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How should we do in the selection and follow-up of systemic conventional treatments in psoriasis?

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Abstract

There is an increasing need for appropriate effective treatment and long-term disease control in patients with psoriasis because of the decreased quality of life, increased physicosocial deficits and associated co-morbidities. Systemic conventional treatments that are the first step in the management of moderate-to-severe plaque psoriasis include methotrexate (MTX), acitretin, cyclosporine and fumarates. MTX is considered the gold standard in the treatment of moderate-to-severe chronic plaque type psoriasis. It is also used to treat pustular psoriasis, erythrodermic psoriasis and psoriatic arthritis. Acitretin monotherapy is less effective than other conventional systemic treatments for plaque psoriasis, while superior to generalized, palmoplantar pustular, and hyperkeratotic variants. Cyclosporine is preferred in the presence of unstable acute clinical conditions (erythrodermic or generalized pustular psoriasis) and also in induction phase of rotational and sequential therapy for severe resistant psoriasis, due to its rapid effect. Dimethyl fumarate, which has similar efficacy to MTX, is an appropriate option in the induction and long-term systemic treatment for adult patients with moderate to severe plaque psoriasis without psoriatic arthritis. Although they are often overshadowed by biologics at the stage of preference by most physicians and patients today, they are classical and inexpensive agents with known long-term results. When the appropriate patient profile and psoriasis type are selected at the right time and necessary laboratory and clinical follow-ups are made, each of them is an effective treatment with reliable and satisfactory results. In this article, important points (recommendations according to patient characteristics, psoriasis type and comorbidities) to be considered in clinical practice when using the conventional anti-psoriatic agents in the treatment of psoriasis are overviewed.

Keywords

Psoriasis, conventional treatment, comorbidity, methotrexate, acitretin, cyclosporine, fumarates

Introduction

Psoriasis is a chronic inflammatory disease and an important public health problem that cannot be cured completely. Its prevalence in the general population is considered to be 1.5–2%. Psoriasis is the most common disease among immune-mediated chronic inflammatory diseases, although its incidence varies greatly between populations [1]. Plaque psoriasis, also known as psoriasis vulgaris, is the most common clinical manifestation of the disease and accounts for approximately 90% of psoriasis patients. The clinical picture varies from case to case. Sometimes, different clinics can be observed in the patient simultaneously or in different time periods [1–3].

Lesions characterized by sharply circumscribed erythematous and pearlescent white scaly plaques may also affect the palmar, plantar, genital areas and nails, apart from the classical involvement sites of the scalp, knees, elbows, and sacral region. Psoriasis often progresses with joint involvement besides the skin [2]. However, co-morbidities such as metabolic syndrome, cardiovascular disease, psychological/psychiatric disorders, inflammatory bowel disease, insulin resistance accompanying psoriasis indicate that the underlying inflammatory process damages many organs [4]. There is a need for appropriate effective treatment and long-term disease control in patients with psoriasis because of the obviously increased quality of life and physicosocial deficits. While only 25% of the patients are satisfied with the treatments applied to them, more than 50% find the treatment moderately sufficient and 20% find it less sufficient [3, 5, 6]. Seventy to eighty percent of patients with psoriasis have limited/localized disease and are managed with topical treatments alone. First-line options in topical treatment of psoriasis are corticosteroids, vitamin D analogues, calcipotriol-betamethasone dipropionate, tazarotene and calcineurin inhibitors [3]. While topical treatments are sufficient and successful in mildly severe psoriasis, which constitutes the majority of cases, it is recommended to initiate systemic treatment without delay in order to prevent co-morbidities and cope with arthritis due to the increased inflammatory effect in moderate and severe cases [5–10].

According to the International Psoriasis Council Delphi consensus, psoriasis patients who are candidates for systemic therapy must meet at least one of three criteria: (1) Body surface area (BSA) ≥ 10; (2) involvement of special areas such as the face, palms, soles, hairy skin and nails that significantly affect the quality of life; (3) unresponsiveness to topical treatment. The guideline group expressed a positive opinion for the use of criteria such as psoriasis area and severity index (PASI), dermatology quality of life index (DLQI), special site involvement and resistance to previous treatments in terms of determining the severity of the disease. Treatment options for mild plaque psoriasis [BSA ≤ 10/PASI ≤ 10/physician global assessment (PGA) ≤ 2 and DLQI ≤ 10] are topical treatments or, in resistant cases, phototherapy. Patients whose quality of life is adversely affected despite the low clinical severity and body area involved in psoriasis are considered as moderate-to-severe plaque psoriasis (BSA ≤ 10/PASI ≤ 10/PGA > 2 and DLQI > 10). This condition usually occurs in the presence of involvement in visible areas, severe involvement of the scalp, genital involvement, palmar/plantar involvement, onycholysis or onychodystrophy of at least two nails, complaints such as itching, pain and burning, recalcitrant plaques and arthritis. Treatment options in such cases are phototherapy, systemic conventional therapies or combination therapies. In moderate-to-severe plaque psoriasis (BSA > 10/PASI > 10/PGA > 2 and DLQI > 10), which have a higher disease burden, systemic conventional therapies, combination therapies or biological therapies are more appropriate [11].

Systemic conventional treatments that are the first step in the management of moderate-to-severe plaque psoriasis include methotrexate (MTX), acitretin, cyclosporine and fumarates [6, 12]. MTX, which has been used in the treatment of psoriasis for more than 50 years, was approved by the American Food and Drug Administration in 1972 for the treatment of resistant severe psoriasis, and is considered the gold standard in the treatment of chronic plaque psoriasis. In addition, acitretin and cyclosporine are agents that have been used in different clinical types of psoriasis for more than 25 years worldwide. Fumarates have also been used as fumaric acid esters in Germany for over 25 years, and since 2017 they have been involved in the treatment of psoriasis in Europe with the dimethyl fumarate form [5–9]. There are more guidelines in the literature on the use and side effects of MTX, which is effective and frequently used in many clinical forms of psoriasis and psoriatic arthritis [13–15].

Systemic agents that have been used for decades to treat psoriasis have their own benefits and risks. While most work by targeting the immune system, others such as acitretin work predominantly by reducing keratinocyte hyperproliferation and restoring normal epidermal differentiation [3–8]. The rate of onset of clinical efficacy, individual patient conditions, and concomitant obesity, psoriatic arthritis, inflammatory bowel disease, and infections [e.g., viral hepatitis, latent tuberculosis, human immunodeficiency virus (HIV)] are all factors that play an important role in switching to or withdrawing from a particular drug [16–19]. The use of biologic agents in the presence of rapid deterioration of psoriasis, involvement of visible areas, functional impairment (such as palmoplantar and genital involvement), severe erythrodermic or generalized pustular psoriasis or joint involvement; it is more appropriate in patients who are unresponsive to conventional systemic therapies (which cannot be controlled by monotherapy or combination therapies and appropriate systemic agents), who develop contraindications or side effects to conventional systemic therapies (due to individual factors such as cumulative toxicity, age, gender, comorbidity, potential drug interactions), and who show rapid relapses (during treatment or within three months after the end of treatment) [3, 5, 6]. Apremilast, an oral, small-molecule phosphodiesterase 4-inhibitor, is also indicated for the treatment of adult patients with active psoriatic arthritis or moderate-to-severe plaque psoriasis who are unresponsive, contraindicated and/or intolerant to phototherapy or other conventional systemic treatments. However, in patients with acute and chronic infections, severe renal dysfunction, low body weight, depression, suicidal thought-behavior and cytochrome P450 enzyme induction drug use, care should be taken to use with patient information and careful monitoring by considering the benefit-harm ratio and dose adjustment. The efficacy of apremilast is lower than that of biologic disease-modifying antirheumatic drugs, but it may be preferred if it is unresponsive to at least one conventional systemic disease-modifying antirheumatic drug in the presence of psoriatic arthritis and the use of biologic agents is not suitable [3, 6, 7].

In this article, important points to be considered in clinical practice when using systemic conventional agents (MTX, acitretin, cyclosporin, fumarates) in the treatment of psoriasis are emphasized. Recommendations according to patient characteristics and psoriasis type (Table 1), recommendations according to comorbidities in patients with psoriasis (Table 2), and laboratory controls recommended at the beginning and follow-up of treatments (Table 3) are summarized in the light of literature [6, 16–19].

MTX

MTX is used to treat severe, treatment-resistant, moderate-to-severe plaque psoriasis, pustular and erythrodermic forms, and psoriatic arthritis. It is considered the gold standard in the treatment of chronic plaque type psoriasis. MTX reduces inflammation in psoriatic arthritis but does not prevent radiographic progression of the disease. This old anti-psoriatic agent, a folic acid antagonist, prevents mitosis and the proliferation of rapidly proliferating cells by reducing DNA synthesis. It exerts anti-inflammatory, immunosuppressive and immunomodulatory effects by suppressing lymphocyte proliferation and cytokine production. The effectiveness of MTX in the treatment of psoriasis is primarily a result of its effect on the immune system [4].

MTX is recommended in the form of a single dose of subcutaneous injection or oral intake (three divided doses with 12-h intervals within 24 h to reduce gastrointestinal side effects) per week. Treatment can be started at normal doses or in risky patients (presence of drug interactions, diabetes mellitus, renal dysfunction or other comorbid conditions) a low dose can be started and the treatment dose can be decided by evaluating laboratory tests after seven days [3, 7]. It is usually started with a test dose of 5–7.5 mg/week and adjusted to 10–25 mg/week according to clinical response. Some clinicians, especially in young patients with good renal function, begin treatment directly with the ideal dose of 15 mg/week MTX. It should be waited 4–8 weeks for the effectiveness to appear. When the slow-acting MTX monotherapy is used in psoriasis, the maximum treatment response usually occurs at 16–24 weeks. Depending on the clinical response and side effects, dose increases up to a maximum of 25–30 mg/week can be done in increments of 2.5–5 mg every 2–4 weeks. After 1–2 months after complete remission, a dose reduction of 2.5 mg/week is made every 1–2 weeks [14]. After remission is achieved, long-term treatment is continued

Table 1. Recommendations according to patient characteristics and psoriasis type

Special conditions	Strong recommendation in favour (Will likely be beneficial)	Weak recommendation in favour (Might be beneficial)	No recommendation (Insufficient evidence)	Weak recommendation against (Will likely not help but cause no harm)	Strong recommendation against (Likely to cause harm)
Children	MTX, acitretin	Cyclosporin	-	Fumarates	-
Adolescents	MTX, acitretin (male), fumarates	Cyclosporin	-	Acitretin (female)	-
Elderly	MTX, acitretin, cyclosporin, fumarates	-	-	-	-
Pregnancy	-	Cyclosporin preferred conventional	-	-	Acitretin (3 years before), MTX (6 months before), fumaretes (6 months before)
Breastfeeding	-	-	-	-	MTX, acitretin, cyclosporin, fumarates
Males wishing to conceive	Acitretin, cyclosporin	Fumarates	-	-	MTX (3 months before)
Nail psoriasis	MTX, acitretin, cyclosporin, fumarates	-	-	-	-
Generalized pustular psoriasis	MTX, acitretin	Cyclosporin	-	-	Fumarates
Erythrodermic psoriasis	MTX, acitretin, cyclosporin	-	-	-	Fumarates
Intermittent treatment	MTX, acitretin, cyclosporin	-	-	Fumarates	-

-: no available agent

Table 2. Recommendations according to comorbidities in patients with psoriasis

Comorbidities	Strong recommendation in favour (Will likely be beneficial)	Weak recommendation in favour (Might be beneficial)	No recommendation (Insufficient evidence)	Weak recommendation against (Will likely not help but cause no harm)	Strong recommendation against (Likely to cause harm)
Psoriatic arthritis	MTX	Cyclosporin	Acitretin, fumarates	-	-
Chronic inflammatory bowel disease: Crohn's disease	-	Acitretin (especially cases with mild paradoxical psoriasis), MTX	Cyclosporin, fumarates	-	-
Chronic inflammatory bowel disease: ulcerative colitis	-	Acitretin (especially cases with mild paradoxical psoriasis), cyclosporin (2nd choice oral treatment)	MTX, fumarates	-	-
Psychiatric disorders	MTX, acitretin, cyclosporin, fumarates	-	-	-	-
Metabolic syndrome	Fumarates	Acitretin, cyclosporin, MTX	-	-	-
Diabetes mellitus/insulin resistance	Acitretin, fumarates	Cyclosporin, MTX	-	-	-
Dyslipidaemia	-	-	MTX, cyclosporin, fumarates	Acitretin	-
Obesity	Fumarates	-	-	Acitretin, cyclosporin, MTX	-
Cardiovascular risk factors	MTX, fumarates	-	-	Acitretin, cyclosporin	-
Advanced heart failure	-	Acitretin, MTX	Fumarates	Cyclosporin	-

Table 2. Recommendations according to comorbidities in patients with psoriasis (*continued*)

Comorbidities	Strong recommendation in favour (Will likely be beneficial)	Weak recommendation in favour (Might be beneficial)	No recommendation (Insufficient evidence)	Weak recommendation against (Will likely not help but cause no harm)	Strong recommendation against (Likely to cause harm)
Ischemic heart disease	-	MTX	Fumarates	Acitretin, cyclosporin	-
Cancer history	-	Acitretin, MTX	Fumarates	Cyclosporin	-
Chronic kidney disease	Stage 1/2 renal insufficiency: use MTX with standard dose	Mild-moderate renal impairment (eGFR ≥ 30 mL/min per 1.73 m^2). Acitretin, MTX, fumarates (carefull dosing/reduced dose)	-	-	Severe renal impairment (eGFR < 30 mL/min per 1.73 m^2), cyclosporin, MTX, fumarates
Demyelinating diseases	Fumarates	MTX	Cyclosporin	Acitretin	-
Concomitant treated tuberculosis	-	Acitretin, fumarates	Cyclosporin, MTX	-	-
Latent tuberculosis	-	Acitretin, fumarates	-	Cyclosporin, MTX	-
HIV with undetectable viral load	-	Acitretin	-	Cyclosporin, MTX, fumarates	-
HIV with detectable viral load	-	Acitretin	-	-	Cyclosporin, MTX, fumarates
Hepatitis C	-	-	Fumarates	Cyclosporin	Acitretin, MTX
Hepatitis B	-	Acitretin, cyclosporin	Fumarates	-	MTX
Solid cancer	-	Acitretin, MTX, cyclosporin, fumarates	-	-	-
Hematological cancer	-	Acitretin, MTX, fumarates	Cyclosporin	-	-
Non-melanoma skin cancer	Acitretin	Fumarates	-	Cyclosporin, MTX	-
Melanoma	-	Acitretin, MTX, fumarates	-	-	Cyclosporin

eGFR: estimated glomerular filtration rate

Table 3. Recommended laboratory controls at treatment initiation and follow-up

Laboratory parameters	MTX	Acitretin	Cyclosporin	Fumarates
Blood count*	X, W1, W2, W4, then every 2–3 months	X, W8, W16	X, W2, W4, then every 4 weeks until month 4	X, every 4 weeks until month 4, therafter every 8 weeks
Liver enzymes**	X, W2, W4, then every 2–3 months	X, W4, W8, then every 3 months	X, W2, W4, then every 4 weeks until month 4	X, every 4 weeks until month 4, therafter every 8 weeks
Creatinine	X, W4, then every 2–3 months	X	X, W2, W4, then every 4 weeks until month 4	X, every 4 weeks until month 4, therafter every 8 weeks
Electrolytes (sodium, potassium)	-	-	X, W2, W4, then every 4 weeks until month 4	-
Magnesium	-	-	Only with indication (muscle cramps). X, W8, W16	-
Fasting blood glucose (if elevated, up HbA1c dosage)	-	X, W8	X, then every 3 months	-

Table 3. Recommended laboratory controls at treatment initiation and follow-up (*continued*)

Laboratory parameters	MTX	Acitretin	Cyclosporin	Fumarates
Cholesterol, triglycerides	-	X, W4, then every 3 months	X (two weeks before and on the day of treatment initiation), W8, W16	-
Urine status	X, every 2 weeks during first two months, thereafter every 2–3 months	-	X, W4, W16	X, every 4 weeks until month 4, therafter every 8 weeks
Uric acid	-	-	X, then every 4 weeks until month 4	-
Albumin	X	-	-	-
Pregnancy test	X	X. Every month during treatment and 1 and 2 months following discontinuation. Avoid pregnancy for 3 years	X	X
HBV/HCV	X	-	X	-
HIV	X	-	X	-
Procollagen III peptide/Fibroscan	Every 6–12 months for PIIIP/1–2 years for Fibroscan	-	-	-
Chest X-ray	X	-	-	-
Liver ultrasound	X	-	-	-

Not all tests are necessary for every patient. Patient history, exposure to risk, and patient characteristics should be considered. More specific testing may be required based on clinical signs, risk, and exposure. X: pretreatment recommended; PIIIP: procollagen type III N-terminal peptide; *: erythrocytes, leucocytes, platelets; **: alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin; -: no available agent

with the lowest effective dose. There is no rebound effect with the sudden discontinuation of MTX. If it is tolerated and necessary follow-ups are carried out, it is not recommended to interrupt treatment after a certain cumulative dose [10, 12].

Absolute contraindications restricting the use of MTX are men and women planning to have children, inadequate contraception (contraception should be recommended until 3 months after discontinuation of the drug), pregnancy (category X; abortive and teratogenic), lactation, hypersensitivity to the drug (e.g., pulmonary toxicity), severe liver disease (alcoholic or nonalcoholic), renal failure, tuberculosis history or other serious infections, immunodeficiency syndromes, active peptic ulcer and hematologic changes (leukocytopenia, thrombocytopenia, anemia). Relative contraindications include renal dysfunction, liver dysfunction, history of hepatitis, congestive heart failure, diabetes mellitus, patient incompatibility, ulcerative colitis, diarrhea and gastritis [6, 7].

The side effects of MTX are often dose-dependent. Common side effects during MTX treatment include gastrointestinal problems (nausea, stomach upset, soft stool), stomatitis or mouth sores, impaired liver function, elevated transaminases, macular punctate rash on the extremities, central nervous system symptoms (headache, weakness, impaired concentration), alopecia, fever and hematologic changes (macrocytosis, bone marrow suppression). Serious side effects include hepatotoxicity (hepatic steatosis, fibrosis, cirrhosis), pulmonary changes (interstitial pneumonitis, alveolitis), infection, bone marrow suppression, lymphoproliferative diseases and nephrotoxicity [7, 19].

In patients receiving MTX, the addition of 1–5 mg/day of folic acid to the treatment except for the days of MTX intake reduces the gastrointestinal, hematological, and hepatic side effects without changing the effectiveness of the drug. Although there is no consensus on the optimal dose for folic acid replacement, it is recommended to administer a single dose of 5 mg at least 24 h after the day MTX is administered. High doses of folic acid (20 mg/week) reduce the effect of MTX [14]. Since MTX is excreted mainly through the kidneys, MTX toxicity may increase according to its stage in case of kidney failure. If there is stage 1 [glomerular filtration rate (GFR) < 90]/stage 2 (GFR = 60–89) renal failure, a standard dose of MTX can be used. In stage 3 (GFR = 30–59) renal failure, it is necessary to use a reduced dose of MTX, but MTX should

not be used if it is stage 4 (GFR = 15–29)/stage 5 (GFR < 15) [14, 18]. Many drugs affect MTX metabolism, causing the drug to reach toxic doses. These drug interactions include those that reduce the renal elimination of MTX (cyclosporine, salicylates, sulfonamides, probenecid, penicillin, colchicine, cyclooxygenase inhibitors), increase bone marrow and gastrointestinal toxicity (ethanol, cotrimaxazole, primethamine, chloramphenicol, sulfonamides, cyclooxygenase inhibitors, cytostatic agents), seperate MTX from the plasma proteins to which it binds (cyclooxygenase inhibitors, probenecid, barbiturates, phenytoin, retinoids, sulfonamides, sulfonylureas, tetracyclines, cotrimaxazole, chloramphenicol), increase intracellular accumulation of MTX (dipyridamole) and hepatotoxicity (retinoids, ethanol, leflunomide). Although alcohol consumption in patients taking MTX is not contraindicated, its use may be allowed once a day in women and 1–2 standard alcoholic beverages in men. Unlike type II diabetes and obesity, alcohol is not associated with increased liver fibrosis in patients with psoriasis, but excessive alcohol consumption increases the risk of hepatotoxicity [7, 14]. Renal dysfunction, advanced age, lack of folate supplementation, drug interactions and improper treatment are risk factors for hematologic toxicity. Elevation in mean erythrocyte volume is a sign of hematologic toxicity due to folate deficiency and requires discontinuation of MTX therapy. In case of thrombocytopenia, leukopenia or anemia, the dose is reduced or the treatment can be discontinued depending on the severity. If these side effects are clinically evident, rescue treatment with folinic acid is performed. Folinic acid (calcium leucovorin) 20 mg (10 mg/m^2) should be given intravenously or intramuscularly, followed doses every 6 h (parenterally or orally) in a way that the patient can tolerate [13, 14].

When MTX is used as monotherapy in psoriasis, it is moderately effective and provides 50–75% healing of skin lesions. Although its effect is lower compared to cyclosporine, it is more suitable for long-term use [12]. Combining MTX with cyclosporine results in lower MTX-induced hepatotoxicity and less cyclosporine-induced nephrotoxicity using both agents at low doses. However, the combination of MTX with cyclosporine is not recommended due to the increased risk of immunosuppression. The combination of MTX with narrowband ultraviolet B (UVB), broadband UVB and psoralen-ultraviolet A (PUVA) has also been found to be highly effective. Low-dose acitretin can be combined with MTX, but caution should be exercised for hepatotoxicity [3, 7]. MTX can also be combined with all biological agents approved for the treatment of psoriasis and psoriatic arthritis. Concomitant use of low-dose MTX in patients receiving anti-tumor necrosis factor (TNF) alpha therapy reduces the risk of antibody development [13, 15].

Acitretin

An important advantage of acitretin, which has immunomodulatory, antiproliferative, antiinflammatory and antiangiogenic effects in psoriasis, is that it is not an immunosuppressive and cytotoxic agent [20–22]. Therefore, acitretin can be preferred in individuals who are immunosuppressive, prone to infection, HIV, hepatitis B or hepatitis C carriers, living in tropical regions or endemic areas for tuberculosis and who have received high UV cumulative dose, have a high risk of skin malignancy, have systemic lupus erythematosus or congestive heart failure [18, 19]. Acitretin is the first choice in the presence of generalized pustular psoriasis, erythrodermic psoriasis and psoriasis associated with HIV [20–23]. It has also been found to be effective in palmoplantar and nail psoriasis [24, 25]. As monotherapy in pustular forms and erythrodermic forms, its effect starts quickly and the success rate is quite high. It is also used successfully in the treatment of psoriasis vulgaris, but it is a slow-acting agent when used as monotherapy in plaque psoriasis. The onset of clinical efficacy is observed in 4–8 weeks, and the apparent response is observed in 3–6 months. For this reason, it is often used in combination with topicals (corticosteroids and calcipotriol) in patients with psoriasis vulgaris [26–28]. When used in combination with phototherapy, lower acitretin and phototherapy cumulative doses may provide more significant efficacy in a shorter time. If acitretin is to be used during phototherapy, it is recommended to start two weeks before the treatment and to increase the ultraviolet dose more slowly. Rapid dose increases may cause photosensitivity [29]. Also, when combined with biological agents, the synergistic effect is observed [30]. Acitretin has moderate efficacy for psoriatic arthritis and is almost never used alone for its treatment [15].

Acitretin is commercially available in soft gelatin capsules as 10 mg and 25 mg doses [20–22]. When used as monotherapy at doses between 0.25–1 mg/kg per day, the effective dose is reported as 25–50 mg/day, and it is generally used at doses of 10–50 mg/day. The daily dose can be taken once or in high doses divided into two or three times a day. Its bioavailability is increased when used in a single dose with a fatty meal or whole milk. Gradual dose escalation is recommended, where side effects are also more comfortable to tolerate. It can be started at a dose of 10–25 mg/day and increased every two weeks if necessary. The optimal dose is 0.3–0.5 mg/kg per day (higher doses in generalized pustular psoriasis, lower doses in erythrodermic psoriasis) and the criterion for an effective dose is mucosal xerosis (cheilitis) [23, 26]. There is no total dose restriction that limits the duration of acitretin therapy. Treatment can be stopped in patients with adequate response, and treatment is planned in the same way in relapses. Maintenance therapy with acitretin is effective and safe [20–22]. In patients requiring long-term treatment, the treatment is continued with the lowest effective dose (frequently 10 mg/day or 25 mg/day) not exceeding 50 mg/day [27, 28].

Since acitretin is a teratogenic agent, it should be preferred in male and postmenopausal female patients. It cannot be used in the presence of pregnancy (category X), and is strictly contraindicated for women who are planning pregnancy and cannot promise contraception until three years after the end of treatment [21]. In retinoid embryopathy, anomalies including craniofacial (microtia, anotia, microphthalmia, cleft palate, micrognathia, facial asymmetry), cardiovascular (large vessel transposition, tetralogy of Fallot, hypoplasia of the aorta, truncus arteriosus), central nervous system (hydrocephaly, microcephaly, mental retardation, cortical agenesis, anophthalmia, meningoencephaly) and skeletal systems, thymic and parathyroid hypoplasia, absence of terminal phalanx, syndactyly, anal and vaginal atresia are occurred [22]. Alcohol use should be restricted due to both the conversion of acitretin to etretinate with a longer half-life and the increased risk of hepatotoxicity. Therefore, the use of alcohol-containing products should be prohibited, especially in women, during treatment and up to two months after acitretin discontinuation [20–22]. It is known that acitretin disappears from the body after two months in female patients who are strictly protected from alcohol. However, it is advocated that many items in daily use, such as various foodstuffs, cough syrups, mouthwashes, and medicines, may contain alcohol, even in small amounts, and that the duration of contraception should be three years even in patients who do not drink alcohol in order to avoid undesirable problems [22]. Contraception should be started one month before the treatment, low-dose progesterone-containing/mini oral contraceptives should not be used, and double contraception (condom + oral contraceptive, intrauterine device + oral contraceptive) should be preferred. The effectiveness of progesterone-only oral contraceptives decreases with the use of acitretin. If pregnancy tests are negative at least twice in the two weeks before starting acitretin, treatment should be started on the second or third day of the next menstrual cycle [6, 7].

Lactation, moderate-to-severe hepatic dysfunction (enzymes > 2 fold), hepatitis, moderate-to-severe renal dysfunction, alcoholism, and blood donation (during treatment and up to three years) are also among absolute contraindications. In addition, women of childbearing age, moderate-severe or drug-controlled hyperlipidemia (especially hypertriglyceridemia), history of hepatitis or pancreatitis, diabetes mellitus, atherosclerosis, concomitant hepatotoxic drug use (such as tetracycline, MTX), heavy alcohol consumption, contact lens use, patient noncompliance, suicidal ideation and pseudotumor cerebri are relative contraindications [20–22].

In terms of acitretin-drug interactions, its use with tetracycline group antibiotics is contraindicated due to the risk of pseudotumor cerebri. Vitamin A supplementation should not be made, and if it is taken, the dose should not be exceeded 2,400–3,000 international units (IU)/day. Acitretin increases free phenytoin levels by decreasing the proteins that bind to phenytoin. Rifampin, phenobarbital and carbamazepine decrease the serum level of retinoids by inducing cytochrome P450 3A4 (CYP3A4). Concomitant use of MTX increases hepatotoxicity, corticosteroids increase hyperlipidemia, antidiabetics increase hypoglycemia, and lipid-lowering agents increase the risk of myotoxicity. If there is a persistent high lipid level, gemfibrozil can be preferred as one of the lipid-lowering agents [21, 22].

The side effects of acitretin are generally dose-dependent. As the dose increases, the side effects increase as well as the effect of the drug. Mucocutaneous side effects such as dryness of the skin and mucous membranes (cheilitis, xerosis, conjunctivitis), thinning and fragility of hair and nails are common with acitretin treatment. Cheilitis is the most important effect that should be observed in all patients and should be considered in dose adjustment [6, 22]. In patients who do not develop cheilitis, the possibility of insufficient drug dose or low absorption (the patient may be taking the drug on an empty stomach) should be reviewed. As other cutaneous side effects, paronychia, pyogenic granuloma, bullous rash, photosensitivity, retinoid dermatitis, and initial psoriasis exacerbation may also develop [21].

Hyperlipidemia [mainly hypertriglyceridemia, hypercholesterolemia, high very low-density lipoprotein (VLDL) level and VLDL/low-density lipoprotein (LDL) ratio, low high-density lipoprotein (HDL) level] and hepatotoxicity (usually reversible elevation of liver function tests, more rarely severe hepatotoxic reaction) should be followed. Liver enzyme increase is usually mild and occurs within 2–8 weeks after starting the treatment and returns to normal within the next 2–4 weeks even if the treatment is continued [3, 10]. Severe or persistent hepatotoxicity occurs in only < 1% of patients. If there is an increase in liver enzymes more than 3 times the upper limit, the treatment should be discontinued; if there is a 2–3 fold increase, the treatment should be interrupted until the transaminases decrease. The risk of cirrhosis and pancreatitis increases in the presence of alcohol use, diabetes and obesity, as well as with familial hypertriglyceridemia. If the level of triglyceridemia is > 5 mmol/L, close follow-up is recommended; and if it is higher than 10 mmol/L or 8 g/L, treatment is discontinued because of the risk of pancreatitis [6, 10]. Since the cardiovascular risk due to hypertriglyceridemia occurs after many years, it carries less risk in the elderly. Therefore, acitretin is a reasonable option in the treatment of psoriasis in the geriatric age group, but in addition to senile xerosis, dryness and itching caused by acitretin may also be an important problem [16, 18].

Musculoskeletal problems such as ligament calcification and diffuse idiopathic skeletal hyperostosis may occasionally develop, but it has been reported that dose adjustments can be made by requesting routine radiographs in the presence of subjective complaints such as muscle, joint and/or bone pain [21]. Other side effects include mood changes (depression, aggressive behavior, suicidality), benign intracranial hypertension, blurred vision, night vision impairment, increased insulin sensitivity, acute myocardial infarction, thromboembolism, hypersensitivity (urticaria, angioedema), capillary leak syndrome, myopathy, rhabdomyolysis, and peripheral neuropathy. Acitretin overdose presents with symptoms of headache, nausea, vomiting, lethargy, and vertigo [10, 22].

Acitretin is an important part of psoriasis treatment. Its most important advantage is that it is used in immunosuppressives, patients with malignancy or in the presence of infection. It is one of the first options in generalized and localized pustular or erythrodermic psoriasis and acts rapidly. Acitretin monotherapy is less effective than other conventional systemic treatments for plaque psoriasis, while superior to generalized, palmoplantar pustular, and hyperkeratotic variants. Therefore, its combination with topicals or narrow-band UVB is recommended in plaque psoriasis [3, 6]. Side effects are usually dose dependent and generally reversible except for hyperosteosis. However, hyperlipidemia is frequently encountered and causes concern, especially in patients at risk of developing metabolic syndrome and cardiovascular side effects. Therefore, good management of hypertriglyceridemia by the physician is of great importance [20–22]. Patients receiving acitretin therapy should be warned to avoid intense ultraviolet exposure (such as sunlight and tanning beds). Patients should also be warned not to use the wax method to remove unwanted hair, as it will cause thinning of the skin and an increase in skin fragility [19].

Cyclosporine

Cyclosporine, recommended for severe resistant psoriasis, can also be used in the treatment of erythrodermic, generalized pustular and/or palmoplantar psoriasis. It can be recommended as a short-term interventional treatment in patients with exacerbation while receiving previous systemic therapy. It is preferred in induction therapy or induction phase of rotational and sequential therapy, due to its rapid effect in psoriasis [3, 6]. Cyclosporine has been shown to be beneficial in reducing peripheral (but not axial)

joint involvement in patients with psoriatic arthritis [15, 18]. It can be used once or twice a day on an empty stomach at doses of 2.5–5 mg/kg per day. Increasing or decreasing dose approach is applied according to clinical necessity. Generally, it is started with 2.5–3 mg/kg per day and continued at this dose for four weeks. If sufficient effect is not achieved in 4–6 weeks or faster control is desired, the dose can be increased by 0.5–1 mg/kg per day every two weeks up to a maximum of 5 mg/kg [31, 32].

A rapid and dramatic improvement is achieved within 12–16 weeks in 80–90% of patients with plaque psoriasis. In people with a high body mass index, the effectiveness of the drug increases with a low-calorie diet and weight loss [3, 33–35]. If there is no adequate response to cyclosporine or if complications develop, the drug will need to be discontinued. However, if it is abruptly terminated, there is a high risk of recurrence in psoriasis, especially in the first 3 months. Therefore, the dose should be reduced gradually and slowly, such as 0.5–1 mg/kg per day at two-week intervals [6, 9, 33]. Most of the side effects are dose and duration related, so it is more appropriate to apply treatment at the lowest effective dose and for the shortest possible duration [34, 35]. Short-term intermittent treatments of 2–4 months are generally recommended in order to avoid nephrotoxicity [35]. Different treatment approaches, such as low-dose long-term or weekend maintenance treatments, have also been found to be effective. It should not be used for longer than 1–2 years, even when used at low doses for a long time [35–40].

Cyclosporine, a nephrotoxic and immunosuppressive agent, is strictly contraindicated in the presence of significant renal failure and uncontrolled arterial hypertension [33, 34]. Severe liver dysfunction, malignancies [especially cutaneous T-cell lymphoma and skin tumors excluding history of treated basal cell carcinoma and *in situ* squamous cell carcinoma (SCC)], cyclosporine susceptibility, presence of serious infection, and concomitant PUVA therapy are also main absolute contraindications. Relative contraindications include being young (< 18 years) or elderly (> 65 years), controlled hypertension, psoriasis triggered by infections or drugs, using drugs that interfere with cyclosporine metabolism (through inhibition of cytochrome P450 CYP3A4) or impair kidney function, previous treatment with long-term MTX, immunosuppressive drugs, and other potentially carcinogenic therapies (PUVA therapy > 200 sessions or > 1,000 J/cm^2, coal tar, arsenic), drug/alcohol abuse, hyperuricemia, hyperkalemia, recent live virus vaccines (at least 1 month prior), primary/secondary immunodeficiency (consult an HIV specialist), poorly controlled diabetes, epilepsy, pregnancy and lactation [6, 10, 34].

Since cyclosporine metabolism can be affected by many drugs that interact with the cytochrome P450 enzyme system, attention should be paid to drug interactions. Drugs that inhibit CYP3A (e.g., some calcium antagonists, antibiotics, azoles, statins mainly atorvastatin and simvastatin, grapefruit juice) increase cyclosporine levels, while drugs that induction CYP3A (e.g., some antibiotics and neuroleptics such as carbamazepine, phenytoin, barbiturates) correlated with decreased cyclosporine levels. When used together with aminoglycosides (e.g., gentamicin, tobramycin), antibiotics such as ciprofloxacin, nonsteroidal anti-inflammatory drugs and fibrates, it may cause increased nephrotoxic effects, and statins may cause worsening of myopathy. Drug interactions in which other mechanisms play a role include increased cyclosporine level with alcohol use, decreased metabolism of MTX, prednisolone, digoxin and simvastain, decreased effect of progesterone-based oral contraceptives, and risk of seizures with high-dose corticosteroids [3, 5, 6]. The risk of hyperkalemia develops if used concomitantly with potassium-sparing diuretics. Cyclosporine is an agent not generally recommended in combination with other agents used in the treatment of psoriasis [34, 35].

Close monitoring is required in terms of nephrotoxicity (increase in serum creatinine, blood urea nitrogen (BUN) and uric acid levels, decrease in GFR and creatinine clearance) and hypertension (vasoconstriction in renal arteries), which are the most common side effects of cyclosporine. Since the risk of kidney failure increases with age and obesity, these people should be more careful. While nephrotoxic effects are acute and reversible with short-term high-dose treatment, they can become chronic and even irreversible (interstitial fibrosis, tubular atrophy, glomerular sclerosis) with long-term treatment. If there is an increase in serum creatinine values of ≥ 30%, it is necessary to control fluid intake. It is recommended to reduce the dose of cyclosporine by a minimum of 25% for a 30–50% increase in creatinine, and to reduce the dose by a minimum of 50% for an increase of ≥ 50% and to be followed for one month. If ≥ 30%

elevation in serum creatinine values still persists, treatment should be discontinued [7]. In the development of hypertension [systolic arterial blood pressure > 160 mmHg/90 mmHg (1 mmHg = 0.133 kPa) in two consecutive measurements], calcium channel blockers (amlodipine, isradipine) should preferably be used as antihypertensives. Since there is a risk of gingival hyperplasia with nifedipine, an increase in cyclosporine levels with diltiazem, nicardipine and verapamil, exacerbation of psoriasis with beta-blockers, and hyperkalemia with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor 2 antagonists, use of these antihypertensive treatments with cyclosporine should be avoided. If blood pressure values do not return to normal, the dose should be reduced by at least 25%, and if this is ineffective, cyclosporine treatment should be discontinued [7, 8, 34].

Among the other side effects of cyclosporine, very common (≥ 10%) side effects are nausea, vomiting, diarrhea, paresthesia, myalgia, headache, burning hands and feet (symptomatic treatment), increased bilirubin and/or transglutaminase levels (if higher than 2 time, the dose should be reduced by 25% and follow-up tests should be done within a month, if the elevation persists, the treatment should be discontinued), and gingival hyperplasia (optimal dental hygiene should be maintained, if insufficient, the treatment dose should be reduced or discontinued); common (≥ 1%, < 10%) side effects are tremor, hypertrichosis (symptomatic treatment), hyperlipidemia (diet, cyclosporine dose should be reduced or discontinued if necessary, concomitant use with anti-hyperlipidemic drugs statins and fibrates should be avoided); rare (≥ 0.1%, < 1%) side effects are gastric ulcer, colitis, convulsions, papillary edema, weight gain, hyperglycemia, acne, anemia; more rare (≥ 0.01%, < 0.1%) side effects are ischemic heart disease, pancreatitis, polyneuropathy, leukopenia, thrombocytopenia; and very rare (< 0.01%) side effects are microangiopathic hemolytic anemia, hemolytic uremia syndrome (symptomatic treatment according to severity of symptoms, or the dose should be reduced or discontinued) [5, 10].

Cyclosporine is the conventional treatment option that can be preferred in the presence of unstable acute clinical conditions such as erythrodermic and generalized pustular psoriasis, where rapid recovery is desired [5–8]. It is not a major teratogenic agent and appears to be a safe alternative that can be used during pregnancy in patients with resistant psoriasis. Cyclosporine is specified as pregnancy category C [16]. It should not be used in obese, hypertensive and elderly patients with renal insufficiency. It should not be used together with ACE inhibitors and thiazide diuretics. It should not be given together with phototherapy and should not be preferred in summer. However, it should be considered in situations where rapid effect is expected. Patients should be followed carefully for infection and malignancy. Intermittent therapy is safer than continuous use [10, 35].

Fumarates (fumaric acid esters)

Fumarates, which show antipsoriatic activity through their antiproliferative, anti-inflammatory, immunomodulatory and antiangiogenic properties, are used as first-line systemic therapy in Germany and the Netherlands. These agents, which have been used in the treatment of psoriasis for more than 30 years in various European countries, are indicated only in adult patients with moderate-to-severe plaque psoriasis. It is not the first choice for unstable and rapidly progressive plaque psoriasis, generalised pustular psoriasis, erythrodermic psoriasis and psoriatic arthritis [5, 6, 41]. The main active ingredient with antipsoriatic effect in Fumaderm® (dimethyl fumarate and calcium, magnesium and zinc salts of monoethyl fumarate; 30 mg and 120 mg tablets) and Skilarence® (dimethyl fumarate, 120 mg tablet; agent approved by the European Medicines Agency in 2017) is dimethyl fumarate [42, 43].

In order to increase drug compliance and reduce the risk of side effects, it is recommended to start with low-dose dimethyl fumarate and gradually increase the dose. A 30 mg Fumaderm® tablet is given once a day in the first week, twice a day in the second week, and three times a day in the third week, and from the fourth week, it is switched to 120 mg tablet once a day and a 120 mg tablet is added once a week for 9 weeks until the maximum daily dose of 720 mg is reached (dimethyl fumarate 120 mg tablet, 3 × 2). In the first weeks, a combination with topicals or phototherapy is recommended to increase the effectiveness of the treatment. No further dose escalation is necessary if clinical response is achieved before the maximum dose is reached. A daily dose of 240–480 mg dimethyl fumarate (120 mg tablet 2–4 times a day) is usually

sufficient for maintenance. Clinical response is achieved at the earliest in 6–8 weeks, with maximum efficacy usually after 24 weeks. If no efficacy is achieved at week 12, treatment should be discontinued. When an adequate response is obtained, the maintenance dose of dimethyl fumarate should be reduced by 120 mg once a month [10, 43, 44]. When new lesions appear, the previous clinical response can be obtained by returning to the previous effective dose. In other words, dimethyl fumarate treatment provides convenience and flexibility to physicians and patients in terms of dose increase and decrease according to clinical response and side effects [10, 42].

Absolute contraindications for fumarates are severe kidney and liver disease, severe gastrointestinal disease (duodenal ulcer or active severe inflammatory bowel disease), malignancies, pregnancy and lactation. Concomitant use with MTX, retinoids, psoralen, cyclosporine, immunosuppressive, cytotoxic and renal toxic drugs are among the relative contraindications. If the leukocyte count is < 3,000/μL or the lymphocyte count is < 1,000/μL, treatment should not be initiated. Treatment should be discontinued when lymphocyte levels fall below < 700/μL (Skilarence®) or < 500/μL (Fumaderm®). Since Skilarence® tablets contain lactose, they are not recommended for use in intolerant cases [10, 41, 42]. Its metabolism is independent of the cytochrome P450 enzyme system and no organ-specific toxicity occurs due to drug metabolism. No dose adjustment is necessary in the elderly and in mild to moderate hepatic and renal dysfunction [42, 45–47]. It is not mandatory to evaluate patients for hepatitis B/C, latent tuberculosis or HIV infection. However, in the presence of active hepatitis, tuberculosis or HIV infection, treatment should not be decided without consulting the relevant specialist. Since the use of fumarates during pregnancy is not recommended, it would be appropriate to check the pregnancy test before treatment. Contraception is not required in male patients [5, 6, 10].

Gastrointestinal system complaints (nausea, stomach cramps, diarrhea) and flushing are the most common side effects of fumarates. Headache, loss of appetite, fatigue, itching, leukopenia and lymphopenia are also common side effects. Lymphopenia, which mostly occurs at the beginning of treatment and during dose increase, is mild in most cases and improves with dose adjustment. Prolonged and severe lymphopenia, which can be seen in approximately 3% of patients, carries a risk for opportunistic infections such as progressive multifocal leukoencephalopathy. Eosinophilia (transient between the 4th and 10th weeks of treatment), proteinuria, increased serum creatinine and liver enzyme levels, and Fanconi syndrome are less common side effects [5, 10, 42].

Fumarates are an appropriate systemic treatment option for patients with moderate to severe plaque psoriasis. It has similar efficacy to MTX treatment. It can be used as the first treatment option in patients with moderate-to-severe plaque psoriasis without psoriatic arthritis. The European S3 Guidelines recommend fumaric acid esters for the induction and long-term systemic treatment of psoriasis vulgaris [5, 6]. Although the use of fumaric acid esters is recommended as the first treatment option in patients who have not used systemic treatment, before biological treatments, they can also be used in patients who do not respond to other systemic treatments, including biological treatments [41–43]. Even with a gradual dose increase, lymphopenia is an important and common side effect, and close follow-up of patients is appropriate in this respect. Particular attention should be paid to opportunistic infections in patients with severe lymphopenia [10, 41, 42].

Conclusions

The treatment plan in psoriasis should be individual, taking into account the age and gender of the patient, the type, severity, extent and specific involvement areas of psoriasis, comorbid/special conditions, previous treatment history, concomitant treatments, and the patient's profession, perception of the disease and compliance with treatment. Although conventional treatments in psoriasis are often overshadowed by biologics at the stage of preference by most physicians and patients today, they are classical and inexpensive agents with known long-term results [6, 12, 48]. As a result, when the appropriate patient profile and psoriasis type are selected at the right time and necessary laboratory and clinical follow-ups are made, each of them is an effective treatment with reliable and satisfactory results.

Abbreviations

BSA: body surface area

DLQI: dermatology quality of life index

GFR: glomerular filtration rate

HIV: human immunodeficiency virus

MTX: methotrexate

PASI: psoriasis area and severity index

PGA: physician global assessment

PUVA: psoralen-ultraviolet A

UVB: ultraviolet B

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