EDITORIAL

Could Interleukin-37 and Vitamin D Alleviate Inflammation in Asthmatic Children

Sabrine Louhaichi[1,2,3], Kamel Hamzaoui[1,2], Agnes Hamzaoui[1,2,3]

[1]Unit Research 12SP15 "Expression Moléculaire des Interactions Cellulaires et Leur Mode de Communication Dans le Poumon profond," A. Mami Hospital, Ariana, Tunisia, [2]Department of Basic Sciences, Université de Tunis El Manar, Faculty of Medicine of Tunis, Tunis, Tunisia, [3]Department of Paediatric and Respiratory Diseases, Division of Pulmonology, Abderrahman Mami Hospital, Pavillon B, Ariana, Tunisia

Asthma is a chronic disorder of the conducting airways that are characterized by reversible airway obstruction, cellular infiltration, and airway inflammation. The response involves the interplay of genetic and environmental factors, as well as the activation of cells in the innate and adaptive immune systems. It is established that the inflammation in asthma involves several subsets of T-lymphocytes. It has been found that peripheral circulation-induced sputum and bronchoalveolar Th17 cells (interleukin [IL-17]) were highly expressed contrasting with a drastic decrease of regulatory T (Treg) cells.[1]

Vitamin D (Vitamin D; [25(OH)D3]), a potent immunomodulator is capable of dampening inflammatory signals in asthmatic immune cells. Hypovitaminosis D is frequent in asthmatic children who live in a Mediterranean country.[2] Data obtained from *in vitro* studies in human asthmatics suggested that Vitamin D could modulate inflammation in the airways by restoring Treg[3] and suppressing Th17 subset cells.[4] Moreover, IL-37, one of the newest IL-1 cytokine families, has emerged as a fundamental inhibitor of innate immune responses and inflammation. IL-37 was reported to abrogate *in vitro* inflammatory cytokines in asthmatic patients.[4]

In this letter, we reported correlations between Vitamin D deficiency and serum IL-37 expression in 150 asthmatic patients (60 mild asthma, 40 moderate asthma, and 50 severe asthma) recruited from the Department of Paediatrics and Respiratory Disease and Homeostasis and Cell Dysfunction Unit Research, A. Mami Hospital (Ariana, Tunisia), using the criteria set by the Global Initiative for Asthma (GINA guidelines).[5]

Regarding [25(OH)D3] categorization in asthmatics, 57 patients (38%) had sufficient serum level (≥30 ng/mL), 51 patients (34%) had insufficient serum level (20–30 ng/mL), and 42 patients (28%) had deficient serum level (<20 ng/mL). Patients with asthma expressed low IL-37 levels (33.38 ± 8.59 pg/mL) compared to varied healthy controls (74.52 ± 15.27 pg/mL). The expression of IL-37 varied according to their Vitamin D status: suffcient, insufficient and deficient with IL 37 levels being 40.25 ± 5.68 pg/mL, 31.11 ± 6.70 pg/mL, and 25.42 ± 5.68 pg/mL, respectively [Figure 1]. The correlation between IL-37 levels and [25(OH)D3] was reported in Figure 2.

Our results show the close relationship between [25(OH)D3] values and IL-37 deficiency in asthmatic patients. Vitamin D and IL-37 deficiency have been associated in asthmatic patients, particularly in patients with severe asthma. Deficiency of Vitamin D and VDR was highly clarified in asthmatic patients both in the peripheral circulation and in induced sputum.[6-8] Recent studies have shown that Vitamin D supplementation reduces the risk of recurrent respiratory infections, virus-induced wheezing, and asthma exacerbations.[9] Vitamin D, through the activation of vitamin receptor (VDR), has been shown to have an immunomodulatory effect on immune cells, dendritic cells, macrophages, B and T lymphocytes, as well as Th17, Treg cells, and structural cells in the airways. Supplementation of Vitamin D alleviates immunity by reducing Th17 cells and increasing regulatory T cells. In the same way, incubation of lymphocytes with recombinant

Address for correspondence:
Kamel Hamzaoui, Department of Basic Sciences, Faculty of Medicine, Bab Saadoun 1007, Université de Tunis El Manar, Tunis, Tunisia. E-mail: kamel.hamzaoui@gmail.com

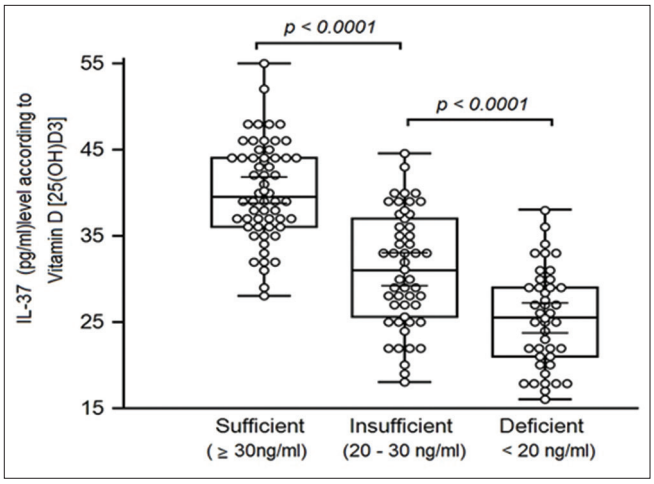

Figure 1: Evaluation of interleukin-37 levels according to (25[OH]D3) categorization in asthmatics. IL-37 and Vitamin D were quantified by enzyme-linked immunosorbent assay. The lines inside the boxes indicate the median; the outer borders of the boxes indicate 25th and 75th percentiles; the bars extending from the boxes indicate the 10th and 90th percentiles. The mean values were compared and P values are indicated in the figures

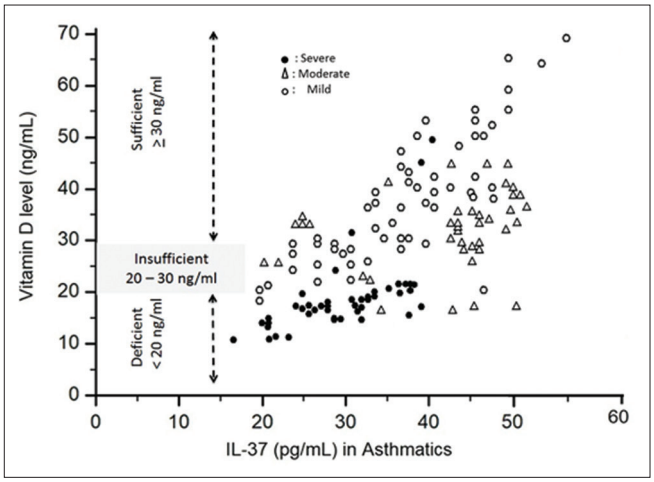

Figure 2: Correlation between Vitamin D levels and interleukin-37 (IL-37) expression in serum from asthmatic patients. Correlation in asthmatics was $r = 0.722$; $P = 0.0001$. Pearson correlation test showed an association between IL-37 and Vitamin D: In mild asthma: 0.767, $P < 0.0001$; in moderate asthma: 0.653, $P = 0.0001$; and in severe asthma: 0.530, $P = 0.0001$

IL-37 (rIL-37) reduces significantly levels of inflammatory cytokines (IL-6, IL-17, and TNF-α).[4] IL-37 exerts potent anti-inflammatory effects through two distinct mechanisms, either extracellular (receptor mediated) or intracellular (nuclear function). Extracellular IL-37 forms a complex with cell surface IL-18 receptor α (IL-18Rα) and IL-1 receptor 8 (IL-1R8), which transduces anti-inflammatory signals. Intracellular IL-37 produced on pro-inflammatory stimuli interacts with Smad3 and traffics through the nucleus, where it modulates gene expression and reduces transcription of pro-inflammatory genes. IL-37 broadly suppresses the responses to LPS in M1 but not M2-like differentiated human blood macrophages followed by decreased expression of IL-1b, IL-6, and TNF-α.[10]

IL-37 and Vitamin D acted *in vivo* positively by restoring homeostasis, but the mode of action and the interaction between these two parameters remains obscure at least. What we can confirm is that both Vitamin D and IL-37 acted to reduce the production of inflammatory mediators, and the sufficient levels of Vitamin D seem to be essential for proper immune function.

REFERENCES

1. Gupta RK, Gupta K, Dwivedi PD. Pathophysiology of IL-33 and IL-17 in allergic disorders. Cytokine Growth Factor Rev 2017;38:22-36.
2. Chinellato I, Piazza M, Sandri M, Peroni DG, Cardinale F, Piacentini GL, *et al.* Serum vitamin D levels and exercise-induced bronchoconstriction in children with asthma. Eur Respir J 2011;37:1366-70.
3. Urry Z, Chambers ES, Xystrakis E, Dimeloe S, Richards DF, Gabryšová L, *et al.* The role of 1α,25-dihydroxyvitamin D3 and cytokines in the promotion of distinct foxp3+ and IL-10+ CD4+ T cells. Eur J Immunol 2012;42:2697-708.
4. Charrad R, Berraïes A, Hamdi B, Ammar J, Hamzaoui K, Hamzaoui A. Anti-inflammatory activity of IL-37 in asthmatic children: Correlation with inflammatory cytokines TNF-α, IL-β, IL-6 and IL-17A. Immunobiology 2016;221:182-7.
5. Global Initiative for Asthma. GINA Guidelines. Global Strategy for Asthma Management and Prevention. Available from: https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention. [Last accessed on 2018 Sep 05].
6. Hutchinson K, Kerley CP, Faul J, Greally P, Coghlan D, Louw M, *et al.* Vitamin D receptor variants and uncontrolled asthma. Eur Ann Allergy Clin Immunol 2018;50:108-16.
7. Tizaoui K, Berraies A, Hamdi B, Kaabachi W, Hamzaoui K, Hamzaoui A. Association of Vitamin D receptor gene polymorphisms with asthma risk: Systematic review and updated meta-analysis of case-control studies. Lung 2014;192:955-65.
8. Lahmar O, Salhi M, Kaabachi W, Berraies A, Ammar J, Soomro MH, *et al.* Association between Vitamin D metabolism gene polymorphisms and risk of Tunisian adults' asthma. Lung 2018;196:285-95.
9. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. J Allergy Clin Immunol 2011;127:1294-6.
10. Li S, Neff CP, Barber K, Hong J, Luo Y, Azam T, *et al.* Extracellular forms of IL-37 inhibit innate inflammation *in vitro* and *in vivo* but require the IL-1 family decoy receptor IL-1R8. Proc Natl Acad Sci U S A 2015;112:2497-502.

How to cite this article: Louhaichi S, Hamzaoui K, Hamzaoui A.Could Interleukin-37 and Vitamin D Alleviate Inflammation in Asthmatic Children.Clin Res Immunol.2018;1(1):1-3.