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**Biomarkers of psoriasis severity and therapy monitoring**

Coimbra S *et al.* Biomarkers role in psoriasis assessment

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**Abstract**

Psoriasis is a chronic, recurrent inflammatory cutaneous disease. Psoriasis patients alternate between periods of remission and periods of exacerbation of the disease. Usually, psoriasis severity is clinically evaluated using tools like Psoriasis Area and Severity Index that present some limitations and subjectivity. Clinicians select the therapy according to psoriasis severity, aiming that patients achieve longer remission periods and improve their quality of life. Biological markers for diagnosis and prognosis of psoriasis help to establish its severity and to monitor the therapeutic response; moreover, biomarkers of psoriasis assist clinicians in their therapeutic decision to treat psoriasis and to choose earlier and more adequate therapeutic strategies, avoiding or minimising worsening of psoriasis. With these markers, they would be able to monitor therapeutics, avoiding unnecessary therapeutic surcharge or changes to a more aggressive therapy. As any attempt to identify these biomarkers should be encouraged, in this review, we will debate published data concerning the proposal of biomarkers to evaluate severity and response to treatment of psoriasis vulgaris.

**Key-words:** Psoriasis; Severity; Monitorization; Markers; Inflammation

**Core tip:** Severity of psoriasis, a chronic, recurrent inflammatory disease, is clinically evaluated by Psoriasis Area and Severity Index that present some limitations and subjectivity. Biological markers for diagnosis and prognosis of psoriasis help to establish its severity and to monitor the therapeutic response; moreover, psoriasis biomarkers assist clinicians in their therapeutic decision to treat psoriasis and to choose earlier and more adequate therapeutic strategies, avoiding or minimizing psoriasis worsening. As any attempt to identify these biomarkers should be encouraged, in this review, we will debate published data concerning the proposal of biomarkers to evaluate severity and response to treatment of psoriasis.

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**INTRODUCTION**

Psoriasis affects about 2%-3% of the World population, and is characterized by epidermal hyperplasia, dilated and prominent blood vessels in the dermis, and by an inflammatory infiltrate of leukocytes, predominantly in the dermis. It is a chronic, recurrent, immune-mediated inflammatory disease, with a recognised genetic predisposition. Several acute phase reactants, cytokines and growth factors are known to play an important role in the pathogenesis of psoriasis. Indeed, it is accepted that different cells are crucial in psoriasis at different stages[[1](#_ENREF_1)], and that the interleukin (IL)-23/T-helper (Th)17 axis is decisive in psoriasis pathogenesis, and its inhibition appears to be crucial for therapeutic achievement[[2](#_ENREF_2),[3](#_ENREF_3)].

Psoriasis patients alternate between periods of remission and periods of exacerbation of the disease. This chronic, unpredictable course of the disease and the need of periodical alternation of drugs or classes of drugs, makes difficult to treat psoriasis. Psoriasis patients require an individual management and long-term planning of therapeutic strategies. The risks *vs* benefits ratio and the cost-effectiveness of the different treatments should be carefully evaluated. A variety of approaches are available for its treatment, ranging from topical agents, for milder and limited forms of psoriasis, to phototherapy, photochemotherapy, systemic and biologic agents, for moderate and severe psoriasis. The main goal of psoriatic therapies is to control the disease and its clinical manifestations, contributing to improve the quality of life of the patient. The therapy is chosen in accordance with skin type, clinical history, patient’s age, the effect on the patient’s quality of life, the response to previous treatments and, obviously, the severity of psoriasis.

The Psoriasis Area and Severity Index (PASI) is the prototype to measure psoriasis severity, being the most widely used tool to assess the severity of the disease in clinical trials and in clinical practice. This system has two major advantages: it is sensitive to changes in the affected skin area and in the severity of the lesions, and, therefore, the changes in PASI score reflect improvement or worsening of the disease. However, it presents some subjectivity and limitations[[4-6](#_ENREF_4)], such as a poor sensitivity to changes in small areas of involvement; thus, it may not be the best tool to be used in patients with mild disease. There are other approaches to asses psoriasis severity, such as the percentage of involved body surface area, the Physician’s Global Assessment, the Lattice System Physician’s Global Assessment, and the National Psoriasis FoundationPsoriasis Score. There are also more specific instruments,focusing on aspects of quality of life that are affected by skindisease, such as the Dermatology Life Quality Index (DLQI)[[7](#_ENREF_7)] , but they are all clinical tools.

Biological markers for diagnosis and prognosis of psoriasis help to establish its severity and to monitor the therapeutic response. The identification in blood of predictive biologic markers of worsening of the disease could be useful for clinical evaluation of psoriasis and to monitor the treatment of the disease. Indeed, biomarkers of psoriasis severity are useful to clinicians in their therapeutic decision to treat psoriasis and to choose earlier and more adequate therapeutic strategies, avoiding or minimising worsening of psoriasis. With these markers, they would be able to monitor therapeutics, avoiding unnecessary therapeutic surcharge or changes to a more aggressive therapy.

Considering that any attempt to identify these biomarkers should be encouraged, we intend to review and debate published data concerning the proposal of biomarkers to evaluate the severity and the response to treatment of psoriasis vulgaris. To avoid a length and complex manuscript, we will only consider biomarker evaluation in psoriasis vulgaris without arthritis.

**INTERLEUKINS AND GROWTH FACTORS**

Nowadays, it is proposed that psoriasis development depends on skin infiltration of Th1/Th17 cells that stimulate macrophages and dermal dendritic cells to release mediators that sustain inflammation and cause abnormal keratinocyte proliferation. The mediators of the Th17 immune system include IL-1, IL-6, IL-23 and transforming growth factor (TGF)-β[[8](#_ENREF_8),[9](#_ENREF_9)]. Additionally, IL-23 and related interleukins seem to be crucial for psoriasis pathogenesis[[10](#_ENREF_10),[11](#_ENREF_11)].

Tumour necrosis factor (TNF)-α, a cytokine of the Th1 pathway, influences the proliferation, activation and differentiation of several cell types, stimulates apoptosis, enhances the synthesis of several cytokines and the expression of some adhesion molecules[[12](#_ENREF_12)]. The neutralization of TNF-α, the basis of some psoriasis therapies, strengthens the important role of this cytokine in the disease. High concentration of TNF-α[[13-22](#_ENREF_13)] and significant and positive correlations with PASI scores[[3](#_ENREF_3),[17-19](#_ENREF_17),[23](#_ENREF_23)] were found in active psoriasis. However, some authors did not find this significant increase[[3](#_ENREF_3),[24](#_ENREF_24),[25](#_ENREF_25)]. Bevelacqua *et al*[[26](#_ENREF_26)] observed that the correlation of TNF-α with psoriasis severity was only found for the severer forms and Nakajima *et al*[[12](#_ENREF_12)] found a negative correlation of TNF-α with PASI[[20](#_ENREF_20)]. These controversial results suggested that TNF-α is essentially produced and act locally, and, therefore, its circulating levels might be lower than at the inflammatory area. Its activity was found to decrease after effective treatments, including narrow-band ultraviolet light B (NB-UVB), psoralen plus UVA (PUVA) and topical therapy[[3](#_ENREF_3),[19](#_ENREF_19),[22](#_ENREF_22)]. However, Emerit *et al*[[27](#_ENREF_27)] found a significant decrease in its levels only after infliximab and etanercept therapies; no changes were found after PUVA and NB-UVB treatments. Borska et al. did not find a decrease in its levels after Goeckerman´s therapy[[25](#_ENREF_25)]. The levels of soluble TNF-α receptor type 1 (sTNF-R1) were found to be increased in active psoriasis and to correlate with PASI[[28](#_ENREF_28),[29](#_ENREF_29)]. TNF-α-converting enzyme from peripheral blood mononuclear cells may contribute to the up-regulation of sTNF-R1 in psoriasis. The raised concentrations of sTNF-R1 in psoriasis were correlated with PASI and were diminished after NB-UVB therapy, suggesting that it may be a marker of the disease severity[[30](#_ENREF_30)].

Interferon (IFN)-γ is important in the early stages of psoriasis, increasing the migration of immune cells into the skin and the activation of monocytes/macrophages, dendritic cells and endothelial cells[[1](#_ENREF_1)]. IFN-γ inhibits apoptosis of keratinocytes, contributing to the hyperproliferation of keratinocytes, and to stimulate epidermal cell proliferation[[31](#_ENREF_31),[32](#_ENREF_32)]. The levels of IFN-γ are elevated in active psoriasis[[15](#_ENREF_15),[17](#_ENREF_17),[18](#_ENREF_18),[21](#_ENREF_21),[24](#_ENREF_24),[33](#_ENREF_33)] and correlate with PASI[[15](#_ENREF_15),[18](#_ENREF_18),[24](#_ENREF_24),[33](#_ENREF_33)]. The improvement of psoriasis, with a significant decrease in PASI, has been associated with a significant decrease in its concentrations[[33](#_ENREF_33)]; moreover, patients with high levels of IFN-γ that did not decrease significantly after treatment show shorter remission periods[[33](#_ENREF_33)]. Yet, Abdel-Hamid *et al*[[17](#_ENREF_17)]reported that TNF-α was a more efficient predictor for disease severity than IFN-γ[[17](#_ENREF_17)], and Tigalonowa *et al*[[34](#_ENREF_34)] did not find any alterations in INF-γ levels after treatment with cyclosporine.

IL-12 is a key cytokine responsible for the induction of Th1 response, leading to the secretion of IFN-γ and homing of T cells in the skin, and the maintenance of the Th1 response. IL-12 shares with IL-23 a common p40 subunit, an attractive therapeutic target in psoriasis, as the ustekinumab efficacy has demonstrated[[35](#_ENREF_35)]. IL-12 concentrations were reported to be increased in patients with psoriasis[[15](#_ENREF_15),[18](#_ENREF_18),[36](#_ENREF_36)], to be correlated with PASI[[15](#_ENREF_15),[18](#_ENREF_18)] and to decrease after psoriasis treatment[[18](#_ENREF_18),[36](#_ENREF_36)]. However, Jacob *et al*[[24](#_ENREF_24)] observed that IL-12 levels were decreased in sera from active untreated psoriasis patients compared with normal controls, and, as Borska *et al*[[36](#_ENREF_36)], they did not find a significant correlation with PASI. These controversial findings compromise its value as a possible biomarker for psoriasis.

In psoriasis, IL-18 is important **for** cellular adhesion[[37](#_ENREF_37)] and synergizes the stimulation of IFN-γ release[[38](#_ENREF_38)]. Its levels seem to be enhanced in psoriatic patients[[15](#_ENREF_15),[18](#_ENREF_18),[39-42](#_ENREF_39)], to be correlated with PASI[[15](#_ENREF_15),[18](#_ENREF_18),[39-42](#_ENREF_39)] and to decrease after treatment[[39](#_ENREF_39)]. Flisiak *et al*[[42](#_ENREF_42)] reported that the combined measurement of plasma IL-18,  TGF-β1, tissue inhibitors of metalloproteinases (TIMP)-1 and matrix metalloproteinase (MMP)-1 has a superior value as a biomarker of psoriasis activity in comparison with IL-18, or with any of the others individually.

Neutrophils are recognized as a component of the leukocyte infiltrate in psoriasis lesions. Its mobilization and degranulation is induced by IL-8, which is produced by keratinocytes. A rise in IL-8 levels has been reported in psoriasis vulgaris patients[[3](#_ENREF_3),[14](#_ENREF_14),[15](#_ENREF_15),[17](#_ENREF_17),[24](#_ENREF_24),[25](#_ENREF_25)], although Deeva *et al*[[43](#_ENREF_43)] did not find it. A study in our lab showed a significant correlation between IL-8 and PASI[[3](#_ENREF_3)]; still, Jacob et al. referred a positive correlation only with the degree of erythema[[24](#_ENREF_24)] and others did not find any significant correlation[[15](#_ENREF_15),[17](#_ENREF_17)]. We also found a significant decrease in its levels after PUVA and after NB-UVB treatment[[3](#_ENREF_3)]. However, Borska *et al*[[25](#_ENREF_25)] reported a significant increase in IL-8 serum concentrations after Goeckerman's therapy.

IL-6, known to be increased in psoriasis[[14](#_ENREF_14),[15](#_ENREF_15),[20-22](#_ENREF_20),[43-45](#_ENREF_43)], mediates T cell activation, stimulates proliferation of keratinocytes and mediates the acute phase response[[15](#_ENREF_15)]. It has been reported that an enhancement in its levels is associated with an in increase in psoriasis severity, as defined by PASI[[21](#_ENREF_21),[22](#_ENREF_22),[44](#_ENREF_44)]. Nonetheless, Bevelacqua et al. reported that the mean value of IL-6 was higher in severe than in mild psoriasis patients and in healthy controls, but there were no differences between mild psoriasis patients and healthy controls, and IL-6 correlated with PASI only for the severer forms of psoriasis[[26](#_ENREF_26)]. Elango *et al*[[45](#_ENREF_45)] observed that only 2 indices of PASI, infiltration and desquamation, showed a positive correlation with IL-6, before and after treatment, and Deeva *et al*[[43](#_ENREF_43)] reported that no correlation was found between psoriasis severity, assessed by PASI, and IL-6. A few successful treatments, such as PUVA[[22](#_ENREF_22),[46](#_ENREF_46)], methotrexate[[45](#_ENREF_45)], etanercept[[47](#_ENREF_47)], were associated with a significant decrease in IL-6 levels. No significant reduction in IL-6 concentrations was found after NB-UVB and topical therapy[[22](#_ENREF_22)]. These studies suggest that IL-6 may not be the best tool, if not combined with other(s) marker(s), to monitor all options of psoriasis treatments.

As referred, the IL-23/Th17 axis is believed to be crucial in psoriasis pathogenesis[[48](#_ENREF_48)]. IL-23 sets in motion several pathways leading to neutrophil recruitment, and stimulates the production of other cytokines, which may directly act on keratinocytes in a TNF-regulated way, resulting in epidermal hyperplasia and/or altered regulation of keratinocyte differentiation. It seems, therefore, that IL-23 is a causative independent factor in psoriasis pathogenesis. Therapies directed to IL-23, such as ustekinumab, that targets the p40 subunit of IL-12 and IL-23, has been used successfully for the treatment of moderate to severe psoriasis[[35](#_ENREF_35)]. In a 12-wk NB-UVB or PUVA therapy, its levels decreased after 3 weeks of treatment, which figured to be crucial to reverse several of the analytical changes found in psoriasis, and to achieve resolution of the lesions[[3](#_ENREF_3)]. As far as we know, there is no data showing a correlation between psoriasis severity and IL-23. The expression of CC chemokine ligand 20 (CCL20) and its receptor CC chemokine receptor 6 (CCR6) is up-regulated in psoriasis[[49](#_ENREF_49),[50](#_ENREF_50)], which may be related to the disease pathogenesis. Indeed, Hedrick et al. found that CCR6 has an important role in IL-23-related responses and identified CCR6 as a potential therapeutic target in psoriasis[[51](#_ENREF_51)]. In opposition to the therapy with calcipotriol, camptothecin or tazarotene, clobetasol treatment inhibited the CCR6 expression in a imiquimod-induced psoriasis-like mouse model[[52](#_ENREF_52)].

IL-22 is the linkage between the infiltrating Th17 cells, driven by IL-23, and keratinocyte hyperplasia and activation. This cytokine is the downstream effector cytokine of IL-23, and can induce many of the pathological features seen in psoriatic skin lesions. The production of IL-22 is up-regulated in psoriatic skin[[53](#_ENREF_53)]; their levels are high in the peripheral blood[[3](#_ENREF_3),[20](#_ENREF_20),[46](#_ENREF_46),[54-57](#_ENREF_54)], and are correlated with the severity of the disease[[20](#_ENREF_20),[46](#_ENREF_46),[54](#_ENREF_54),[55](#_ENREF_55)], suggesting an important role for IL-22 in the pathogenesis of psoriasis. Moreover, a 12-wk successful PUVA or NB-UVB treatment induced a significant decrease in its levels after 6 weeks of therapy[[3](#_ENREF_3)]; treatments with calcipotriol alone or combined with NB-UVB, with NB-UVB, and with etanercept were also associated with a decrease in IL-22 concentrations[[56](#_ENREF_56),[57](#_ENREF_57)]; no changes were found after treatment with acitretin[[57](#_ENREF_57)]. However, some studies did not find significant correlations between IL-22 and psoriasis severity[[3](#_ENREF_3),[57](#_ENREF_57)]. Shimauchi *et al*[[55](#_ENREF_55)]reported that IL-22 can be used as useful biomarker of psoriasis severity, however, it is not a good predictor of the biologic response for biologic therapies.

IL-17, produced by Th17 cells, is a critical component in the establishment and perpetuation of inflammation. It induces the production of pro-inflammatory cytokines, mainly by endothelial cells and macrophages[[58](#_ENREF_58)], and activates keratinocytes to produce interleukins, such as IL-8[[12](#_ENREF_12)]. Increased levels of IL-17 were found in blood of psoriatic patients[[3](#_ENREF_3),[18](#_ENREF_18),[56](#_ENREF_56),[57](#_ENREF_57)], and they seem to correlate with psoriasis severity[[18](#_ENREF_18),[57](#_ENREF_57)]. Romani *et al*. and our group[[3](#_ENREF_3),[59](#_ENREF_59)] did not find this correlation. Romani *et al*[[59](#_ENREF_59)] and Arican *et al*[[15](#_ENREF_15)] found that IL-17 levels in patients were similar to controls. IL-17 concentrations decreased significantly after treatment with calcipotriol, PUVA, NB-UVB, and NB-UVB combined with calcipotriol[[3](#_ENREF_3),[56](#_ENREF_56)]. As observedfor IL-22, etanercept reduced IL-17, but acitretin therapy did not change its levels[[57](#_ENREF_57)]. Some of these findings suggest a limited applicability of IL-22 and IL-17 levels as monitors of psoriasis therapy.

IL-21 seems to play an important role in a variety of inflammatory diseases, such as psoriasis. It is highly expressed in psoriatic plaques and promotes the proliferation of epidermal cells in mice[[60](#_ENREF_60)]. Serum IL-21 levels were reported to be enhanced in psoriasis[[20](#_ENREF_20),[61](#_ENREF_61)] and to correlate with PASI[[61](#_ENREF_61)]; this correlation was not found by Nakajima *et al*[[20](#_ENREF_20)].

Vascular endothelial growth factor (VEGF) contributes to improve the vascularization of the lesions[[62](#_ENREF_62)], to stimulate epidermal hyperplasia, vascular growth and leukocyte infiltration in the skin[[63](#_ENREF_63)]; through its receptors, it appears to play an important role in regulating psoriatic keratinocyte activity[[64](#_ENREF_64)], to increase the permeability of the endothelium and to induce vasodilatation[[65](#_ENREF_65)]. Several authors reported that its levels are significantly high in plasma in the active stage of the disease[[3](#_ENREF_3),[43](#_ENREF_43),[66-71](#_ENREF_66)]. Nonetheless, Shimauchi *et al*[[55](#_ENREF_55)] did not find significant differences in VEGF levels between psoriasis patients and controls. Flisiak *et al*[[72](#_ENREF_72)] reported that the increase of serum VEGF becomes significant **only** in patients with medium and severe activity of the disease, and that soluble VEGF receptor 1 (sVEGFR1) was higher than VEGF in serum of patients with low psoriasis activity. A significant positive correlation has been reported between PASI and VEGF[[18](#_ENREF_18),[55](#_ENREF_55),[67-70](#_ENREF_67),[72](#_ENREF_72)] and sVEGFR1[[72](#_ENREF_72)]; yet, according to Deeva *et al*[[43](#_ENREF_43)] severity of skin symptoms do not correlate with plasma VEGF concentrations. VEGF levels appear to be reduced by standard topical therapy[[68](#_ENREF_68)], PUVA therapy[[3](#_ENREF_3),[71](#_ENREF_71)] and acitretin combined with PUVA[[67](#_ENREF_67)]; the effect of UVB irradiation in VEGF levels is more controversial[[3](#_ENREF_3),[70](#_ENREF_70),[71](#_ENREF_71)] and the effect of retinoids combined with NB-UVB was associated with an increase in VEGF circulating values[[71](#_ENREF_71)]. Besides, VEGF levels were reported to serve as sensitive biomarkers, but not as predictors of therapeutic response to biological therapies in patients with psoriasis[[55](#_ENREF_55)].

According to Nockowski *et al*[[73](#_ENREF_73)] serum concentrations of TGF-β1, an inhibitor of keratinocyte hyperproliferation, were significantly increased in psoriasis; the circulating levels are higher in patients with more severe disease than in those with mild psoriasis, and, actually, TGF-β1 concentrations seem to correlate with disease severity[[39](#_ENREF_39),[42](#_ENREF_42),[73](#_ENREF_73),[74](#_ENREF_74)]. Zaher *et al*[[75](#_ENREF_75)] found correlations between TGF-β1 and extent of the disease and PASI and, as Flisiak *et al*[42] they did not observe significantly higher levels of TGF-β1 in active psoriasis[[42](#_ENREF_42),[74](#_ENREF_74),[75](#_ENREF_75)]. Enhanced levels of TGF- β1 for patients with a PASI lower than 15 were not found[[76](#_ENREF_76)]. As referred previously, the combination of plasma TGF-β1, IL-18, TIMP-1 and MMP-1 has a superior value as a biomarker of psoriasis activity than each one separately[[42](#_ENREF_42)]. Increased TGF-β1 levels in patients with mild psoriasis decreased after biological drug treatment, which was accompanied by a reduction in PASI[[77](#_ENREF_77)], and after treatment with salicylic acid and/or sulphur followed by dithranol ointment[[76](#_ENREF_76)].

The levels of the anti-inflammatory cytokine IL-10 were reported to be decreased[[18](#_ENREF_18)] or below detection levels in psoriatic patients[[24](#_ENREF_24)], and negatively correlated with PASI[[18](#_ENREF_18)].  Another study, by Borska *et al*[[36](#_ENREF_36)] reported that IL-10 concentrations were significantly higher in psoriatic patients, and decreased after treatment. Deeva *et al*[[43](#_ENREF_43)] reported that mild-to-moderate psoriasis vulgaris patients showed higher levels of IL-10, and did not find any correlation between PASI and IL-10. The controversial data do not confirm IL-10 as a reliable biomarker for psoriasis.

Fibroblast growth factor levels correlated to PASI before psoriasis treatment[[70](#_ENREF_70)], and its values were diminished by Goeckerman's therapy[[70](#_ENREF_70)], but as far as we know, no more published data concerning its relationship with psoriasis activity and/or severity exists.

**PENTRAXINS**

C-reactive protein (CRP), a short-chain pentraxin produced in the liver, is a positive acute phase protein that increases rapidly in the presence of inflammation, a hallmark of psoriasis. Elevated CRP levels result from the interaction between pro-inflammatory cytokines, namely IL-6, TNF-α and IL-1, their receptors and inhibitory factors[[78](#_ENREF_78)]. TNF-α induces secretion of IL-6, which stimulates hepatic production of CRP, an effect that can be enhanced by IL-1β. The development of high-resolution CRP assays, has allowed clinicians to explore the potential role of these assays to detect low-grade inflammation, in diagnosing and predicting pathologic conditions.

Increasing concentrations of CRP have been widely reported in mild, moderate and severe forms of active psoriasis[[69](#_ENREF_69),[78-95](#_ENREF_78)]. Only a few reports did not observe significantly increased values[[96](#_ENREF_96),[97](#_ENREF_97)], probably because high-resolution assays were not used, included different clinical forms of psoriasis, or patients that were not at the active stage of psoriasis, or were under treatment with anti-psoriatic regimens. The majority of data reveals CRP as a potential marker of psoriasis severity, since its levels correlate with disease severity, as defined by PASI[[69](#_ENREF_69),[79](#_ENREF_79),[84](#_ENREF_84),[87](#_ENREF_87),[90](#_ENREF_90),[93-95](#_ENREF_93),[98](#_ENREF_98)], few studies did not report these findings[[81](#_ENREF_81),[99](#_ENREF_99)], and Kanelleas *et al*[[82](#_ENREF_82)] only found significant correlations after treatment. CRP levels decreased significantly after successful treatments with several types of psoriasis therapies[[88](#_ENREF_88)], such as phototherapy, alone or combined with coal tar[[79](#_ENREF_79),[81](#_ENREF_81),[83](#_ENREF_83),[97](#_ENREF_97)], photochemotherapy[[78](#_ENREF_78),[79](#_ENREF_79)], systemic[[78](#_ENREF_78)] and biologic agents[[82](#_ENREF_82),[91](#_ENREF_91),[92](#_ENREF_92),[98](#_ENREF_98)]. Moreover, our group has recently proposed the CRP value after treatment, as an important determinant of the length of remission of psoriasis, at least for patients treated with phototherapy or topical therapy[[100](#_ENREF_100)]. Thus, CRP concentration is a potential marker to access the severity of psoriasis, to monitor the treatment and to predict the length of remission of psoriasis, especially if combined with PASI.

Pentraxin 3 (PTX3), a long chain pentraxin, is produced in response to inflammatory signals by macrophages, dendritic cells and endothelial cells. PTX3 and CRP reflect different sides of the inflammatory process[[101](#_ENREF_101)]. Enhanced PTX 3 levels are found in active psoriasis[[26](#_ENREF_26),[81](#_ENREF_81),[102](#_ENREF_102)]; Ctirad *et al*[[81](#_ENREF_81)] did not find increased values of PTX3. Significant correlations between PTX3 concentrations and psoriasis severity have been reported[[26](#_ENREF_26),[102](#_ENREF_102)]. After effective Goeckerman's, NB-UVB and PUVA therapies, PTX3 values decreased significantly[[81](#_ENREF_81),[102](#_ENREF_102)]. PTX3, combined with PASI and CRP, seems to be important for the clinical evaluation and monitoring of psoriasis.

We must emphasize that CRP and PTX3 evaluation, although sensitive, lacks specificity, as they are also increased in different types of inflammatory diseases. Therefore, the presence of inflammatory comorbidities should be considered when using these biomarkers to assess psoriasis.

**MARKERS OF OXIDATIVE STRESS**

It has been suggested that increased reactive oxygen species, such as nitric oxide (NO) and malondialdehyde (MDA), may play a part in the pathogenesis of psoriasis. The balance between oxidant and antioxidant agents seems to be altered in psoriasis. In psoriasis patients, a significant increase in NO and MDA and a decrease in superoxide dismutase (SOD) levels was reported[[103](#_ENREF_103),[104](#_ENREF_104)]. Some authors did not find a significant correlation between PASI and NO, MDA, SOD and total antioxidant status[[103](#_ENREF_103),[105](#_ENREF_105)], while others reported a significant correlation between PASI and MDA, NO, SOD, catalase and total antioxidant status[[104](#_ENREF_104),[106](#_ENREF_106)]. MDA levels decreased after treatment with PUVA, NB-UVB, infliximab and etanercept, yet without reaching baseline levels[[27](#_ENREF_27)].

Methylglyoxal serum level, that reflects oxidative and carbonyl stress status, increases in psoriasis patients and is associated with psoriasis severity, assessed by PASI[[107](#_ENREF_107)].

Considering the controversial data, it seems that although oxidative stress has a crucial role in psoriasis pathogenesis, markers of redox status / oxidative stress may not be the best translators of psoriasis severity.

Increased lipid oxidation is also associated with psoriasis. One of the major and early lipid peroxidation product is oxidized low-density lipoprotein (oxLDL)[[108](#_ENREF_108)]. The levels of autoantibodies against oxLDL (auAb-oxLDL), an indirect evidence of LDL oxidation, seem to be increased in psoriasis[[109](#_ENREF_109),[110](#_ENREF_110)], and, according to Orem *et al*[[110](#_ENREF_110)] the levels of auAb-oxLDL are correlated with PASI score. There is no data concerning the effect of psoriasis therapies in auAb-oxLDL concentrations.

**ADIPOKINES**

The adipokine adiponectin, which is adipose-tissue specific, is known to inhibit the inflammatory response and to protect against metabolic and cardiovascular diseases[[111](#_ENREF_111),[112](#_ENREF_112)], as it plays an important role in lipid metabolism and atherogenesis[[113](#_ENREF_113)]. Moreover, adiponectin reduces the production of TNF-α, IL-6, IFN-γ, the expression of monocyte cell adhesion molecules, the phagocytic activity of macrophages and, therefore, its transformation to foam cells; adiponectin also increases insulin sensitivity and the repair of damaged vasculature[[114](#_ENREF_114),[115](#_ENREF_115)]. The high molecular weight (HMW) form is considered the active fraction, and, therefore, it is considered a better marker of metabolic disturbances than total adiponectin. Data concerning adiponectin in psoriasis are controversial. Reduced adiponectin levels have been associated with psoriasis, at least in overweight/obese patients[[22](#_ENREF_22),[116-118](#_ENREF_116)], and were correlated inversely with PASI[[69](#_ENREF_69)]. Yet, increased concentrations of total adiponectin that correlate positively with PASI were reported[[20](#_ENREF_20)]; HMW adiponectin levels were described to be decreased and negatively correlated with PASI[[20](#_ENREF_20)]. However, according to the meta-analysis performed by Zhu *et al*[[119](#_ENREF_119)] adiponectin and HMW adiponectin levels are not significantly different in patients with psoriasis, compared with controls. These authors suggested that the levels of total adiponectin and HMW adiponectin may not be associated with psoriasis *per se* and that the relationship between psoriasis and adiponectin needs to be clarified[[119](#_ENREF_119)].

Resistin is expressed by cells from the stromal compartment of the adipose tissue, particularly by macrophages and by peripheral monocytes that are up-regulated during their differentiation to macrophages. High resistin levels are reported to be associated with the atherosclerotic process, and insulin resistance; resistin has been shown to increase the expression of several pro-inflammatory cytokines, including TNF-α and IL-6, suggesting an involvement in inflammation[[120](#_ENREF_120)]. Psoriasis patients seem to present enhanced levels of resistin[[22](#_ENREF_22),[121](#_ENREF_121)]. A study performed by our team found that the severer psoriasis forms presented significantly higher values when compared to moderate forms and controls[[22](#_ENREF_22)]. The PASI score was found to correlate with serum resistin concentrations[[69](#_ENREF_69),[121](#_ENREF_121),[122](#_ENREF_122)].

High levels of leptin, another adipokine adipose-tissue specific, seem to enhance Th1 immune responses, and increase macrophage activity, with production of different cytokines. Serum leptin levels were reported to be significantly higher in psoriasis patients[[22](#_ENREF_22),[59](#_ENREF_59),[116](#_ENREF_116),[117](#_ENREF_117),[123](#_ENREF_123),[124](#_ENREF_124)], particularly in those with severe psoriasis[[125](#_ENREF_125)] and/or with higher body mass index[[22](#_ENREF_22)], and to positively correlate with PASI[[125](#_ENREF_125)]. Nonetheless, others authors did not find these significant results[[126](#_ENREF_126)].

Data concerning the more recent discovered adipokines and its relationship with psoriasis is limited. Ghrelin seems to take part in the development of metabolic syndrome and its concentrations are decreased in some pathologic conditions, such as obesity and type 2 diabetes[[127](#_ENREF_127)]. A strong negative correlation between PASI and ghrelin was reported, yet, ghrelin concentrations were not different from controls and did not suffer a significant alteration after cyclosporine treatment of psoriasis[[126](#_ENREF_126)]. Patients with psoriasis also showed considerably enhanced serum levels of visfatin[[128](#_ENREF_128),[129](#_ENREF_129)], an inflammatory adipokine, with significant positive correlation with disease severity and duration[[128](#_ENREF_128)]; however, this increase in its levels was not always found[[91](#_ENREF_91)]. According to Takahashi *et al*[[56](#_ENREF_56)] the levels of omentin were decreased in psoriasis patients and negatively correlated with PASI scores. However, Romani et al. did not find these significant differences for omentin; instead, they observed higher baseline serum concentrations of retinol binding protein (RBP)-4 and lipocalin-2, that correlated both with PASI[[59](#_ENREF_59)]. Although Ismail et al. described lower omentin concentrations in psoriasis, the correlation with disease severity was not found[[128](#_ENREF_128)]. Concerning RBP-4, and oppositely to the previously referred results by Romani *et al*[[59](#_ENREF_59)], Gerdes *et al*. observed that RBP-4 is independently decreased in psoriasis[[129](#_ENREF_129)], and Karadag *et al*[[130](#_ENREF_130)] did not find significant differences in its basal concentrations compared to controls, although a decrease was found after treatment with anti-TNF-α agents.

In what concerns the changes in adipokine levels following different types of psoriasis treatments, data is controversial. In summary, therapies, such as topics, NB-UVB, TNF-α inhibitors, did not induce significant alterations in the levels of adiponectin, visfatin, leptin, ghrelin, resistin and apelin[[22](#_ENREF_22),[131](#_ENREF_131),[132](#_ENREF_132)]. However, an increase in adiponectin concentrations was reported after PUVA[[22](#_ENREF_22)] and cyclosporine[[126](#_ENREF_126)] therapies. Corbetta *et al*[[133](#_ENREF_133)] did not observe any alteration in adiponectin circulating values after retinoid therapy, but reported a decrease in resistin levels; in opposition, Ozdemir *et al*[[126](#_ENREF_126)] observed an increase in resistin concentrations after cyclosporine treatment. Phototherapy induced no remarkable change in the levels of leptin, but decreased resistin levels[[134](#_ENREF_134)]. Therefore, adipokines may not be the best tools to monitor psoriasis activity.

**OTHER POTENTIAL BIOMARKERS**

Elastase, released at inflammatory sites, when neutrophils are stimulated by a variety of compounds, mediates inflammation and tissue damage, by inducing activation of other inflammatory cells and by inducing degradation of matrix proteins and clotting factors[[135](#_ENREF_135)]. Its levels are known to be increased in active psoriasis[[79](#_ENREF_79),[80](#_ENREF_80)] and seem to be crucial for the formation and enlargement of psoriatic plaques. Orem *et al*[[136](#_ENREF_136)] reported that elastase correlates with PASI, but only in the active period of the disease; accordingly, we also found a trend towards a correlation between elastase and PASI[[79](#_ENREF_79)]. We also found a significant decrease in elastase levels after PUVA and NB-UVB therapy, but not after topical therapy (calcipotriol and betamethasone dipropionate, combined or alternatively)[[79](#_ENREF_79)].

TNF-α and IFN-γ increase the expression of inter-cellular adhesion molecule-1 (ICAM-1), promoting skin infiltration of T cells and other inflammatory cells, such as monocytes. The levels of the soluble form of ICAM-1 (sICAM-1) were reported to be higher in psoriasis patients than in controls, to correlate with disease severity[[25](#_ENREF_25),[29](#_ENREF_29),[41](#_ENREF_41),[137-140](#_ENREF_137)], and to decrease after NB-UVB therapy[[137](#_ENREF_137)], but not after dithranol combined with UVB therapy[[141](#_ENREF_141)]. In opposition, Takahashi *et al*[[18](#_ENREF_18)] reported that in psoriasis patients, sICAM-1 concentrations were not significantly different from those of controls and were not associated with PASI. Krasowska *et al*[[142](#_ENREF_142)] also observed that its levels are not related with psoriasis severity.

The levels of E-selectin, another classical marker of endothelial dysfunction, are significantly elevated in psoriatic patients and positively correlated with disease severity[[140](#_ENREF_140),[143](#_ENREF_143)]. Long *et al*[[137](#_ENREF_137)] found that serum levels of soluble E-selectin decreased significantly after NB-UVB treatment, but were not correlated with PASI score before therapy, which is in accordance with Borska *et al*[[25](#_ENREF_25)]data.

The levels of adenosine deaminase, a nonspecific marker of T cell activation,  are increased in psoriasis , and decreased after cyclosporine, etanercept, and PUVA therapies, suggesting that it may be a good marker of psoriasis activity, but it did not correlate with PASI[[144](#_ENREF_144),[145](#_ENREF_145)], thus, it is not a good marker for psoriasis severity.

Soluble IL-2 receptor (sIL-2R) seems to correlate with disease activity in psoriasis[[146](#_ENREF_146),[147](#_ENREF_147)]. The levels of sIL-2R decreased after treatment with PUVA and cyclosporine[[146](#_ENREF_146),[147](#_ENREF_147)], but did not change with NB-UVB treatment[[148](#_ENREF_148)].

In psoriasis patients, a rise in serum levels of neopterin, a non-specific marker of the activation of cell-mediated immunity, that correlates with PASI was reported[[149](#_ENREF_149)]. Urine neopterin levels are also elevated in psoriatic patients and reduced significantly after etanercept treatment, however, no correlation with PASI was found[[150](#_ENREF_150)].

Other analytical parameters were occasionally reported to be related with psoriasis severity. For instance, hydrogen sulfide [H(2)S], that seems to be a signalling molecule with both pro- or anti-inflammatory effects, was significantly decreased and negatively correlated with clinical psoriasis severity[[151](#_ENREF_151)]. Nonetheless, its relationship with psoriasis has not been clearly elucidated.  Procollagen III peptide levels were found to relate with psoriasis severity[[138](#_ENREF_138)]. Higher platelet factor 4 levels were found in psoriasis and correlated with PASI scores[[152](#_ENREF_152)]. Additionally, endothelin-1 seems to be increased in sera of psoriatic patients, to associate with PASI [[153](#_ENREF_153),[154](#_ENREF_154)] and to decrease after PUVA therapy[[154](#_ENREF_154)]. Plasma platelet-derived microparticles were higher in psoriasis, presented a significant correlation with PASI, and reduced after clinical improvement[[152](#_ENREF_152)]. Prolactin levels were increased in psoriatic patients and reduced after tacalcitol ointment; moreover, there was a correlation between the baseline levels and PASI [[155](#_ENREF_155)]. Finally, the levels of themicroRNA (miR)-1266, apparently one of the regulators of IL-17, were considerably higher in psoriasis patients than in control subjects and showed an inverse association, although weak, with PASI and body surface areas of involved skin, which lead the authors to propose it as a marker of disease activity [[156](#_ENREF_156)]; however, further studies are warranted to clarify the role of miR-1266 in psoriasis pathogenesis.

**CONCLUDING REMARKS**

For most of the potential biomarkers there are studies with divergent results, compromising their definition as markers of psoriasis severity and/or monitors of therapy. In several cases, their levels are altered in active psoriasis, but may or may not be correlated with PASI, and may or may not be reversed by different therapies. Differences in the study design, characteristics of patients and controls enrolled in the study, psoriasis severity and its assessment, among other factors, may account for these discrepancies. Nonetheless, in most cases the alterations seem to reflect more the involvement of the biomarker in psoriasis pathogenesis, rather than to reflect directly psoriasis severity and/or activity. Moreover, the use of some of these biomarkers must consider other inflammatory comorbidities that may be misleading, as they are not specific for psoriasis.

**C**onsidering adipokines, although several studies referred a possible association between their levels and disease severity, this correlation seems to be dependent of the body weight of the patient and/or to be more pronounced in the severer forms, that are usually associated with higher adiposity. This raises the question: patients with severe psoriasis forms and with low adipose mass present also alterations in these adipokines levels? And do they relate with psoriasis activity?

Considering that psoriasis is an immunologic, inflammatory chronic disease, it is not surprising that most of the potential biomarkers of psoriasis are inflammatory/immunologic markers or are somehow related with the inflammatory process. In spite of some controversial data, it appears that a bio-panel by combining the most promising inflammatory biomarkers may become a reliable alternative to accesses psoriasis severity and to monitor the response to therapy. A summary of the reported data about these biomarkers and its relation with psoriasis activity, severity and therapy is presented at Table 1.

With several and more consistentdata, we might propose CRP, one of the most sensitive markers of inflammation, as the most promising biomarker to evaluate psoriasis severity and to monitor the response to different types of treatment of psoriasis. However, since there is no consistent data for mild psoriasis forms, it seems that the combination of CRP values with other analytical or clinical markers would be valuable. Thus, the need to search for an accurate marker or a combination of clinical and/or analytical markers, to support therapeutic decisions, needs further studies. We believe, considering the current data, that the association between CRP levels and PASI score, provides a valuable bio-panel to evaluate psoriasis severity and to monitor its treatments. Moreover, as CRP and PASI are both predictors of the length of psoriasis remission[[100](#_ENREF_100)], their evaluation at end of thetreatment may help to decide if the treatment should be continued to achieve lower CRP values and longer periods of remission.

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**Table 1 Potential inflammatory biomarkers and its relation with psoriasis activity, severity and therapy.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Studies reports** | **about its levels** |  |  |
| **Biomarker** | **In active psoriasis** | **Correlation with severity** | **After therapy** | **Relation (after therapy) with length of psoriasis remission** |
| TNF-α | Increased levels[[13-22](#_ENREF_13)]  Mild psoriasis with higher levels than controls, lower than severe psoriasis[[26](#_ENREF_26)] | Correlated positively[[3](#_ENREF_3),[17-19](#_ENREF_17),[23](#_ENREF_23)]  Only for severe psoriasis[[24](#_ENREF_24)] | Improved[[3](#_ENREF_3),[19](#_ENREF_19),[22](#_ENREF_22)]  Only for infliximab and etanercept[[27](#_ENREF_27)] | No report |
|  | Not altered[[3](#_ENREF_3),[24](#_ENREF_24),[25](#_ENREF_25)] | Correlated negatively [[20](#_ENREF_20)] | Not improved for PUVA and NB-UVB[[27](#_ENREF_27)];  and for Goeckerman´s therapy[[25](#_ENREF_25)] |  |
| IFN-γ | Increased[[15](#_ENREF_15),[17](#_ENREF_17),[18](#_ENREF_18),[21](#_ENREF_21),[24](#_ENREF_24),[33](#_ENREF_33)] | Correlated positively[[15](#_ENREF_15),[18](#_ENREF_18),[24](#_ENREF_24),[33](#_ENREF_33)] | Improved[[33](#_ENREF_33)] | Longer length of remission if decreased [[33](#_ENREF_33)] |
|  |  | Not correlated[[21](#_ENREF_21)] | Not improved[[34](#_ENREF_34)] |  |
|  |  | Not the best predictor[[17](#_ENREF_17)] |  |  |
| IL-12 | Increased levels[[15](#_ENREF_15),[18](#_ENREF_18),[36](#_ENREF_36)] | Correlated positively[[15](#_ENREF_15),[18](#_ENREF_18)] | Improved[[18](#_ENREF_18),[36](#_ENREF_36)] | No report |
|  | Decreased levels[[24](#_ENREF_24)] | Not correlated[[24](#_ENREF_24),[36](#_ENREF_36)] |  |  |
| IL-18 | Increased levels[[15](#_ENREF_15),[18](#_ENREF_18),[39-42](#_ENREF_39)] | Correlated positively[[15](#_ENREF_15),[18](#_ENREF_18),[39-42](#_ENREF_39)] | Improved[[39](#_ENREF_39)] | No report |
|  |  | Combined with TGF-β1, TIMP-1 and MMP-1 - superior value as predictor[[42](#_ENREF_42)] |  |  |
| IL-8 | Increased levels[[3](#_ENREF_3),[14](#_ENREF_14),[15](#_ENREF_15),[17](#_ENREF_17),[24](#_ENREF_24),[25](#_ENREF_25)] | Correlated positively[[3](#_ENREF_3)] | Improved[[3](#_ENREF_3)] | No report |
|  | Not increased[[43](#_ENREF_43)] | Correlation only with erythema [[24](#_ENREF_24)] | Increased significantly [[25](#_ENREF_25)] |  |
|  |  | Not correlated[[15](#_ENREF_15),[17](#_ENREF_17)] |  |  |
| IL-6 | Increased levels [[14](#_ENREF_14),[15](#_ENREF_15),[20-22](#_ENREF_20),[43-45](#_ENREF_43)] | Correlated positively[[21](#_ENREF_21),[22](#_ENREF_22),[44](#_ENREF_44)]  for severe psoriasis only[[26](#_ENREF_26)] | Improved[[45-47](#_ENREF_45)]  for PUVA[[22](#_ENREF_22)] | No report |
|  | Higher levels in severer forms than in mild and in controls; no differences between mild forms and controls[[26](#_ENREF_26)] | Correlation only with desquamation and infiltration[[45](#_ENREF_45)] | Not improved for NB-UVB and topical therapy[[22](#_ENREF_22)] |  |
|  |  | Not correlated[[43](#_ENREF_43),[46](#_ENREF_46)] |  |  |
| IL-22 | Increased levels[[3](#_ENREF_3),[20](#_ENREF_20),[46](#_ENREF_46),[54-56](#_ENREF_54)] | Correlated positively [[20](#_ENREF_20),[46](#_ENREF_46),[54](#_ENREF_54),[55](#_ENREF_55)] | Improved[[3](#_ENREF_3),[56](#_ENREF_56)]  Only for etanercept[[57](#_ENREF_57)] | No report |
|  |  | Not correlated[[3](#_ENREF_3),[57](#_ENREF_57)] | Not improved for acitretin[[57](#_ENREF_57)] |  |
|  |  |  | Only in high-responders; not predictor of biologic therapeutic response[[55](#_ENREF_55)] |  |
| IL-17 | Increased levels[[3](#_ENREF_3),[18](#_ENREF_18),[56](#_ENREF_56),[57](#_ENREF_57)] | Correlated positively[[18](#_ENREF_18),[57](#_ENREF_57)] | Improved[[3](#_ENREF_3),[56](#_ENREF_56)]  Only for etanercept [[57](#_ENREF_57)] | No report |
|  | Not altered[[15](#_ENREF_15),[59](#_ENREF_59)] | Not correlated[[3](#_ENREF_3),[59](#_ENREF_59)] | Not improved for acitretin [[57](#_ENREF_57)] |  |
| VEGF | Increased levels[[3](#_ENREF_3),[43](#_ENREF_43),[66-71](#_ENREF_66)]  Only im medium and severe psoriasis[[72](#_ENREF_72)] | Correlated positively[[18](#_ENREF_18),[55](#_ENREF_55),[67-70](#_ENREF_67),[72](#_ENREF_72)] | Improved[[3](#_ENREF_3),[67](#_ENREF_67),[68](#_ENREF_68)]  Only for PUVA[[71](#_ENREF_71)] | No report |
|  | Not increased[[55](#_ENREF_55)] | Not correlated[[43](#_ENREF_43)] | Discordant results with NB-UVB[[3](#_ENREF_3),[70](#_ENREF_70),[71](#_ENREF_71)] |  |
|  |  |  | Increased values with retinoids combined with NB-UVB[[71](#_ENREF_71)] |  |
|  |  |  | Only in high-responders; not predictor of biologic therapeutic response[[55](#_ENREF_55)] |  |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| IL-21 | Increased levels [[20](#_ENREF_20),[61](#_ENREF_61)] | Correlated positively[[61](#_ENREF_61)] | No report | No report |
|  |  | Not correlated [[20](#_ENREF_20)] |  |  |
| TGF-β1 | Increased levels[[73](#_ENREF_73)] | Correlated positively[[39](#_ENREF_39),[42](#_ENREF_42),[73-75](#_ENREF_73)] | Improved[[77](#_ENREF_77)]. | No report |
|  | Not increased[[74](#_ENREF_74),[75](#_ENREF_75)]  At least for patients with a PASI < 15[[76](#_ENREF_76)] | Combined with IL-18, TIMP-1 and MMP-1 - superior value as predictor[[42](#_ENREF_42)] | The decrease was not significantly[[76](#_ENREF_76)] |  |
| IL-10 | Decreased[[18](#_ENREF_18)] | Correlated negatively[[18](#_ENREF_18)] |  | No report |
|  | Below detection levels [[24](#_ENREF_24)] | Not correlated[[43](#_ENREF_43)] | Decreased[[36](#_ENREF_36)] |  |
|  | Increased[[36](#_ENREF_36),[43](#_ENREF_43)] |  |  |  |
| CRP | Increased levels[[69](#_ENREF_69),[78-95](#_ENREF_78)] | Correlated positively [[69](#_ENREF_69),[79](#_ENREF_79),[84](#_ENREF_84),[87](#_ENREF_87),[90](#_ENREF_90),[93-95](#_ENREF_93),[98](#_ENREF_98)] | Improved[[78](#_ENREF_78),[79](#_ENREF_79),[81-83](#_ENREF_81),[88](#_ENREF_88),[91](#_ENREF_91),[92](#_ENREF_92),[97](#_ENREF_97),[98](#_ENREF_98)] | Longer length of remission if decreased; predictor of length of remission[[100](#_ENREF_100)] |
|  | Not increased[[96](#_ENREF_96),[97](#_ENREF_97)] | Correlated after treatment[[82](#_ENREF_82)] |  |  |
|  |  | Not correlated[[81](#_ENREF_81),[99](#_ENREF_99)] |  |  |
| PTX3 | Increased levels[[26](#_ENREF_26),[81](#_ENREF_81),[102](#_ENREF_102)] | Correlated positively[[26](#_ENREF_26),[102](#_ENREF_102)] | Improved[[81](#_ENREF_81),[102](#_ENREF_102)] | No report |
|  |  | Not correlated[[81](#_ENREF_81)] |  |  |

CRP: C-reactive protein; IL: Interleukin; IFN: Interferon; MMP: Matrix metalloproteinase; NB-UVB: Narrow-band ultraviolet light B; PTX3: Pentraxin 3; PUVA: Psoralen plus ultraviolet light A; TGF: Transforming growth factor; TIMP: Tissue inhibitors of metalloproteinases; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.