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**Maurizio Rossini**

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Dear Colleagues,

In this issue, you will first find an update on the possible role of vitamin D in various dermatological diseases, as its deficiency may contribute to the pathogenesis of some skin diseases, both neoplastic and immune-mediated.

As a rheumatologist, I am particularly interested in psoriasis, the incidence and severity of which has been shown in numerous studies to be associated with vitamin D deficiency and the treatment of which has involved the use of topical vitamin D analogues for years.

The association of psoriasis with arthritic manifestations is frequent and well known. Indeed, psoriatic arthritis is classified amongst the Spondyloarthritis (SpA), representing a heterogeneous group of chronic inflammatory rheumatological diseases that share genetic, radiological and clinical characteristics, including the possible involvement of the entheses, axial skeleton and sacroiliac joints as well as peripheral joints. Copious evidence shows that specific inflammatory cytokines are involved in the pathogenesis of SpA (IL17, IL23, TNF- $\alpha$ , IL6). In particular, IL17 plays a pathogenetic role both in joint exertion and in entheses and bone. Recent evidence also indicates that metabolic as well as immunological factors are additionally involved in the pathogenesis of SpA, including in particular those modulating bone metabolism, such as DKK1, sclerostin and PTH, as has been shown<sup>1-5</sup>. On such pathogenic, immunological and metabolic components, there is a scientific rationale for believing that vitamin D – often described as deficient in patients with SpA<sup>6-10</sup> – may play an important role. Yet, in addition to playing an important role in the regulation of phosphate-calcium metabolism, including PTH control, vitamin D is also recognised for its immunomodulatory and anti-inflammatory actions<sup>11</sup>. In fact, vitamin D can act by endocrine mechanism (the typical regulatory action of bone metabolism) but also autocrine-paracrine signalling, thanks to the presence within individual cells of the enzyme 1- $\alpha$ -hydroxylase capable of producing the active metabolite 1,25(OH)<sub>2</sub> vitamin D. Both the vitamin D receptor and 1- $\alpha$ -hydroxylase are expressed by different types of immune cells including macrophages, T-cells, dendritic cells, monocytes and B-cells. Preclinical studies indicate that vitamin D exerts biological effects on both the innate and adaptive immune systems, including on the production of proinflammatory cytokines.

It is known that vitamin D deficiency is associated with increased serum levels of pro-inflammatory mediators, including IL-6 and TNF- $\alpha$ , which are related to both the development and progression of inflammatory rheumatological diseases like SpA. What's more, we have recently observed that in healthy yet vitamin D-deficient subjects, supplementation with vitamin D results in a significant reduction in IL-6 and IL-17 levels<sup>12</sup>.

The second article in this issue is dedicated to the ongoing debate on the choice between cholecalciferol and calcifediol. The authors conclude that on the basis of knowledge of physiology and current scientific evidence, cholecalciferol should be considered the therapy of first choice in the prevention and treatment of vitamin D deficiency, and that the use of calcifediol should be limited to special situations, such as malabsorption syndromes, severe obesity or liver failure.

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		% difference compared to 31 months 17 <sup>th</sup> APRIL-19 <sup>th</sup> OCTOBER (PRE NOTE 96)		31 MONTHS 19 <sup>th</sup> NOVEMBER-22 <sup>nd</sup> MAY (POST NOTE 96)	
	IN THE NOTE	ATC 5	Number of packs	Gross expenses	
Alfacalcidol	NO	A11CC03	45,9%	54,5%	
Calcitriol	NO	A11CC04	-4,8%	-3,9%	
Cholecalciferol	YES	A11CC05	-21,3%	-16,4%	
Calcifediol	YES	A11CC06	41,1%	49%	
Cholecalciferol + calcium	YES	A12AX	-27,1%	-28,9%	
<b>TOTAL ATC IN THE NOTE</b>			<b>-19,6%</b>	<b>-15,7%</b>	
<b>TOTAL ATC NOT IN THE NOTE</b>			<b>8,5%</b>	<b>18,2%</b>	

  

<b>IN THE NOTE</b>	Average gross monthly ATC POST 21,341,970
	Average gross monthly ATC ANTE 25,331,506
<b>AVERAGE MONTHLY SAVINGS</b>	<b>3,989,536</b>

  

<b>IN THE NOTE</b>	Average gross monthly ATC POST 2,027,640
	Average gross monthly ATC ANTE 1,714,870
<b>AVERAGE MONTHLY INCREASE</b>	<b>312,770</b>

  

**Average monthly savings observed over the last 19 months in the ATC in the note: 2,807,326**

**FIGURE 1.**

NOTE 96 – Monitoring consumption trends of the note relative to vitamin D. Office for Pharmaceutical Expenditure Monitoring and Relations with the Regions. Italian Medicines Agency (AIFA). Last analysed: May 2022. Analysis on 31 months after the introduction of the note ([https://www.aifa.gov.it/documents/20142/1030827/NOTA\\_96\\_31mesi\\_08.11.2022.pdf](https://www.aifa.gov.it/documents/20142/1030827/NOTA_96_31mesi_08.11.2022.pdf)).

Also in the “Particular Warnings” of Note 96 of the Italian Medicines Agency (AIFA)<sup>13</sup>, it is pointed out that the main evidence of antifracturative efficacy has been conducted using cholecalciferol, which appears to be the molecule of reference for this recommendation, and that the clinical documentation in this area of use for hydroxy analogues is very limited. It should thus be a matter of concern that AIFA’s monitoring of vitamin D consumption following Note 96<sup>14</sup>, in view of expenditure savings due to the reduction in the use of cholecalciferol, shows an upswing in the consumption of calcifediol and alfacalcidol, being negligible from an economic point of view but not from a point of view of appropriateness (Fig. 1).

What do you think? Happy reading!

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