Journal of Pharmacological Sciences 144 (2020) 52–56

Contents lists available at ScienceDirect

Journal of Pharmacological Sciences

journal homepage: www.elsevier.com/locate/jphs

Current Perspective

Predictive role of vitamin A serum concentration in psoriatic patients treated with IL-17 inhibitors to prevent skin and systemic fungal infections

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ARTICLE INFO

Article history:
Received 19 February 2020
Received in revised form
1 May 2020
Accepted 11 May 2020
Available online 11 June 2020

Keywords:
All-trans retinoic acid
Vitamin A
Interleukin 17
Interleukin-17 inhibitors
Fungal pathogens
Psoriasis
Biological therapy

ABSTRACT

The use of biological drugs in psoriasis is replacing traditional therapies due to their specific mechanism and limited side effects. However, the use of Interleukin 17 inhibitors and the modification of its cytokine pathway could favor the risk of fungal infections.

All-trans retinoic acid is an active metabolite of vitamin A with anti-inflammatory and immunoregulatory properties through its capacity to stimulate both innate and adaptive immunity and to its effects on proliferation, differentiation and apoptosis in a variety of immune cells. Furthermore, it has been recently discovered that All-trans retinoic acid has a direct fungistatic effect against Candida and Aspergillus Fumigatus.

On the basis of these new insights, in the current review, we suggest that the evaluation of serum level of All-trans retinoic acid or vitamin A should be considered as a predictive marker for the development of fungal infections among psoriatic patients treated with Interleukin 17 inhibitors.

In clinical practice, vitamin A test could be added in the routine hospital diagnostic management for a better selection of psoriatic patients eligible to Interleukin 17 inhibitors.

1. Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disorder, affecting 2–3% of the world's population. It is characterized by the formation of sharply demarcated, scaly, erythematous plaques.[1] The etiology of the disorder is uncertain, but it is theorized an ensemble of genetic and environmental aspects leading to an impaired immunological activation in psoriatic patients.[2] The efficacy of biologic agents in the treatment of psoriasis is well known; nevertheless, 15–40% of patients fail to respond to these treatments.[3] The high cost of these therapies related to their administration highlight the need to study those patients who may most likely benefit from a different treatment.[4] Predictive tests should be used to select the appropriate therapy for the right patient. Indeed, genetic factors have been studied in genome wide association studies: interleukin 23 receptor (IL23R), IL-23, interleukin 12B, IL-12B, and HLA-C*06, all strongly related to psoriasis.[5,6] The critical role of the IL23/Th17 axis at tissue level is indicated by the increased levels of IL-23, IL-23R and Th17 cytokines revealed in psoriatic skin, with the latter increased in lesional versus non-lesional skin.[7] Th17 development is sustained by IL-23 predominantly produced by dendritic cells. Th17 cells produce IL-17A, IL-17F and IL-22. IL-17A and IL-22 stimulate keratinocyte proliferation and tumor necrosis factor alpha (TNF-α), chemokine

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Peer review under responsibility of Japanese Pharmacological Society.

https://doi.org/10.1016/j.jphs.2020.06.003

(C-X-C motif) ligand (CXCL1) and CXCL8 production. TNF-α stimulates inflammatory cells – such as lymphocytes, monocytes and neutrophils - from the peripheral blood into the skin via dendritic cell activation.[8] Several molecular pathways associated with psoriasis pathogenesis are involved in host defence mechanisms that protect against common infections - such as IL-17 pathway - fundamental to fight fungal pathogens.[9] Fungal infections have been frequently observed in psoriatic patients.[10] These infections could exacerbate psoriatic plaques and stigmata, thus worsen the patient's quality of life (see daily life quality index, DLQI).[11] Conventional treatment of psoriatic disease includes immunosuppressors, such as corticosteroids, cyclosporine or methotrexate (MTX), and biological therapy such as tumor necrosis factor-α (TNFα) inhibitors for patients with a persistent disease activity.[12] Many systemic psoriasis therapies - such as corticosteroids and IL-17 inhibitors[13]-may increase the risk of developing oral, cutaneous and genitourinary candidiasis.[9] Predisposition to fungal infections in psoriasis patients and health controls could be linked to comorbidities, i.e. diabetes[14] and also to the deficit of some oligoelements such as zinc.[15] Recently, we have demonstrated a protective role of vitamin A and its active metabolite, all-trans-retinoic acid (ATRA) against fungal pathogens, showing direct fungistatic effect.[16]

Vitamin A is a fat-soluble vitamin required for the proper functioning of a diverse array of metabolic and physiologic activities.[17]

Beyond its well-documented role in reproduction, embryogenesis and maintenance of body tissues, vitamin A has attracted considerable attention due to its immunomodulatory effects on both the innate and the adaptive immune responses. In infectious diseases, vitamin A has been shown to have a host-protective effect in infections of bacterial, viral or protozoan origin, but also against *C. albicans*.[18]

On the basis of these new insights, in this review, we suggest that the evaluation of serum level of vitamin A and its active metabolite, ATRA, could be considered as a predictive marker for the development of fungal infections among psoriatic patients. In clinical practice, vitamin A analysis could be added in the routine hospital diagnostic management for a better selection of psoriatic patients eligible to IL-17 inhibitors.

2. Candidiasis in psoriatic patients

Patients affected by moderate-to-severe psoriasis are often treated with TNFα inhibitors, interleukin IL 12/23 inhibitors and more recently IL17 inhibitors.[8] These agents are known to increase the patients' risk of developing mycotic infections, such as *Pneumocystis jirovecii* pneumonia, histoplasmosis and candidiasis.[9,19] Picciani et al. showed that 26% (37/140) of patients with psoriasis tested positive for oral candidiasis compared to 0% (0/140) healthy controls.[20] Sarvtin et al. found that Candida spp. were isolated in 15% of skin specimens from patients affected by psoriatic disease compared to 4% of healthy controls.[21]

Candidiasis and other fungal infections could be successfully managed with antifungal therapies. Therefore, the development of a fungal infection does not usually require modifications to psoriasis treatment regimens. There are many drugs that can protect against fungal infections, though they need to be monitored. On the other hand, fungal infections can trigger or exacerbate psoriasis through the production of pro-inflammatory cytokines[7]: 20%–50% of psoriatic patients are affected by metabolic syndrome - considered as systemic inflammation – which includes diabetes and predisposition to opportunistic pathogens as *Candida* spp.[22] At the same time, *Candida albicans* induces IL-1b, IL-6, and IL-23 secretion by dendritic cells (DCs), and IL-17 secretion by T cells, thus it favors and worsens the development of psoriasis.[23]

3. The role of IL17 and Th17

The central role of interleukin 17A (IL-17A) in the pathogenesis of psoriasis is well known. It is a member of the IL-17 family which comprises six members, namely IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. IL-17A and IL-17F are the most closely related and have overlapping biological functions. IL-17A is produced by Th17 cells, NK cells, γδT cells and innate lymphoid cells (ILCs), but also myeloid cells, B-cells, mast cells, neutrophils and macrophages. IL-17A and IL-17F signal through the heterodimeric receptor IL-17RA/IL-17RC, which is located on keratinocytes, endothelial cells and fibroblasts.[24–27] Therefore, new monoclonal antibodies targeting this cytokine or its receptors for therapeutic purposes may be very useful.[8] At the same time, IL-17A plays a protective role against infections, especially those caused by *C.* spp and other fungal pathogens. *C. albicans* is a commensal yeast normally present in small areas of healthy adult skin and is part of the natural flora of the mucous membranes.[28] Innate and acquired host defence mechanisms are responsible for keeping the pathogen in a commensal state. Several studies suggested that patients with immune defects affecting the IL-17 signalling pathway may suffer from chronic mucocutaneous candidiasis, a disorder characterized by persistent or recurrent nails, skin, oral or genital mucosae diseases.[28–31] The IL-17 pathway is involved in the inflammatory target that triggers and sustains the psoriatic disease. Zielinski et al. have described two types of human TH17 cells with distinct effector function and differentiation requirements. *C. albicans*-specific TH17 cells produced IL-17 and IFN-γ, but no IL-10, sustaining defence against *Candida* infection.[32] Saunte et al. analyzed the prevalence of Candida infection in patients treated with IL-17 inhibitors. Candida infections were reported in 4.0% of patients treated with Brodalumab, 2.1% with Secukinumab, and 3.3% with Ixekizumab, compared to 0.3%, 2.3% and 0.8% of those assigned to placebo, Ustekinumab or Etanercept, respectively.[9] This suggested that although the incidence of Candida infection increased only in a small percentage of patients during anti-IL-17 treatment, patients undergoing this therapy should be examined for fungal infection and treated as required.[9]

From a clinical point of view, mechanisms that enhance IL-17A responses may help prevent or treat *C. albicans* cutaneous infections in humans. Conversely, therapeutic blockade of IL-17A–mediated immune responses may result in increased skin infections with *C. albicans*. Patients treated with these inhibitors should be closely monitored for cutaneous infections with *C. albicans* or even other pathogens controlled by IL-17A–mediated immune responses.

4. Protective role of vitamin A and ATRA against fungal pathogens

Vitamin A is a nutrient obtained through the diet either as provitamin-A (carotenoids) or as preformed vitamin A (retinol and retinyl esters). ATRA is an active metabolite of vitamin A with anti-inflammatory and immunoregulatory properties.[33] Recent studies support the hypothesis that the effectiveness of ATRA - alone or combined with other drugs - is associated with its capacity to stimulate both innate and adaptive immunity through its effects on proliferation, differentiation and apoptosis in a variety of immune cells. ATRA triggers a decline in the Th17 population, increasing CD4+ Tregs, stabilizing Tregs, and promoting suppressive B cells.[34] Recent studies have described important inadequacies of vitamin A[35] in critically ill patients and associated this deficiency with an

increased risk of mortality. Thus, monitoring the serum levels of vitamins A might have far-reaching prophylactic and therapeutic implications in severe infections. Vitamin A has been shown to decrease lipopolysaccharide-induced expression of pro-inflammatory cytokines such as TNFα and IL-6, or chemokines such as MIP-1α and MIP-1β in human macrophages and dendritic cells.[36] Vitamin A deficiency has been associated with an increased susceptibility to severe infectious diseases.[37] Several authors demonstrated the protective role of ATRA against bacterial and fungal infections through an indirect immunological effect both in vitro and in vivo. Complementing the therapy of acute promyelocytic leukaemia with ATRA resulted in a lower incidence of systemic mycosis in treated patients.[16] More recently, we documented also the direct fungistatic effect of ATRA at 0.5–1 mM concentration on *Aspergillus fumigatus* and *C. albicans* offering a promising opportunity of systemic therapy for opportunistic fungal pathogens. Despite an increasing interest in the immuno-modulatory role of ATRA, its specific role in the immune response to fungal infections has never been explored.[38] This was the first evidence on the efficacy of ATRA in controlling fungal pathogens in clinical subjects. Therefore, we suggest evaluating serum values of vitamin A or ATRA and eventually treat the deficit before starting the IL-17 inhibitors therapy.

5. Vitamin A regulation: retinoid nuclear receptors

Vitamin A uptake from plasma is mediated by cell surface receptor stimulated by retinoic acid 6 (STRA6).[39] Intracellular retinoid bioavailability is regulated by the presence of specific cytoplasmic retinol and retinoic acid binding proteins, CRBPs and CRABPs. In the cytoplasm, vitamin A and derivatives are bound to cytoplasmic proteins: CRBPs which comprised four isoforms, CRBP-1 and CRBP-2 and CRBP-3 and CRBP-4. CRBP-1, are the most represented isoform in many tissues. Cellular retinoic acid binding proteins (CRABPs) comprise two isoforms, CRABP-1 and CRABP-2. CRBPs specifically bind retinol, while CRABPs and well-characterized members of the fatty acid binding proteins (FABPs) bind retinoic acid. Cellular retinoic acid binding proteins may regulate the interactions between retinoic acids and their nuclear receptors by regulating the concentration of retinoic acids.[40] Retinoids can activate gene expression by specific nuclear retinoid acid receptors. The RA signal is transduced, on the nucleus, by two retinoid receptors: the retinoic acid receptor (RAR) and the retinoid X receptor (RXR). Both RARs and RXRs are members of the nuclear receptor superfamily of ligand-activated transcription factors and mainly act as heterodimers to activate the transcription of target genes in the presence of their ligand, all-trans RA. The family nuclear receptors, NRs, comprising steroid, thyroid hormone and vitamin D3 receptors include also retinoid receptors, which are DNA-binding proteins working as trans-acting transcription modulating factors.

One of the major actors of the RA signalling pathway is the retinoic acid receptor (RAR). RARs mainly take steps as heterodimers with the retinoid x receptors (RXRs) to activate the transcription of target genes in the presence of their ligand, all-trans RA.[40] In human beings, there are three rar genes (rarα, rarβ and rarγ) and three rxr genes (rxrα, rxrβ and rxrγ), each encoding several isoforms.[41] Upon binding of RA, the RAR-RXR heterodimer binds to DNA on specific sequences called retinoic acid response elements (RAREs), which, most frequently, consist of direct repeats (DRs).[41]

The regulation of RAR-target gene activation by RA is controlled not only by simple on/off conformational switches of RARs, but also by kinase signalling pathways. These signalling pathways target several actors in retinoid regulatory processes through phosphorylations that fine-tune the RA response via rapid changes in chromatin organization, RAR dynamics, coregulator interactions, and structural and functional shifts in protein-DNA interactions.

6. Vitamin A and psoriasis

Vitamin A derivatives have been widely used to treat psoriasis. Patients have responded favorably both to topical and oral administration of these drugs.[42,43] However, the mechanisms that cause vitamin A impairment in psoriasis remain unknown.

The detection of vitamin A-related molecules in psoriatic skin lesions is very limited. Vitamin A deficiency has often been reported in psoriasis patients. For instance, Rollman and Vahlqist[44] investigated the vitamin-A status of 107 patients with psoriasis and 37 healthy controls. Also, a study by Majewski et al.[45] looked at the systemic levels of vitamin A and found a decrease in all psoriasis patients compared to controls. Additionally, their study found the levels correlated with disease activity — levels were lower if the disease was more active. Therefore, many researchers proposed that retinol metabolism was altered in psoriasis lesional skin, based on the increased synthesis of retinoic acid. Recently, Wang et al. found that the demand for vitamin A in psoriatic skin lesions was upregulated in a murine model of psoriasis.

Hence, it seems that psoriatic patients are already more susceptible to ATRA deficiency than healthy controls and this lack could be the basis of the higher frequency of *Candida* colonization in psoriatic patients than in another dermatosis.

Indeed, dermatologists should focus on the presence of oropharyngeal or genitourinary candidiasis when examining a patient with psoriasis.

Based on our experience with currently available psoriasis treatments, we suggest evaluating each individual case.

Dermatologists should investigate critical areas such as nails, scalp and skin folds, also performing cutaneous, nails swab and stool culture, before beginning the treatment. Particularly, the differential diagnosis between nail psoriasis and onychomycosis must be done by fungal culture. The National Psoriasis American Foundation included in the treatment guidelines the importance of

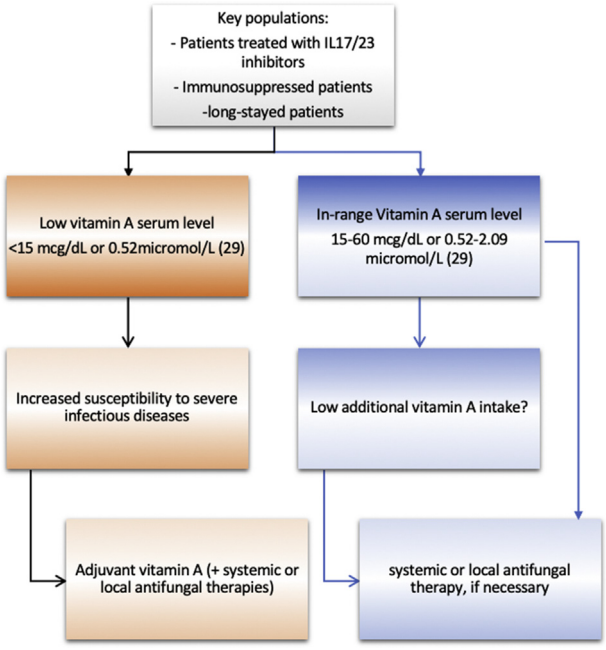

Fig. 1. Clinical algorithm in key populations.

excluding the presence of fungal infections in psoriatic patients before starting the therapy.[46]

In clinical practice, after culture confirmation of mucosal or nail fungal infection, we propose to measure vitamin A or ATRA serum level to rebalance any eventual deficit. This issue is crucial for psoriatic patients treated with IL17inhibitors (Fig. 1).

ATRA could lead to a better diagnostic management and prevention mainly in patients with contraindications to classic antifungal drugs due to chronic renal failure, liver disease, therapy with CYP3A4 inducing drugs.

Conclusion

The evaluation of Vitamin A in daily routine, or ATRA if possible, must be considered in the near future for many kinds of patients, mainly in those affected by psoriasis due to the key role of Vitamin A, and its esters, in preventing and controlling fungal pathogens. Therefore, vitamin A analysis could be used in routine hospital diagnostic management in order to establish the target therapy for each psoriatic patient, above all those treated with IL-17 inhibitors.

Author contributions

E. C., T. C., A. V. have conceived the ideas; T. C. and E. C. have written draft and main file; S. M., C. L., R. G., A. D., E. D., E. C., L. B. have corrected draft and made revisions.

Ethics statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page have been adhered to. No ethical approval was required as the research in this article related to micro-organisms.

Declaration of Competing Interest

The authors report no conflicts of interest in this work.

Acknowledgments

We thank Denis Mariano for his technical editing assistance.

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