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Psoriasis: A Comprehensive Review on the Aetiopathogenesis and Recent Advances in Long-Term Management of Patients with Plaque Psoriasis

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Abstract

Immense changes have been introduced in psoriasis treatment, including successful systemic treatment of inflammation and education of psoriatic patients. The focus of this review is the latest developments in the understanding of the aetiopathogenesis of psoriasis, the significance of its comorbidities, treatment possibilities and long-term management using the latest insight provided by pharmacogenetics and identification of biomarkers. The successful control of the disease leads to reduction of myocardial infarction and long-term cardiovascular risk but is usually achieved after various therapeutic attempts until the best-matched treatment for the individual is identified. There is a high unmet medical need for revealing biomarkers associated with disease prognosis, comorbidities, response to therapy and adverse effects. More studies have to be performed for identification and validation of biomarkers and implementation of personalized medicine into clinical practice.

Keywords

Biologicals, Psoriasis, Pharmacotherapy, Dermatology

1. Introduction

Understanding the basic mechanisms which lead to disease and using that knowledge to develop appropriate medication—which is safe, effective and leads to

stable outcomes or cure—have always been the two primary goals in the history of medicine.

The latest scientific advances have led to new pathogenesis conceptions of psoriasis and long-term management approaches. For many years psoriasis was perceived as a cosmetic nuisance. A common inflammatory pathology coexists between psoriasis and many chronic inflammatory diseases including psoriatic arthritis, cardiovascular disorders, metabolic syndrome, diabetes mellitus and others. This suggests that severe psoriasis is a chronic systemic inflammatory disorder, which may cause a state of insulin resistance, consequent endothelial cell dysfunction and atherosclerosis, and may lead to myocardial infarction or stroke [1] [2] [3]. Data demonstrate a 50% increased risk of mortality in patients with severe psoriasis compared with the general population and/or patients with mild psoriasis [4] [5]. A broader and more systematic approach in management of psoriatic patients with earlier introduction of more aggressive systemic therapy in patients at higher risk is required to lower systemic inflammation and long-term cardiovascular/mortality risk. However, introduction of systemic therapy can be associated with severe side effects including risk of infections. Using biomarkers for the non-invasive prediction of disease prognosis (including onset of comorbidities, response to therapy, dosing and/or appearance of toxic side effects) to a given therapy would be a major step toward a personalized approach in the management of psoriasis and its comorbidities—*i.e.* optimisation of the treatment and management of connected risks.

This review is an overview of the current understanding of the etiopathogenesis of psoriasis, the significance of its comorbidities, treatment possibilities and long-term management using the latest insights provided by pharmacogenetics and identification of biomarkers.

2. Disease Burden, Epidemiology and Etiopathogenesis

Psoriasis is a chronic inflammatory, immune-mediated skin disease with a complex aetiology affecting 2% to 3% of adults. Prevalence rates of psoriasis have a worldwide geographic variation, reflecting influence of both genetic and environmental factors. The results of a systematic review also confirmed that psoriasis is less common in children. Gender prevalence of psoriasis is inconclusive [6] [7] [8] [9].

Psoriasis manifests as inflammatory lesions on either the skin and/or joints, and it has a major impact on the quality of life. Wide disease spectrum is caused by the complex interaction of genetic, environmental and immunological factors. Clinically, psoriasis is highly variable with respect to lesional characteristics (*i.e.* morphology, distribution), the severity and course of disease and the presence of associated diseases. The typical presentation of psoriasis on the skin is a sharply demarcated erythrosquamous plaque which appears infiltrated and reddened and sometimes also contains silvery scales, which are a sign of hyperparakeratosis. The psoriatic plaque is itchy in approximately two-thirds of patients,

approximately a quarter of patients report that their skin hurts, lesions bleed and/or are bothered by water (Table 1). It was estimated that less than 10% of patients never experience irritated skin, and slightly more (12.3%) never experience burning or stinging. Symptoms are more severe in women and they tend to increase in severity with the increasing clinical severity of psoriasis [10]. The lesions are often distributed symmetrically on the elbows, knees, other parts of the legs, scalp, lower back, face, palms, soles of the feet and in body folds. However, they can also be found in other places such as fingernails, toenails, genitals, and even inside the mouth [11]. Psoriasis may present as chronic, stable plaques or may present acutely, with a rapid progression and widespread involvement. It can result in a generalised exfoliative erythroderma if it is progressive or uncontrolled, but it may also develop at the site of trauma or injury, which is known as Koebner's phenomenon [7] [10] [11] [12]. In 2005 the International Psoriasis Council (IPC) proposed a simplified classification of plaque psoriasis based on clinical phenotypes. The most common type, which affects 80% to 90% of patients, is classic psoriasis, also called plaque psoriasis or *psoriasis vulgaris* (this is what is usually referred to by the term "psoriasis"). Other less common types are guttate, pustular and erythrodermic psoriasis. They are further subtyped based on distribution, anatomical localization, size and thickness of plaques, onset and disease activity: for example inverse, palmo-plantar, drug-associated psoriasis, etc. [10] [13] [14]. Onset of the disease may occur at any age. A bimodal age of onset has been recognised in several large studies: Type I is characterised by onset before the age of 40 years, with a peak age of onset for first presentation at 15 to 20 years of age (*i.e.* early onset) and Type II presenting after the age of 40 years with a distinct peak at 55 - 60 years (*i.e.* late onset). Type I psoriasis, which accounts for more than 75% of cases, is correlated with more severe disease states and with fewer concurrent infectious diseases. Patients with type I have more affected first-degree relatives. Type I psoriasis is strongly associated with human leucocyte antigen (HLA)-Cw6 [15] [16].

3. Pathogenesis

The main histopathological features of psoriasis are epidermal thickening (acanthosis), incomplete terminal keratinocyte differentiation with retention of the

Table 1. Classification of psoriasis and clinical symptoms [7] [17].

Phenotype	Subtype	Patient reported symptoms (% overall)*	Onset
Plaque Guttate Pustular Erythrodermic	Inverse Palmo-plantar Psoriatic nail disease Psoriatic arthropathy Drug-associated Koebnerized psoriasis	Hurts (26.0) Burns/stings (46.1) Itches (63.8) Water bothers (23.9) Irritated (59.7) Sensitive (39.0) Bleeds (25.4)	Type I: before 40 (peak 15 - 20 y) Type II: after 40 (peak 55 - 60 y)

*The prevalence of symptoms is higher in women and tends to increase with clinical severity.

nucleus by corneocytes (parakeratosis), elongation of the rete ridges extending downward between dermal papillae (papilomatosis), blood vessel dilation and immune cell infiltration in the skin. Neutrophils accumulate into parakeratotic scales, lymphocytes (mainly CD8+ T cells) are interspersed between keratinocytes and T cells (mainly CD4+) and dendritic cells (DC) are heavily infiltrated in the dermis (**Figure 1(c)**) [18].

A variety of cells and mediators of both the innate and adaptive immune systems are involved in the pathogenesis of psoriasis. Their involvement changes as the disease progresses. The immune pathways that are activated by psoriasis are the same as the immune circuits in normal skin although their activity is greatly amplified. In the initiation phase injured or stressed keratinocytes release antimicrobial peptide (AMP) cathelicidin LL-37. LL-37 is an important effector molecule of innate immunity in the skin with broad antimicrobial activity. It is synthesized by epithelial cells but is also provided by infiltrating immune cells which transport LL-37 to infected or wounded skin. In healthy skin keratinocytes cathelicidin expression is barely detected. LL-37 was recognised as a critical factor for the activation of the auto-inflammatory cascade implicated in psoriasis: it increases cytokine and chemokine liberation from local cells and leucocytes, has a chemotactic effect on a large number of immune cells, enhances the proliferation of endothelial cells and influences angiogenesis [19]. In psoriatic skin the innate tolerance to self-DNA is attenuated. Formation of condensed aggregated structures of LL-37 with DNA/RNA, released by stressed or dying skin cells, converts otherwise non-stimulatory self-nucleic acids into a potent trigger of plasmocytoid dendritic cells (pDCs) via toll-like receptor (TLR) to produce INF-α that initiates innate and adaptive immunity responses [20] [21]. Keratinocyte-derived IL-1β, IL-6, TNF-α and self-nuclear acid-LL37 complexes can activate dendritic cells (DCs) to promote the activation and proliferation of skin-resident and newly recruited T cells, forming Th1, Th17, Th22 and producing IL-23, TNF-α and nitric oxide radicals (NO) (**Figure 1(b)**).

It is generally accepted that chronic psoriatic disease state occurs when mature dermal DCs and inflammatory myeloid DCs produce cytokines such as IL-23 and IL-12. IL-23 stimulates T17 (Th17 and Tc17) to release IL-17A, IL-17F, IL-22 and IFN-γ which further act on keratinocytes to promote production of T cells, neutrophil-attracting chemokines and AMPs, amplifying psoriatic inflammation. Chemokines favour the recruitment of more Th17 cells, while IL-22 impairs keratinocyte terminal differentiation and induces epidermal hyperplasia, while IFN-γ further activates dermal DCs to produce cytokines (**Figure 1(c)**) [13] [22]. Studies have also identified an over expression of IL-9 receptors in psoriatic skin lesions together with increased IL-9 producing Th9 cells. Although their pathogenic relevance is yet to be confirmed, the presence of these cells in psoriatic skin lesions and their ability to enhance proliferation and the production of inflammatory cytokines from other T cells suggest that they have a role in initiating and maintaining cutaneous inflammation. Th9 cells are preferentially skin-tropic

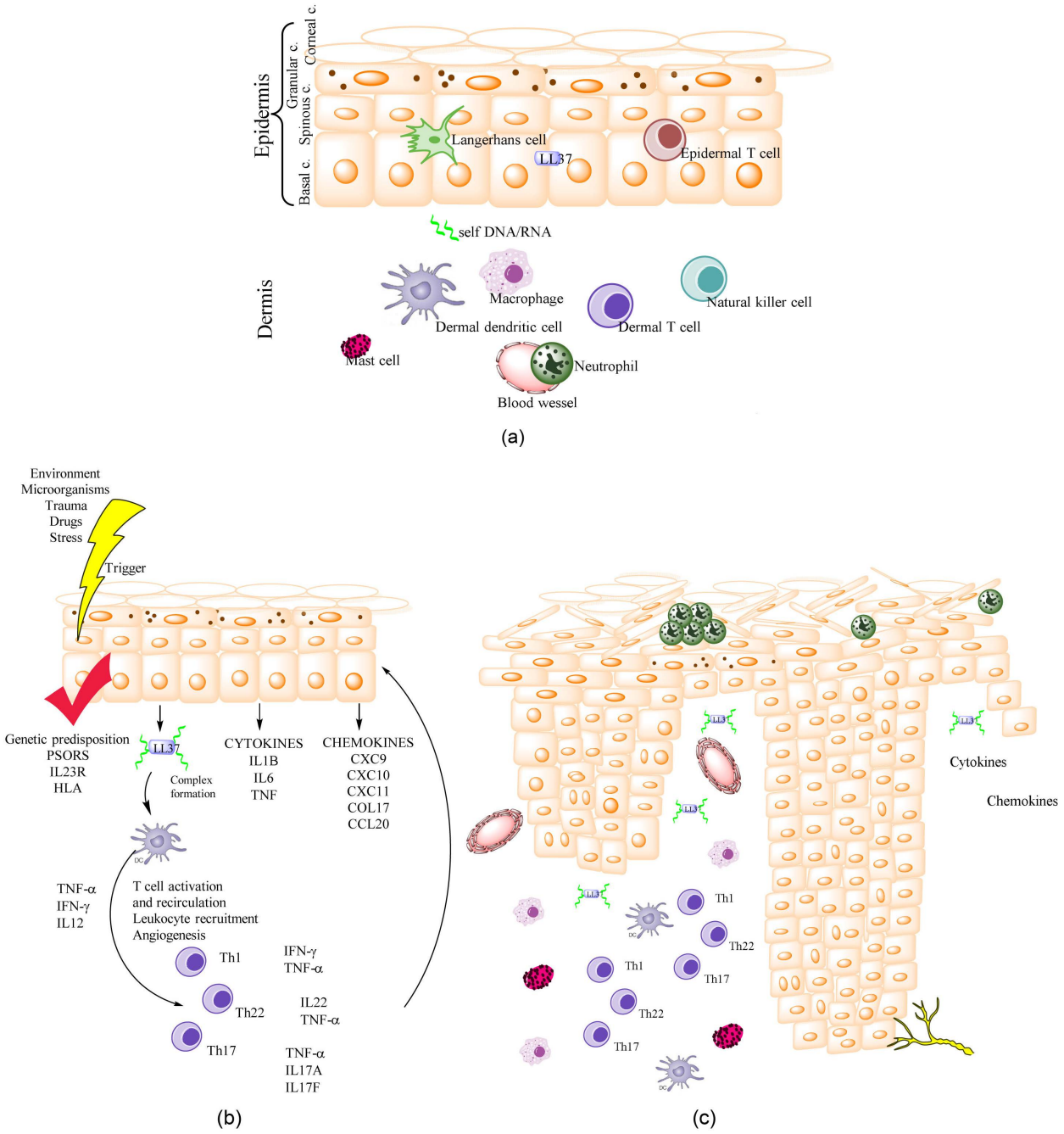

Figure 1. Immunopathogenesis of psoriasis. (a) Healthy skin. The epidermis is an initial site of host immune responses and defence mechanisms against environmental and pathogenic insults. It is composed of proliferating basal and differentiated keratinocytes (e.g. spinous, granular and corneal layers). The nucleus is lost as granular keratinocytes transition to corneacytes. The epidermis contains Langerhans cells and antimicrobial peptides which act as the body's major barrier against pathogens. (b) External triggers in heathy skin with genetic predisposition for psoriasis activate the immune pathways. Formation of self DNA/RNA complex with LL-37 and release of cytokines and chemokines activate dendritic cells. Secreted pro-inflammatory mediators and cytokines induce naive T cells to differentiate into effector T cells (Th17, Th1, Th22) which further release cytokines and pro-inflammatory mediators. These mediators act on keratinocytes leading to their activation, proliferation and production of AMPs, chemokines and cytokines. (c) The final result of this cross-talk of innate and adaptive immune response is psoriatic lesion with epidermal hyperplasia and thickening with impaired terminal keratinocyte differentiation and hyper-parakeratosis, infiltration of neutrophils in epidermis, elongation of the rete ridges, blood vessel dilatation, recruitment, activation and infiltration of immune cells in the skin, and activation of cutaneous nerves.

or skin-resident and are present in both healthy and diseased human skin. It was proposed that IL-9 may play a role in the development of psoriatic lesions through Th17-associated inflammation and angiogenesis [23] [24] [25].

4. Comorbidities

Occurrence of psoriasis is characterized by numerous relapses and remissions, with the manifestations not limited to the skin. The visible symptoms of disease can stigmatize patients, causing heavy psychological burden. Psoriatic patients commonly suffer from accompanying conditions such as psoriatic arthritis, the prevalence among patients with psoriasis ranges from 6% to 39% [26]. Several observational studies have also demonstrated the association of psoriasis with increased risk of other diseases including cardiovascular disease, metabolic syndrome, obesity, cancer, chronic obstructive pulmonary disease, depression, osteoporosis, Crohn's disease, uveitis and liver disease, all of which shorten the life expectancy of psoriatic patients [27] [28] [29] [30]. Data demonstrate that patients with severe psoriasis have a 50% increased risk of mortality, whereas patients with milder psoriasis have no overall increased risk [27] [31] [32]. The direct link between psoriasis and many of the possibly associated diseases is the presence of chronic inflammation and, in particular, elevated levels of the multifunctional cytokine tumour necrosis factor-α (TNF-α). The increase of inflammatory burden brought by psoriasis causes a state of insulin resistance, resulting in endothelial cell dysfunction and atherosclerosis. At the level of coronary, carotid or cerebral arteries, this cascade causes myocardial infarction or stroke (so called "psoriatic march") [1]. Although obesity occurs twice as often in patients with psoriasis as in control patients without psoriasis across all age groups, it does not appear to be one of the factors known to trigger the onset of disease. There is a positive correlation between obesity (*i.e.* Body Mass Index—BMI) and severity of psoriasis. Patients with psoriasis are more likely to be obese than non-psoriatic controls. Studies suggest that psoriasis may improve after weight-loss surgery, and also provide some preliminary evidence that weight-loss surgery may reduce the need for medical therapy for psoriasis [32] [33] [34] [35]. The aetiology of this strong association between obesity and psoriasis is not understood. For a long time it was believed that psoriasis had a casual effect on obesity due to the profound changes on an individual's physical, social, and mental well-being. Obesity may nevertheless be biochemically linked to psoriasis by a common underlying pathophysiology, both psoriasis and obesity being chronic inflammatory states. Human adipose tissue as an active endocrine organ which produces and releases many cytokines such as TNF-α and IL-6, chemokines like IL-8, monocyte chemoattractant protein (MCP-1), and bioactive proteins, such as adipokines (e.g. adiponectin and leptin) may contribute to the development of metabolic changes, endothelial dysfunction, and atherosclerosis by promoting activation of T cells and monocytes, driving both Th1 and Th17 immune responses and at the same time impairing the function of regulatory T cells [32]

[36]. Obesity may, thus, potentiate the inflammation of psoriasis while at the same time facilitating the development of metabolic syndrome [36]. Both psoriasis and obesity independently confer cardiovascular risk and when present in the same patient may augment mortality risk [22]. Weight loss in obese patients has been correlated with decreases in serum concentrations of inflammatory mediators, including TNF-*α*, IL-6, CRP, fibrinogen, and markers of endothelial dysfunction, and with a concomitant increase in adiponectin and IL-10, which exert anti-inflammatory and insulin-sensitizing effects [35].

5. Psoriasis Severity Measures and Goals of Treatment

Psoriasis is usually diagnosed by clinical assessment; histological confirmation is needed only in rare cases. Severity of the skin lesions and their impact on the quality of patient's life is assessed by indexes developed to help guide treatment decisions and to assess the outcomes and the chance of successful treatment. The most widely used measures for assessing severity of plaque psoriasis are the Body Surface Area (BSA), the Physician's Global Assessment (PGA), the Psoriasis Area and Severity Score (PASI) and the Dermatology Life Quality Index (DLQI). The PASI index uses surface area in addition to an assessment of the extent of inflammation, induration and scaling. The DLQI is a superior and widely accepted measure of severity when the patients' quality of life is significantly impaired due to the involvement of visible areas, major parts of the scalp, genitals, palms and/or soles, onycholysis or onychodystrophy and/or pruritus leading to excoriation [37].

Despite the utility of generalized scoring, the assessment of psoriasis by empirical measures can be inadequate: only a skillful and attentive clinical assessment can determine that an individual's disease has gone "completely beyond their control" in ways significant to the individual. For example, itching (pruritus is the most bothersome and commonly reported symptom) is not captured in any of the assessment tools. This suggests that patient's and physician's assessments of the impact of the symptoms of psoriasis may differ [38]. In 2011, a European consensus statement on severity of psoriasis and definition of treatment goals in moderate to severe psoriasis was accepted. Mild psoriasis was defined as a condition meeting all of the following criteria: PASI ≤ 10, BSA ≤ 10% and DLQI ≤ 10. Moderate to severe plaque psoriasis was defined as condition meeting the following two criteria: PASI >10 or BSA 10%, and DLQI >10. Special clinical situations may change mild psoriasis to moderate to severe, e.g. involvement of visible areas, major parts of the scalp, genitals or palms and/or soles, severe nail involvement, pruritus leading to scratching and the presence of single recalcitrant plaques [39] [40].

In 2020 the International Psoriasis Council (IPC) proposed a patient centred recategorization of psoriasis severity assessment. Based on the results of a modified Delphi study approach, categorization of mild, moderate and severe psoriasis classification should be omitted and replaced by classification as either can-

didates for topical therapy or candidates for systemic treatment. The basis for the suggested categorization is >10% BSA as severity criterion which is further supplemented with a justification which includes involvement of special areas (scalp, genitals, palms, soles, or nails; involvement of visible areas; recalcitrant plaques) and failure of topical therapy as criteria for more severe disease. This approach aims to reduce miss-categorization and subsequent undertreatment of psoriasis [41].

Casual relationships between systemic comorbidities and common inflammatory denominator with psoriasis were confirmed many years ago, yet their severity is not routinely assessed by dermatologists. To achieve efficacious treatment through the control of clinical symptoms and comorbidities, thereby increasing quality of life, definition of the treatment goals is essential. Before initiation of treatment the severity of the disease should be graded and categorized as either candidates for topical or systemic therapy (**Table 2**). It is important that this division is not changed afterwards by the response to the treatment because, in the majority of patients, termination of the treatment will result in relapse or recurrence. In some patients discontinuation of treatment may also result in deterioration beyond the baseline severity, an effect known as rebound [40].

According to the European consensus statement on psoriasis treatment, the treatment goal is to reduce cutaneous signs and symptoms by at least 75% as measured by the PASI score (so called PASI75), and to guarantee a good quality of life, as measured by a DLQI score of 5 or less. With ability of the new therapeutic options in the last few years, expectations regarding treatment goals also increased, with the ultimate goal of therapy now being the complete or almost complete clearing of skin lesions which correlates with an at least 90% improvement—so called PASI90 [42]. Treatment failure or inadequate response to therapy is defined by the consensus statement as the failure to achieve an improvement in PASI score of 50%—*i.e.* PASI50. When in the range between PASI50 and PASI75, the decision whether or not the treatment goals have been met depends on the measure of quality of life—the dermatology life quality index (DLQI) [40] [43].

The greatest benefit of the classification of psoriasis into either mild or moderate to severe and the establishment of clear treatment goals is the ability to take timely and appropriate corrective action in response to the failure of a specific systemic therapy [40]. The first corrective action when the treatment goal has not been reached is usually adding topical therapy and/or dose adjustment—*i.e.* increasing the dose or, if feasible, shortening of dosing intervals. If this fails, the second corrective action is to introduce combination of systemic therapy, which also reduces the concern of accumulating monotherapy toxicity. A carefully prescribed combination therapy that takes into account differences in pharmacodynamics, pharmacokinetics, and the associated toxicities of different individual systemic therapies may lead to greater efficacy while minimizing toxicity [44]. Combination therapy should consist of phototherapy with either conventional

Table 2. Treatment algorithm and treatment goals for psoriasis vulgaris [40].

Candidate for topical treatment (mild plaque psoriasis)	If BSA ≤10% and PASI ≤10 and DLQI ≤10 Treat with topical therapy Determine response		
	If Psoriasis remains mild continue treatment regimen	If condition worsens treat as for moderate/severe psoriasis	
Candidate for systemic treatment (moderate to severe plaque psoriasis)	If BSA >10% or PASI >10 or PASI ≤10 and DLQI >10 Initiate systemic (non-biologic) therapy and/or phototherapy Determine response (measured by percentage change in PASI score)*		
	Good = ΔPASI ≥75 and DLQI ≤5 Continue treatment regimen	Partial = ΔPASI ≥50 <75 and DLQI ≤5, continue treatment regimen and DLQI >5, modify treatment regimen	Failed = ΔPASI ≤50 Modify treatment regimen
	If the patient failed the treatment or has a contraindication or intolerance to conventional systemic therapy Initiate biologic therapy Determine response (measured by percentage change in PASI score)*		
	Good = ΔPASI ≥75 and DLQI ≤5 Continue treatment regimen	Partial = ΔPASI ≥50 <75 and DLQI ≤5, continue treatment regimen and DLQI >5, modify treatment regimen	Failed = ΔPASI ≤50 Modify treatment regimen
	Modification strategies: • Increase the dose • Shorten intervals between doses • Add a topical • Add another systemic • Change the drug		

*Assessment should be performed at the end of the induction phase of therapy. This is the point when the optimal clinical response of a given drug can be expected *i.e.* after 16 - 24 weeks. Δ = in comparison to baseline.

systemic therapy or biologic or combination of biologic and conventional systemic therapy, starting with the conventional therapy at the lowest recommended dosage (e.g. 5 - 10 mg/week for methotrexate). If neither corrective action, *i.e.* dose adjustment by increasing the dose or decreasing of dosing intervals or combination therapy, gives an adequate response or achieves treatment goals, switching to another biological should be considered as the last option (Table 2).

6. Management and Prevention

The historically narrow view of health care as an effort to reduce symptom severity or reverse disease progression has given way to a more comprehensive view that effective treatment should be patient-centred and focus on improving

the patient's functional level and overall well-being [7] [11] [41] [45] [46].

Comprehensive management of psoriasis includes early detection and appropriate management of comorbidities, including psoriatic arthritis, cardiovascular diseases, and depression. The significant reduction in quality of life, the psychosocial disability and consequently reduced work efficiency of psoriatic patients underline the need for prompt, effective treatment, long-term disease control, psychical and emotional support and patient counselling by means of standardized modular training containing relevant information on disease management and advice on a healthy lifestyle [42] [47] [48]. Diseases associated with psoriasis can affect processes involved in absorption, distribution and elimination of drugs: alcoholism impairs liver function, obesity affects drug distribution, diabetes can impair kidney function, Crohn's disease can reduce absorption from the gastrointestinal tract, smoking can impact the efficacy of some drugs etc. It is thus important for dermatologists to be aware of the likelihood of concomitant comorbid conditions and the possible impact of their associated inflammatory conditions. Physicians from other specialities should also be aware of the potential impact of their management strategies on psoriasis and the possible exacerbation of psoriasis by treatments prescribed for other conditions [49].

Many of the comorbidities of psoriasis have similar inflammatory and pathogenic mechanisms which involve cytokine dysregulation. Because of this, drugs targeting inflammation and/or suppressing the immune response are often used to treat psoriasis and related comorbidities: it seems that controlling psoriasis with aggressive systemic therapy, thus lowering inflammation, also reduces the incidence of myocardial infarction (MI) and long-term cardiovascular risk (**Figure 2**). Literature data suggest a statistically significant reduction in MI risk in patients treated with biologic therapy, and oral agents and/or phototherapy compared with patients treated with topical agents [29] [50] [51] [52]. Since most of this evidence is observational and based on patients with rheumatoid arthritis, further research is necessary to better delineate the effect of these systemic medications on cardiovascular events and other comorbid conditions

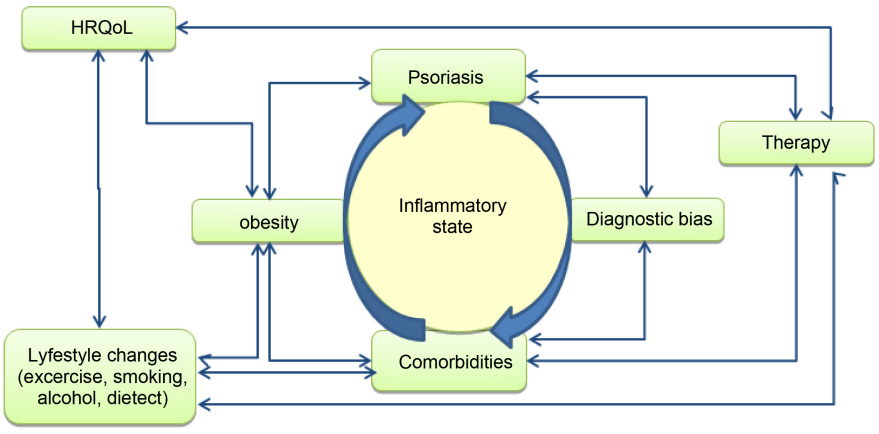

Figure 2. Schematic overview of possible factors influencing the association between inflammation, psoriasis, comorbidities and therapy. HRQoL, health-related quality of life.

in patients with psoriasis [50] [53].

Despite the availability of a number of treatment options, surveys have shown that patients with psoriasis are not managed optimally to clear their skin symptoms, to control the risk of major medical comorbid diseases and to improve their health-related quality of life (HRQoL): patients are frequently prescribed with an ineffective treatment for too long, while a large proportion of patients with psoriasis do not receive any treatment at all [29] [38] [39] [40] [50] [54]. Epidemiological studies conducted in Germany and elsewhere, as well as patient surveys in Europe and the United States, have indicated that mean disease activity in patients with psoriasis is high and quality of life is low, even among those patients who are seen regularly by dermatologists. Only about half of psoriatic patients indicated that they had seen a physician in the previous 12 months for their condition. Among those, 19% stated that this is because they do not believe their physician can help. These findings are accompanied by data showing low treatment satisfaction and a demand for more efficacious, safe, and practical therapies [34] [55].

7. Treatment of Psoriasis

The portfolio of current therapeutic options for patients with psoriasis is wide. Unfortunately, patients do not respond to therapy uniformly. Successful control of the disease is usually achieved after several therapeutic attempts, when the best-matched approach for a specific patient at his or her disease stage is identified.

7.1. Conventional Therapy

Topical treatment is the first line of therapy for psoriasis. Topicals such as emollients, keratolytics, glucocorticosteroids, vitamin D derivatives, or combinations of those are usually sufficient to manage mild disease presentation and are the mainstay of treatment in all forms of psoriasis. Topical calcineurin inhibitors tacrolimus and pimecrolimus are used for difficult-to-treat sites, such as the intertriginous areas or the face. The inconvenience of treatment frequently limits the use of topical therapies [56].

Phototherapy or systemic treatment should always be offered to patients with moderate to severe disease. Established phototherapy includes narrow-band UVB, and to a lesser extent PUVA (psoralen + UVA) photochemotherapy. Phototherapy is an effective, but time-consuming treatment, and the potential carcinogenic effects of PUVA limit its long-term use [56].

Conventional systemic therapies for psoriasis include methotrexate, cyclosporin, acitretin and fumaric acid esters (see **Table 3**) [39] [43] [55] [56] [57]. Cyclosporin is usually prescribed for short periods, in contrast, methotrexate and acitretin can be used as long-term maintenance therapy of psoriasis. A novel oral phosphodiesterase-4 (PDE4) inhibitor apremilast has been approved in Europe and USA with comparable efficacy to methotrexate in patient to moderate-to-severe

Table 3. Conventional systemic therapy of psoriasis [59]-[64].

Systemic therapy	Mode of action	Dosing regime	Therapy specific absolute contraindications	Special considerations
Acitretin	Synthetic aromatic analogue of retinoic acid. Mechanism not fully understood, modulates epidermal differentiation and proliferation, also has anti-inflammatory and immunomodulatory effect. No immunosuppressive effect.	daily	Severe renal or hepatic impairment pregnancy, breastfeeding, alcoholism, blood donation, severe hyperlipaemia, comedication with MTX, tetracyclines, vitamin A containing products, retinoids	Teratogenic-avoidance during pregnancy is mandatory. Effective contraceptive measures up to three years after discontinuation of therapy
Apremilast	Inhibitor of phosphodiesterase 4 (PDE4); elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-*α*, IL-23, IL-17 and other inflammatory cytokines	daily	Pregnancy	Dose reduction is needed in patients with severe renal impairment. Special caution in patients with unexplained and clinically significant weight loss
Cyclosporin	Immunosuppressive agent, calcineurin inhibitors	daily	Renal impairment, insufficiently controlled arterial hypertension, severe infectious disease, history of malignancy, current malignancy, simultaneous PUVA therapy, combination with products containing Hypericum perforatum (St. john's worth), combination with medicines that are substrate for P-glycoprotein or OATP transporter	Potential for multiple drug interactions. Usually for short periods only.

Continued

Fumaric acid esters	Mechanism not fully understood; conventional hypothesis is based on the idea that dimethyl fumarate interferes with the cellular redox system by modulating intracellular thiols, thereby increasing the level of reduced glutathione. These increased glutathione levels may finally lead to an inhibition of the translocation of NF-κB into the nucleus. The main activity is considered to be immunomodulatory, producing a shift from Th1/Th17 profile to a Th2 phenotype	daily	Severe disease of the gastrointestinal tract, Hepatic and/or renal impairment, pregnancy or breastfeeding	Not FDA approved for psoriasis
Methotrexate	A folic acid antagonist. Its main effect is inhibition of DNA synthesis but it also acts directly both on RNA and protein synthesis. MTX also inhibits 5-aminoimidazole-4-carboxamide ribonucleotide tranformylase, leading to an increase in endogenous adenosine which has an anti-inflammatory effect.	weekly	Severe infections, severe liver disease, renal failure, conception (men and women)/breastfeeding, alcohol abuse, bone marrow dysfunction/haematological changes, immunodeficiency, acute peptic ulcer, stomatitis, ulcerations of the oral cavity, significantly reduced lung function	Special caution in geriatric patients
Tofacitinib	Janus kinase (JAK) inhibitor	daily	Active tuberculosis, serious infections such as sepsis or opportunistic infections. Severe hepatic impairment. Pregnancy or lactation.	Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients Currently approved for psoriatic arthritis only EU or USA

OATP: organic-anion-transporting polypeptides.

psoriasis [58]. More detailed information on their mode of action, dosing regimen, contraindications and other special consideration are described in the **Table 3** [59]-[64].

The major limitation of long-term use of conventional systemic treatment is poor tolerability and cumulative toxicity including liver toxicity from methotrexate, renal toxicity from cyclosporine, and skin carcinogenesis from phototherapy, above all when psoralens are used with ultraviolet A (PUVA) [42].

7.2. Therapy with Biologics

Several biologics have been approved for the treatment of moderate to severe psoriasis (**Table 4**) and in general show better tolerability and safety compare to conventional systemic treatment. An overall increased risk for infections including herpes zoster and *Candida* may be the only major concern associated with TNF-α and IL-17 inhibitors [42] [65]-[74]. All of them are monoclonal antibodies, except etanercept, which is a fusion protein. Adalimumab, etanercept, infliximab and certolizumab pegol inhibit TNF-α and are also approved for the treatment of psoriatic arthritis. Ustekinumab blocks interleukins 12 and 23 and is also approved for both indications. Several other biologicals have been approved in the last 5 years: the anti-IL-17 agents secukinumab (the first anti-IL-17 agent, approved for both indications), ixekizumab (also approved for psoriatic arthritis) and brodalumab, as well as anti IL-23 agents guselkumab, tildrakizumab and risankizumab. Several biosimilar to adalimumab, infliximab and etanercept have already been approved and marketed in the EU and elsewhere.

At present, the use of biologics is limited to patients unresponsive to, intolerant of, or with contraindications to conventional systemic psoriasis therapies and/or PUVA. This second-line use is in part because of the high direct costs for drugs, which are in the order of ten-times higher than for conventional systemic drugs [56]. A recent Cochrane meta-analysis review revealed that the biologic treatments (anti IL-17, anti-IL-12/23, anti-IL-23 and anti-TNF-α biologics) were significantly more effective that the small molecules (apremilast, tofacitinib) and the conventional systemic agents in terms of achieving PASI90, PASI75 and PGA improvement with no significant difference between any of the treatments and placebo for the risk of serious adverse events (SAE). In terms of efficacy measured as PASI90 infliximab, all of the anti-IL17 biologicals (bimekizumab, brodalumab, ixekizumab, secukinumab) and anti-IL23 biologicals (guselkumab and risankizumab, but not tildrakizumab) were significantly more effective compared to ustekinumab and anti-TNF-αs adalimumab, certolizumab and etanercept. Furthermore adalimumab and ustekinumab were shown to be significantly more effective than certolizumab and etanercept. The meta-analysis revealed no significant difference between tofacitinib or apremilast and between cyclosporine and methotrexate [9].

The choice of treatment from among systemic agents will thus depend on their safety profiles, individual contra-indications, and cost effectiveness [75]

Table 4. Biologics for the treatment of psoriasis [65]-[75] [88].

Agent	Mechanism of action	Agent specific absolute contraindication	Comment
Adalimumab	Anti-TNF-α human monoclonal antibody	Active tuberculosis or other severe infections such as sepsis, and opportunistic infections. Moderate to severe heart failure (NYHA class III/IV).	Subcutaneous application every 2 weeks; Washout period 6 - 10 weeks; Registered biosimilars on the market
Brodalumab	Anti-IL-17 Rec A human monoclonal antibody	Crohn's disease Clinically important active infections (e.g. active tuberculosis)	Subcutaneous application, maintenance dosing every 2 weeks subcutaneously
Etanercept	TNF-α receptor, chimeric human-murine fusion protein	Active infections (including sepsis, or risk of sepsis, tuberculosis and other opportunistic infections, chronic or localised infections)	Subcutaneous application once or twice weekly; Washout period 1 - 2 weeks; Registered biosimilars on the market
Guselkumab	Anti IL-23 fully human immunoglobulin G1 lambda (IgG1λ) monoclonal antibody	Clinically important active infection (e.g. active tuberculosis)	Subcutaneous application, maintenance dosing every 8 weeks
Infliximab	Anti-TNF-α chimeric human-murine monoclonal antibody	Active tuberculosis Significant active infection, abscesses, and opportunistic infections Chronic heart failure (NYHA class III/IV). Hypersensitivity to murine proteins.	Intravenous application, maintenance dosing every 8 weeks; Washout period 3.5 - 6 weeks; Registered biosimilars on the market
Ixekizumab	Anti-IL-17A and IL-17A/F recombinant humanised monoclonal antibody	Clinically important active infections (e.g. active tuberculosis).	Subcutaneous application, maintenance dosing every 4 weeks Infections and treatment-emergent adverse events were more common in the ixekizumab group than in the etanercept and placebo groups
Risankizumab	Anti IL-23 humanized IgG1 monoclonal antibody	Clinically important active infection (e.g. active tuberculosis)	Subcutaneous application, maintenance dosing four times per year

Continued

Secukinumab	Anti-IL-17A human monoclonal antibody	Severe hypersensitivity reactions to the active substance or to any of the excipients Clinically important, active infection (e.g. active tuberculosis).	Subcutaneous application, maintenance dosing every 4 weeks; Washout period 11 - 19 weeks
Tildrakizumab	Anti IL-23 humanized IgG1/k monoclonal antibody	Clinically important active infection (e.g. active tuberculosis)	Subcutaneous application, maintenance dosing four times per year
Ustekinumab	Anti-IL-12/23 human monoclonal antibody	Clinically important active infection (e.g. active tuberculosis.	Subcutaneous application, maintenance dosing every 12 weeks; Washout period 9 - 15 weeks

Washout period defined as period of 3 - 5 times drug's half-life. NYHA—The New York Heart Association Classification.

[76] [77] [78]. The available therapies for psoriasis today are effective in resolving skin symptoms or clearing skin by reverting the pathologic skin changes. Good control or even complete remission can be achieved in the majority of patients. However, no available treatment is able to cure the disease or to induce life-long, disease-free remission. Even after skin is completely cleared from the disease, the underlying disease activity may still be high. If the treatment is interrupted, terminated or the dose of medication is reduced the skin symptoms of psoriasis rapidly reappear in most cases. The data also show that the overall efficacy of systemic therapy itself may diminish with time. Long-term survival varies among systemic treatment options [79]-[85]. Long-lasting, safe and effective therapy is thus the most important requirement of any management concept that requires continuous effective therapy with predictable risks of toxicity and side effects.

Safety and efficacy are the primary concern in the long-term management of (every) disease. Due to the existing risk of experiencing adverse events with any agent that suppresses the immune system, careful monitoring of patients before, during, and after use of such agents is important to ensure patient safety [86]. The collective data from national and international databases and registries of psoriatic patients on biologics show that biologics, unlike most traditional systemic therapies, do not exhibit cumulative toxicity and therefore have a good safety profile in the long-term, continuous management of patients with moderate to severe psoriasis [55] [56] [81] [82] [87].

8. Drug Survival

In general, psoriatic patients require life-long treatment. Consequently their adherence to the selected treatment is the most important factor in successful

management of the disease. Adherence to treatment is generally related to drug efficacy, experienced adverse events, convenience, cost and other factors which influence patients' satisfaction with the treatment. The assessment of length of adherence to treatment is an important marker of treatment success. Time to drug discontinuation, also called "drug survival" or "drug retention", is receiving more attention as an important parameter reflecting the long-term management and therapeutic performance of psoriatic treatments with biologics in real-life settings. Studies show that the discontinuation of biologics during long-term treatment is mainly driven by the gradual loss of efficacy, more than it is by adverse events. The occurrence of adverse events accounts for approximately 10% of all drug discontinuations. Rates of adverse reactions leading to discontinuation vary between biologics, being the highest for infliximab (14.6%) and the lowest for ustekinumab (3.1%). The most frequent adverse events were minor infections, mostly associated with adalimumab and infliximab and relatively infrequently associated with etanercept and ustekinumab. Discontinuation due to loss of efficacy was most commonly associated with etanercept whereas ustekinumab showed to have the least frequent discontinuation due to loss of efficacy [80] [89].

The statistically significant predictors of discontinuations of biologics in patients with psoriasis reported in most of the studies and/or reviews are the type of the biologic, the patient's gender and previous exposure to biologics. A shorter drug survival for all biologics was confirmed in female patients and bio-experienced patients who were previously exposed to one or more biologics. Data from registries show dramatic reduction of drug survival in patients who previously received and discontinued another biologic [81]. Ustekinumab shows a clear superiority in terms of long-term efficacy in bio-naive patients. One of the explanations might be more frequent dose adjustment during treatment as part of the treating physician's choice with either shortening dose interval or dose increase from 45 mg to 90 mg (or both) which recaptures efficacy in approximately 45% of patients who would otherwise have lost clinical response [81] [90]. Among biologicals investigated for drug survival ustekinumab requires the fewest dosing and/or visits to dermatologists and shows the lowest rates of adverse reactions which may increase patient satisfaction compared to other biologics and increase adherence. [83] Comparisons between anti-TNF-α and anti-IL-17 agents are inconclusive and/or contradicting, most likely due to the methodological differences among studies *i.e.* adherence to the prescribing protocols, dose adjustments, combination therapies which may help to explain the discrepancies between findings [81] [82] [83] [84] [89] [91] [92] [93] [94]. Biologics tend to have a shorter survival in bio-experienced patients who previously received and discontinued another biologic. Several explanations have been proposed, such as higher rate of antibody catabolism independent of their specificity, production of anti-drug antibodies and an immunological reorchestration where long-term suppression of a single cytokine would cause an induction of other pro inflamma-

tory cytokines with the redundant function. Among these explanations the last explanation is the most convincing [81].

9. Biomarkers and Pharmacogenetics of Psoriasis

The existence of a genetic predisposition to psoriasis is supported by family and population studies and higher concordance rates in monozygotic compared to dizygotic twins. The psoriasis genetic landscape emerging from genome-wide association studies (GWAS) includes 36 independent psoriasis associated genetic regions in the Caucasian population. Associated regions include skin-specific and immune-related genes belonging to either innate or adaptive immunity. In fact, the genome regions most strongly associated with the development of psoriasis are those associated with the immune system. More than 12 major psoriasis susceptibility (PSORS) loci have been identified by linkage disequilibrium in family-based studies. Several candidate genes at each PSORS locus contribute to the disease [13]. Psoriasis susceptibility loci include: PSORS1 (177900) on 6p21.3; PSORS2 (602723) is caused by mutation in the *CARD*14 gene (607211) on chromosome 17q25; PSORS3 (601454) on 4q; PSORS4 on 1q21; PSORS5 (604316) on 3q21; PSORS6 (605364) on 19p; PSORS7 (605606) on 1p; PSORS8 (610707) on 16q; PSORS9 (607857) on 4q31; PSORS10 (612410) on 18p11; PSORS11 (612599) on 5q31-q33; PSORS12 (612950) on 20q13; PSORS13 (614070) is conferred by variation in the *TRAF3IP2* gene (607043) on 6q21; PSORS14 (614204) is caused by mutation in the *IL36RN* gene (605507) on chromosome 2q13 and PSORS15 (616106) which is conferred by variation in the *AP1S3* gene (615781) on 2q36 [95].

The strongest susceptibility locus is PSORS1, which lies within the class I region of the major histocompatibility complex (MHC). The *HLA-C**0602 allele of the MHC Class I molecule HLA-C is considered to be the primary associated allele; it is connected with more severe disease and early onset (*i.e.* Type I psoriasis). Recently two gene mutations have been found to independently induce psoriasis: *IL36RN* and *CARD*14; the two have an effect on both the skin and the immune system. Mutations in *IL36RN* gene are reported to be connected to generalized, pustular psoriasis and are connected with the increased production of cytokines downstream of NF-κβ. The over-activity of fundamental immunological processes and pathways during psoriasis imply that the same genes which affect antigen presentation could affect psoriasis (e.g. *HLA-C* and *ERAP*1), NF-κβ signalling (*TNFAIP*3, *TNIP*1, *TRAF3IP2* and *CARD*14), the IL-23/IL-17 axis pathway (*IL*-23, *IL12B*, *and IL23R*) and type I IFN pathway (*IL28RA*, *RNF*114). The gene *CDKAL*1 is associated with psoriasis and comorbid diseases such as type II diabetes mellitus and Crohn's disease. Mutations of the *IL-23R* gene are suspected to be associated with psoriasis, psoriatic arthritis and Crohn's disease [13] [96] [97] [98].

More than 30 Single Nucleotide Polymorphisms (SNPs) were identified by GWAS targeted toward psoriasis [99] [100] [101]. SNPs hold the key to defining

the risk of an individual's susceptibility to various illnesses and response to therapy. However, their relationship to the clinical manifestation of psoriasis and individual response to available treatments in psoriasis are yet to be revealed. Thus far an association between two SNPs in the gene that encodes a protein belonging to TNF-α signalling—TNFAIP3—and the improved response to anti-TNF-α therapy has been described [102]. Studies also show that patients with HLA-Cw*06+ allele respond better and faster to ustekinumab, a biologic that blocks the IL-12/IL-23 pathway [103]. Studying genetic variations of psoriatic patients on MTX therapy, the association of SNPs within the efflux transporter genes ABCC1 (ATP-binding cassette, subfamily C, member 1) and ABCG2 (ATP-binding cassette, subfamily G, member 2) with good response by the means of efficacy, and SNPs in ABCC1, SLC19A1 (solute carrier family 19, member 1), and ADORA2a (adenosine receptor A2a) with toxicity has been confirmed [104]. However, pharmacogenetic research in psoriasis has been hampered by small populations and confounding factors, which precludes the use of the presented findings until further validation. Additionally, studies should be performed with the most recently approved drugs, such as anti-IL-23 biologics, several anti-IL-17 biologics and apremilast [105].

Evidence for the role of microRNAs (miRNA), small noncoding RNA molecules that post-transcriptionally regulate gene expression, in the pathogenesis of inflammatory skin disorders support the utility of using miRNAs as biomarkers for psoriasis. More than 100 miRNA reproducibly exceeded the detection threshold in the serum of patients with psoriasis. The most abundant are preferentially expressed by leucocytes (e.g. miR-223, miR-146a, miR-142-3p), endothelial cells (miR-126), liver cells (miR-122) or by multiple tissue and cell types (e.g. miR-16, the miR-17-92 cluster, miR-21) [106]. Increased plasma miR-33 positively correlates with insulin levels and insulin resistance [107]. Correlation of severity of the disease was seen with miR-1266, miR-146a, miR-369-3p, miR-143 and miR-223 in the serum of psoriatic patients. An increasing number of studies confirm the impact of systemic therapies on specific psoriasis related miRNAs [108]. Despite high potential of miRNAs as diagnostic and prognostic biomarkers in psoriasis no routine test for their detection is available on the market. More studies have to be performed for the identification and validation of psoriasis biomarkers. The success of such studies will enable the implementation of the concept of personalized medicine into clinical practice.

10. Conclusion

Psoriasis is a systemic inflammatory disorder with complex pathogenic interactions between the innate and adaptive immune system. For effective control of skin manifestation and associated conditions, appropriate long-term management is required: keeping the patient at the centre of care is of prime importance. Results of the Multifunctional Assessment of Psoriasis and Psoriatic Arthritis Survey published in 2014 indicate that about half of psoriatic patients who

received systemic treatment for their condition found their therapies bothersome: in case of traditional oral medications primarily because of adverse effects, inconvenience and the need for laboratory monitoring, while patients on biologics indicated therapy bothersome primarily because of fear of injection, inconvenience and adverse effects [38]. These findings suggest that some patients may not initiate or continue effective therapies regardless of the increased mortality risk associated with systemic comorbidities.

Patients with psoriasis must be educated about the increased risk of systemic comorbidities if treatment is abandoned, and about how successful systemic treatment of inflammatory disease lowers the overall risk of mortality. They must be educated about the importance of non-drug interventions as an effective measure for managing psoriasis such as weight loss, diet, exercise, cessation of smoking and alcohol intake. Education should be routinely used in clinical practice together with identification of the patient's preferences, such as mode of administration and access to the selected treatment [4] [35] [39] [42] [54] [109].

Despite high potential of several promising candidate biomarkers for monitoring the initiation and progress of the disease and its response to treatment no routine test is yet available on the market. Pharmacogenetic research in psoriasis is rapidly progressing due to the high clinical and public health need to find biomarkers that can be associated with disease prognosis, onset of comorbidities (such as cardiovascular disease, metabolic syndrome, psoriatic arthritis, etc.), pharmacological/clinical response to therapy and/or adverse effects to treatment. To enable comprehensive management, future treatment algorithms should include disease manifestation and severity, coexistence of systemic comorbidities, likelihood of treatment response and appearance of toxic side effects to selected treatment (based on biomarkers) as well as patient satisfaction. More work needs to be done to further identify and validate the most promising candidate biomarkers with the final goal of implementation the concept of personalized medicine in management of psoriatic patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Boehncke, W.-H., Boehncke, S., Tobin, A.-M. and Kirby, B. (2011) The "Psoriatic March": A Concept of How Severe Psoriasis May Drive Cardiovascular Comorbidity. *Experimental Dermatology*, **20**, 303-307. https://doi.org/10.1111/j.1600-0625.2011.01261.x

[2] Reich, K. (2012) The Concept of Psoriasis as a Systemic Inflammation: Implications for Disease Management. *Journal of the European Academy of Dermatology and Venereology*, **26**, 3-11. https://doi.org/10.1111/j.1468-3083.2011.04410.x

[3] Kerdel, F. and Don, F. (2018) The Importance of Early Treatment in Psoriasis and Management of Disease Progression. *Journal of Drugs in Dermatology*, **17**, 737-742.

[4] Gelfand, J.M., Troxel, A.B., Lewis, J.D., Kurd, S.K., Shin, D.B., Wang, X., *et al*. (2007) The Risk of Mortality in Patients with Psoriasis: Results from a Population-Based Study. *Archives of Dermatology*, **143**, 1493-1499. https://doi.org/10.1001/archderm.143.12.1493

[5] Svedbom, A., Dalén, J., Mamolo, C., Cappelleri, J.C., Mallbris, L., Petersson, I.F. and Ståhle, M. (2015) Increased Cause-Specific Mortality in Patients with Mild and Severe Psoriasis: A Population-Based Swedish Register Study. *Acta Dermato-Venereologica*, **95**, 808-815. https://doi.org/10.2340/00015555-2095

[6] Parisi, R., Symmons, D.P.M., Griffiths, C.E.M. and Ashcroft, D.M. (2013) Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. *Journal of Investigative Dermatology*, **133**, 377-385. https://doi.org/10.1038/jid.2012.339

[7] Langley, R.G., Krueger, G.G. and Griffiths, C.E. (2005) Psoriasis: Epidemiology, Clinical Features, and Quality of Life. *Annals of the Rheumatic Diseases*, **64**, ii18-ii25. https://doi.org/10.1136/ard.2004.033217

[8] Queiro, R., Tejón, P., Coto, P., Alonso, S., Alperi, M., Sarasqueta, C., *et al*. (2013) Clinical Differences between Men and Women with Psoriatic Arthritis: Relevance of the Analysis of Genes and Polymorphisms in the Major Histocompatibility Complex Region and of the Age at Onset of Psoriasis. *Clinical and Developmental Immunology*, **2013**, Article ID: 482691. https://doi.org/10.1155/2013/482691

[9] Sbidian, E., Chaimani, A., Afach, S., Doney, L., Dressler, C., Hua, C., *et al*. (2020) Systemic Pharmacological Treatments for Chronic Plaque Psoriasis: A Network Meta-Analysis. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD011535.pub3

[10] Griffiths, C.E.M., Christophers, E., Barker, J.N.W.N., Chalmers, R.J.G., Chimenti, S., Krueger, G.G., *et al*. (2007) A Classification of Psoriasis Vulgaris According to Phenotype. *British Journal of Dermatology*, **156**, 258-262. https://doi.org/10.1111/j.1365-2133.2006.07675.x

[11] Mrowietz, U. and Reich, K. (2009) Psoriasis—New Insights into Pathogenesis and Treatment. *Deutsches Ärzteblatt International*, **106**, 11-19. https://doi.org/10.3238/arztebl.2009.0011

[12] Kurd, S.K., Troxel, A.B., Crits-Christoph, P. and Gelfand, J.M. (2010) The Risk of Depression, Anxiety, and Suicidality in Patients with Psoriasis: A Population-Based Cohort study. *Archives of Dermatology*, **146**, 891-895. https://doi.org/10.1001/archdermatol.2010.186

[13] Lowes, M.A., Suárez-Fariñas, M. and Krueger, J.G. (2014) Immunology of Psoriasis. *Annual Review of Immunology*, **32**, 227-255. https://doi.org/10.1146/annurev-immunol-032713-120225

[14] Nestle, F.O., Daniel, H., Kaplan, D.H. and Barker, J. (2009) Mechanism of Disease: Psoriasis. *The New England Journal of Medicine*, **361**, 496-509. https://doi.org/10.1056/NEJMra0804595

[15] Henseler, T. and Christophers, E. (1995) Disease Concomitance in Psoriasis. *Journal of the American Academy of Dermatology*, **32**, 982-986. https://doi.org/10.1016/0190-9622(95)91336-X

[16] Henseler, T. and Christophers, E. (1985) Psoriasis of Early and Late Onset: Characterization of Two Types of Psoriasis Vulgaris. *Journal of the American Academy of Dermatology*, **13**, 450-456. https://doi.org/10.1016/S0190-9622(85)70188-0

[17] Sampogna, F., Gisondi, P., Melchi, C.F., Amerio, P., Girolomoni, G. and Abeni, D. (2004) Prevalence of Symptoms Experienced by Patients with Different Clinical Types of Psoriasis. *British Journal of Dermatology*, **151**, 594-599.

https://doi.org/10.1111/j.1365-2133.2004.06093.x

[18] Alwan, W. and Nestle, F.O. (2015) Pathogenesis and Treatment of Psoriasis: Exploiting Pathopysiological Pathways for Precision Medicine. *Clinical and Experimental Rheumatology*, **33**, S2-S6.

[19] Reinholz, M., Ruzicka, T. and Schauber, J. (2012) Cathelicidin LL-37: An Antimicrobial Peptide with a Role in Inflammatory Skin Disease. *Annals of Dermatology*, **24**, 126-135. https://doi.org/10.5021/ad.2012.24.2.126

[20] Lande, R., Gregorio, J., Facchinetti, V., Chatterjee, B., Wang, Y.-H., Homey, B., *et al*. (2007) Plasmacytoid Dendritic Cells Sense Self-DNA Coupled with Antimicrobial Peptide. *Nature*, **449**, 564-569. https://doi.org/10.1038/nature06116

[21] Benezeder, T. and Wof, P. (2019) Resolution of Plaque-Type Psoriasis: What Is Left behind (and Reinitiates the Disease). *Seminars in Immunopathology*, **41**, 633-644. https://doi.org/10.1007/s00281-019-00766-z

[22] Di Meglio, P., Perera, G.K. and Nestle, F.O. (2011) The Multitasking Organ: Recent Insights into Skin Immune Function. *Immunity*, **35**, 857-869. https://doi.org/10.1016/j.immuni.2011.12.003

[23] Schlapbach, C., Gehad, A., Yang, C., Watanabe, R., Guenova, E., Teague, J.E., *et al*. (2014) Human TH9 Cells Are Skin-Tropic and Have Autocrine and Paracrine Proinflammatory Capacity. *Science Translational Medicine*, **6**, 219ra8. https://doi.org/10.1126/scitranslmed.3007828

[24] Schon, M.P. and Erpenbeck, L. (2018) The Interleukin-23/Interleukin-17 Axis Links Adaptive and Innate Immunity in Psoriasis. *Frontiers in Immunology*, **9**, 1323. https://doi.org/10.3389/fimmu.2018.01323

[25] Singh, T.P., Schön, M.P., Wallbrecht, K., Gruber-Wackernagel, A., Wang, X.-J. and Wolf, P. (2013) Involvement of IL-9 in Th17-Associated Inflammation and Angiogenesis of Psoriasis. *PLoS ONE*, **8**, e51752. https://doi.org/10.1371/journal.pone.0051752

[26] Gelfand, J.M., Gladman, D.D., Mease, P.J., Smith, N., Margolis, D.J., Nijsten, T., *et al*. (2005) Epidemiology of Psoriatic Arthritis in the Population of the United States. *Journal of the American Academy of Dermatology*, **53**, 573. https://doi.org/10.1016/j.jaad.2005.03.046

[27] Nijsten, T. and Wakkee, M. (2009) Complexity of the Association between Psoriasis and Comorbidities. *Journal of Investigative Dermatology*, **129**, 1601-1603. https://doi.org/10.1038/jid.2009.55

[28] Yeung, H., Takeshita, J., Mehta, N.N., Kimmel, S.E., Ogdie, A., Margolis, D.J., *et al*. (2013) Psoriasis Severity and the Prevalence of Major Medical Comorbidity: A Population-Based Study. *JAMA Dermatology*, **149**, 1173-1179. https://doi.org/10.1001/jamadermatol.2013.5015

[29] Armstrong, E.J., Harskamp, C.T. and Armstrong, A.W. (2013) Psoriasis and Major Adverse Cardiovascular Events: A Systematic Review and Meta-Analysis of Observational Studies. *Journal of the American Heart Association*, **2**, e000062. https://doi.org/10.1161/JAHA.113.000062

[30] Augustin, M., Reich, K., Glaeske, G., Schaefer, I. and Radtke, M. (2010) Co-Morbidity and Age-Related Prevalence of Psoriasis: Analysis of Health Insurance Data in Germany. *Acta Dermato- Venereologica*, **90**, 147-151. https://doi.org/10.2340/00015555-0770

[31] Kim, N., Thrash, B. and Menter, A. (2010) Comorbidities in Psoriasis Patients. *Seminars in Cutaneous Medicine and Surgery*, **29**, 10-15. https://doi.org/10.1016/j.sder.2010.01.002

[32] Sterry, W., Strober, B.E., Menter, A. and International Psoriasis Council (2007) Obesity in Psoriasis: The Metabolic, Clinical and Therapeutic Implications. Report of an Interdisciplinary Conference and Review. *British Journal of Dermatology*, **157**, 649-655. https://doi.org/10.1111/j.1365-2133.2007.08068.x

[33] Farias, M.M., Achurra, P., Boza, C., Vega, A. and de la Cruz, C. (2012) Psoriasis Following Bariatric Surgery: Clinical Evolution and Impact on Quality of Life on 10 Patients. *Obesity Surgery*, **22**, 877-880. https://doi.org/10.1007/s11695-012-0646-8

[34] Hossler, E.W., Wood, G.C., Still, C.D., Mowad, C.M. and Maroon, M.S. (2013) The Effect of Weight Loss Surgery on the Severity of Psoriasis. *British Journal of Dermatology*, **168**, 660-661. https://doi.org/10.1111/j.1365-2133.2012.11211.x

[35] Gisondi, P., Del Giglio, M., Di Francesco, V., Zamboni, M. and Girolomoni, G. (2008) Weight Loss Improves the Response of Obese Patients with Moderate-to-Severe Chronic Plaque Psoriasis to Low-Dose Cyclosporine Therapy: A Randomized, Controlled, Investigator-Blinded Clinical Trial. *The American Journal of Clinical Nutrition*, **88**, 1242-1247.

[36] Johnston, A., Arnadottir, S., Gudjonsson, J.E., Aphale, A., Sigmarsdottir, A.A., Gunnarsson, S.I., *et al*. (2008) Obesity in Psoriasis: Leptin and Resistin as Mediators of Cutaneous Inflammation. *British Journal of Dermatology*, **159**, 342-350. https://doi.org/10.1111/j.1365-2133.2008.08655.x

[37] Mattei, P.L., Corey, K.C. and Kimball, A.B. (2014) Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): The Correlation between Disease Severity and Psychological Burden in Patients Treated with Biological Therapies. *Journal of the European Academy of Dermatology and Venereology*, **28**, 333-337. https://doi.org/10.1111/jdv.12106

[38] Lebwohl, M.G., Bachelez, H., Barker, J., Girolomoni, G., Kavanaugh, A., Langley, R.G., *et al*. (2014) Patient Perspectives in the Management of Psoriasis: Results from the Population-Based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *Journal of the American Academy of Dermatology*, **70**, 871-881. https://doi.org/10.1016/j.jaad.2013.12.018

[39] Mrowietz, U., de Jong, E.M., Kragballe, K., Langley, R., Nast, A., Puig, L., *et al*. (2014) A Consensus Report on Appropriate Treatment Optimization and Transitioning in the Management of Moderate-to-Severe Plaque Psoriasis. *Journal of the European Academy of Dermatology and Venereology*, **28**, 438-453. https://doi.org/10.1111/jdv.12118

[40] Mrowietz, U., Kragballe, K., Reich, K., Spuls, P., Griffiths, C.E., Nast, A., *et al*. (2011) Definition of Treatment Goals for Moderate to Severe Psoriasis: A European Consensus. *Archives of Dermatological Research*, **303**, 1-10. https://doi.org/10.1007/s00403-010-1080-1

[41] Strober, B., Ryan, C., van de Kerkhof, P., van der Walt, J., Kimball, A.B., Barker, J., *et al*. (2020) Recategorization of Psoriasis Severity: Delphi Consensus from the International Psoriasis Council. *Journal of the American Academy of Dermatology*, **82**, 118-122. https://doi.org/10.1016/j.jaad.2019.08.026

[42] Gisondi, P., Del Giglio, M. and Girolomoni, G. (2017) Treatment Approaches to Moderate to Severe Psoriasis. Review. *International Journal of Molecular Sciences*, **18**, 2427. https://doi.org/10.3390/ijms18112427

[43] Nast, A., Boehncke, W.H., Mrowietz, U., Ockenfels, H.M., Philipp, S., Reich, K., *et al*. (2012) German S3-Guidelines on the Treatment of Psoriasis Vulgaris (Short Version). *Archives of Dermatological Research*, **304**, 87-113. https://doi.org/10.1007/s00403-012-1214-8

[44] Armstrong, A.W., Bagel, J., Van Voorhees, A.S., Robertson, A.D. and Yamauchi, P.S. (2016) Combining Biologic Therapies with Other Systemic Treatments in Psoriasis: Evidence-Based, Best-Practice Recommendations from the Medical Board of the National Psoriasis Foundation. *JAMA Dermatology*, **151**, 432-438. https://doi.org/10.1001/jamadermatol.2014.3456

[45] Rapp, S.R., Feldman, S.R., Exum, M.L., Fleischer, A.B. and Reboussin, D.M. (1999) Psoriasis Causes as Much Disability as Other Major Medical Diseases. *Journal of the American Academy of Dermatology*, **41**, 401-407. https://doi.org/10.1016/S0190-9622(99)70112-X

[46] Fortune, D.G., Richards, H.L., Main, C.J. and Griffiths, C.E. (2002) Patients' Strategies for Coping with Psoriasis. *Clinical and Experimental Dermatology*, **27**, 177-184. https://doi.org/10.1046/j.1365-2230.2002.01055.x

[47] Smith, C.H., Anstey, A.V., Barker, J.N.W.N., Burden, A.D., Chalmers, R.J.G., Chandler, D.A., *et al.* (2009) British Association of Dermatologists' Guidelines for Biologic Interventions for Psoriasis 2009. *British Journal of Dermatology*, **161**, 987-1019. https://doi.org/10.1111/j.1365-2133.2009.09505.x

[48] Tlaker-Zunter, V. (2015) Treatment of Psoriasis. In: Miljkovic, J., Ed., *Monograph on Psoriasis*, Slovenian Dermatologist Association, Maribor, 73-83. (In Slovenian)

[49] Grzelj, J. and Sollner Dolenc, M. (2020) The Role of Xenobiotics in Triggering Psoriasis, Review. *Archives of Toxicology*, **94**, 3959-3982. https://doi.org/10.1007/s00204-020-02870-8

[50] Wu, J.J., Poon, K.Y., Channual, J.C. and Shen, A.Y. (2012) Association between Tumor Necrosis Factor Inhibitor Therapy and Myocardial Infarction Risk in Patients with Psoriasis. *Archives of Dermatology*, **148**, 1244-1250. https://doi.org/10.1001/archdermatol.2012.2502

[51] Bettiol, A., Pirolo, R., Bolcato, J., Franchin, G., Deambrosis, P., Giusti, P. and Chinellato, A. (2015) The Impact of Innovative Biologic Drugs in the Management of Psoriatic Patients. *International Journal of Pharmacy and Pharmaceutical Sciences*, **3**, 43-49. http://www.openscienceonline.com/journal/osjpp

[52] von Stebut, E., Boehncke, W.H., Ghoreschi, K., Gori, T., Kaya, Z., Thaci, D. and Schäffler, A. (2020) IL-17A in Psoriasis NAD beyond: Cardiovascular and Metabolic Implications. Review. *Frontiers in Immunology*, **10**, 3096. https://doi.org/10.3389/fimmu.2019.03096

[53] Mrowietz, U., Elder, J.T. and Barker, J. (2006) The Importance of Disease Associations and Concomitant Therapy for the Long-Term Management of Psoriasis Patients. *Archives of Dermatological Research*, **298**, 309-319. https://doi.org/10.1007/s00403-006-0707-8

[54] Mrowietz, U., Steinz, K. and Gerdes, S. (2014) Psoriasis: To Treat or to Manage? *Experimental Dermatology*, **23**, 705-709. https://doi.org/10.1111/exd.12437

[55] Pathirana, D., Ormerod, A.D., Saiag, P., Smith, C., Spuls, P.I., Nast, A., *et al.* (2009) European S3-Guidelines on the Systemic Treatment of Psoriasis Vulgaris. *Journal of the European Academy of Dermatology and Venereology*, **23**, 1-70. https://doi.org/10.1111/j.1468-3083.2009.03389.x

[56] Boehncke, W.-H. and Schön, M.P. (2015) Psoriasis. *The Lancet*, **386**, 983-994. https://doi.org/10.1016/S0140-6736(14)61909-7

[57] Menter, A., Gelfand, J.M., Connor, C., Armstrong, A.W., Cordoro, K.M., Davis, D.M.R., *et al.* (2020) Joint American Academy of Dermatologye National Psoriasis Foundation Guidelines of Care for the Management of Psoriasis with Systemic Nonbiologic Therapies. *Journal of the American Academy of Dermatology*, **82**, 1444-

1486. https://doi.org/10.1016/j.jaad.2020.02.044

[58] Armstrong, A.W., Betts, K.A., Sundaram, M., Thomason, D. and Signorovitch, J.E. (2016) Comparative Efficacy and Incremental Cost per Responder of Methotrexate versus Apremilast for Methotrexate-Naive Patients with Psoriasis. *Journal of the American Academy of Dermatology*, **75**, 740-746. https://doi.org/10.1016/j.jaad.2016.05.040

[59] Acitretin (acitretin) (2020) Summary of Product Characteristics. MHRA. https://mhraproducts4853.blob.core.windows.net/docs/5a585f38defdbb4817e0c4740df6a5bfc0e4049b

[60] Otezla (apremilast) (2020) Summary of Product Characteristics. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003746/WC500182627.pdf

[61] Neoral (ciclosporin) (2020) Summary of Product Characteristics. MHRA. https://mhraproducts4853.blob.core.windows.net/docs/a59cd1e88632a366f8e5a5aa1934e60bf139a7d1

[62] Fumaderm (Dimethyfumarate, Ethylhydrogenfumarate Salts) (2020) Summary of Product Characteristic. Fachinfo Service. https://www.fachinfo.de/suche/fi/000847

[63] Methotrexate (2020) Summary of Product Characteristics. EMC. https://www.medicines.org.uk/emc/product/511/smpc#gref

[64] Xeljanz (tofacitinib) (2020) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf

[65] Humira (adalimumab) (2020) Summary of Product Characteristic. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf

[66] Kyntheum (brodalumab) (2020) Summary of Product Characteristic. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/kyntheum-epar-product-information_en.pdf

[67] Enbrel (etanercept) (2020) Summary of Product Characteristics. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000262/WC500027361.pdf

[68] Tremfya (guselkumab) (2020) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/tremfya-epar-product-information_en.pdf

[69] Remicade (infliximab) (2020) Summary of Product Characteristics. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf

[70] Taltz (ixekizumab) (2020) Summary of Product Characteristics. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003943/WC500205804.pdf

[71] Skyrizi (risankizumab) (2020) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/skyrizi-epar-product-information_en.pdf

[72] Cosentyx (secukinumab) (2020) Summary of Product Characteristic. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003729/WC500183129.pdf

[73] Ilumetri (tildrakizumab) (2020) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/ilumetri-epar-product-information_en.pdf

[74] Stelara (ustekinumab) (2020) Summary of Product Characteristics. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000958/WC500058513.pdf

[75] Menter, A., Warren, R.B., Langley, R.G., Merola, J.F., Kerr, L.N., Dennehy, E.B., *et al*. (2017) Efficacy of Ixekizumab Compared to Etanercept and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis and Non-Pustular Palmoplantar Involvement: Results from Three Phase 3 Trials (UNCOVER-1, UNCOVER-2 and UNCOVER-3). *Journal of the European Academy of Dermatology and Venereology*, **31**, 1686-1392. https://doi.org/10.1111/jdv.14237

[76] Galván-Banqueri, M., Gil, R.M., Ramos, B.S. and Paloma, F.J.B. (2013) Biological Treatments for Moderate-to-Severe Psoriasis: Indirect Comparison. *Journal of Clinical Pharmacy and Therapeutics*, **38**, 121-130. https://doi.org/10.1111/jcpt.12044

[77] Jabbar-Lopez, Z.K., Yiu, Z.Z.N., Ward, V., Exton, L.S., Mohd Mustapa, M.F., Samarasekera, E., *et al*. (2017) Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis. *Journal of Investigative Dermatology*, **137**, 1646-1654. https://doi.org/10.1016/j.jid.2017.04.009

[78] Kim, I.H., West, C.E., Kwatra, S.G., Feldman, S.R. and O'Neill, J.L. (2012) Comparative Efficacy of Biologics in Psoriasis: A Review. *American Journal of Clinical Dermatology*, **13**, 365-374. https://doi.org/10.2165/11633110-000000000-00000

[79] Gisondi, P., Tessari, G., Di Mercurio, M., Del Giglio, M. and Girolomo, G. (2013) Retention Rate of Systemic Drugs in Patients with Chronic Plaque Psoriasis. *Clinics in Dermatology*, **1**, 8-14.

[80] Menting, S.P., Sitaram, A.S., Bonnerjee-van der Stok, H.M., de Rie, M.A., Hooft, L. and Spuls, P.I. (2014) Drug Survival Is Not Significantly Different between Biologics in Patients with Psoriasis Vulgaris: A Single-Centre Database Analysis. *British Journal of Dermatology*, **171**, 875-883. https://doi.org/10.1111/bjd.13001

[81] Gniadecki, R., Bang, B., Bryld, L.E., Iversen, L., Lasthein, S. and Skov, L. (2015) Comparison of Long-Term Drug Survival and Safety of Biologic Agents in Patients with Psoriasis Vulgaris. *British Journal of Dermatology*, **172**, 244-252. https://doi.org/10.1111/bjd.13343

[82] Gniadecki, R., Kragballe, K., Dam, T.N. and Skov, L. (2011) Comparison of Drug Survival Rates for Adalimumab, Etanercept and Infliximab in Patients with Psoriasis Vulgaris. *British Journal of Dermatology*, **164**, 1091-1096. https://doi.org/10.1111/j.1365-2133.2011.10213.x

[83] Umezawa, Y., Nobeyama, Y., Hayashi, M., Fukuchi, O., Ito, T., Saeki, H. and Nakagawa, H. (2013) Drug Survival Rates in Patients with Psoriasis after Treatment with

Biologics. *The Journal of Dermatology*, **40**, 1008-1013. https://doi.org/10.1111/1346-8138.12353

[84] van den Reek, J.M., Zweegers, J., Kievit, W., Otero, M.E., van Lümig, P.P., Driessen, R.J., *et al*. (2014) "Happy" Drug Survival of Adalimumab, Etanercept and Ustekinumab in Psoriasis in Daily Practice Care: Results from the BioCAPTURE Network. *British Journal of Dermatology*, **171**, 1189. https://doi.org/10.1111/bjd.13087

[85] Warren, R.B., Smith, C.H., Yiu, Z.Z.N., Ashcroft, D.M., Barker, J.N.W.N., Burden, A.D., *et al*. (2015) Differential Drug Survival of Biologic Therapies for the Treatment of Psoriasis: A Prospective Observational Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). *Journal of Investigative Dermatology*, **135**, 2632-2640. https://doi.org/10.1038/jid.2015.208

[86] Panchal, M.R., Coope, H., McKenna, D.J. and Alexandroff, A. (2013) Long-Term Safety of Biologics in the Treatment of Psoriasis. *Psoriasis*: *Targets and Therapy*, **4**, 1-9. https://doi.org/10.2147/PTT.S26168

[87] Nast, A., Gisondi, P., Ormerod, A.D., Saiag, P., Smith, C., Spuls, P.I., *et al*. (2015) European S3-Guidelines on the Systemic Treatment of Psoriasis Vulgaris—Update 2015. *Journal of the European Academy of Dermatology and Venereology*, **29**, 2277-2294. https://doi.org/10.1111/jdv.13354

[88] Gisondi, P., Geat, D., Pizzolato, M. and Girolomoni, G. (2019) State of the Art and Pharmacological Pipeline of Biologics for Chronic Plaque Psoriasis. *Current Opinion in Pharmacology*, **46**, 90-99. https://doi.org/10.1016/j.coph.2019.05.007

[89] Lin, P.T., Wang, S.H. and Chi, C.C. (2018) Drug Survival of Biologics in Treating Psoriasis: A Meta-Analysis of Real-World Evidence. *Scientific Reports*, **8**, Article No. 16068. https://doi.org/10.1038/s41598-018-34293-y

[90] Menter, A., Papp, K.A., Gooderham, M., Pariser, D.M., Augustin, M., Kerdel, F.A., *et al*. (2016) Drug Survival of Biologic Therapy in a Large, Disease-Based Registry of Patients with Psoriasis: Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *Journal of the European Academy of Dermatology and Venereology*, **30**, 1148-1158. https://doi.org/10.1111/jdv.13611

[91] Esposito, M., Gisondi, P., Cassano, N., Ferrucci, G., Del Giglio, M., Loconsole, F., *et al*. (2013) Survival Rate of Antitumour Necrosis Factor-α Treatments for Psoriasis in Routine Dermatological Practice: A Multicentre Observational Study. *British Journal of Dermatology*, **169**, 666-672. https://doi.org/10.1111/bjd.12422

[92] Lunder, T., Zorko, M.S., Kolar, N.K., Suhodolcan, A.B., Marovt, M., Leskovec, N.K. and Marko, P.B. (2019) Drug Survival of Biological Therapy Is Showing Class Effect: Update Results Form Slovenian National Registry of Psoriasis. *International Journal of Dermatology*, **58**, 631-641. https://doi.org/10.1111/ijd.14429

[93] Egberg, A. and Skov, L. (2019) Drug Survival of Secukinumab and Ixekizumab for Moderate-to-Severe Plaque Psoriasis. *Journal of the American Academy of Dermatology*, **81**, 173-178. https://doi.org/10.1016/j.jaad.2019.03.048

[94] Yiu, Z.Z.N., Mason, K.J., Hampton, P.J., Reynolds, N.J., Smith, C.H., Lunt, M., *et al*. (2020) Drug Survival of Adalimumab, Ustekinumab and Secukinumab in Patients with Psoriasis: A Prospective Cohort Study from the British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR). *British Journal of Dermatology*, **2**, 294-302. https://doi.org/10.1111/bjd.18981

[95] OMIM (2020) Online Mendelian Inheritance in Man. http://www.omim.org

[96] Trembath, R.C., Clough, R.L., Rosbotham, J.L., Jones, A.B., Camp, R.D., Frodsham, A., *et al*. (1997) Identification of a Major Susceptibility Locus on Chromosome 6p and Evidence for Further Disease Loci Revealed by a Two Stage Genome-Wide Search

in Psoriasis. *Human Molecular Genetics*, **6**, 813-820. https://doi.org/10.1093/hmg/6.5.813

[97] Di Meglio, P., Villanova, F., Napolitano, L., Tosi, I., Terranova Barberio, M., Mak, R.K., *et al*. (2013) The IL23R A/Gln381 Allele Promotes IL-23 Unresponsiveness in Human Memory T-Helper 17 Cells and Impairs Th17 Responses in Psoriasis Patients. *Journal of Investigative Dermatology*, **133**, 2381-2389. https://doi.org/10.1038/jid.2013.170

[98] Foulkes, A. and Warren, R. (2015) Pharmacogenomics and the Resulting Impact on Psoriasis Therapies. *Dermatologic Clinics*, **33**, 146-160. https://doi.org/10.1016/j.det.2014.09.011

[99] Rahman, P., Inman, R.D., Gladman, D.D., Reeve, J.P., Peddle, L. and Maksymowych, W.P. (2008) Association of Interleukin-23 Receptor Variants with Ankylosing Spondylitis. *Arthritis & Rheumatology*, **58**, 1020-1025. https://doi.org/10.1002/art.23389

[100] Prieto-Pérez, R., Cabaleiro, T., Daudén, E., Ochoa, D., Roman, M. and Abad-Santos, F. (2013) Genetics of Psoriasis and Pharmacogenetics of Biological Drugs. *Autoimmune Diseases*, **2013**, Article ID: 613086. https://doi.org/10.1155/2013/613086

[101] Villanova, F., Di Meglio, P. and Nestle, F.O. (2013) Biomarkers in Psoriasis and Psoriatic Arthritis. *Annals of the Rheumatic Diseases*, **72**, ii104-10. https://doi.org/10.1136/annrheumdis-2012-203037

[102] Tejasvi, T., Stuart, P.E., Chandran, V., Voorhees, J.J., Gladman, D.D., Rahman, P., *et al*. (2012) TNFAIP3 Gene Polymorphisms Are Associated with Response to TNF Blockade in Psoriasis. *Journal of Investigative Dermatology*, **1323**, 593-600. https://doi.org/10.1038/jid.2011.376

[103] Talamonti, M., Botti, E., Galluzzo, M., Teoli, M., Spallone, G., Bavetta, M., *et al*. (2013) Pharmacogenetics of Psoriasis: HLA-Cw6 But Not LCE3B/3C Deletion nor TNFAIP3 Polymorphism Predisposes to Clinical Response to Interleukin 12/23 Blocker Ustekinumab. *British Journal of Dermatology*, **169**, 458-463. https://doi.org/10.1111/bjd.12331

[104] Warren, R.B., Smith, R.L., Campalani, E., Eyre, S., Smith, C.H., Barker, J.N., *et al*. (2008) Genetic Variation in Efflux Transporters Influences Outcome to Methotrexate Therapy in Patients with Psoriasis. *Journal of Investigative Dermatology*, **128**, 1925-1929. https://doi.org/10.1038/jid.2008.16

[105] Ovejero-Benito, M.C., Muñoz-Aceituno, E., Reolid, A., Saiz-Rodríguez, M., Abad-Santos, F. and Daudén, E. (2018) Pharmacogenetics and Pharmacogenmics in Moderate to Severe Psoriasis. *American Journal of Clinical Dermatology*, **19**, 209-222. https://doi.org/10.1007/s40257-017-0322-9

[106] Pivarcsi, A., Meisgen, F., Xu, N., Ståhle, M. and Sonkoly, E. (2013) Changes in the Level of Serum microRNAs in Patients with Psoriasis after Antitumour Necrosis Factor-*α* Therapy. *British Journal of Dermatology*, **169**, 563-570. https://doi.org/10.1111/bjd.12381

[107] García-Rodríguez, S., Arias-Santiago, S., Orgaz-Molina, J., Magro-Checa, C., Valenzuela, I., Navarro, P., *et al*. (2014) Abnormal Levels of Expression of Plasma microRNA-33 in Patients with Psoriasis. *Actas Dermo-Sifiliográficas*, **105**, 497-503. https://doi.org/10.1016/j.ad.2013.11.010

[108] Hawkes, J.E., Nguyen, G.H., Fujita, M., Florell, S.R., Duffin, K.C., Krueger, G.G. and O'Connell, R.M. (2016) microRNAs in Psoriasis. *Journal of Investigative Dermatology*, **136**, 365-371. https://doi.org/10.1038/JID.2015.409

[109] Frankel, H.C., Han, J., Li, T. and Qureshi, A.A. (2012) The Association between Physical Activity and the Risk of Incident Psoriasis. *Archives of Dermatology*, **148**, 918-924. https://doi.org/10.1001/archdermatol.2012.943