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A modern approach to the treatment of plaque psoriasis

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Psoriasis is a common chronic inflammatory skin disease which affects 0.5–1 % of children and 2–3 % of the adult population. In Croatia, 1.6 % of the population suffer from psoriasis. Distribution of the disease is bimodal, with the first peak at the age of 20–30, and the second at the age of 50–60. The etiopathogenesis of the disease is multifactorial, the key factors being genetic predisposition combined with immunological disorders, environmental factors and skin barrier damage. There are several clinical variants of the disease. The main signalling pathways in psoriasis include TNF-α, IL-23 and IL-17. Topical agents are used for the treatment of the mild form, and the systemic conventional therapy is used for the treatment of moderate to severe forms of the disease. In cases where's no response, or intolerance or contraindications are present, new targeted medications are to be administered. Development in the field of immunogenetics of psoriasis leads to personalized medicine.

Keywords: psoriasis, topical treatment, conventional systemic therapy, small molecules, biologicals

Psoriasis is a common chronic inflammatory skin disease which affects 0.5–1 % of children and 2–3 % of the adult population (1). It affects approximately 125 million people in the world. Prevalence ranges from 0.91 % in the USA to 8.5 % in Norway (2). Prevalence patterns vary across the world. In line with the beneficial effects of the UV radiation, there are fewer cases of psoriasis in countries closer to the equator compared to the countries that are further away.

In Croatia, approximately 70,000 people suffer from psoriasis, which represents 1.6 % of the population (3). Distribution of the disease is bi-modal, with the first peak at the age of 20–30, and the second at the age of 50–60. Despite the improvements in therapy and consequently in life-expectancy, patients affected by psoriasis are still more likely to die prematurely (4).

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The etiopathogenesis of the disease is multifactorial, the key factors being genetic predisposition combined with immunological disorders, environmental factors and skin barrier damage. Environmental factors that have been identified so far are drugs (imiquimod, lithium, beta blockers, IFNs and even anti-TNFs), infections (streptococcal throat infections), a physical trauma (Koebner phenomenon), smoking, alcohol and stress (5). Psoriatic lesional skin has increased levels of *S. pyogenes* and *S. aureus* compared to non-lesional and healthy skin (1). Psoriasis is a complex disease with more than 30 single nucleotide polymorphisms contributing to the risk of the disease (6). Two gene mutations, that can induce psoriasis independently (IL-36RN and CARD14), have been identified. There are at least 12 major PSORS psoriasis susceptibility loci identified (6). More than 60 % of patients suffering from psoriasis carry the HLA Cw0602, the disease loci associated haplotype (1). If one of the parents has psoriasis, their children have a 20 % chance of developing the disease, whereas if both of the parents are affected, the risk rises to 65 % (1). There is a 70 % probability of monozygotic twins to be affected by psoriasis and 20 % for dizygotic twins (1).

Nowadays, psoriasis is considered a systemic inflammatory disease and not just a skin disease. The notion of psoriatic march describes the cutaneous inflammation leading to a cascade of events that increases the risk of CVD in patients with severe psoriasis (2). There is a strong association between psoriasis and cardio-metabolic diseases, gastrointestinal diseases kidney disease, malignancy, infection and mood disorders. Furthermore, there are studies that point out the emerging comorbidities such as obstructive pulmonary disease, peptic ulcer, sexual dysfunction and sleep apnea. Some studies suggest that psoriasis is an independent risk factor for MACE (MI, stroke, death to CVD) (7). Lymphoma is also associated with psoriasis. This can be attributed to the pathophysiology of psoriasis or its treatment since methotrexate and cyclosporine have been associated with lymphoma. Patients with psoriasis have an increased risk of squamous cell carcinoma because of certain psoriatic treatments such as PUVA (8).

There are several clinical variants of the disease out of which the most important are chronic plaque psoriasis (85–90 %), eruptive guttata psoriasis, pustular psoriasis and erythrodermic psoriasis (5) (Fig. 1–3).

Chronic plaque psoriasis is characterized by well-demarcated erythematous plaques with adherent silver scales (9). Psoriasis guttata (or eruptive psoriasis) is a form of psoriasis usually preceded by streptococcal infection of the upper respiratory tract and is characterized by numerous tiny erythematosquamous lesions, the size of a droplet (10). One third of children affected by this form of psoriasis develop plaque psoriasis later in life (11).

Generalized pustular psoriasis is a rare but life-threatening disease. It is characterized by the episodic appearance of sterile pustules together with widespread skin and systemic inflammation (5). An erythrodermic psoriasis is a form of psoriasis marked by generalized erythema and exfoliation. This is a potentially life-threatening condition with systemic manifestations such as hypothermia, oedema, myalgia and malaise. It can be provoked by abrupt withdrawal of drugs like methotrexate or corticosteroids from the therapy (11).

Psoriatic arthritis affects between 1.3 and 34.7 % of patients diagnosed with psoriasis. The clinical symptoms vary with the most common being enthesitis, peripheral arthritis, spondylitis, dactylitis (Global report) and arthritis mutilans (12).

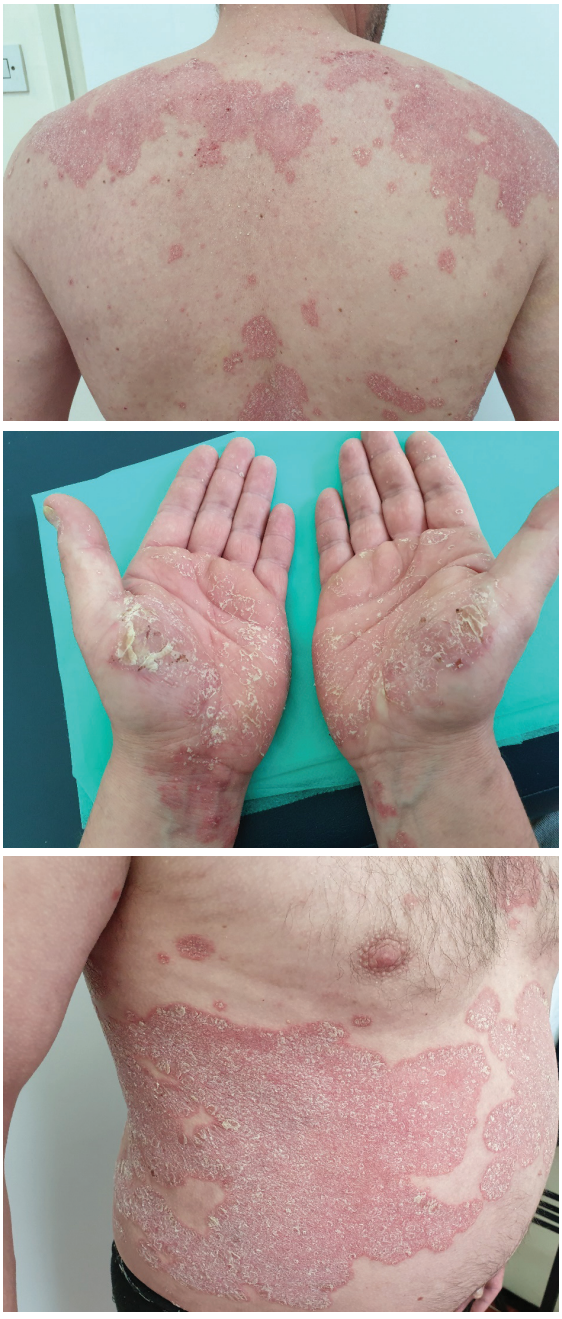

Fig. 1. Clinical presentation of plaque psoriasis: a) on the back, b) on the palms, c) on the trunk. The patient gave written consent to the authors for the use of these photographs.

Psoriasis is a highly visible condition and patients have to endure social stigma due to the nature of the disease (2). They feel ashamed and guilty, the disease has a detrimental effect on their interpersonal relationships, sexual well-being and capacity for intimacy (1).

The severity of the disease is associated with a higher level of systemic inflammation. Psoriasis shares many inflammatory processes and predisposing factors with its comorbidities and associated diseases (7).

Today, it is widely accepted that the main signalling pathways in psoriasis include TNF-α, IL-23 and IL-17. It has been established that different cytokines dominate in various clinical presentations of psoriasis, *e.g.* interferon γ dominates in the acute erythrodermic psoriasis, TNF-α, IL-23/IL-17 in the chronic plaque psoriasis, and IL-36/IL-1 in pustular psoriasis (13). The TNF-α-IL-23-Th17 axis seems to be pivotal in the pathogenesis of plaque psoriasis. Aberrant dermal dendritic cells produce TNF-α and IL-23 which stimulate Th17 and Tc17 cells to migrate into the epidermis where they identify epidermal autoantigens and start producing IL-17 and IL-22 (13).

Additional important effector cells such as neutrophils, mast cells and monocytes, mediators and potential autoantigens are being investigated as a possible new targeted therapy.

Melanocytes, but not the keratinocytes, have been identified as target cells of an HLA--Cw6 restricted CD8 T cell clone found in the psoriatic plaques (14).

Before selecting the treatment, it is necessary to establish the severity of the disease. When estimating the severity of chronic plaque psoriasis, three scales are commonly used and those are: PASI score (psoriasis area and severity index), BSA (body surface area) and DLQI (dermatological quality of life index). PASI score is the most commonly used method for the evaluation of the severity of the disease on a scale from 0 to 72. This method takes into account the skin surface covered with psoriatic lesions as well as the degree of erythema, induration and desquamation of the lesions. BSA is a method used to establish the percentage of skin covered with psoriatic lesions. DLQI is a scale which is used to estimate the effect of psoriasis on the patient's everyday life, social interaction and his overall well-being.

According to the guidelines, mild psoriasis is defined by PASI and/or BSA and/or DLQI levels equal or less than 10, and moderate and severe psoriasis have PASI and/or BSA and/or DLQI levels exceeding 10 (3).

Topical therapy

Topical agents are used for the treatment of the mild form of the disease.

Emollients keep the skin moist and soft, thus minimizing the itching, tenderness or subsequent development of psoriatic lesions at the sites of potential trauma. They are an important addition to psoriasis treatment (15).

Mid to high-potency topical corticosteroids reduce inflammation rapidly and induce regression of lesions, especially when applied under occlusion. Long-term treatment can lead to skin atrophy, telangiectasia or stretch marks. Topical corticosteroids can be applied in intermittent regimen in patients with quick recurrence of psoriatic lesions. Non-fluorinated corticosteroids are used for facial, genital and intertriginous lesions (15, 16).

Calcineurin inhibitors. Although not officially approved**,** both tacrolimus ointment and pimecrolimus cream have proven to be helpful in the treatment of intertriginous and

facial psoriasis. They penetrate well in the skin folds and the risk of prolonged corticosteroid use is avoided. Possible risk of lymphoma and skin cancer in patients on topical calcineurin inhibitors was reported but subsequent studies have not confirmed it (17).

Vitamin D analogues calcipotriol and tacalcitol reduce the proliferation of keratinocytes and modulate T cell and dendritic cell function. Combination of calcipotriol and potent corticosteroids has shown better clinical results and tolerance compared with either agent used as a monotherapy (18).

Tars and dithranol are used less frequently nowadays, as well as topical retinoids such as tazarotene.

Along with topical drugs, phototherapy and different forms of systemic therapy such as retinoids, methotrexate and cyclosporine are used for the treatment of moderate to severe psoriasis (3).

Photo- and photochemotherapy

In patients who do not respond adequately to local therapy, narrow band (311 nm wavelength) UVB phototherapy is a good treatment option (3, 15, 19). The initial dose of UVB light is determined by the skin phototype and/or minimal erythema dose. The dose is gradually increased during the therapy. This treatment is usually administered 3 to 5 times per week for 3 to 4 weeks. It is especially effective in treating psoriasis guttata (20, 21).

PUVA photochemotherapy combines UVA irradiation and photosensitizer psoralen. It induces the remission of psoriasis by repeated controlled phototoxic reactions. Psoralen is a furocoumarin, which is found in many plants. Psoralen molecules intertwine with DNA strands and, when exposed to UVA, form DNA adducts and thus inhibit cell proliferation. They can be used systemically, topically and as bath therapy (16). The initial dose of UVA light is determined by the skin phototype and/or the minimal phototoxic dose. The treatments are administered up to four times per week during three to four weeks. Chronic adverse effects include increased risk of squamous cell carcinoma, skin ageing and the development of PUVA lentigines and even melanoma (16).

Conventional systemic therapy

Retinoids – acitretin is an aromatic retinoid, a derivative of vitamin A, with antiproliferative and anti-inflammatory effect. In treating plaque psoriasis, retinoids are nowadays usually combined with UVB (Re-UVB) or PUVA (Re-PUVA) in order to increase the effect of phototherapy and to decrease the exposure to UV-light. As monotherapy for plaque psoriasis, acitretin is prescribed in a daily dose of 20–50 mg for 2 to 4 weeks (or more if needed), regardless of the patient's weight. The standard dose for the treatment of psoriatic erythroderma is 0.25 to 0.5 mg kg^{-1}, and for pustular psoriasis 0.75 to 1 mg kg^{-1}. Maintenance dose for all types of psoriasis is 0.125–0.5 mg kg^{-1} (22). The side effects of acitretin are dose-related and are almost always reversible upon the drug withdrawal. The most common side effects are dryness of the lips, cheilitis, and dryness of other areas of the skin, eyes and of the nasal mucosa. Night vision might be disturbed. Effluvium might occur. In around half of the patients elevated cholesterol and triglyceride levels are reported and in about 25 % of liver function tests are abnormal. Rare adverse changes comprise bone and joint pain and elevated intracranial pressure. The main contraindication to

the use of acitretin is pregnancy, due to its teratogenicity. In case of use in women of childbearing potential, pregnancy test as well as reliable contraceptive measures must be administered during therapy and two to three years after discontinuing the drug (22).

Methotrexate is the folic acid antagonist. It is effective as long-term therapy for both psoriasis and psoriatic arthritis. Methotrexate inhibits the enzyme dihydrofolate reductase which leads to inhibition of purine synthesis. In lower doses, it induces the apoptosis of activated T cells, and at higher it blocks the DNA synthesis and cell proliferation. Methotrexate is administered orally or subcutaneously once a week. The initial dose is 7.5 mg per week. This can be gradually elevated up to the maximum dose of 25 mg (22). The acute side effects of methotrexate include erosions on the oral mucosa, gastrointestinal problems such as diarrhea, bleeding, ulcers, bone marrow suppression (thrombocytopenia, leukopenia, anemia) and effluvium. Chronic side effects might include pulmonary fibrosis, hepatotoxicity, chronical renal impairment and troubles with spermatogenesis. Absolute contraindications to its use are severe infections, bone marrow suppression, pregnancy, peptic ulcer, alcoholism, and impaired liver function (22).

Cyclosporine is a highly and rapidly effective cyclic polypeptide, a calcineurin inhibitor which inhibits T cell activation and IL-2 cytokine production. The recommended initial dose is 2.5 mg kg^{-1}. This level can be continued if the patients show improvement after one month of treatment, but if not, the dose can be elevated to 5 mg kg^{-1} (22). Cyclosporine is used for the treatment of pustular psoriasis as well but in a higher initial dose. It is seen as an interventional therapy and is not recommended for long-term treatment. The lowest possible maintenance dose should be used. Cyclosporine can cause renal impairment, with increased creatinine and potassium levels and decreased glomerular filtration rate. Renal vascular damage might occur and it is irreversible. Other common adverse effects are gingival hyperplasia, hypertrichosis and tremor (16). Contraindications include hypersensitivity to cyclosporine, malignancies other than epidermal carcinomas, unregulated hypertension, renal impairment, severe infections and concomitant PUVA therapy (19).

Dimethyl fumaric esters are licensed as the induction therapy for moderate to severe psoriasis in Germany (23). Their mechanism of action seems to be immunomodulatory, inducing apoptosis of activated T cells and alteration of the cytokine secretion. The initial dose of 0.2 mg per day is slowly increased to avoid the severity of side effects such as flushing, nausea, vomiting and heartburn. The maximum dose is 1.2 mg per day, but most patients require 0.4 to 0.8 mg. During the first week, eosinophilia appears, whereas later on lymphopenia develops. Proteinuria is a serious adverse effect (16, 22).

If patients, suffering from moderate to severe psoriasis, do not respond, cannot tolerate or have a contraindication for the conventional systemic therapy (PUVA, retinoids, methotrexate, cyclosporine), they become candidates for the administration of new targeted medications such as small molecules and biologics, according to the European or local guidelines (19, 23).

Targeted therapies – Small molecules

Apremilast is an oral medication used for the treatment of moderate to severe plaque psoriasis. By increasing the level of cAMP, this phosphodiesterase-4 inhibitor reduces the production of various mediators that play a crucial role in the development of psoriasis

(24). The standard dosage is 30 mg twice daily after 6 days of gradually increasing the dosage. Apremilast appears to be effective for nail psoriasis and for palmoplantar and scalp psoriasis (25). This drug is also effective in psoriatic arthritis. PASI 75 response is achieved in 33 % of patients in the sixteenth week of the treatment. It is shown as a relatively safe and effective treatment in the combination with systemic, biologic or phototherapy in the treatment of chronic plaque psoriasis, reflected by achieving PASI 75 (26). Recommended laboratory controls include complete blood count, liver enzymes and renal function. Apremilast has a very good safety profile due to its non-immunosuppressive mechanism of action (26). Diarrhea is the most common side effect, whereas others include vomiting, dyspepsia, abdominal pain, upper respiratory infections, fatigue, insomnia, migraine, weight loss (23). The most severe side-effect is depression, including suicidal ideation (22).

Targeted therapies – Biologics

Medications that specifically target TNF-α, IL-23/IL-12, IL-17 and IL-23 are currently available (Table I). Biologics are generally well tolerated and mostly used as a monotherapy. TNFα inhibitors are effective in both psoriasis and psoriatic arthritis. Suggested controls include blood count, liver enzymes, CRP, creatinine, urine analysis. Prior to the therapy, initiation pregnancy test, HBV, HCV, HIV and tuberculosis screening including chest X-ray is advised. Breastfeeding, demyelinating disease, active chronic hepatitis B, active tuberculosis, localized infections and congestive heart failure (NYHA III/IV) are absolute contraindications for the administration of TNFα inhibitors. Injection site reactions, infections, bone marrow suppression, demyelinating disease, drug-induced lupus, lymphoma and solid malignancies are possible adverse events. Formation of antibodies against anti TNFs might reduce the response to therapy (27). Combination with methotrexate might prevent the formation of antibodies (19).

Adalimumab, initially used for treating patients suffering from rheumatoid arthritis, is a humanized monoclonal antibody targeting TNFα. The initial dosage is 80 mg subcutaneously, followed by 40 mg every two weeks, starting one week after the first dose (19, 22). The clinically significant response is expected after four weeks. PASI 75 is achieved in 53–80 % patients. Formation of antibodies against adalimumab is reported in 6 to 50 percent of patients treated which might reduce the response to the therapy (27). Adalimumab biosimilars comprise adalimumab-atto and adalimumab-admb. A randomized trial that compared adalimumab with adalimumab-atto in 350 patients with moderate to severe psoriasis showed similar efficacy and safety after 16 weeks of treatment in both treatment groups (28).

Infliximab is a chimeric monoclonal antibody against TNF-α. It has a faster onset of action compared to other commercially available biologic agents. The recommended dosage is 5 mg kg^{-1} administered in intravenous infusion at weeks 0, 2 and 6 and every eight weeks subsequently (19, 21). A clinically significant response is expected after 1 to 2 weeks. About 80 % of patients achieve PASI 75, ten weeks after therapy initiation. Anti-infliximab antibodies have been reported in 5 to 55 percent of patients who receive infliximab (29). Switching to infliximab-dyyb, a biosimilar to infliximab is not inferior to the original therapy (30).

Etanercept is the antagonist of the TNF-α receptor. The standard dosage for etanercept is 25 mg twice a week or 50 mg once a week. In overweight patients or in severe psoriasis 50 mg can be given twice a week up to three months, followed by a dose of 25 mg

twice a week or 50 mg once a week (19, 22). PASI 75 is achieved in 33 or 49 % of patients after 12 weeks. The formation of anti-etanercept antibodies has been reported, but unlike the antibodies against adalimumab and infliximab, they do not seem to reduce the efficacy of the treatment (27).

IL-12/IL-23 inhibitors. Ustekinumab is a human monoclonal antibody that targets p40 subunit shared by IL-12 and IL-23. Dosage of ustekinumab is weight-based. The recommended dosage for adults weighing ≤ 100 kg is 45 mg ustekinumab given at weeks 0, 4, and every 12 weeks thereafter. A 90 mg dosage is recommended for adults weighing > 100 kg. Ustekinumab can also improve psoriatic arthritis (19, 22). This medication showed PASI 75 response in 75 % of the patients who received 45 mg and in 69 % who received 90 mg (31). Risk of major adverse cardiovascular events was detected in early phase clinical trials with ustekinumab. However, subsequent larger trials have not confirmed this finding (32, 33). Possible side effects include headache and nasopharyngitis. Anti-ustekinumab antibodies have been reported in 4 to 6 patients treated, but the effect of the antibodies on the treatment efficacy is yet to be established (27).

IL-17 targeted therapies are effective in both psoriasis and psoriatic arthritis. In patients treated with IL-17 inhibitors, the development or exacerbation of inflammatory bowel disease have been noticed (34). Candida infections are more common under this treatment (13).

Secukinumab is an anti-IL-17A monoclonal antibody. The standard dosage is 300 mg subcutaneously once a week at weeks 0, 1, 2, 3 and 4 and every four weeks thereafter (23, 34). Dosage of 150 mg is adequate for some of the patients.

Ixekizumab is a humanized monoclonal antibody against IL-17A. The standard dosage for ixekizumab is 160 mg at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, 12 and every four weeks thereafter (15).

Brodalumab is an anti-IL-17 receptor A monoclonal antibody. The recommended dosage is 210 mg given at weeks 0, 1, and 2 and then every two weeks (15).

IL-23 targeted therapies. Guselkumab is a human immunoglobulin G1 lambda monoclonal antibody that targets p19 subunit of IL-23. The standard dose is 100 mg at weeks 0, 4 and every eight weeks thereafter. Its efficacy for psoriatic arthritis is still under evaluation. At week 16, PASI 75 response was achieved in 85.1 % and PASI 90 in 73.3 % of patients (35). Common adverse events include upper respiratory infections, tinea and herpes simplex infections, arthralgia, diarrhea and gastroenteritis.

Tildrakizumab is a human immunoglobulin G1 kappa monoclonal antibody targeting p19 subunit of IL-23. The standard dose is 100 mg subcutaneously at weeks 0, 4 and every twelve weeks thereafter. It has demonstrated a 74 % PASI 75 and 52 % PASI 90 response in the sixteenth week of therapy (36).

Risankizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody selective to IL-23 protein produced in Chinese Hamster Ovary cells using recombinant DNA technology. It has shown 88 % PASI 75, 81.5 % PASI 90 and 48 % PASI 100 at week 12. Despite having received the last injection at week 16, 26 % of patients remained clear after 48 weeks (PASI 100) (37).

Targeted therapies in special patient populations: biologics should be avoided during pregnancy, anti-TNFs should be discontinued 1 to 2 weeks before surgery and can be re-

Table I. Biologics approved for psoriasis

Biologic drug	Target	Administration	Treatment algorithm	Approved for psoriatic arthritis
Etanercept	TNFα	subcutaneous	25 mg twice a week or 50 mg once a week. In overweight patients or in severe psoriasis 50 mg can be given twice a week up to three months, followed by a dose of 25 mg twice a week or 50 mg once a week	+
Infliximab	TNF-α	intra-venous	5 mg kg^{-1} on week 0,2 and 6, then every 8 weeks	+
Adalimumab	TNF-α	subcutaneous	80 mg initial dose, then 40 mg every 2 weeks, starting one week after the initial dose	+
Ustekinumab	IL-12 / IL-23 p40	subcutaneous	45 mg (≤ 100kg) or 90 mg (> 100 kg) on week 0 and 4, then every 12 weeks	+
Secukinumab	IL-17A	subcutaneous	300 mg on week 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks	+
Ixekizumab	IL-17A	subcutaneous	160 mg week 0, then 80 mg week 2, 4, 6, 8, 10, 12, then 80 mg every 4 weeks	+
Brodalumab	IL-17A receptor	subcutaneous	210 mg on week 0, 1, and 2, then every 2 weeks	+
Guselkumab	IL-23 p19	subcutaneous	100 mg at weeks 0, 4 then every 8 weeks	
Tildrakizumab	IL-23 p19	subcutaneous	100 mg subcutaneously at weeks 0, 4 and then every 12 weeks	
Risankizumab	IL-23 p19	subcutaneous	150 mg (two 75 mg injections) administered by subcutaneous injection at week 0, week 4, and then every 12 weeks	

sumed after 1 to 2 weeks after, live vaccines are contraindicated, biologics should be avoided in patients with active malignancy and lymphoma (13). The following biologics are approved for the use in children: etanercept (from 6 years of age), ustekinumab (from 12 years of age) and adalimumab (from 4 years of age) (38). Certolizumab pegol is considered safe for use in pregnancy and breastfeeding (38).

Therapeutic goals

According to the treatment guidelines, PASI 75 is still the gold standard (19, 22, 23). However, as new therapies show higher efficacy and patient expectations became higher, today PASI 90 (almost clear skin) and PASI 100 (clear skin) are becoming new treatment targets. These new targets are associated with the improvement in the patient's quality of

life (39). Group of authors suggest cut-off of „5" for both PASI and DLQI, where dermatologists should consider changing the treatment if the target is not achieved (14). The aim of the treatment is to prevent progression or development of comorbidities and to control systemic inflammation (40).

Treatment of patients with psoriasis and comorbid conditions

For patients with psoriasis and psoriatic arthritis, TNF inhibitors are the suggested first option. If there is no response, IL-17 inhibitors should be considered. If arthritis is mild and psoriasis severe, ustekinumab might be the option. In patients with psoriasis and multiple sclerosis, ustekinumab and IL-17 inhibitors are the right treatment option, while TNF inhibitors should be avoided, due to possible worsening of the disease. Patients with psoriasis and congestive heart failure can be treated with ustekinumab and IL-17 inhibitors, while all TNF inhibitors should be avoided. In patients with psoriasis and inflammatory bowel disease adalimumab, infliximab and ustekinumab would be the best treatment option. Ustekinumab is still considered the first option for patients with psoriasis and hepatitis B. IL-17 inhibitors should be considered as the second option. TNF inhibitors reduce host immune defences and might allow reactivation of hepatitis B. Therefore, TNF inhibitors are considered as a third option. Before initiating the TNF inhibitors, screening for hepatitis B should be performed. Vaccination is recommended to all non-immune patients. Screening for latent tuberculosis infection should be performed in all patients planned for biologics. Anti-TB prophylaxis for a minimum of 1–2 months should be provided to all of the patients before initiating the therapy. The first option for this patient group is ustekinumab followed by IL-17 inhibitors and anti-TNFs as the last option (38).

CONCLUSIONS

Some authors suggest the term moderate psoriasis should be reintroduced and small molecules, such as apremilast or dimethyl fumaric esters, might be considered as an ideal first-line therapy for patients with moderate psoriasis, whereas biologics might be regarded as a first-line therapy for severe psoriasis (14). Many studies have given us an insight into the coexistence of psoriasis and other serious systemic diseases. An interdisciplinary approach of different specialities is needed for the diagnosis and treatment of comorbidities and associated diseases. Comorbidities and associated diseases have a direct influence on dermatologist's decision regarding the treatment of a patient with psoriasis. The choice of the treatment is based on the safety profile of the treatment, patient's comorbidities and special indication profile (13). Developments in the field of immunogenetics of psoriasis enable new research of different forms of targeted therapy which could enable personalised medicine. The goal of individualised treatment is the best possible response to therapy and the best possible safety profile. Implementation of personalized medicine is possible because different biomarkers have been identified by genetic and epigenetic testing. They correlate with the severity of the disease (HLA Cw*0602 is associated with early onset and severe form of psoriasis), they monitor the efficacy of therapy in relation to the pathogenetic mechanism (IL-23/IL-17 axis), and they predict the treatment efficacy (TNFAIP3 gene and response to anti-TNF therapy, or HLA Cw*0602 and ustekinumab) (41).

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