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REVIEW

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Novel concepts in psoriasis: histopathology and markers related to modern treatment approaches

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Abstract

Psoriasis is a chronic autoimmune disease affecting over 2% of the worldwide population. From an anatomopathological point of view, psoriasis is characterized by immune cells infiltration, epidermal hyperproliferation, and abnormal keratinocyte differentiation. Understanding the pathogenesis of psoriasis will allow clinicians to manage this complex disease. Under these conditions, the application of effective treatments requires a thorough knowledge of all the pathogenetic mechanisms that lead to psoriasis. Numerous immunopathological pathways play crucial roles in the development of new therapies, such as biological therapies, which have been a breakthrough in psoriasis's treatment. Pharmacogenetics is an essential factor in the patient's response to treatment. One important pathway targeted by modern treatments is the interleukin (IL)-23/T-helper (Th)17 axis. Like IL-17 inhibitors, IL-23 blockers are a very effective therapy for this autoimmune disease. It is considered that micro-ribonucleic acids (microRNAs) are the starting point for any autoimmune disease. Studying certain microRNA (miR) involved in the inflammatory pathway in psoriasis can find direct targets to future treatments that can even be more specific than actual biological therapies. As such, miR-210 has proven to be up-regulated in psoriasis, also leading to the up-regulation of the Th1/Th17 axis. On the other hand, miR-187 was found to be down-regulated, influencing the outcome of psoriasis by increasing the proliferation of IL-6 stimulated keratinocytes and consecutively generating epidermal thickening. In this review, we are aiming to do an up-to-date briefing of psoriasis histopathology and pharmacogenetic factors that are considered for the accurate evaluation of treatment response.

Keywords: psoriasis, histopathology, pharmacogenetics, microRNA, biological therapies.

Introduction

Psoriasis is an autoimmune disease affecting over 2% [1, 2] of the global population without a fully understood pathophysiology path.

The most common form is vulgar psoriasis, being involved in more than 80% of the total cases of psoriasis [3, 4]. It is clinically characterized by papulosquamous plaques, with a clear demarcation from normal skin and asymmetrical debut usually involving elbows, scalp, and knees [5, 6]. Apart from plaque psoriasis, there are also other clinical forms, such as inverse or flexural psoriasis, characterized by red scales, with a particular shiny aspect, that can sometimes be misdiagnosed with seborrheic dermatitis due to specific localization and often greasy scales [5, 7]. Von Zumbusch psoriasis or general psoriasis, pustular, inverse, and guttate psoriasis are other less frequent forms, while erythroderma is an extremely severe condition that can emerge from any form of psoriasis [8, 9].

Clinical evidence plays a key role in the diagnosis approach of this disease [10]. The most important score used in evaluating the severity of the disease, as well as the remission under treatment, is Psoriasis Area and Severity Index (PASI) score. It includes four anatomic sites: head, arms, trunk, and legs, each of those being assessed for typical lesions, such as desquamation, induration, and erythema [11]. The maximum score that can be achieved is 72, equivalent to the most severe and almost complete form of erythroderma [5, 12].

Aim

In this narrative review, we aim to present the latest knowledge in the medical literature regarding the implications of pharmacogenetics in the response to psoriasis' treatment. The main objectives are to state whether there could be a possible predictable marker in this pathology's outcome, as well to present the newest treatment directions based on individualized pharmacogenetic treatment, which could be a breakthrough in future medicine.

Histopathological features and immunopathology

One major approach in understanding the mechanisms

behind the disease is to study the histopathological (HP) aspect of the skin. There are three important HP features in psoriasis: leukocyte infiltration, vessel dilation both of which are present in the dermis, and epidermal hyperplasia. Correlations between HP aspects and clinical features are essential for a full understanding of this diseases' natural outcome. The early macule at the debut of the disease is characterized by a mere lymphocytic infiltrate in the proximity of more prominent blood vessels. The next step in the natural evolution is epidermal hyperplasia and the appearance of scaly papules characterized by parakeratosis. At this point, neutrophilic infiltration appears, which together with parakeratosis form in the horny layer a specific HP lesion: the Munro abscess (Figures 1 and 2). Sometimes, when necrotic epidermal cells form a structure in the shape of a collar surrounding neutrophilic infiltration, a spongiform pustule of Kogoj is formed (Figures 3 and 4). Generally speaking, the classical HP presentation of psoriasis plaques is characterized by elongation of rete ridges, parakeratotic, neutrophilic infiltration, and a more thinned subpapillary plate. The histopathology of the lesions is mostly reversible, starting with fibrosis, and a decrease in the number of neutrophils [5, 13]. Jiang *et al.* studied the implication of the psoriatic keratinocyte exosome release, as well as their function in the outcome of the disease. Their findings show a clear relationship between keratinocytes exosomes and the expression of proinflammatory factors involved in the development of psoriasis. This can be explained by the role keratinocyte exosomes play in inducing neutrophil activation [14] and by such in the perpetuation of inflammation. The most important conclusion stated in their study is that psoriasis' inflammation is characterized by a tight "communication" between keratinocyte exosomes and neutrophils [14]. There is a pathological interaction among skin cells, immune cells, and numerous biological signaling molecules [15].

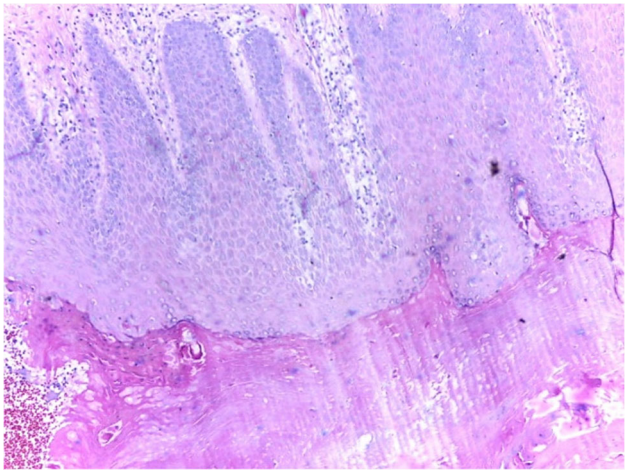

Figure 1 – ***HP patterns of psoriasis, chronic phase: regular acanthosis, hypogranulosis, hyperkeratosis, parakeratosis. HE staining, ×100. HE: Hematoxylin–Eosin; HP: Histopathological.***

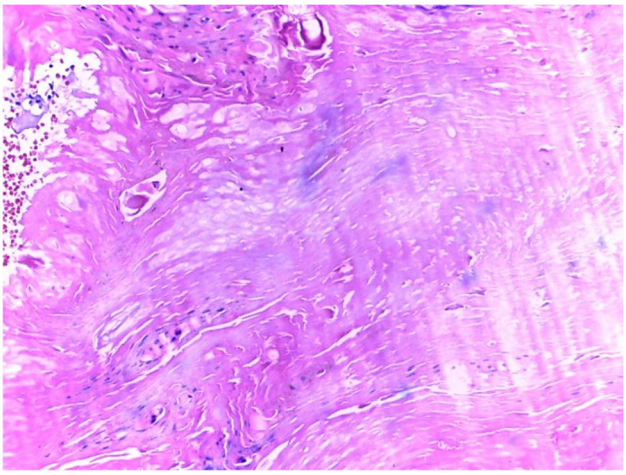

Figure 2 – ***HP patterns of psoriasis, chronic phase: parakeratosis, hyperkeratosis, Munro microabscesses. HE staining, ×200.***

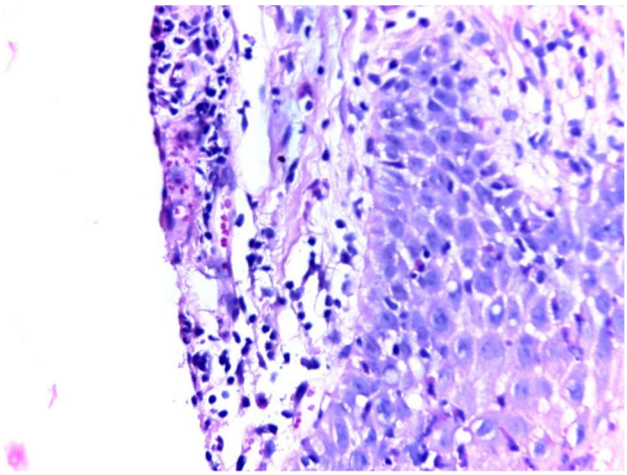

Figure 3 – ***HP patterns of psoriasis, acute phase: congested capillaries, pustules of Kogoj, perivascular lymphocytic infiltrate. HE staining, ×200.***

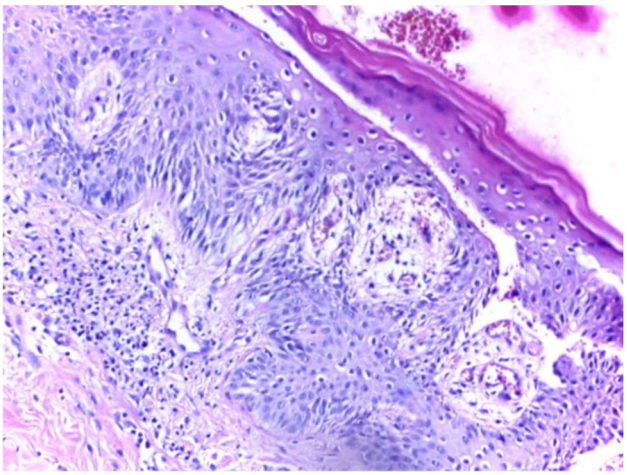

Figure 4 – ***HP patterns of psoriasis, acute phase: elongation and fusion of rete ridges, congested and tortuous capillaries in the edematous dermal papillae, perivascular lymphocytic infiltrate. HE staining, ×200.***

The most studied feature in psoriasis, vessel dilation, is most likely caused by the rise of vascular endothelial growth factor (VEGF). This pathway is signaled by tumor necrosis factor-alpha (TNF-α), targeted by TNF-α blockers, such as Infliximab, Etanercept, Adalimumab, etc. [16, 17]. Understanding the immunopathology behind this disease could give us better control of the progression of the lesions and thus a great improvement of patients' quality of life.

Yet very little is known regarding specific predictors of this disease, or the factors that can lead to clinical remission [18]. The immunopathological pathway is triggered in the first phase by keratinocytes which fulfill the role of activating dendritic cells, leading to a cytokine release, including interleukin (IL)-12 and IL-23 [19, 20]. Those two ILs will subsequently activate type 1 and type 17 T-helper (Th1, Th17) cells [21]. All these factors (ILs, cytokine increased number, TNF-α) amplify keratinocyte activation and thus maintenance of inflammation [22–24].

Most recent studies are based on IL-23/Th17 axis, according to which IL-23 activates Th17, which synthetizes IL-17 [25–28]. Figure 5 shows a brief overview of the immunopathological pathways triggered in psoriasis, as well as the site of action of most important biological therapies [29, 30].

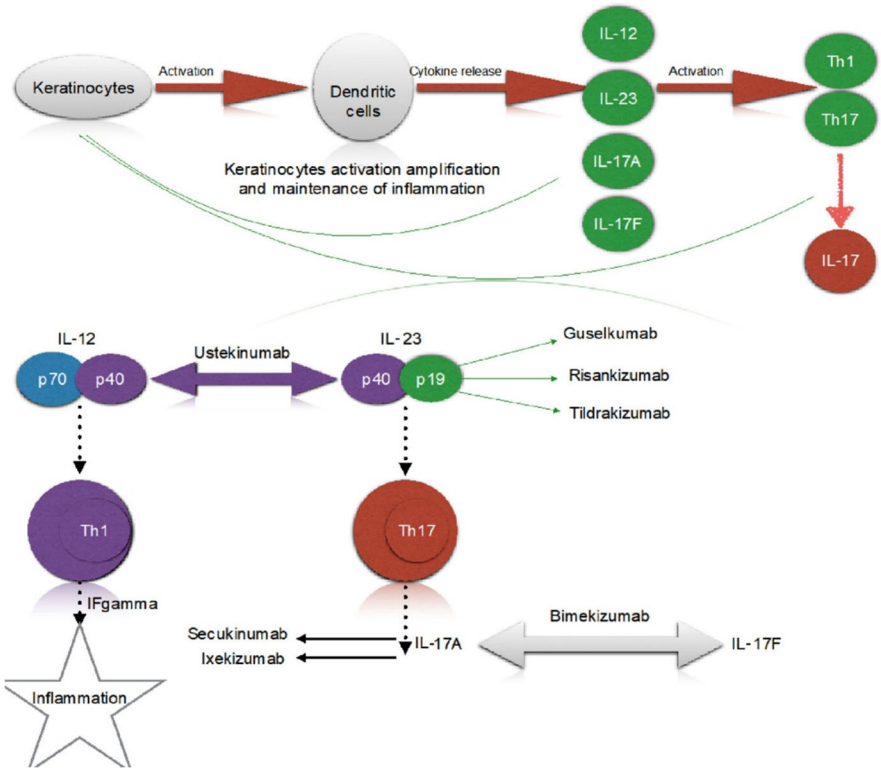

Figure 5 – ***Immunopathology in psoriasis. IF: Interferon; IL: Interleukin; Th: T-helper.***

Involvement of ILs in the onset and evolution of psoriasis

IL-17 plays a major role in the immunopathogenesis of psoriasis [31]. IL-17 is a family of cytokines that includes six different cytokines, the highest potency having the IL-17A cytokine [32]. Important sources for this proinflammatory cytokine are Th17 lymphocytes, gamma delta T ($\gamma\delta$T) lymphocytes, and mucosal-associated invariant T (MAIT) cells, type 3 innate lymphoid cells (ILC3s) [33]. IL-17F is more than 50% homologous to IL-17A (55%) and has the same sources (Th17, $\gamma\delta$T cell, ILC3s). Although both IL-17A and IL-17F cytokines are more expressed in psoriatic plaque and the serum of psoriatic patients, IL-17F has a higher potency in inducing IL-6 and IL-8 in normal keratinocytes compared to IL-17A [34].

The IL-23/Th17 axis has been identified as a major factor in the pathogenesis of psoriasis. IL-23 has modulatory effects on the maintenance of Th17 cells. IL-23 is produced by dendritic cells, monocytes, and macrophages (antigen-presenting cells) [35]. Like IL-17 inhibitors, IL-23 blockers are a very effective therapy for this autoimmune disease.

Immunomodulatory treatment of psoriasis

Depending on the form and severity of the disease, treatment can vary from topical to systemic, with biological therapies as the last resort therapy but also the highest efficiency [36–38]. The role of biological therapies is to suppress the immune-mediated process that leads to inflammation in most autoimmune diseases. Depending on the pathway targeted by each agent there is a wide variety of biological therapies to be used for treating moderate to severe forms of psoriasis [33, 39, 40].

TNF-α blockers were the first agents used as targeted therapy in psoriasis. They were followed by monoclonal antibodies against IL-17, IL-23, and IL-12/IL-23 [41]. TNF-α is an agent produced by both immune cells and non-immune cells, such as T-cells, dendritic cells, macrophages, neutrophils, but especially mature dendritic cells [42]. TNF-α activates the inflammatory pathways mainly in keratinocytes and endothelial cells [43]. Thus, TNF-α blockers modify the nuclear factor-kappa B (NF-κB) pathway through a strong interaction with TNF-α receptors. The result of this interaction is maintaining the inactivity of the NF-κB dimer [44]. TNF influences the expression of intercellular adhesion molecule-1 (ICAM-1) in skin cells by stimulating the adhesion of circulating leukocytes and also stimulating the production of proinflammatory cytokines, such as IL-1 and IL-6 [43]. At present, Etanercept, Infliximab, and Adalimumab are available for the treatment of psoriasis [45]. Certolizumab is only recommended for adult patients with active psoriatic arthritis [46] (Table 1) [47–55].

Table 1 – ***TNF-α inhibitors in psoriasis***

Drug name/study reference	Approved indications	Mechanism of action	Dosage forms/routes of administration
Etanercept Nguyen & Koo (2009) [47] Michailidou *et al.* (2014) [48] Papp *et al.* (2007) [49]	*FDA*/*EMA* Plaque psoriasis Psoriatic arthritis Ankylosing spondylitis Rheumatoid arthritis Polyarticular juvenile idiopathic arthritis	▪ binds specifically to the cell surface of soluble TNF; ▪ blocks the interaction of TNF-*α* and TNF-*β* with their receptors; ▪ down-regulates the expression of E-selectin, ICAM-1 (adhesion molecules that are responsible for leukocyte migration); ▪ decreases serum levels of IL-1, IL-6, and matrix metalloproteinase.	Solution for parenteral administration or powder for solution for injection (subcutaneous)
Infliximab Netherlands Yearbook (1985) [50] ZYPREXA FDA (2009) [51] Gall & Kalb (2008) [52]	*FDA*/*EMA* Psoriasis Psoriatic arthritis Ankylosing spondylitis Ulcerative colitis Crohn's disease Rheumatoid arthritis	▪ binds both soluble and membrane-bound TNF-*α*; ▪ decreases epidermal T-cell infiltration; ▪ down-regulates angiopoietin and thus modulate angiogenesis; ▪ decreases keratinocyte differentiation.	Powder for concentrate for solution for infusion (intravenous use) Solution for parenteral administration (subcutaneous)
Adalimumab AMGEVITA EMA (2017) [53] HUMIRA FDA (2021) [54] Markus *et al.* (2019) [55]	*FDA*/*EMA* Psoriasis Psoriatic arthritis Axial spondyloarthritis Crohn's disease Ulcerative colitis *Hidradenitis suppurativa* Rheumatoid arthritis Juvenile idiopathic arthritis Uveitis	▪ binds both soluble and membrane-bound TNF-*α*; ▪ decreases inflammatory cytokines; ▪ blocks TNF-*α* signaling and inflammatory cascade.	Solution for parenteral administration (subcutaneous)

EMA: *European Medicines Agency*; FDA: *Food and Drug Administration*; ICAM-1: Intercellular adhesion molecule-1; IL: Interleukin; TNF: Tumor necrosis factor.

IL-17 is a key factor in the immunopathogenesis of psoriasis [31]. IL-17 is a family of cytokines involved in the chronic inflammation in psoriasis consisting of six different cytokines, among which IL-17A has the highest potency [32]. The most important sources for this proinflammatory cytokine are Th17 lymphocytes, *γδ*T lymphocytes, as well as MAIT cells, and ILC3s [33]. IL-17F is more than 50% homologous to IL-17A (55%) and has the same sources (Th17, *γδ*T cell, ILC3s). Although both IL-17A and IL-17F cytokines are more expressed in psoriatic plaque and the serum of psoriatic patients, IL-17F has a higher potency in inducing IL-6 and IL-8 in normal keratinocytes compared to IL-17A [34].

Currently, there are IL-17 inhibitors available for the treatment of moderate-severe plaque psoriasis: two monoclonal antibodies targeting IL-17A (Secukinumab, Ixekizumab), one targeting both IL-17A and IL-17F (Bimekizumab), and one against IL-17 receptors (Brodalumab) [31, 56] (Table 2) [48, 57–65]. The importance of a direct treatment target of specific cytokines involved in this pathology cannot be understated, leading not only to an important minimization of the adverse effects of immunosuppressive therapy but also to impressive improvements in HP lesions [66].

Table 2 – ***New generation biological agents in psoriasis (I)***

Drug name/study reference	Approved indications	Mechanism of action	Dosage forms/routes of administration
Secukinumab Deodhar *et al.* (2019) [57] Krueger *et al.* (2019) [58] Mercurio *et al.* (2020) [59]	*FDA*/*EMA* Plaque psoriasis Psoriatic arthritis Ankylosing spondylitis	▪ selectively inhibits IL-17A; ▪ influences the immune function of keratinocytes; ▪ inhibits the release of chemokines and antimicrobial peptides; ▪ decreases neutrophil accumulation and psoriasis inflammation.	Solution for parenteral administration or lyophilized powder for reconstitution (subcutaneous)
Ixekizumab Genovese *et al.* (2020) [60] Michailidou *et al.* (2019) [48] Craig & Warren (2020) [61]	*FDA* Plaque psoriasis Psoriatic arthritis Ankylosing spondylitis	▪ blocks the action of IL-17A, binding this cytokine with high affinity and specificity; ▪ decreases the activation and proliferation of keratinocytes	Solution for parenteral administration (subcutaneous)
Bimekizumab Oliveira *et al.* (2021) [62] Freitas & Torres (2021) [63]	*EMA* Plaque psoriasis	▪ inhibits both IL-17A and IL-17F.	Solution for parenteral administration (subcutaneous)
Brodalumab Rivera-Oyola *et al.* (2020) [64] Puig (2017) [65]	*FDA*/*EMA* Plaque psoriasis	▪ binds IL-17A receptor (has high affinity); ▪ locks the biological activities of IL-17 family cytokines (IL-17A, IL-17A/F, IL-17F, and IL-25).	Solution for parenteral administration (subcutaneous)

EMA: *European Medicines Agency*; FDA: *Food and Drug Administration*; IL: Interleukin.

The next step in psoriasis' pathophysiology pathway is the IL-23/Th17 axis, which has been identified as a major factor in the persistent chronic inflammation, characteristic of this pathology. IL-23 has modulatory effects on the maintenance of Th17 cells, and by this, in the constant production of IL-17. IL-23 is mainly produced by dendritic cells, monocytes, and macrophages (antigen-presenting cells) [67]. Like IL-17 inhibitors, IL-23 blockers are a very effective therapy for this autoimmune disease (Table 3) [35, 67–69].

Table 3 – ***New generation biological agents in psoriasis (II)***

Drug name/study reference	Approved indications	Mechanism of action	Dosage forms/routes of administration
Tildrakizumab Sakkas *et al.* (2019) [67]	Moderate-to-severe plaque psoriasis	▪ binds (with high affinity) to the p19 subunit of IL-23; ▪ inhibits IL-23 signaling.	Solution for parenteral administration (subcutaneous)
Guselkumab Tsukazaki & Kaito (2020) [35] Nogueira & Torres (2019) [68]	Moderate-to-severe plaque psoriasis Active psoriatic arthritis	▪ inhibits IL-23 specifically.	Solution for parenteral administration (subcutaneous)
Risankizumab Blair (2020) [69]	Moderate-to-severe plaque psoriasis	▪ selectively bind to the IL-23 p19 subunit; ▪ inhibits the interaction with the specific receptor; ▪ decreases expression of IL-17A, IL-17F, IL-21, and IL-22.	Solution for parenteral administration (subcutaneous)

IL: Interleukin.

The concentration of IL-12/IL-23p40 and IL-23p19 micro-ribonucleic acid (microRNA, miR) was observed to be higher in lesions compared to normal skin. Also, IL-17A, IL-17F, and IL-22, the cytokines induced by IL-12 and IL-23 are increased in lesions *vs.* non-lesioned skin.

IL-12 and IL-23 stimulate the activity of Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2) and activate the signal transducer and activator of transcription (STAT) family of transcription factors, IL-12 especially STAT4 and IL-23 STAT3 [70].

IL-23 is a proinflammatory cytokine produced by dendritic cells and activated macrophages. IL-23 is considered to produce negative effects through the production of inflammatory mediators, such as IL-17, IL-22, TNF-*α*, and thus pathological consequences occur [71]. The effect of IL-23 in psoriasis is considered to be the consequence of its effect on IL-17, an important cytokine with a role in the cascade of inflammation [72]. The most important biological therapies used nowadays in psoriasis, as well as their site of action, are presented in Table 4 [37, 73–76].

Table 4 – ***Biological therapies in psoriasis and their site of action***

Biological therapies/study reference: Trembath *et al.* (1997) [75]; Capon *et al.* (2002) [76]			
TNF-*α*	***Adalimumab*** (approved)	***Etanercept*** (approved)	***Infliximab*** (approved)
IL-12/ IL-23p40	***Ustekinumab*** (approved)	***Briakinumab*** (withdrew from market due to severe adverse effects)	–
IL-23p19	***Tildrakizumab*** (phase III)	***Risankizumab*** (phase II)	***Guselkumab*** (phase III)
IL-17A	***Secukinumab*** (approved)	***Ixekizumab*** (phase III)	***Brodalumab*** (unstudied)

IL: Interleukin; TNF-*α*: Tumor necrosis factor-alpha.

Genetic changes in psoriasis

Psoriasis' genetic background involves several genes, psoriasis susceptibility (*PSORS*)*1–7*, but according to literature human leukocyte antigen (*HLA*)-*Cw6* represents a highly important disease allele at *PSORS1* [77]. *PSORS1* is located in the major histocompatibility complex (MHC) region on chromosome 6p, and it is thought to play a major role in the immunopathological pathway of this disease [78–80]. The specific roles of this allele are not yet fully elucidated, but original studies targeting *HLA-Cw6* status showed implications in the severity of the disease, quicker onset, and most important, variations in terms of response to treatment [80].

One major pathological factor is represented by *HLA-Cw6*, which is considered to be highly associated with psoriasis susceptibility alleles. This review aims to state the possible connection between the level of *HLA-Cw6* and the response to different types of biological agents [74].

Burlando *et al.* stated that there might be a connection between the high expression of *HLA-Cw6* and a longer-lasting response to treatments targeting TNF-*α*, IL-17, and IL-12/IL-23. Therefore, *HLA-Cw6* could play the role of a predictor for the achievement and maintenance of clinical remission. Throughout their study, their main aim was the PASI score and patients' comorbidities. Thus, patients with a severe PASI score (more than 15) were treated with Secukinumab or Ixekinumab, biological agents targeting IL-17, while younger patients or patients who due to traveling were unable to follow treatments involving more frequent doses were given Ustekinumab, targeting IL-12/ IL-23. Last but not least, patients with a moderate PASI score were treated with anti-TNF-*α* agents, such as Adalimumab, Etanercept, Infliximab). The response to treatment showed yet no link between the base level of *HLA-Cw6* and the maintenance of PASI90 after being reached at week 16, which suggested that *HLA-Cw6* status could not be considered an "overall prognostic factor" [74]. On the other hand, when taken into consideration separately, drugs targeting IL-12/IL-23 and IL-17 showed a better response in those with an *HLA-Cw6* positive (POS) status, while drugs targeting TNF-*α* were opposingly showing more efficiency on those with an *HLA-Cw6* negative (NEG) status [81, 82]. Costanzo *et al.* state that the efficiency of Secukinumab on patients with psoriasis is independent of *HLA-Cw6* status. These findings are yet contrary to other studies which suggest a link between *HLA-Cw6* and the response to other biological agents, such as Adalimumab and Ustekinumab [80]. For their study, the response to treatment assessed by the PASI90 score reached on week 16 was similar in POS and NEG groups [74, 81]. Similar results at week 16 were found by Burlando *et al.* who did not find any difference between POS and NEG groups [74]. On the other hand, after evaluating the rate of maintenance for PASI90 at week 48, showed a higher rate of response for those in the POS group, so as opposed to no relationship between treatment response and IL-17 treatment, drugs targeting IL-23/IL-12 and TNF-*α* pathways might have a better long-lasting response for patients with an *HLA-Cw6* POS status. On the other hand, though, Gallo *et al.* found a worse response to treatment for drugs targeting TNF-*α* pathway on *HLA-Cw6* POS groups only for PASI75 [73].

Dand *et al.* have conducted a study a longitudinal study based on data from 1326 patients which concluded that *HLA-Cw6* is a predictive biomarker on the response of

biological therapies with Adalimumab and Ustekinumab. Moreover, the state that patients with *HLA-Cw6* NEG are more likely to respond to Adalimumab than to Ustekinumab. Furthermore, patients with *HLA-Cw6* POS are more likely to have inactive psoriasis, and thus could be treated in the long term with Ustekinumab, which also has the advantage of longer doses intervals. One important aspect suggested by their study is that *HLA-Cw6* status only interacts with the biological drug, and not with the biological native status, and so the different rate of response between Adalimumab and Ustekinumab could be explained [73].

Another possible role of *HLA-Cw6* status is the link to certain clinical forms of psoriasis. Thus, Mallon *et al.* found a direct implication of *HLA-Cw6* POS status and the development of guttae psoriasis. This clinical form of psoriasis is usually diagnosed in young adults and is developed consequently to a streptococci infection. In most cases, the streptococcal infection is hard to be proven due to prior antibiotic therapies. Their findings show a 100% carriage of *HLA-Cw6* allele in patients diagnosed with guttate psoriasis, compared to only 20% in the healthy group. It is not yet understood the functional role of HLA-C in psoriasis, but there is most certainly a consensus regarding its implications in the progression and outcome of the disease [83] (Table 5).

Table 5 – *Link between HLA-Cw6 status and response to biological treatment according to literature*

Study reference	*HLA-Cw6* POS	*HLA-Cw6* NEG
Dand *et al.* (2019) [73]	▪ more likely to develop unactive psoriasis; ▪ no advantage was found on using Adalimumab over Ustekinumab.	▪ more likely to respond to Adalimumab than to Ustekinumab; ▪ 46.6% of patients with NEG status have severe psoriasis.
	▪ selecting the treatment based on *HLA-Cw6* status could improve the response to treatment, reaching PASI90 in the first 12 months for over 30% of the patients; ▪ stratifying patients over HLA status, rather than aged (psoriasis type I/II) could be a more useful approach for a better treatment response.	
Costanzo *et al.* (2018) [81]	▪ response to Secukinumab showed no link to the *HLA-Cw6* status, as POS and NEG groups reached PASI90 at week 16 on close percentages.	
Burlando *et al.* (2020) [74]	▪ similar response for reaching PASI90 at week 16 on *HLA-Cw6* POS and NEG groups.	
	▪ higher rate of PASI90 maintenance at week 48.	
Gallo *et al.* (2013) [84]	▪ worse response for *HLA-Cw6* at PASI75 for Adalimumab and Etanercept.	

HLA: Human leukocyte antigen; NEG: Negative; PASI: Psoriasis Area and Severity Index; POS: Positive.

Molecular lesions in psoriasis and future alternative therapies

Another high interest point in literature is the study of molecular mechanisms triggered by microRNAs. In psoriasis, one of the most discussed genes is miR-210. It is believed that once a patient genetically predisposed to psoriasis is exposed to environmental factors, activated dendritic cells stimulate the production of IL-23, IL-6, as well as IL-12, and TNF-α. The previously mentioned ILs will consecutively activate autoregressive Th1, Th17, Th22 cells, which will finally result in producing proinflammatory cytokines that will in the end amplify the immune response in psoriasis [85]. MicroRNAs are non-coding RNA molecules that have the role of negatively regulating gene expression at the post-transcriptional level [86]. There are several microRNAs that are considered to be of interest regarding psoriasis patients. Wu *et al.* have studied the importance of miR-210 overexpression over the inflammatory pathways triggered in psoriasis, moreover, they also stated a link between increased levels of inflammatory cytokines, such as IL-23, and the overexpression of miR-210 in cluster of differentiation (CD)4+ T-cells in patients with active psoriasis lesions and higher severity index (PASI score). These findings alongside all studies regarding microRNAs in psoriasis are of vital importance in the future development of targets treatments. As such, intradermal injections of miR-210 inhibitor could be a viable alternative to biological treatments especially for patients with a poor answer or severe adverse effects. Another important finding of their study was that miR-210 might have an affinity to upregulate Th1 and Th17 *in vivo* cell differentiation and at the same time downregulate the differentiation of Th2. This pathological pathway triggered by miR-210 led to an increase in the severity of psoriasis lesions proving that the higher the expression of miR-210, the higher the severity scores. Furthermore, the most important outcome of their study showed that suppressing miR-210 leads to an improvement of skin lesions in psoriasis [85].

Some numerous other microRNAs are somehow linked to the pathophysiology of psoriasis lesions. Another recent study conducted by Tang *et al.* showed that downregulation of miR-187 is related to the activity of the disease. Moreover, they proved that stimulating the expression of miR-187 can improve the outcome of the disease by inhibiting the proliferation of IL-6 stimulated keratinocytes, which led to a decrease in the epidermal hyperplasia in a mouse model. The pathway behind this important discovery is the inhibition of CD276 by miR-187. CD276 is an immunoregulatory protein, with yet unknown implications in the hyper-proliferation of keratinocytes in psoriasis skin. To assess the possibility of a future treatment targeting miR-187, they administrated miR-187 agomir to mouses with induced psoriasis lesions. The outcomes showed a decrease in the epidermal thickening. Also, the decrease of acanthosis after HP analysis proved a good response to the experimental treatment. Dermal cell infiltration showed no modification consecutive to this treatment, however. Another important marker for cell proliferation is the expression ok Ki67, which was considerably decreased after miR-187 agomir was administrated [87].

Bian *et al.* studied the importance of decreased levels of miR-340 in patients with active psoriasis. They also used mice with Imiquimod (IMQ)-induced psoriasis that presented in the first place with low levels of miR-340. Consecutive, they administrated miR-340 agomir and which led to a decrease in the epidermal thickening similar to the results after miR-187 agomir was administrated. They also proved that experimental treatment with miR-340 agomir leads to an important downregulation of the expression of IL-17A, and thus limits the local inflammation [88].

Another important aspect that must be evaluated regarding pharmacogenetic profile for patients diagnosed with psoriasis is whether the levels of microRNAs vary after therapies. A study conducted by Wipasiri *et al.* in 2020 investigates the downregulation of miR-155 in patients with symptomatic psoriasis (PASI score over 10) before and after being treated with Methotrexate and narrow-band ultraviolet B (UVB). They compared levels of miR-155, miR-135b, as well as miR-125b in normal skin, as well as in skin affected by psoriasis. The most relevant increase was for the levels of miR-155 before the beginning of the therapy. miR-155 is responsible according to them for inhibiting apoptosis of keratinocytes in psoriasis skin, as well as for increasing cell viability in the same conditions, leading to the abnormal keratinocytic proliferation that characterizes skin affected by psoriasis. They concluded that after patients were treated with Methotrexate and narrow-band UVB levels of miR-155 were importantly diminished [89]. This can easily explain the rapid clinical response after immunosuppressive therapy is started, due to Methotrexate's capacity to increase keratinocyte apoptosis by stimulating apoptosis markers, such as caspase-3 and caspase-9 [90].

Even though studies are yet at an incipient level, it is clear that there is a strong connection between the expression of certain microRNAs and the development of psoriasis lesions. Future studies must be carried out to be able to find alternative directed treatments especially for patients with a poor response to biological agents, which are considered nowadays the last resort therapy (Table 6).

Table 6 – ***Possible future treatments based on microRNAs***

MicroRNA/study reference	Up/down regulation in psoriasis	Physiopathological implications	Future implications
miR-210 Wu *et al.* (2018) [85]	Up	▪ increased IL-23; ▪ upregulation of Th1 and Th17 *in vivo*.	Possible intradermal injections with miR-210 inhibitor as adjuvant therapies?
miR-187 Tang *et al.* (2019) [87]	Down	▪ increased proliferation of IL-6 stimulated keratinocytes; ▪ epidermal thickening.	Decrease in epidermal thickening after intradermal injection with miR-187 agomir.
miR-340 Bian *et al.* (2018) [88]	Down	▪ increased levels of IL-17A.	Decrease in epidermal thickening after intradermal injection with miR-340 agomir.
miR-155 Soonthornchai *et al.* (2021) [89]	Up	▪ inhibition of keratinocyte apoptosis in psoriasis.	Narrow-band UVB can lower level of miR-155 and thus decrease epidermal thickening.
miR-369-3p Hou *et al.* (2016) [91]	Up	▪ correlated to the disease's severity (PASI).	Possible intradermal administration of miR-369-3p inhibitor.
miR-205 An *et al.* (2017) [92]	Down	▪ linked to epidermal thickening in psoriasis similar to the development of keloid lesion due to VEGF production.	Upregulation of miR-205 can improve epidermal thickening, as well as keloid lesions.

IL: Interleukin; miR: Micro-ribonucleic acid (RNA); PASI: Psoriasis Area and Severity Index; Th: T-helper; UVB: Ultraviolet B; VEGF: Vascular endothelial growth factor.

Conclusions

Psoriasis is an autoimmune disease with a complex pathogenetic background. Mainly, psoriasis represents a clinical diagnostic, due to the clinical specific aspects. The HP examination is mandatory to be performed any time the clinical aspects or response to therapy is uncommon. MicroRNAs are considered the starting point to any HP pathway behind all autoimmune diseases and seem to be the answer to our problem. Studying certain microRNA involved in the inflammatory pathway in psoriasis can find direct targets to future treatments that can even be more specific than actual biological therapies. Data in the literature shows that intradermal injection of either agomirs or antagomirs directed to specific microRNAs can dramatically improve the morphopathology of psoriasis affected skin. These possible future treatments can play a major role not necessarily by replacing actual biological treatments, but most probably by potentiating their beneficial effects. The most important breakthrough in modern pharmacology is to personalize the treatment to every patient. Individually treating each patient is thought to enhance the desired effect of the therapy, as well as to decrease to a minimum possible the incidence of adverse effects. Furthermore, being able to link the response to treatment to the genetic status of the patient, can improve the outcomes of therapy.

Conflict of interests

The authors declare that they have no conflict of interest.

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