

V Conclusion

Oral **cholecalciferol** 100,000 IU every two weeks as **monotherapy** is **safe, well tolerated and efficient to reduce disease activity** in **CIS** patients and early **RRMS**.

Cholecalciferol could represent an **inexpensive**, **safe** and **well-tolerated** therapeutic alternative after a CIS, especially in populations with limited access to DMTs. It could benefit at the **population level** after exclusion of high-risk hypercalcemia and represent the best candidate for **add-on therapy** evaluation in the therapeutic strategy for MS. Assessment of VD efficacy on **disability** is needed.

IV Discussion

- Our results align with a pilot study evaluating VD efficacy as **monotherapy** for 48 weeks in 30 patients with **untreated optic neuritis** [3] and with **add-on therapy studies CHOLINE and SOLAR**, negative for their primary endpoint (reduction of MS relapses) but suggesting benefits on **MRI activity**, in combination with IFN-β1a. [5,6]
- Our results contrast with the **PreVANZ study** testing three daily VD doses on lower patient numbers with shorter treatment duration, and higher drop-out rates. [4] Effects of high-dose pulse therapy *vs*. daily oral VD supplementation could be different.
- The **relative risk reduction (34%) for disease activity** observed here was similar to that of some platform therapies in CIS patients (teriflunomide in TOPIC trial and slightly less than interferon β-1a and -1b in REFLEX and BENEFIT trial). [7-9]
- Our results showed **efficacy** and **good safety** of high-dose VD in patients with **RRMS according to 2017 McDonald criteria**.
- VD did not reduce relapse in this study, possibly due to the low number of relapses (60/303) as a disease modifying treatment was started in case of MRI activity.
- NEDA-3 at 24 months could not be assessed since EDSS was not measured frequently enough to assess 3- or 6-month confirmed disability accumulation.
- VD efficacy should be assessed on activity and disability among 2024 revised criteria MS patients and pre-clinical stages.

Acknowledgments

- D-Lay MS Investigators : Dominique AUFAUVRE, Xavier AYRIGNAC, Aurélien BENOILID, Julien BIBERON, Damien BIOTTI, Bertrand BOURRE, David BRASSAT, Gauthier CALAIS, Clarisse CARRA DALLIERE, Olivier CASEZ, Giovanni CASTELNOVO, Nathalie CAUCHETEUX, Jonathan CIRON, Pierre CLAVELOU, Mickael COHEN, Nicolas COLLONGUES, Laura COULOUME, Marc COUSTANS, Jérôme DE SÈZE, Véronique DEBURGHGRAEVE, Loreen DELALANDE, Nathalie DERACHE BELPALME, Romain DESCHAMPS, Richard DEVY, Anne-Laure DUBESSY, Françoise DURAND-DUBIEF, Gilles EDAN, Mirela FAIGHEL, Caroline FROMENT TILIKETE, Agnès FROMONT, Nicolas GAILLARD, Nicolas GAILLARD, Damien GALANAUD, Olivier GOUT, Anne-Marie GUENNOC, Patrick HAUTECOEUR, Olivier HEINZLEF, Anne KERBAT, Caroline LANCIN GARCIA, David LAPLAUD, Emmanuelle LE PAGE, Christine LEBRUN-FRESNAY, Flora LEJEUNE, Céline LOUAPRE, Adil MAAROUF, Laurent MAGY, Elisabeth MAILLART, Julie MAS, Laure MICHEL, Alexis MONTCUQUET, Thibault MOREAU, Chantal NIFLE, Olivier OUTTERYCK, Caroline PAPEIX, Ivania PATRY, Sophie PITTION-VOUYOVITCH, Aurelia SCHUNCK, Frédéric TAITHE, Violaine TALMANT, Eric THOUVENOT, Ayman TOURBAH, Aurelian UNGUREANU, Mathieu VAILLANT, Sandra VUKUSIC, Anne WACONGNE, Sandrine WIERTLEWSKI, Jennifer YEUNG
- Steering Committee: Eric THOUVENOT, Pascale FABBRO-PERAY, Thibault MURA, William CAMU
- Data and Safety Monitoring Board: Jean PELLETIER, Nicolas MOLINARI, Dominique HILLAIRE-Buys, Jean-Luc FAILLIE
- BESPIM and others : Christophe DEMATTEI, Manon RIVAL, Brigitte LAFONT, Hanane AGHERBI, Dimitri RENARD, Carey SUEHS, Pierre RATABOUL, Zahrâ MEZGUELDI, Sarah KABANI, Marion CHEVRON, Marie-Paule FRANCESCHI, Dorian MULTEDO, the CRAs, RBC and Pharmacy teams.

Literature

1. Munger KL, Levin LI, Hollis BW,et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 2006;296(23):2832–8.
2. Galoppin M, Kari S, Soldati S, et al. Full spectrum of vitamin D immunomodulation in multiple sclerosis: mechanisms and therapeutic implications. Brain Commun 2022;4:fcac171.
3. Derakhshandi H, Etemadifar M, Feizi A, et al. Preventive effect of vitamin D3 supplementation on conversion of optic neuritis to clinically definite multiple sclerosis: a double blind, randomized, placebo-controlled pilot clinical trial. Acta Neurol Belg 2013;113(3):257–63.
4. Butzkueven H, Ponsonby A-L, Stein MS, et al. Vitamin D did not reduce multiple sclerosis disease activity after a clinically isolated syndrome. Brain 2023;awad409.
5. Hupperts R, Smolders J, Vieth R, et al. Randomized trial of daily high-dose vitamin D 3 in patients with RRMS receiving subcutaneous interferon β-1a. Neurology2019;10.1212/WNL.0000000000008445.
6. Camu W, Lehert P, Pierrot-Deseilligny C, et al. Cholecalciferol in relapsing-remitting MS: A randomized clinical trial (CHOLINE). Neurol Neuroimmunol Neuroinflamm 2019;6(5):e597.
7. Miller AE, Wolinsky JS, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13(10):977–86.
8. Comi G, De Stefano N, Freedman MS, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol 2012;11(1):33–41.
9. Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006;67(7):1242–9.