Review paper

Acitretin in psoriasis treatment – recommended treatment regimens

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Abstract

Acitretin is a synthetic retinoid, a pharmacologically active metabolite of etretinate. It is characterized by very favourable pharmacological profile: its period of half-life is approximately 2 days, it is nearly 50 times less lipophilic than etretinate, and its efficacy in the treatment of psoriasis is comparable to etretinate. The mechanism of its action is not yet fully understood, but it is known that acitretin normalizes all processes typical for psoriasis. The paper discusses in details the indications for acitretin, its efficacy in monotherapy and combination therapy, the principles of alternate therapy, and also the most common side effects during treatment. In addition, we classify the most important recommendations to be aware of before, during and after treatment.

Key words: acitretin, psoriasis, efficacy, combination therapy, alternate therapy.

Introduction

Retinoids are a group of natural and synthetic analogues of vitamin A. Three generations of the compounds can be distinguished including: generation 1. – natural monoaromatic (retinol, tretinoin, isotretinoin, alitretinoin), generation 2. – synthetic monoaromatic retinoids (etretinate, acitretin) and generation 3. – synthetic polyaromatic retinoids (bexarotene and other topically applied retinoids) [1, 2].

Psoriasis therapy is usually based on etretinate or acitretin; isotretinoin is not routinely recommended for treatment due to lower therapeutic efficacy [3]. Bexarotene has not, as yet, found practical applications in psoriasis treatment, the primary indication for the drug being lymphomas of the skin.

It needs stressing that the first reports about the beneficial effects of etretinate in patients suffering from psoriasis go back to 1975 [4]. The main limitations on the widespread use of etretinate were its long half-life (ca. 120 days) and teratogenic activity. Etretinate use in women of reproductive age entailed the necessity of effective long-term contraception. Consequently, studies were undertaken in the 1980s to investigate acitretin, a new derivative of etretinate. Compared to etretinate, acitretin is almost 50 times less lipophilic and has a markedly shorter half-life (ca. 2 days) [5, 6]. Since 1997, acitretin (marketed in Poland under the trade name of Neotigason) has practically replaced etretinate in psoriasis treatment worldwide. Unfortunately, there is evidence that acitretin can be converted back to etretinate, especially during concomitant alcohol intake – Figure 1.

Mechanism of action of acitretin

The tentative mechanism of action of acitretin, which has not been entirely elucidated, is shown in Figure 2 [6]. It must be noted that the retinoid normalizes all processes typically involved in the development of psoriatic lesions:

- it reduces excessive proliferation of keratinocytes and their abnormal differentiation;
- it impedes inflammatory infiltration by inhibiting the chemotaxis of polynuclear lymphocytes from blood vessels into psoriatic epidermis and the release of inflammatory mediators by neutrophils;
- it exerts anti-inflammatory activity by influencing cyclooxygenase and lipoxygenase, and thus affecting the metabolism of products of arachidonic acid;
- it has immunomodulatory properties and suppresses angiogenesis processes (both directly, i.e. by reducing the migration of endothelial cells and creating new ves-

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sels; and indirectly, i.e. by limiting the production of VEGF by human keratinocytes) [7, 8];
- it inhibits the synthesis of IL-6, a cytokine which plays a vital role in the process of differentiation of the T cell subpopulation Th0 to Th17 [9, 10].

General pharmacological properties of acitretin

The molar mass of acitretin is 326 g/mol (etretinate: 354 g/mol). Acitretin binds to plasma proteins extensively (bound fraction: 99%), while the main transporters of this retinoid are albumins (for etretinate: both albumins and lipoproteins) [11]. According to various estimates, the oral bioavailability of acitretin varies from 36% to 95% (etretinate: from 30% to 70%) and increases up to twofold if the drug is taken with food (especially fat-rich meals). At the same time, it should be noted that there is significant individual variation in the rate of absorption of the drug and, therefore, its serum concentration which, however, is unaffected by body weight. Peak serum concentration of acitretin is reported to occur 4 h after oral administration. Acitretin is nearly 50 times less lipophilic than etretinate [12]. It does not accumulate in the fatty tissue, which means that it has a considerably shorter half-life (etretinate, on the other hand, it accumulates in the fatty tissue, from which it is slowly released) [13]. The half-life of acitretin is ca. 2 days (etretinate: 80-175 days) [14]. Acitretin is metabolized in the liver (in a process involving cytochrome P450) and excreted in urine and faeces. The main active metabolite of acitretin is 13-*cis*-acitretin [15].

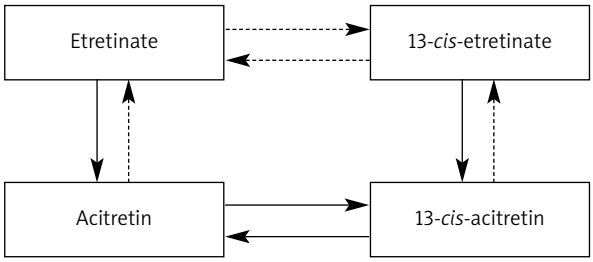

Fig. 1. Diagram illustrating mutual conversions of acitretin and etretinate

Multiple studies have shown that acitretin may be converted back to etretinate (particularly after alcohol intake). A correlation has been found between the amount of alcohol intake and etretinate concentration in blood serum. On the other hand, no association has been shown between the duration of treatment (and hence total drug

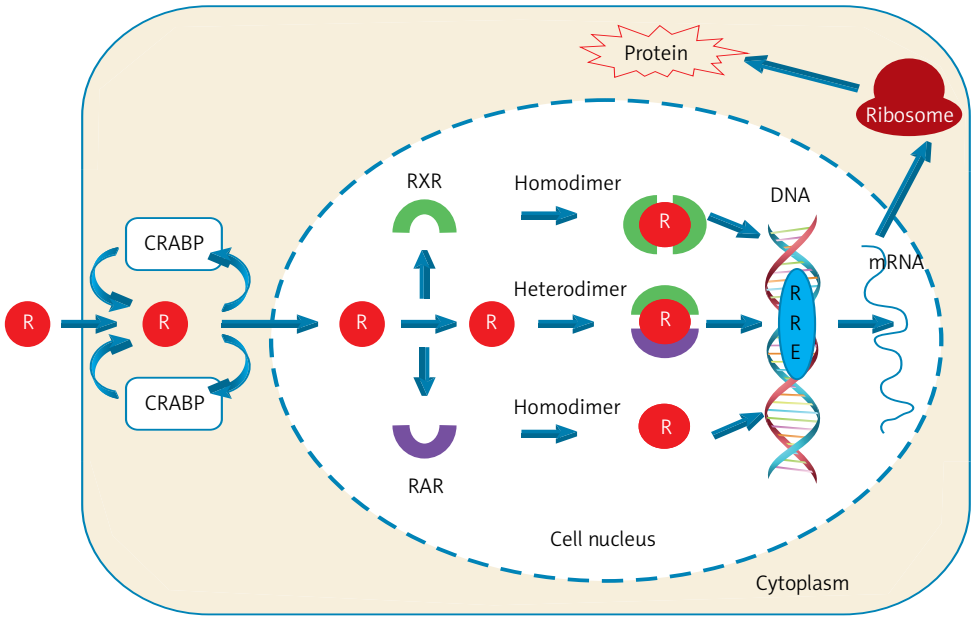

Fig. 2. Mechanism of action of acitretin
Similarly to other retinoids, acitretin binds inside the cell with a specific protein carrier: CRABP (*cellular retinoic acid binding protein*). The carrier protein has two subtypes: CRABP I and II. CRABP II expression is the dominant pattern in the epidermis of patients suffering from psoriasis.
After being transported to the cell nucleus, it activates specific RARs (*retinoic acid receptors*) and RXRs (*retinoid X receptors*). The receptors are structurally similar to receptors for glucocorticosteroids and thyroid hormones. They are found in the epidermis, sebaceous glands, hair follicles and in the immune system, performing the function of transcription factors. The processes described above activate specific short sequences of DNA (RAREs and RXREs) located in promoter regions of certain genes (including genes responsible for cell growth and differentiation), causing either stimulation or inhibition of the process of transcription of specific genes.
R – acitretin, DNA – deoxyribonucleic acid, mRNA – matrix ribonucleic acid

dose) and etretinate detection [16]. It is also worthwhile to note that chromatographic studies have shown the conversion to apply to acitretin only, not to its main metabolite – 13-*cis*-acitretin.

The drug crosses the placenta and is excreted in milk. Based on results of animal experiments it can be assumed that an infant breastfed by a mother treated with acitretin could absorb a daily dose of ca. 50 µg of the drug [17]. Acitretin has no metabolic interference with endogenous vitamin A in the skin. After the discontinuation of treatment it is rapidly eliminated from the epidermis, following which adverse skin and mucosal reactions subside within several days [18].

Acitretin in monotherapy – recommended dosage and efficacy

Acitretin monotherapy is extremely effective in pustular psoriasis, very effective in psoriatic erythroderma and moderately effective in plaque psoriasis. The efficacy data come from numerous clinical studies.

A significantly higher efficacy of acitretin vs. placebo in the treatment of palmoplantar pustulosis was demonstrated in two randomized clinical trials. In one trial, a five-fold reduction in the number of skin lesions was achieved after 4 weeks of therapy with the retinoid at a dose of 50 mg/day (compared to the 1.4-fold reduction obtained in the placebo group) [19]. Similar results were also recorded in another trial which additionally showed acitretin to be comparably effective to etretinate [20].

Clinical effects produced by acitretin and placebo in the treatment of psoriasis vulgaris were compared in four randomized trials and one open multi-centre clinical trial. Acitretin and etretinate were compared in four randomized trials. It is worthwhile to summarize the results of at least several of them.

Murray *et al.* reported that 12 months of treatment with acitretin administered at doses between 25 mg and 50 mg resulted in the achievement of PASI 50 in 76% of study patients and PASI 75 – in 46% [21]. Similar findings were recorded by Kragbelle *et al.* who noted PASI 50 in 85% of patients and PASI 75 in 52% of patients after 12 weeks of treatment with acitretin used at a daily dose of 40 mg [22]. Lassus *et al.* focused on comparing the efficacy of the retinoid depending on the dose (10 mg, 30 mg or 50 mg) in a group of 80 patients with psoriasis. After 8 weeks of therapy the overall mean PASI reduction was: 61% in the group treated with acitretin at 10 mg, 79% in the acitretin 30 mg group and 86% in the acitretin 50 mg group (30% in the placebo group) [23].

Acitretin dosage regimens in the treatment of different forms of psoriasis are listed in Table 1.

Table 1. Dosage recommendations for acitretin monotherapy

Plaque psoriasis		
Starting dose (usually used for 4 weeks of therapy): 0.3-0.5 mg/kg/day, typically 10-25 mg/day	Therapeutic dose (the starting dose is usually increased every 2 weeks over 2 consecutive months of treatment) 0.5-0.8 mg/kg/day, typically up to 50 mg/day	• As a rule, the therapeutic dose is set at a level that ensures dryness and slight epidermal exfoliation within the *rubor labiorum* • The efficacy of therapy is routinely assessed after 8 weeks of treatment • Acitretin monotherapy is only moderately effective in psoriatic erythroderma, which is why combination treatment is often necessary • Duration of treatment – usually up to 6 months
Psoriatic erythroderma		
Starting dose: typically 10-30 mg/day	The starting dose is often sufficiently effective. If not, it can be increased up to 50 mg/day	• Acitretin monotherapy is very effective in psoriatic erythroderma • Duration of treatment – usually up to 6 months
Palmoplantar pustulosis		
Starting dose: typically 50 mg/day	Sometimes the dose can be reduced to 25 mg/day	• To maintain remission, retinoids must be used at high doses (50 mg/day) on a continuous basis. Exacerbations sometimes occur even during active therapy • Duration of treatment – usually ca. 12 months
Generalized pustular psoriasis		
Starting dose: typically 50 mg/day	Maintenance dose: typically 25 mg/day	• In a large group of patients, acitretin used in monotherapy results in complete clinical remission, while the emergence of new lesions is often suppressed after several dozen hours of treatment • Duration of treatment – usually approx. 1-4 months

Note: Acitretin treatment in patients suffering from arthropatic psoriasis typically begins with maximum doses of the retinoid which are then reduced to 0.2-0.3 mg/kg b.w./day. On account of its higher efficacy, however, Re-PUVA is a more commonly used method

Combination therapy (acitretin coupled with other systemic or topical drugs) – recommended dosage regimens and efficacy

In order to achieve satisfactory clinical effects in patients suffering from plaque psoriasis (sometimes also palmoplantar pustulosis, psoriatic erythroderma or arthropatic psoriasis), it is often necessary to introduce a combined treatment modality based on acitretin and SUP/PUVA phototherapy. As a result, adverse reactions associated with both therapeutic methods are reduced and efficacy is enhanced. It is also possible to combine acitretin with biological drugs, topical therapy with vitamin D_3 derivatives, corticosteroids of cignolin (Table 2).

On the other hand, acitretin combination with methotrexate is not recommended (even though it is highly effective, while isolated reports have not provided evidence for increased hepatic toxicity) [24] and ciclosporin (alternating therapy is possible) [25].

As pointed out above, when acitretin monotherapy is ineffective, it is usually coupled with UVB phototherapy (acitretin + UVB = Re-UVB) or PUVA (acitretin + PUVA = Re-PUVA) or, alternatively, with PUVA-*soak* for palmoplantar pustulosis.

Re-PUVA currently seems the most effective method of treatment for severe forms of plaque psoriasis. Compared to acitretin monotherapy or PUVA, Re-PUVA significantly accelerates clinical remission (the period of treatment is reduced by an average of 18 days) but also decreases the accumulated dose of UVA by 30-50% (as compared with the cumulative dose required for PUVA alone) [30]. An additional benefit of this therapeutic combination is the anti-tumour activity of retinoids. It is a crucial aspect, considering the high risk of non-melanoma skin cancers in patients treated with PUVA.

The data have been successfully verified in a number of clinical trials. Tanew *et al.* observed a complete or significant clinical improvement in 96% of patients suffering from severe plaque-type psoriasis treated with Re-PUVA (as opposed to 80% of patients treated with PUVA alone). Moreover, the authors concluded that the method made it possible to reduce the radiation dose by 42% [31]. Similar results were obtained in other studies: Sommerbung *et al.* [32], Saurat *et al.* [33], Lauharanta *et al.* [34], Muchenberger *et al.* [35] and Nijsten *et al.* [36].

Re-UVB is applied in patients who are contraindicated for Re-PUVA, in the treatment of more superficial lesions and in younger patients, since PUVA carries a carcinogenic risk. Using the method, satisfactory clinical effects emerge during a longer period than in Re-PUVA treatment, nevertheless faster and in a greater percentage of cases than in acitretin monotherapy or UVB treatment.

Lebwohl *et al.* reported that a 3-month Re-UVA therapy had brought a 75% PASI score reduction – compared with 35% – among patients treated with UVB phototherapy and 42% – among patients treated with acitretin alone [37]. Similar results were also reported by other authors including Spuls *et al.* [38], Ruzicka *et al.* [39], Lowe *et al.* [40] and Kampitak *et al.* [41].

Alternating therapy (ciclosporin → acitretin) – recommended treatment regimen

Alternating therapy is a therapeutic method in which after achieving clinical remission with the first drug (in this case ciclosporin which, despite ensuring rapid

Table 2. Acitretin in combination therapy – recommended combinations

Type of therapy	Recommendation	Notes
Phototherapy	++	Enhanced efficacy; reduced cumulative dose of UV radiation (lower risk of distant adverse effects, e.g. carcinogenesis) and lower dose of acitretin (better treatment tolerance)
Ciclosporin	–	No evidence for enhanced efficacy. The metabolism of both products involves cytochrome P450
Methotrexate	–	Increased hepatic toxicity. The combination (though extremely uncommon) seems very effective in the most severe cases of psoriasis, particularly pustular and erythrodermic types). Acitretin at 25-50 mg/day should be introduced and, in the event of therapeutic failure, methotrexate in weekly courses of 15-20 mg should be added to therapy. There have been literature reports of isolated cases of toxic hepatitis after combined methotrexate and etretinate treatment [26]
Fumaric acid esters	–	No evidence for enhanced efficacy
Etanercept	+	One randomized clinical trial demonstrating similar efficacy of combination therapy with acitretin (0.4 mg/kg/day) and etanercept (25 mg/week), and etanercept (50 mg/week) [27]
Other biological drugs	+/–	Isolated reports suggesting enhanced efficacy
Topical treatment with vitamin D_3 derivatives	++	Synergistic mechanisms of action result in significantly more rapid remission than in monotherapy, and lower accumulated dose of acitretin. High efficacy of the combination has been confirmed in two randomized clinical trials performed in large cohorts of patients [28, 29]

Table 3. Diagram presenting Re-PUVA/Re-UVB treatment regimen

Phototherapy added to acitretin treatment	
Add acitretin (50 mg/day) for ca. 2 weeks	Reduce the dose of acitretin (typically to 10-25 mg/day) + Add PUVA or UVB (at doses reduced by 30-50%, as retinoids cause thinning of the corneal layer of the epidermis)
Acitretin added to phototherapy	
No expected effects after UVB/PUVA treatment	Reduce the radiation dose by 30-50% + Add acitretin (10-25 mg/day) (after ca. 1-2 weeks)

regression of skin manifestations, cannot be used on a long-term basis because of nephrotoxicity) another drug is introduced (e.g. acitretin which is usually better tolerated and safer, and ensures a longer remission period). The first drug is then gradually phased out and remission is maintained with the second drug. The regimen thus comprises three phases, as shown in Table 4 below.

Rules governing switching between systemic therapies

If one therapy proves ineffective or serious adverse reactions develop during treatment, it may become necessary to switch to another therapeutic modality. New therapy should be selected on the basis of the following criteria: the patient's clinical condition (severity of skin lesions, concomitant diseases), the patient's drug history, efficacy of previous therapies and any therapy-associated adverse reactions, costs of treatment and, naturally, the patient's expectations. Rules which must be observed while switching systemic therapies are presented in Table 5.

Contraindications to acitretin treatment

1. Absolute contraindications:
   - severe hepatic disorders,
   - renal failure,
   - pregnancy, lactation,
   - alcohol abuse,
   - therapy with drugs interacting with acitretin.
2. Relative contraindications:
   - hepatic/renal disorders,
   - reproductive period in women and men,
   - history of pancreatitis,
   - no patient compliance,
   - diabetes,
   - hyperlipidaemia.

Drugs interacting with acitretin

Before introducing acitretin the patient's medical history must be taken, including all previously used drugs. Also, the patient must be instructed to consult the physician before taking any new drug because acitretin (as any other drug) interacts with other therapeutic agents, which may lead to adverse reactions.

Drugs which most commonly cause interactions with acitretin are listed in Table 6.

Recommended tests prior to starting and during acitretin treatment

Safe acitretin therapy requires patient compliance and observance of a number of vital rules listed in Table 7.

This is particularly important for women of reproductive age due to the teratogenic properties of acitretin. For reproductive-age female patients it is always necessary to make sure that they understand and accept the necessity to use ongoing effective contraception (sign a relevant statement). It should also be noted that effective contraception should also be used by women with a history of infertility.

Table 4. Alternating therapy regimen: ciclosporin → acitretin

Phase 1 – achievement of remission (months: 0-1)	**Phase 2A – drug switch (months: 2-3)**	**Phase 2B – drug switch (months: 4-7)**	**Phase 3 – maintenance of remission (months: > 7)**
Add ciclosporin (5 mg/kg/day)	Continue ciclosporin treatment (≤ 5 mg/kg/day) + Add acitretin (25 mg/day; the dose can be gradually increased by 10 mg/day)	Reduce ciclosporin dosage (max. by 1 mg/kg/month) + Continue acitretin treatment	Continue acitretin treatment alone; add SUP/PUVA phototherapy (optionally)

Table 5. Rules governing switching between systemic therapies

Methotrexate (Mtx) → acitretin	Acitretin → methotrexate (Mtx)
Reduce Mtx dose gradually ↓ Introduce acitretin when the weekly dose of Mtx is 7.5 mg and Mtx therapy was used for 2 months ↓ Monitor hepatic function test results	Mtx can be introduced at the desired dose, without any adjustment period (regardless of the acitretin dose used) + Acitretin dosage can be reduced gradually or acitretin can be discontinued abruptly ↓ Monitor hepatic function test results
Ciclosporin → acitretin	**Acitretin → ciclosporin**
Add acitretin (10-25 mg/day) to full-dose ciclosporin treatment. ↓ Reduce the dosage of ciclosporin gradually, over a period of more than 3 months + Increase the dose of acitretin gradually, depending on the observed clinical response ↓ Monitor lipid profile results	Ciclosporin can be introduced at the desired dose, without any adjustment period (regardless of the acitretin dose used) + Acitretin dosage can be reduced gradually or acitretin can be discontinued abruptly ↓ Monitor lipid profile results

Note! Since the concentration of acitretin in sperm is insignificant, the drug probably is not a teratogenic agent.

Patients with a history/family history of diabetes, alcohol disease or disorders of lipid metabolism should be monitored more frequently than specified in Table 8 due to an increased risk of hypertriglyceridaemia.

Adverse reactions during acitretin treatment

The list of adverse reactions that may develop during acitretin therapy is very long. For the most part, these are dose-dependent symptoms which either lessen or subside completely after dose reduction or completion of treatment (Table 9).

The most serious risk associated with acitretin treatment is teratogenicity. There is also a risk of bone abnormalities (especially when the drug is used in children) which must always be duly considered, since the abnormalities are irreversible.

Teratogenicity

According to the FDA pharmaceutical pregnancy categories, acitretin is classified as category X, which means that it may cause congenital disorders, spontaneous abortion or premature birth.

Defects observed in retinoic acid embryopathy include: CNS abnormalities (hydrocephalus, microcephaly), eye defects (microphthalmia), skeletal and craniofacial abnormalities, external ear defects (congenital absence of pinna, absence/malformation of the external auditory meatus), cardiovascular disorders (e.g. cardiac septal defects) as well as abnormalities of the thymus and parathyroid glands [42].

Table 6. Drugs most commonly interacting with acitretin

Drugs	Interaction type
Tetracyclines	Idiopathic intracranial hypertension
Cholesterol-lowering medications	Increased risk of muscle damage
Vitamin A	Increased activity of retinoids
Methotrexate, antifungal imidazoles	Increased hepatic toxicity
Phenytoin	Displacement of acitretin from bindings with carrier proteins
Low dose progesterone contraceptive pills (“mini-pills”)	Reduced contraceptive efficacy
Anti-diabetic medications	Risk of hypoglycaemia; frequent glucose monitoring is essential, especially in the initial phase of treatment.
Glucocorticosteroids	Risk of hyperlipidaemia

Table 7. Recommendations before, during and after acitretin therapy

Recommendations before initiating acitretin treatment
1. Assessment of disease severity (PASI, BSA) and the patient's quality of life (DLQI)
2. Patient's detailed medical history, particularly previous drug use, liver/kidney diseases as well as disorders of the musculoskeletal system (if necessary, a radiographic examination should be performed)
3. Women of reproductive age should be informed of the teratogenic activity of acitretin and the need to use effective methods of contraception on an ongoing basis, starting 4 weeks before the initiation of treatment, during the entire period of treatment and for 2 years after the completion of therapy (a relevant statement must be signed) *Note! The therapy cannot commence until the second/third day of normal menstruation occurring after the start of contraception, provided that a pregnancy test gives a negative result*
4. Female patients must be informed that no alcohol intake is allowed during acitretin therapy and for 2 months after the completion of treatment (due to the risk of conversion to etretinate). Patients of both sexes must be instructed that no honorary blood donation is allowed during the treatment and for one year after the completion of therapy *Note! Men should not consume alcohol during therapy because it interferes with lipid metabolism and elevates the level of liver aminotransferases*
5. Laboratory tests – Table 8
Recommendations during acitretin treatment
1. Periodic assessment of disease severity and the patient's quality of life
2. Acitretin should be taken with fat-rich foods or milk *Note! Patients with high triglyceride and/or cholesterol levels should follow a diet. Recommended foods include fibre-rich meals, natural sterols (nuts, plant oils and fish such as salmon, sardines, herring, mackerel), meat consumption limited to poultry and veal, reduced intake of high GI carbohydrates (sweets, white bread). Alcohol intake is excluded*
3. Women of reproductive age should use effective methods of contraception (as above) and take pregnancy tests once a month for the entire duration of treatment
4. Ban on alcohol intake and honorary blood donation
5. Limited exposure to UV radiation (as retinoids cause skin thinning)
6. Avoiding laser treatment and waxing as a depilation method (increased skin susceptibility to irritancy)
7. Application of special lipsticks for lipid replenishment and body emollients. Due to the risk of conjunctival xerosis, patients should not wear contact lenses
8. Monitoring of laboratory test results – Table 8
Recommendations after acitretin treatment
1. Effective contraception in women of reproductive age
2. Ban on alcohol intake and honorary blood donation

PASI – Psoriasis Area and Severity Index, BSA – body surface area, DLQI – Dermatology Life Quality Index

Skin and mucosal symptoms

They are the most common and the most inconvenient symptoms for the patient. They include skin and mucosal dryness; pruritus; erythema (especially of the face); increased skin irritancy (observed in 50-75% of patients, sometimes accompanied by a mild symptom resembling Nikolsky's sign; blepharitis and conjunctivitis; cheilitis – in over 75% of patients; erythematous exfoliative skin lesions typically located on the extensor surfaces of forearms and palms (retinoid dermatitis) – 50-75% of patients; excessive sweating; *rhinitis sicca* and nose bleeds; nail plate abnormalities – brittle and soft nails (up to 25-50% of patients); whitlow; hair loss (affecting up to 50-75% of patients treated with acitretin, more common in women; hair typically grows back on discontinuation of treatment) [43, 44].

Note! During the first four weeks of acitretin therapy some patients may experience an exacerbation of psoriatic lesions, which often (unnecessarily) discourages them from continuing therapy.

Effect on the liver and lipid metabolism

A temporary increase in results of liver function tests is observed in ca. 15% of patients treated with the retinoid.

Table 8. Schedule of recommended additional medical tests

Recommended tests	Frequency [weeks]						
	Before therapy	1	2	4	8	12	16
Peripheral CBC	+				+		+
Liver function tests (ALT, AST, GGTP, FA, bilirubin)	+			+	+		+
Creatinine and urea	+						
Glucose	+						
Triglycerides, total cholesterol, HLD and LDL	+			+	+		+
Pregnancy test	+	Once a month during therapy and for 2 years after the completion of treatment					
Bone radiography	For persisting pain						

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGTP – γ-glutamyl transpeptidase, FA – alkaline phosphatase, HDL – high-density lipoprotein, LDL – low-density lipoprotein

Table 9. Adverse reactions accompanying acitretin treatment

Very common	Symptoms resulting from excess of vitamin A (dry skin, cheilitis)
Common	Conjunctivitis (usually in contact lens wearers), hair loss, hyperlipidaemia, photosensitivity, muscle and joint pain
Rare	Gastrointestinal complaints, hepatitis, jaundice, bone abnormalities
Very rare	Idiopathic intracranial hypertension, colour vision disturbances, nocturnal amblyopia

Hypertriglyceridaemia occurs in 25-50% and hypercholesterolaemia in 10-30% of patients. It must be noted, though, that the disorders enumerated above are more common in patients with additional risk factors including diabetes, obesity, alcohol abuse, smoking or history/family history of hyperlipidaemia [45]. Results of liver function tests, as well as triglyceride and cholesterol levels, usually return to baseline values within 4-8 weeks after the discontinuation of acitretin.

Note! Treatment must be discontinued if:

- *transaminase activity is significantly elevated (three times above the upper limit of normal),*
- *the cholesterol level is higher than 300 mg/dl,*
- *the triglyceride level is higher than 500 mg/dl (risk of acute pancreatitis).*

Bone lesions

Acitretin treatment may also lead to the formation of diffuse calcifications in ligaments and bone thickening within the vertebra. They usually develop in the anterior cervical ligament or in the lumbar spine (DISH, *diffuse idiopathic skeletal hyperostosis*).

Note! Radiology examinations should not be routinely performed even in prolonged acitretin treatment [46]. They are indicated only in the patients who develop abnormal symptoms of the musculoskeletal system.

Caution should also be exercised when etretinate or acitretin is used in children (due to isolated reports of premature epiphyseal fusion) [47, 48].

Other adverse reactions

Other adverse symptoms include fatigue, drowsiness, malaise, muscle and joint pain, candidal vulvovaginitis, nausea and, very rarely, benign intracranial hypertension – *pseudotumor cerebri* (manifestations: headache, nausea, vomiting and visual disturbances; there is one literature report of the condition developing after acitretin therapy) [49].

Note! Even though experiments in mice have shown acitretin to delay the process of wound healing, the findings have not been confirmed in human studies. As a result, it is not necessary to stop treatment prior to surgery [50].

Conclusions

Acitretin is a long-established drug with a proven efficacy against psoriasis symptoms. Acitretin therapy should be considered in patients with pustular psoriasis (both generalized and palmoplantar pustulosis) or psoriatic erythroderma. For plaque psoriasis a more beneficial therapeutic option is combination treatment, e.g. with UVB

phototherapy, PUVA or topical agents. In addition, the retinoid is effective in arthritic psoriasis.

For acitretin therapy to be safe, a number of rules must be followed, especially in reproductive-age women due to teratogenic properties, and hence good patient compliance is vital.

The drug should not be used at doses exceeding 50 mg/day, regardless of body weight. This dosage regimen makes it possible to reduce adverse reactions (better tolerance of treatment) and provides a better safety profile both in short- and long-term therapy.

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