

## SHORT COMMUNICATION

### The Potential Effect of the Tumour Necrosis Factor- $\alpha$ Inhibitors on Vitamin D Status in Psoriatic Patients

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Vitamin D is deeply involved in calcium-phosphorus metabolism and in bone homeostasis (1). One of its metabolisms, 25-hydroxyvitamin D<sub>3</sub>, (25(OH)D<sub>3</sub>) is the best marker of vitamin D status since its half-life is 2–3 weeks and it reflects the total vitamin D amount derived from diet, sun exposure and the liver conversion (2).

Not only does vitamin D inhibit cellular proliferation, promote cellular differentiation, it also exerts an immune-regulatory effect on tumour necrosis factor (TNF)- $\alpha$  and chemokine expression (2). Some studies confirm the critical role of vitamin D in physiopathology and in therapeutic approach to several dermatological diseases, including psoriasis (3).

A recent study emphasised that vitamin D deficiency is very frequent in patients with chronic plaque psoriasis and in those with psoriatic arthritis, especially in wintertime (4). TNF- $\alpha$  inhibitors have radically changed the therapeutic management of psoriatic patients with comorbidities (5,6).

The aim of the present study was to evaluate whether the 24 week administration of TNF- $\alpha$  inhibitors could influence the vitamin D, PTH and calcium serum levels in psoriatic patients.

## MATERIALS AND METHODS

We conducted a retrospective case control study on patients with psoriasis receiving TNF- $\alpha$  inhibitors; clinical and laboratory data were obtained from the database of Dermatological Clinic of United Hospitals of Ancona.

This analysis was approved by Polytechnic Marche University Ethical Committee, and conducted in accordance with the Ethical Principles of Declaration of Helsinki.

Inclusion criteria were the following: a clinical diagnosis of moderate to severe chronic plaque type psoriasis carried out by a trained dermatologist (PASI > 10, DLQI > 10, BSA > 10), no phototherapy or sun exposure in the last 4 weeks before and during the investigation period, no history of previous biological therapies or alcohol abuse (no more than 2 glasses of wine per day). Patients suffering from other clinical type of psoriasis, and/or patients receiving concomitant treatments with the ability to influence vitamin D status, and/or patients suffering from bowel disease with malabsorption of vitamin D were excluded from the study. All these data were obtained from medical records previously compiled and stored.

One hundred and twenty patients met the above described criteria. Among them, 42 patients had been treated with etanercept (50 mg/bi-weekly for 12 weeks and 25 mg/bi-weekly for further 12 weeks) and 38 patients with adalimumab (40 mg/ every other week for 24 weeks).

As controls, we selected 20 psoriatic patients treated with cyclosporine (4 mg/kg/day for 24 weeks), 20 patients treated with acitretin (25 mg/day for 24 weeks) and 70 healthy controls recruited from the same household of psoriatic patients, in order to minimise the differences linked to dietary habits and lifestyle.

All patients followed a Mediterranean diet which is characterised by low saturated fat (<7–8% of energy), an abundance of plants foods, minimally processed, seasonally fresh foods, food with low sugar content consumed a few times per week, olive oil as the principal source of fat, and low consumption of cheese, red meat and wine (7). In order to avoid the confounding factor related to seasonal fluctuations of vitamin D, that could create a bias in the interpretation of collected data, we selected only T0-T24 sera obtained from patients and controls between October–November 2010 and March–April 2011.

The body mass index (BMI) was evaluated after a 12 h overnight fast and without clothes and shoes, and estimated by calculating body weight (kg)/height (m<sup>2</sup>).

All frozen-thawed serum samples obtained from the selected 80 psoriatic patients both before (T0) and after 24 weeks of treatment with TNF- $\alpha$  inhibitors (T24) and from the 70 selected healthy controls were equilibrated to room temperature for 30 min before use. Blood specimens had been previously refrigerated at –80°C and repeated freeze-thaw had been avoided. Serum levels of 25(OH)D<sub>3</sub> (ng/ml), parathyroidea hormone (pg/ml) and calcium (mg/dl) were measured using 25(OH)D<sub>3</sub> ELISA (Calbiotech), Intact-PTH ELISA and Calcium Detection Kit (Colorimetric) (Abcam). The circulating levels of vitamin D were interpreted according to the consensus statement on deficiency/insufficiency of vitamin D: deficiency of 25(OH)D<sub>3</sub> for serum levels less than 20 ng/ml, insufficiency in the range 20–32 ng/ml, and sufficiency in the range of 33–80 ng/ml (8).

All data were analysed using Graph-Pad Prism (version 5.0, El Camino REAL, San Diego, CA). The normal distribution of continuous variables was verified with Kolmogorov-Smirnov test. Statistical non-parametric analyses included the Mann Whitney test for continuous variables. For all the analyses a *p*-value of <0.05 was considered to be statistically significant.

## RESULTS

The psoriatic group consisted of 75 men and 45 women, mean age of 44.4 ± 14.5 years, whereas the healthy group included 40 men and 30 women, mean age 48.7 ± 13.7 years. Psoriasis patients did not differ in age and sex distribution, PASI, BMI, dietary and smoke habits and sun exposure; they had therefore been considered as a whole group at baseline.

At baseline, both study and control group showed similar serum levels of 25(OH)D<sub>3</sub>, PTH and calcium: median 25(OH)D<sub>3</sub> serum levels were in the range of sufficiency (Table I).

Table I. Characteristics of psoriatic patients before and after treatment with anti-tumour necrosis factor- $\alpha$  inhibitors, cyclosporine or acitretin and of healthy controls

	Baseline/patient			Post-treatment			Healthy controls	
	anti-TNF (T0/TNF) (n=80) Mean $\pm$ SD	Cyclosporine (T0/cyc) (n=20) Mean $\pm$ SD	Acitretin (T0/ret) (n=20) Mean $\pm$ SD	anti-TNF (T24/TNF) (n=80) Mean $\pm$ SD	Cyclosporine (T24/cyc) (n=20) Mean $\pm$ SD	Acitretin (T24/ret) (n=20) Mean $\pm$ SD	Baseline (T0/h) (n=70) Mean $\pm$ SD	T24 (T24/h) (n=70) Mean $\pm$ SD
PASI score <sup>a</sup>	20.53 $\pm$ 3.56	19.69 $\pm$ 4.56	16.86 $\pm$ 4.23	4.43 $\pm$ 3.26	4.53 $\pm$ 3.40	15.81 $\pm$ 4.36	n.d.	n.d.
BMI <sup>b</sup> , kg/m <sup>2</sup>	18.36 $\pm$ 4.64	18.65 $\pm$ 6.93	18.60 $\pm$ 6.74	22.10 $\pm$ 6.43	18.54 $\pm$ 6.86	18.62 $\pm$ 6.84	18.55 $\pm$ 6.78	18.53 $\pm$ 6.73
25(OH)D3 <sup>c</sup> , ng/ml	40.15 $\pm$ 7.99	41.29 $\pm$ 7.43	41.41 $\pm$ 6.26	24.27 $\pm$ 9.97	41.76 $\pm$ 9.62	41.43 $\pm$ 9.45	39.15 $\pm$ 7.99	39.20 $\pm$ 7.78
PTH, mg/ml	37.65 $\pm$ 9.56	37.50 $\pm$ 9.69	37.28 $\pm$ 9.68	37.65 $\pm$ 9.76	37.45 $\pm$ 9.71	37.35 $\pm$ 9.73	36.44 $\pm$ 6.53	36.39 $\pm$ 6.50
Calcium, mg/dl	8.67 $\pm$ 1.18	8.72 $\pm$ 1.33	8.63 $\pm$ 1.14	8.70 $\pm$ 1.23	8.73 $\pm$ 1.26	8.68 $\pm$ 1.15	8.98 $\pm$ 0.50	8.95 $\pm$ 0.49

<sup>a</sup>T24/TNF vs T0/TNF; T24/CYC vs T0/CYC ( $p < 0.05$ ). <sup>b</sup>T24/TNF vs T0/TNF ( $p < 0.05$ ). <sup>c</sup>T0/TNF vs T24/TNF; ( $p < 0.05$ ).

In the psoriatic group, mean PASI score was significantly decreased after 24 weeks of treatment with anti-TNF- $\alpha$  therapy and cyclosporine. Only in the psoriatic patients treated with TNF- $\alpha$  inhibitors, a significant BMI increase was evident (Table I).

Serum levels of 25(OH)D3 were significantly decreased in the psoriatic patients receiving anti-TNF- $\alpha$  therapy compared to baseline values, to cyclosporine and acitretin group and to T0–T24 healthy control values, overlapping the range of insufficiency with median serum levels of  $\sim 24$  ng/ml. PTH and calcium serum levels were not influenced by any of the above therapies for psoriasis (Table I).

No significant 25(OH)D3, PTH and calcium serum levels modifications were detected in healthy controls after 24 weeks (Table I).

## DISCUSSION

In the last decades, interesting data have been reported on the role of vitamin D on psoriasis, a Th1–Th17 immuno-mediated inflammatory disease (2, 9–15).

It has already been demonstrated that TNF- $\alpha$  directly stimulates the differentiation of osteoclasts from bone marrow macrophages *in vitro* as well as indirectly via osteoblasts (16). Based on this evidence, it could be inferred both a serum level calcium decrease and a compensatory increase in circulating vitamin D in patients receiving TNF- $\alpha$  inhibitors.

Our results showed that at baseline 25(OH)D3 serum levels did not show statistically significant differences between psoriasis patients and healthy controls, whereas at T24 the values in psoriatic patients receiving TNF- $\alpha$  inhibitors approached vitamin D insufficiency. It could be hypothesised that the block of TNF- $\alpha$  inflammatory pathways exerts a negative feedback on the enzymatic machinery of vitamin D synthesis either in the skin or in the liver and kidney.

Furthermore, our data showed a BMI increase after biologic therapy and this might be responsible for the associated vitamin D insufficiency, confirming data from Orgaz-Molina et al. (17): one possible explanation is a sequestration of vitamin D in fat.

The main limitation of the study is its retrospective nature (18), which did not allow us to evaluate the effect of TNF- $\alpha$  inhibitors on serum levels of 25(OH)D3 over a long period of treatment, a critical role of season (in terms of sun exposure) on circulating vitamin D levels cannot be completely excluded.

A potential protective role for 25(OH)D3 in the metabolic profile of patients with psoriasis has recently been demonstrated (4). Thus oral vitamin D supplementation could be tried to prevent a further decrease in serum 25(OH)D3 levels during long-term anti-TNF- $\alpha$  treatment associated with a risk of osteoporosis.

*The authors declare no conflict of interest.*

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