Acad Med J 2025;5(Suppl 1):S1-S8.
UDC: 616.517-085
https://www.doi.org/10.53582/AMJ255101s
Guidelines

GUIDELINES FOR SYSTEMIC TREATMENT OF PATIENTS WITH PSORIASIS AT THE UNIVERSITY CLINIC FOR DERMATOLOGY – SKOPJE

Sotirovski Tomica, Damevska Katerina, Peshikj Nebojsha, Mirchevska Arsovska Elena, Filipovikj Dejan, Batkoska Shekutkoska Bojana, Simeonovski Viktor, Najdova Anita, Popovski Tomche, Doneva Simonov Kamelija, Stoicovska Ema

University Clinic for Dermatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
email: tomicasot@gmail.com

Abstract

Psoriasis is a chronic autoimmune disease that causes inflammation in your skin and encompasses several disease subtypes (plaque, inverse, guttate, pustular, erythrodermic, nail and sebopsoriasis), requiring a standardized approach to diagnosis and treatment. According to current recommendations, the treatment involves the use immunosuppressants and biologic therapy which has already been approved as a first-line treatment for moderate to severe psoriasis in Europe and USA. These guidelines are made for the needs of the University Clinic for Dermatology – Skopje and are based on the European guidelines on the systemic treatment of psoriasis (EuroGuiDerm Guidelines on the systemic treatment of Psoriasis vulgaris, 2020). They include a system for grading disease severity, and recommendations for treatment and monitoring. Systemic treatment modalities included in these guidelines are: acitretin, ciclosporin, methotrexate, adalimumab, apremilast, brodalumab, certolizumab, pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab.

Objectives of the guidelines

The primary objective of these guidelines is to provide guidance for the optimal choice of treatment for adult patients with moderate to severe plaque psoriasis, aiming to reduce disease-induced morbidity and improve the disease-related quality of life.

The recommendations are evidence-based, considering the results of systematic reviews obtained with rigorous methods and the practical experience of experts.

Target group of users of the guidelines

The Guideline is primarily intended for dermatologists at the University Hospital for Dermatology in Skopje.

Methodology

These guidelines are based on EuroGuiDerm, Guideline on the systemic treatment of Psoriasis vulgaris – Methods&Evidence Report, available on the EDF website:

https://www.guidelines.edf.one/guidelines/psoriasis-guideline [1]

Guideline development and consensus process

The chapters and recommendations were developed by a working group of specialist physicians at the Dermatology Clinic with extensive experience in clinical dermatology and

the treatment of patients with psoriasis, as well as resident physicians involved in the technical preparation of the text.

Each chapter and all recommendations were reviewed, discussed, and amended where necessary. The Expert Collegium and then the Management Board of the PHI Dermatology Clinic, Skopje, reviewed and adopted the Guideline with the necessary consensus.

Psoriasis severity

The most accepted tool for determining the severity of skin symptoms in psoriasis is the Psoriasis Area and Severity Index (PASI) score, introduced in 1978 [2]. The Dermatology Life Quality Index (DLQI) is the most commonly used questionnaire to assess the impact of psoriasis on health-related quality of life HRQoL. It consists of 10 questions related to symptoms, mental health, impact on daily life, leisure time, work, school, interpersonal relationships, and the burden of psoriatic treatment[3]. The questionnaire, translated into Macedonian and validated by Cardiff University in 2012, is an integral part of this Guideline (Annex 1). Permission was sought from the authors to use this questionnaire.

The Expert Collegium at the University Clinic of Dermatology Skopje has endorsed the use of PASI and DLQI for assessing the severity of psoriasis.

The first European consensus to define the goals of treatment for moderate to severe psoriasis was introduced in 2011[4]. According to that consensus, moderate to severe psoriasis was defined as PASI > 10 or BSA > 10 and DLQI > 10, and mild form of psoriasis PASI ≤ 10 and BSA ≤ 10 and DLQI ≤ 10 [4].

Treatment goals

Successful treatment is defined as improvement of PASI by at least 75%. Unsuccessful treatment is not achieving od PASI improvement of 50%. Achieving PASI improvement between 50% and 75% and improving DLQI score by 5 or less is considered a successful treatment [4].

There are a number of measures that can be applied to increase the effectiveness of therapy, such as increasing the dose, reducing the time between two therapies or adding another medicine (combination therapy); however, with certain medications this may constitute therapy outside the protocols, as such variations are not part of the drug's instructions for use. When dose adjustments are ineffective or inappropriate, changing the medication is an important step. Because there is little evidence on how to switch from one drug to another, the global a consensus program provides guidelines based on evidence from the literature and expert opinion [5].

Treatment modalities included in these guidelines are the conventional approach (acitretin, ciclosporin, methotrexate), biological therapy targeting TNF (adalimumab, etanercept, certolizumab, pegol, infliximab), biological therapy targeting IK-12/23p40 (ustekinumab), IL-17A (ixekizumab, secukinumab), IL-17RA (brodalumab), IL-23p19 (guselkumab, Risankizumab, tildrakizumab) and the group of so called “small molecules” (apremilast).

This discussion will be limited to the treatment modalities currently available within our clinical setting, as these constitute the only options presently accessible in this context.

Acitretin

Instructions for use

Pre-treatment:

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI)
- History and clinical examination should focus on musculoskeletal problems. If patient reports complaints, further imaging investigation may be performed Exclude pregnancy/breastfeeding: patient must be informed explicitly and extensively about the teratogenic risk of the medication, the necessity of effective long-term contraception (three years after cessation of treatment), and the possible consequences of becoming pregnant while taking retinoids; written documentation of this informational interview should be obtained
- Note that during and up to three years after treatment, blood donation is not permitted
- Laboratory parameters (blood count, liver enzymes, serum creatinine, pregnancy test, blood glucose, triglycerides, cholesterol, HDL) [6,7,8]

During treatment:

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI/Skindex-29 or -17)
- Take capsules with a meal containing some fat or with whole milk to improve absorption
- In order to prevent elevation of serum lipids and liver enzymes, alcohol abstinence and a low-fat and low-carbohydrate diet are advised.
- Preventing pregnancy is mandatory. After satisfactory contraception for at least one month prior to treatment, start treatment on second or third day of the menstrual cycle. . Double contraception is recommended (e. g., condom + pill; IUD/Nuva Ring + pill; cave: no low-dosed progesterone preparations/mini-pills) during and up to three years after end of therapy; effectiveness of oral contraceptives is reduced by acitretin
- Ask patient about spine and joint complaints at follow-up visits. If patient reports complaints, further imaging investigation may be performed
- Laboratory parameters (blood count, liver enzymes, pregnancy test, triglycerides, cholesterol, HDL) [6,7,8]

Post-treatment:

- Reliable contraception in women of child-bearing age for up to three years after therapy, double contraception, as described above, is recommended
- Patients may not donate blood for up to three years after the discontinuation of therapy

Adverse drug reactions [9,10]

- Hypertriglyceridemia
- Dryness of skin and mucosa
- Possibility of hair loss

Contraindications[11]

Absolute contraindications:

- Severe renal or hepatic dysfunction or hypertriglyceridemia

- As there are many other treatment options available, women of child-bearing age should generally not be treated with acitretin. Breastfeeding is also an absolute contraindication.
- Alcoholism
- Blood donation

Relative contraindications:

- Diabetes mellitus
- Hypertriglyceridemia
- History of pancreatitis

Ciclosporin (CsA)

Instructions for use [6,7]

Pre-treatment:

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI)
- History and clinical examination should focus on previous and concomitant diseases (e. g., arterial hypertension; severe infections; malignancies, including cutaneous malignancies; renal and liver diseases) and concomitant medication (see drug interactions)
- Measurement of the blood pressure on two separate occasions
- Laboratory parameters (full blood count, liver enzymes, Na, K, Mg, serum creatinine, urine status, uric acid, pregnancy test, cholesterol, triglycerides, HBV, HIV)
- Reliable contraception (caution: reduced efficacy of progesterone-containing contraceptives)
- Regular gynecologic screening according to national guidelines
- Consultation on vaccination; susceptibility to infections (take infections seriously, seek medical attention promptly); drug interactions (inform other treating physicians about therapy); avoidance of excessive sun exposure; use of sunscreens

During treatment:

During therapy with low dose ciclosporin (CsA; 2.5 to 3 mg/kg daily), follow-up intervals may be extended to two months or more. Shorter intervals may be needed in patients with risk factors, after dose increases, or those who must take concomitant medications that are likely to contribute to adverse drug reactions. Objective assessment of the disease (such as PASI/BSA/PGA; arthritis) [6,7,8]

- HRQoL (such as DLQI)
- Clinical examination should focus on status of skin and mucous membranes (hypertrichosis, gingival changes), signs of infections, gastrointestinal or neurological symptoms (tremor, dysaesthesia), musculoskeletal/joint pain
- Repeat recommendation for sun avoidance and sun protection
- Check of concomitant medication
- Measurement of blood pressure
- Laboratory parameters (full blood count, liver enzymes, Na, K, Mg, serum creatinine, urine status, uric acid, cholesterol, triglycerides)
- Reliable contraception
- Regular gynecologic screening according to national guidelines

- If creatinine is significantly elevated and/or patient on therapy for > one year, perform creatinine clearance (or creatinine-EDTA clearance where available).
- Determination of the CsA level is recommended in selected cases

Post-treatment:

- After discontinuation of CsA, patients should be followed up for skin cancer, especially in case of extensive prior therapeutic or natural UV exposure

Adverse drug reactions[10]:

- Kidney abnormalities
- Malignancies
- Infections

Contraindications[12]

- Impaired renal function
- Insufficiently controlled arterial hypertension
- Severe infectious disease
- History of malignancy (possible exceptions: treated basal cell carcinoma, history of squamous carcinoma in situ)
- Current malignancy
- Simultaneous PUVA therapy or extensive previous UV exposure with high risk of cutaneous malignancy
- Severe hepatic diseases (e.g. liver failure)
- Breastfeeding

Methotrexate (MTX)

Instructions for use [13]

MTX should be preferentially given subcutaneously once weekly for increased safety (oral intake has higher risk for overdosing as patients are more likely to take tablets daily instead of once weekly) and improved bioavailability (MTX is a prodrug that is polyglutaminated into its active in vivo moiety; polyglutamination is linked to efficacy) 46. The recommended initial and maintenance dose is usually 15 mg MTX once weekly. In case of insufficient response, the dose can be increased up to 20 mg MTX once weekly. A further increase up to 25 mg MTX is only beneficial for a small subgroup of patients, no further dose-increase is recommended 47. S.c. dosing is recommended in patients with suboptimal response to oral treatment and may be considered as the starting route of administration in high need patients.

Pre-treatment:

- History and clinical examination
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI)
- Laboratory controls (blood count, liver enzymes, serum creatinine, urine status, pregnancy test, HBV/HCV, HIV, serum albumin)
- Chest X-ray
- Reliable contraception in women of child-bearing age (starting after menstruation), and also in men

- If abnormalities in liver screening are found, refer patient to specialist for further evaluation

During treatment:
- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI)
- Check concomitant medication
- Clinical examination
- Laboratory controls (blood count, liver enzymes, serum creatinine, serum albumin)
- Reliable contraception in women of child-bearing age, and also in men
- 5 mg folic acid once weekly 24 hours after MTX
- Advise alcohol abstinence

Post-treatment:
- Women should be advised not to become pregnant for at least six month and men must not conceive for at least three months thereafter

Adverse drug reactions:
- Myelosuppression
- Hepatotoxicity
- Hypoalbuminemia and reduced renal function increase the risk of ADR
- Nausea, malaise
- Hair loss
- Depression
- Infections

Contraindications
Absolute contraindications:
- Severe infections
- Severe liver disease
- Renal failure
- Pregnancy / breastfeeding
- Alcohol abuse
- Bone marrow dysfunction/haematologic changes
- Immunodeficiency
- Acute peptic ulcer
- Significantly reduced lung function

Relative contraindications:
- Kidney or liver disorders
- Old age
- Ulcerative colitis
- History of hepatitis
- Lack of compliance
- Active desire to become pregnant
- Gastritis
- Obesity (BMI>30)

- Diabetes mellitus
- Previous malignancies

Secukinumab [14,15,16,17]

Instructions for use

Pre-treatment:

- Physicians are encouraged to enrol their patients in a registry (if available)
- Objective assessment of disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI)
- Medical history and physical examination including prior exposure to treatments, malignancies, infections, inflammatory bowel disease
- Recommended measures include:
  - Check for skin cancer
  - Check for lymphadenopathy
  - Laboratory parameters (full blood count, liver enzymes, serum creatinine, urine status, pregnancy test, CRP, HBV/HCV, HIV, tuberculosis)
  - Exclusion of tuberculosis
  - Check for evidence of active infection
  - Check need for vaccines
- Reliable contraception

During treatment:

- Objective assessment of the disease (such as PASI/BSA/PGA; arthritis)
- HRQoL (such as DLQI)
- Laboratory parameters (full blood count, liver enzymes)
- Medical history and physical examination focusing on infections (in particular upper respiratory tract infections, candida, tuberculosis), contraception, signs or symptoms of inflammatory bowel disease

Post-treatment:

- After discontinuation of secukinumab, patients should be followed up with medical history and physical examination
- For information regarding the ongoing need for contraception immediately following biologic treatment cessation, please see chapter “wish for child / pregnancy

Adverse drug reactions:

- Infections
- Neutropenia
- Crohn's disease
- Candidiasis

Contraindications

Absolute contraindications:

- Clinically important active infections

Relative contraindications:

- Pregnancy or breastfeeding
- Inflammatory bowel disease

Conflict of interest statement. None declared.

References:

1. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: treatment and monitoring recommendations. *J Eur Acad Dermatol Venereol*. 2020;34(11):2461–98. doi:10.1111/jdv.16915
2. Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238–44. doi:10.1159/000250393
3. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210–6. doi:10.1111/j.1365-2230.1994.tb01167.x
4. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res*. 2011;303(1):1–10.
5. Mrowietz U, de Jong EM, Kragballe K, et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2014;28(4):438–53. Nast A, Spuls PI, van der Kraaij G, et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab - EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2017;31(11):1951–63. doi:10.1111/jdv.14390
6. Pathirana D, Ormerod AD, Saiag P, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol*. 2009;23(Suppl 2):1–70.
7. Gisondi P, Altomare G, Ayala F, et al. Italian guidelines on the systemic treatments of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(5):774–90. doi:10.1111/jdv.14014
8. Kragballe K, Jansen CT, Geiger JM, et al. A double-blind comparison of acitretin and etretinate in the treatment of severe psoriasis. Results of a Nordic multicentre study. *Acta Derm Venereol*. 1989;69(1):35–40.
9. Samarasekera EJ, Sawyer L, Parnham J, Smith CH. Assessment and management of psoriasis: summary of NICE guidance. *BMJ*. 2012;345:e6712. doi:10.1136/bmj.e6712
10. Amatore F, Villani AP, Tauber M, Viguier M, Guillot B. French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults. *J Eur Acad Dermatol Venereol*. 2019;33(3):464–83. doi:10.1111/jdv.15377
11. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. *J Am Acad Dermatol*. 2009;61(3):451–85. doi:10.1016/j.jaad.2009.06.037
12. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
13. European Medicines Agency. Cosentyx - Summary of product characteristics (Annex I). 01/04/2016. Cosentyx -EMEA/H/C/003729 -II/0008.2016.
14. Deodhar A, Mease PJ, McInnes IB, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. *Arthritis Res Ther*. 2019;21(1):111. doi:10.1186/s13075-019-1876-6
15. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut*. 2012;61(12):1693–700.
16. Novartis Pharmaceuticals Corporation. Secukinumab (AIN457) - Advisory Committee Briefing Material: Available for Public Release. U.S. Food and Drug Administration. 2014.