BASELINE VITAMIN D LEVELS AND MULTIPLE SCLEROSIS ACTIVITY IN RELAPSING REMITTING PATIENTS TREATED WITH FINGOLIMOD

L.Ferre'[1,2], G.Sferruzza[1,2], E.Mascia[2], F.Clarelli[2], G.Dalla Costa[1], M.Radaelli[1], F.Sangalli[1], A. Nuara[1,4], C.Guaschino[1,2], M.A.Rocca[1,3], M.Filippi[1,3], F.Martinelli Boneschi[1,2], G.Comi[1,2], V.Martinelli[1], F.Esposito[1,2]

[1] Department of Neurology, San Raffaele Scientific Institute - Milan (Italy); [2]Laboratory of Human Genetics of Neurological Disorders, CNS Inflammatory Unit & INSPE, San Raffaele Scientific Institute, Milan (Italy); [3] Neuroimaging Research Unit, INSPE - Milan (Italy); Experimental Neurophysiology Unit, INSPE-Milan (Italy)

BACKGROUND AND AIMS

Several studies highlighted the role of 25-hydroxy-vitamin D (VitD) in modulating either the risk of developing multiple sclerosis (MS) and the level of disease inflammatory activity. Moreover higher VitD levels in patients treated with the first line drug interferon beta-1b, were associated with lower MS activity observed on MRI. The present study aimed at investigating the correlation between VitD levels and disease activity in patients treated with fingolimod (FTY), in order to identify a possible synergic effect between VitD and FTY.

PATIENTS AND METHODS

We enrolled in the study 235 relapsing remitting (RR) MS patients treated at the San Raffaele Hospital in Milan, Italy, with available VitD levels at the time of FTY start: they were prospectively followed for 2 years with neurological examinations every 3 months and brain MRI scans every year. The main clinical and demographic characteristics of the patients are listed in Table 1.

Due to seasonal variation, baseline VitD levels were adjusted for the month of blood collection using a periodic regression and accounting for sex and age at blood collection as previously described [Munger et al, 2006].

We performed:

- a linear regression analysis considering the ARR, the number of new/enlarging T2 lesions and gadolinum enhancing (Gd+) lesions at brain MRI scans performed during FTY treatment as outcomes; a logistic regression was applied when considering the NEDA (non-evidence of disease activity) status at 2 years. Both an univariable and a multivariable analysis, including baseline clinical variables, were performed. Moreover, after analysing the whole cohort we performed a separate analysis for patients previously treated with natalizumab (NTZ patients, n=59) and NO NTZ patients, never treated with the drug (n=166).
- a cox regression analysis to test for a relationship between basal VitD levels and the time to first relapse.
- a categorical analysis classifying VitD levels into 4 categories retrieved from the literature (Category 1: <50 nmol/l; Category 2: 50-75 nmol/l; Category 3: <75-100 nmol/l; Category 4: >100 nmol/l). The number of patients in each VitD category is shown in Figure 1.

Female:Male	**163:72**
Mean Age at Onset	**28.5** (±8.8)
Mean Disease Duration	**9.9** (±7.1)
Mean Age at T0	**38.4** (±9.6)
Median EDSS	**2** (1-6)
Mean ARR 2y pre	**0.75** (±1.1)
Mean n° of T2 lesions at bl	**0.88** (±1.4)
Mean n° of Gd+ lesions at bl	**0.62** (±1.3)

Table 1: clinical and demographic characteristics of included patient:

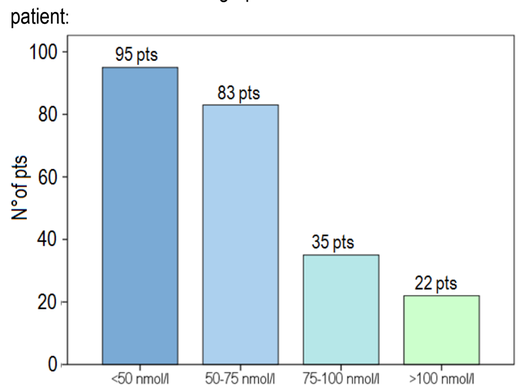

Figure 1: Proportion of patients in each VitD category

RESULTS

Analysing ARR, MRI parameters and NEDA-3 status, we found no association between VitD and a positive response to FTY treatment when considering the whole cohort. However, considering NTZ and NO NTZ pts separately, we found that in the first group NEDA patients showed a trend towards higher VitD levels (p:0.05, Fig 2A). No differences were seen between NEDA and EDA (evidence of disease activity) patients in the NO NTZ group (Fig 2B)

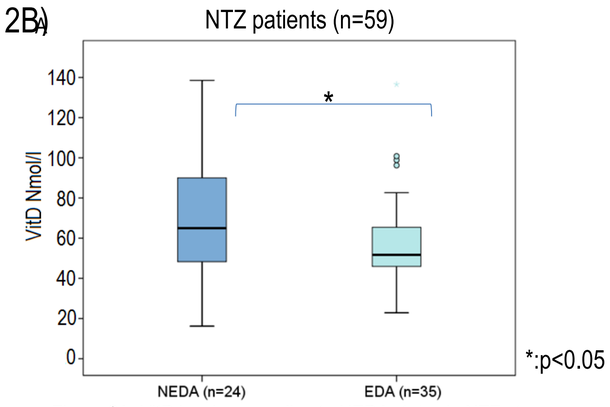

Figure 2A: VitD levels according to NEDA status in NTZ pts

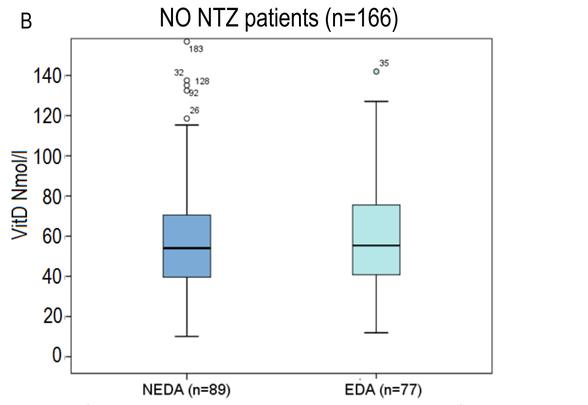

Figure 2B: VitD levels according to NEDA status in NO NTZ pts

On the contrary, when considering the four VitD categories, we found that patients with the highest level of VitD (Category 4) had a significantly lower number of new/enlarging T2 lesion at the baseline MRI scan as compared to Category 1 (0.37 vs 1.05, p: 0.008, Fig3) and to all the first 3 categories considered together (p:0.01 data not shown)

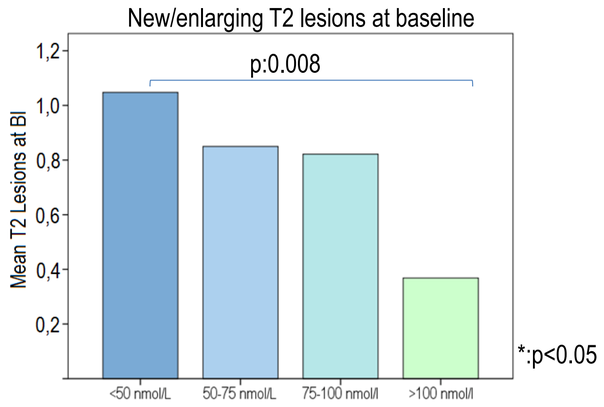

Figure 3: Mean n° of new/enlarging T2 lesions at the baseline brain MRI scan, according to VitD Categories

Category 4 also had a significantly lower number of new/enlarging T2 lesions at 1 and 2 year of follow up compared to Category 1 (p:0.037 and 0.005) and Category 2 (p:0.024 and 0.015) (Fig 5A and B) and to patients with VitD < 100 nmol/l

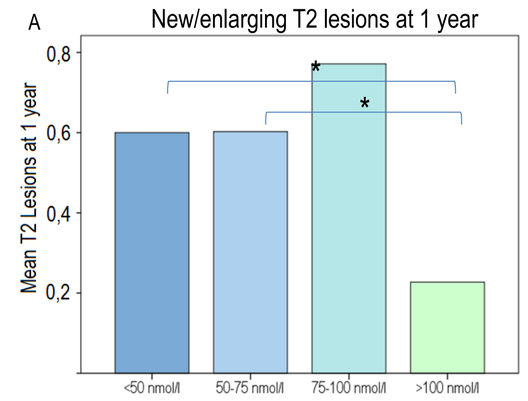

Figure 5A: Mean n° of new/enlarging T2 lesions at 1 year brain MRI scan, according to VitD Categories

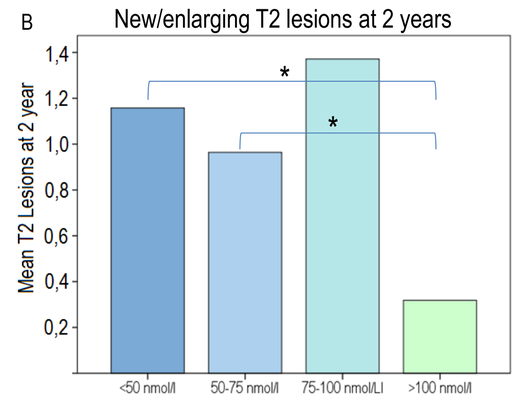

Figure 5B: Mean n° of new/enlarging T2 lesions at 2 years brain MRI scan, according to VitD Categories

*:p<0.05

Likewise, the number of Gd enhancing lesions at the 2 year MRI scan was significantly lower in Category 4 patients with respect to Category 1 (p: 0.03, Fig 6B)

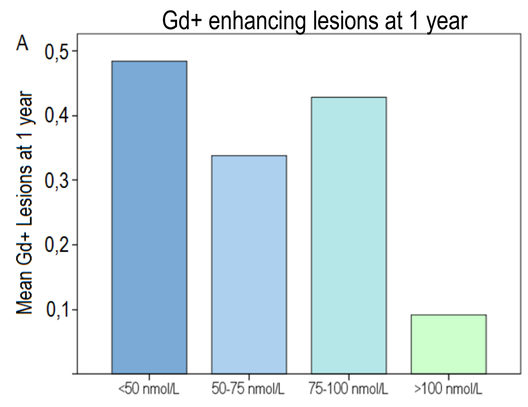

Figure 6A: Mean n° Gd+ enhancing lesions at 1 year brain MRI scan, according to VitD Categories

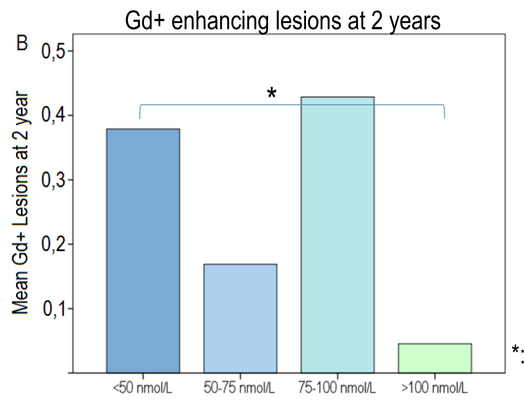

Figure 6B: Mean n° of Gd+ enhancing lesions at 2 years brain MRI scan, according to VitD Categories

CONCLUSIONS

- 25OHVitD levels at baseline seem not to be associated with response to FTY treatment when considering the whole cohort, maybe due to the already powerful action of the treatment that could mask the protective effect of VitD. However, in the NTZ group, that showed a greater inflammatory activity, higher VitD levels were associated to NEDA status.
- Patients with very high level of 25OHVitD >100 nmol/l (>40 ng/ml) showed a trend towards a lower neuroradiological disease activity at baseline and during the 2 year follow up. This could suggest that higher target of 25OHVitD than usually considered could be beneficial for MS patients
- Further studies are needed to confirm our data, considering the limitations of the present study (single 25OHVitD measurement and few patients in Category 4)

DISCLOSURES

L. Ferre', F. Clarelli, G. Sferruzza, E. Mascia,. Radaelli, F. Sangalli, G. Dalla Costa have nothing to disclose. M.A. Rocca received speakers honoraria from Biogen Idec, Novartis, Genzyme, Sanofi-Aventis and Excemed and receives research support from the Italian Ministry of Health and Fondazione Italiana Sclerosi Multipla. M. Filippi is Editor-in-Chief of the Journal of Neurology; serves on scientific advisory board for Teva Pharmaceutical Industries; He received compensation for consulting services and/or speaking activities from Biogen Idec, Excemed, Novartis, and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Teva Pharmaceutical Industries, Novartis, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, Cure PSP, Alzheimer's Drug Discovery Foundation (ADDF), the Jacques and Gloria Gossweiler Foundation (Switzerland), and ARiSLA (Fondazione Italiana di Ricerca per la SLA). F. Martinelli Boneschi received compensation for activities with Teva Neuroscienze as speaker and/or advisor. G. Comi received compensation for consulting services with the following companies: Novartis, Teva, Sanofi, Genzyme, Merck, Biogen, Excemed, Roche, Almirall, Chugai, Receptos, Forward Pharma and compensation for speaking activities from Novartis, Teva, Sanofi, Genzyme, Merk, Biogen, Excemed, Roche. V. Martinelli received honoraria for consulting and speaking activities from Biogen-Idec, Merck, Bayer, TEVA, Novartis and Genzyme. F. Esposito received honoraria from TEVA and Merck. ***This study is supported by the "Fondazione Italiana Sclerosi Multipla", project 2013/R/13***