Peroxisome proliferator-activated receptor agonists (PPARs): a promising prospect in the treatment of psoriasis and psoriatic arthritis*

Os receptores ativados pelo proliferador de peroxissoma (PPAR): uma perspectiva promissora na condução da psoríase e artrite psoriásica

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20132653

Abstract: Psoriasis is a polygenic, inflammatory and progressive disease, characterized by an abnormal differentiation and hyperproliferation of keratinocytes, associated with impaired immunologic activation and systemic disorders, while psoriatic arthritis is a chronic inflammatory articular disease. Pathophysiology of psoriasis comprises a dysfunction of the immune system cells with an interactive network between cells and cytokines supporting the initiation and perpetuation of disease and leading to inflammation of skin, enthesis and joints. Recent studies have shown an important role of systemic inflammation in the development of atherosclerosis. Corroborating these findings, patients with severe Psoriasis have marked incidence of psoriatic arthritis, cardiovascular diseases, hypertension, dyslipidemia, obesity and diabetes mellitus, showing an increased risk for acute myocardial infarction, which suggests that the condition is not restricted to the skin. Nuclear receptors are ligand-dependent transcription factors, whose activation affects genes that control vital processes. Among them the peroxisome proliferator-activated receptor is responsible for establishing the relationship between lipids, metabolic diseases and innate immunity. In the skin, peroxisome proliferator-activated receptors have an important effect in keratinocyte homeostasis, suggesting a role in diseases such as psoriasis. The peroxisome proliferator-activated receptors agonists represent a relevant source of research in the treatment of skin conditions, however more clinical studies are needed to define the potential response of these drugs in patients with psoriasis and psoriatic arthritis.
Keywords: Arthritis, psoriatic; PPAR alpha; Psoriasis

Resumo: A psoríase é uma doença poligênica, inflamatória, progressiva e recorrente, caracterizada por um ciclo evolutivo acelerado dos queratinócitos, associado à ativação imune desordenada e a alterações sistêmicas correlacionadas, sendo a artrite psoriásica o comprometimento articular inflamatório crônico que pode ocorrer em pacientes com a doença cutânea. Na inflamação autoimune, uma rede interativa entre células e citocinas suporta o início e a perpetuação da doença. A fisiopatologia da psoríase e da artrite psoriásica compreende uma disfunção das células do sistema imune e da rede de citocinas, levando à inflamação de pele, enteses e articulações. Estudos recentes têm demonstrado um papel importante da inflamação sistêmica no desenvolvimento da aterosclerose. Corroborando esses achados, pacientes portadores de psoríase grave apresentam marcada incidência de artrite psoriásica, doença cardiovascular, hipertensão arterial sistêmica, dislipidemia, obesidade e diabetes mellitus, evidenciando um risco aumentado para infarto agudo do miocárdio e sugerindo que a doença não se restringe à pele. Os receptores nucleares são fatores de transcrição ligante-dependente cuja ativação afeta genes controladores de processos vitais. Entre eles, destacam-se os receptores ativados pelo proliferador de peroxissoma, responsáveis por estabelecer a relação entre os lipídios, doenças metabólicas e imunidade inata. Na pele, os receptores ativados pelo proliferador de peroxissoma têm ação importante na homeostase dos ceratinócitos, exibindo uma função pró-diferenciação, antiproliferativa e imunomoduladora, sugerindo um papel relevante em doenças como a psoríase. Os agonistas dos receptores ativados pelo proliferador de peroxissoma representam uma relevante fonte de investigação no tratamento de doenças da pele. No entanto, estudos clínicos são necessários para definirmos o potencial de resposta dessas drogas em pacientes com psoríase e artrite psoriásica.
Palavras-chave: Artrite psoriásica; PPAR alfa; Psoríase

Received on 26.03.2013.
Approved by the Advisory Board and accepted for publication on 24.04.2013.
* Work performed at Pernambuco Federal University Clinics Hospital (HC- UFPE) – Recife (PE), Brazil.
Conflict of interest: None
Financial Support: None

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INTRODUCTION

Psoriasis (Pso) is a polygenic, inflammatory, progressive and recurrent disease, characterized by an accelerated evolutive cycle of keratinocytes, associated with disorganized immune activation and correlated systemic abnormalities, whilst psoriatic arthritis (APso) is a chronic inflammatory articular disorder that can occur in patients with the cutaneous disease form.[1,2]

Besides the recognized impairment in patients' quality of life - since psoriasis implies double suffering as the skin alterations effectively damage the patient's appearance and socializing, plus the crippling potential of APSO - there is an increased morbidity and mortality which has been related to the presence of metabolic syndrome (MS), cardiovascular disease (CVD), inflammatory bowel disease and malignancy, with consequent reduction in life expectancy.[3,4]

In autoimmune inflammation, an interactive network between cells and cytokines supports the beginning and perpetuation of disease. The pathophysiology of Pso and APSO comprehend dysfunctions of immune system cells and cytokine network, leading to inflammation of skin, joints and entheses.[5]

Several cytokines, expressed in keratinocytes of patients with psoriasis, have been recognized as inducing epidermal proliferation and inflammatory cell chemotaxis. Among these we highlight cytokines IL-6, IL-8 and more recently, IL-15, IL-19, IL-10 and IL-20.[6] Antigen presenting cells that are infiltrated in skin lesions also contribute to local production of cytokines such as IL-18, IL-23 and TNF-α. Additionally, studies have shown that cytokines IL-18 and IL-23 are involved in production of IFNγ by Th1 cells.[7,8] Furthermore, APSO is also characterized by an increased production of IL-6, IL-12, IL-17A, IL-18 and IL-23 and reduced IL-10.[5]

Recently, in addition to the important role of IFNγ and IL-12 produced by Th1 cells, IL-17, produced by Th17 cells have demonstrated an even more relevant role in triggering autoimmune inflammatory diseases such as Pso and APSO, characterizing them as diseases mediated by Th1/Th17 cells.[7,9,10] Th17 cells are also characterized by the production of IL-22, markedly involved in the pathogenesis of psoriasis.[11]

IL-23 is the cytokine responsible for maintaining the effector Th17 phenotype. In an experimental model it was demonstrated that blocking monoclonal antibodies of the IL-12p40 subunit, common to IL-12 and IL-23, improved APSO and Pso. Associated to these findings, the subunits IL-23p19 and IL-12p40 were identified in higher concentration in psoriatic plaques when compared to the patient's healthy skin.[12]

In recent decades, knowledge on psoriasis's immunopathogenesis triggered a dramatic change in the therapeutic arsenal for moderate to severe psoriasis. Anti-TNF therapies have demonstrated greater efficacy in several clinical aspects.[13-15] However, among adverse events are higher incidence of serious infections such as reactivation of latent tuberculosis, susceptibility to opportunistic infections and neoplasms, as well as the possibility of loss of long-term efficacy.[5] In order to provide more security, new biological treatments such as ustekinumab, a human monoclonal antibody against the p40 subunit of IL-12/IL-23, has also been used in the treatment of moderate to severe Pso and more recently APso.[16]

The high cost of new treatments, which sometimes precludes their prescriptions, and the relative scarcity of substances with long sustained therapeutic responses in controlled clinical trials, stimulates research on new drugs that offer both efficacy and a good safety profile.

PSORIASIS AND CO-MORBIDITIES

Recent studies have demonstrated an important role of systemic inflammation in the development of atherosclerosis. The similarity of immunological factors implicated in the formation of atheromatous plaques with those involved in the installation and progression of chronic inflammatory diseases such as Pso, made it possible to establish a relationship with the incidence of cardiovascular diseases (CVD).[17]

Corroborating these findings, patients with severe Pso also have marked incidence of APso, cardiovascular diseases (CVD), hypertension (HBP), dyslipidemia (DLP), obesity and diabetes mellitus (DM), indicating an increased risk for acute myocardial infarction (AMI), all of which suggests that the disease is not confined to the skin.[18]

Sommer *et al* studied a group of patients with Pso, and identified a higher prevalence of MS in these patients compared to the control group.[19] Cohen *et al* studied 340 patients with psoriasis and 6,643 controls, identifying the association of the disease with AMI, DM, hypertension, obesity and DLP, especially in men between 35 and 50 years old.[20]

As it occurs in Pso, chronic inflammation by Th1 cells participate in the pathophysiology of obesity, DM, atherosclerosis, SM and MI. High levels of Th1 cytokines (such as IL -2 and IFN), besides adhesion molecules and angiogenic factors (capable of promoting angiogenesis and adipogenesis, epithelial proliferation and alteration of insulin receptors and metabolism of lipids) have been observed in both Pso as in coronary artery disease.

Inflammatory molecules and hormones produced in cases of obesity, diabetes and atherosclerosis may influence the pathogenesis of Pso, both favoring

the susceptibility to the disease and predisposing to greater severity.[21] Endorsing these findings is the detection of over 20 genic *loci* consisting of numerous genes that affect the susceptibility to Pso and which are also related to susceptibility to MS, MD, familial hyperlipidemia, and CVD. Figure 1 shows the association of Pso with other systemic diseases of a chronic inflammatory nature.

Obesity is associated with chronic inflammatory response, characterized by abnormal production of adipokines and activation of certain pro-inflammatory signaling pathways, resulting in the induction of various biological markers of inflammation.[22] On the other hand, a decrease in body weight is accompanied by a reduction or normalization of these biological parameters.[23] This association is significant and several animal models suggest that these inflammatory processes have a causal relationship not only with obesity, but also with its comorbidities, such as insulin resistance, diabetes and CVD.[22] Among cytokines implied in the association between obesity, inflammation and insulin resistance, tumor necrosis factor (TNF) is considered one of the main triggers of the inflammatory process that characterizes these metabolic states and also a link between these comorbidities and psoriasis.[22]

In lean subjects, adipocytes secrete adiponectin at high concentrations, resulting in anti-atherogenic and pro-insulinic action in the liver, adipose tissue and muscles, besides reducing the synthesis of TNF. In obese patients, the process is somewhat different, with an infiltration of resistin and TNF-secreting macrophages in the adipose tissue. Meanwhile adipocytes synthesize and release leptin, which exerts a positive feedback effect on TNF, thus aggravating the inflammation and promoting atherosclerosis, liver and muscle resistance to insulin. All this factors lead to dyslipidemia, the main feature of metabolic syndrome (Figure 1).[22]

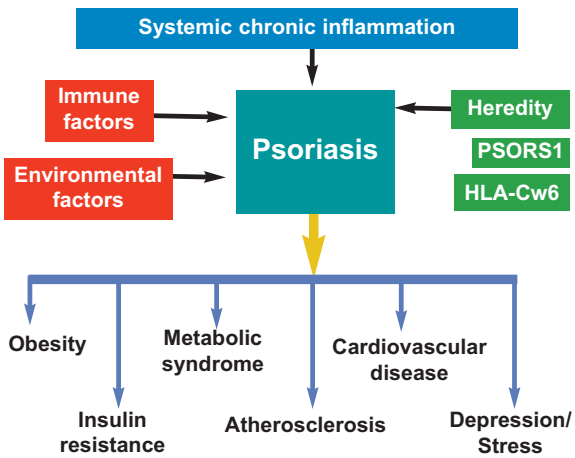

Figure 1: Psoriasis and its associations to systemic diseases of a chronic inflammatory nature

Epidemiological evidences, clinical findings and Pso's pathophysiology demonstrate the importance of recognizing it as a systemic disease, assessing the risks of inflammatory progression and occurrence of comorbidities, as well as the need to intervene in a less conservative manner in selected cases.

PEROXISOME PROLIFERATOR ACTIVATED RECEPTORS (PPAR)

Nuclear receptors are ligand-dependent transcription factors, which activation affects genes controlling vital processes. Among them, we highlight peroxisome proliferator activated receptors (PPARs), responsible for establishing the link between lipid metabolic disorders and innate immunity. PPARs are activated by fatty acids and their derivatives, intermediated by membrane receptors that establish the communication between nucleus and cell surface.[24] Three proteins, encoded by distinct genes, have been identified: PPARα, PPARβ and PPARγ. The PPARs are ligand-dependent transcription factors that regulate target gene expression by binding to specific PPREs (peroxisome proliferator responsive elements) located at regulatory sites in each gene. The receptor binds to PPRE as a heterodimer, together with an additional factor protein, 9-cis-retinoic acid (RXR) receptor.[25,26]

Unsaturated fatty acids, eicosanoids, components of oxidized low-density (LDL) and very low-density lipoproteins (VLDL) and also linoleic acid derivatives are regarded as endogenous ligands of PPARs.[27] In addition, a variety of pharmacological exogenous ligands have been used in research and clinical practice, including fibrates and thiazolidinediones. Table 1 lists the main known PPAR ligands.

PPAR's conformation is altered and stabilized under the action of agonist ligands, creating a binding site, with subsequent recruitment of transcriptional coactivators, resulting in increased gene transcription.[25,26] In the liver, activation of PPARα promotes fatty acid oxidation, synthesis of ketone bodies and glucose accumulation via induction of the synthesis of several proteins, such as fat carriers and acyl-CoA oxidase.[28] PPARα is predominantly expressed in tissues that are able to oxidize fatty acids such as liver, heart, muscle, kidney and brown adipose tissue (Table 1).[29]

Studies provide evidence of the involvement of PPARs ligands in controlling inflammatory response, since their activation resulted in the inhibition of transcription of pro-inflammatory cytokines (IL-1 and TNF-α), inflammatory genes (NOS and COX-2) and matrix metalloproteinases (MMP-1 and MMP-13).[25,30]

Table 1: Endogenous and exogenous PPARs ligands (HETE = hydroxyeicosatetraenoic acid; HODE = hydroxyoctadecadienoic acid)

Receptor	Endogenous ligands	Exogenous ligands
PPARα	Unsaturated fatty acids, saturated fatty acids, B4 leukotrienes, 8-HETE	Clofibrate, fenofibrate, gemfibrozil, GW7647, WY14643
PPARβ	Unsaturated fatty acids, saturated fatty acids, carbaprostacyclin, VLDLs	GW501516, L-165041
PPARγ	Unsaturated fatty acids, 15-deoxi-Δ, prostaglandin J2, 15-HETE, 9-HODE and 13-HODE, oxidize LDL	Rosiglitazone, pioglitazone, troglitazone, ciglitazone, tyrosine farglitazar derivatives, GW7845
PPAR α and γ	There is no endogenous ligands for both receptors	Muraglitazar, ragaglitazar, tesaglitazar

It is also important that PPAR agonist ligands have been implicated in inhibiting the production of IL-17 and IFNγ by CD4 + cells[31,32] In combination with PPARγ, PPARα has also mediated the elimination of cholesterol by macrophages.[33] Due to its role as a modulator of lipid homeostasis and inflammation, PPARs have been identified as potential therapeutic targets in a variety of chronic inflammatory diseases such as atherosclerosis, rheumatoid arthritis and inflammatory bowel disease.[34-39]

Thiazolidinediones are PPARs' synthetic ligands and their activation can significantly attenuate the expression of proinflammatory cytokines, suppress angiogenesis in various models of inflammatory disease, inhibit proliferation and promote differentiation in a variety of malignant and non-malignant tissues.[22,40-43]

THE ROLE OF PPARs IN METABOLIC SYNDROME

Obesity and peripheral insulin resistance, key features of MS, are closely associated with a low degree of inflammation.[44] In the adipose tissue, chronic nutritional excess leads to macrophage infiltration, resulting in local inflammation, which potentiates insulin resistance.[45] In obesity, both adipocytes and macrophages infiltrating the tissue produce inflammatory cytokines, such as TNF and IL-6 and also express TLRs (Toll-like receptors).[46] TLR signaling pathways seem to contribute to the development of obesity associated with insulin resistance, demonstrating the connection between innate immune response and metabolism. It is worth noting that the communication between TLRs and PPARs has been widely documented.[46,47]

In adipocytes, PPARβ inhibits the activation and reduces the production of proinflammatory cytokines linked to insulin resistance. Also involved are IL-4 and IL-3, secreted by eosinophils involved in inflammation, which contributes to maintain the activation of macrophages infiltrated in the adipose tissue.[48] As occurs in the adipose tissue, the presence of PPARβ in the liver has an important role in attenuating toxicity resulting from the inflammatory cascade, which is beneficial to hepatic steatosis.[24] In vessels, PPARs exert local and distant anti-inflammatory effects, preventing atherogenesis. PPARα expression in macrophages will modulate inflammation and cholesterol transport into the cell. In hepatocytes, PPARα expression inhibits the secretion of inflammatory proteins, enabling the modulation of systemic inflammation, which is associated to vascular response.[24]

PPARs have been used as targets in the treatment of MS, DM and DLP.[49-52] Clinical studies suggested that the therapeutic benefits of PPARγ ligands are mediated in part by the release of adiponectin.[53] Diabetic patients and patients with coronary heart disease have elevated levels of adiponectin after exposure to thiazolidinediones, which reduce cholesterol levels and improve hypertension control. Adiponectin released through the stimulation of PPARγ ligands has also been shown to play a protective role against the vascular injury observed in diabetics.[53]

PSORIASIS AND PPARS' LIGANDS – TREATMENT PERSPECTIVES

In the skin, PPARs have an important role in keratinocytes' homeostasis, exhibiting pro-differentiating, antiproliferative and immunomodulatory functions, which suggest a role in diseases such as psoriasis.[54] All three PPAR subtypes have been isolated from human keratinocytes, with prevalence of PPARβ over PPARα and PPARγ. In psoriasis' hyperproliferative

epidermis, expression of α and γ subtypes is reduced, while the expression of β subtypes is increased.[55]

Several studies point to the involvement of PPARα in the mechanism of epidermal barrier development and its proliferation and differentiation. In models of fetal rat skin, activators of these receptors, like clofibrates and oleic and linoleic acids proved to be able to accelerate the development of skin barrier, as evidenced by the reduction of transdermal water-loss, increase in epidermal stratification and maturity of stratum corneum.[56] In addition, PPARα ligands are able to promote differentiation and restore homeostasis in hyperproliferative mice skin besides regulating epidermal apoptosis.[57] Hanley *et al* showed that in cultured human keratinocytes treated with clofibrate or other PPAR ligands, there was an increased expression of involucrin and transglutaminase, essential to the formation of stratum corneum.[58]

Confirming these findings, diabetic patients treated with troglitazone showed improvement in their psoriatic plaques.[59] In addition to relieving the symptoms of patients with chronic psoriasis, the administration of this drug has modified the abnormal phenotype of transplanted psoriatic skin.[56]

Ellis *et al* performed an open trial with five volunteers with plaque Pso using troglitazone. Results showed that all patients improved substantially during treatment.[55] In the same study, 10 samples of skin with and without active lesions were cultured and treated with troglitazone, ciglitazone and 15-deoxy-12,14-D-prostaglandin, with further observation demonstrating inhibition of keratinocyte proliferation both in normal as well as in psoriatic skin. Furthermore, treatment with troglitazone normalized histological changes of psoriatic skin and reduced the epidermal hyperplasia in animal models of psoriasis compared to non-treated controls ($p < 0.05$).

Bongartz *et al* evaluated the tolerability and disease activity parameters in an open pilot study with 10 patients with active APso, treated with pioglitazone.[60] After 12 weeks of treatment, the authors observed a 38% reduction of PASI, statistically significant reduction of average number of painful and/or swollen joints, and improvement in the score function (Health Assessment Questionnaire). However, 25% of patients did not respond to treatment and adverse events such as edema of the limbs and weight gain were documented.

Pilot studies in patients with plaque psoriasis demonstrated that PPAR agonists for topical use did not lead to an improvement in skin homeostasis.[54] Furthermore, patients with plaque psoriasis treated orally with thiazolidinediones, showed improvement in cutaneous symptoms.[55,59,61,62] These observations indicate that, to be beneficial, the activation of PPARs must be systemic and not local.

Although the exact mechanism for the effect of PPAR agonists is not yet known and it is not even possible to define which isotype (PPARβ / g) would be more beneficial in the treatment of the disease, these seem to be of particular importance, judging by the results of *in vitro* and *in vivo* studies in the treatment of patients with psoriasis.

The thorough knowledge of the immunology of psoriasis gathered in recent years, as well as the understanding of the role of cytokines, and the clinical improvement resulting from the interruption of inflammatory pathways, encouraged an expansion of therapeutic possibilities, which has stimulated the discovery of new drugs with a limited scope of adverse events.[62]

FINAL CONSIDERATIONS

PPAR agonists represent a class of promising anti-inflammatory and immunomodulating agents that can be used in the treatment of Pso and APso. Dyslipidemia and the dramatic increase in liver enzymes seen in some of the patients with moderate to severe psoriasis prevent the administration of drugs such as acitretin and methotrexate.

Due to their diverse biological activities on keratinocytes, PPAR agonists represent a significant source of investigation in the treatment of skin diseases. These drugs undoubtedly act in the hyperproliferative and undifferentiated condition of diseased keratinocytes, appearing as a promising therapeutic promise. However, clinical studies are needed to define the potential impact of these drugs in the treatment of patients with Pso and APso. ❑

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How to cite this article: Lima EA, Lima MMDA, Marques CDL, Duarte ALBP, Pita IR, Pita MGR. Peroxisome proliferator-activated receptor agonists (PPARs): a promising prospect in the treatment of psoriasis and psoriatic arthritis. An Bras Dermatol. 2013;88(6):1029-35.