DOI: 10.4274/turkderm.galenos.2022.89577
Turkderm-Turk Arch Dermatol Venereol 2022;56(Suppl 1):21-5

Acitretin

Asitretin

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Abstract

Acitretin is a synthetic retinoid and an active metabolite of etretinate. It shows its action in psoriasis treatment by suppressing proliferation and enhancing the differentiation of keratinocytes. It differs from other systemic anti-psoriatic agents in that it is not immunosuppressive or cytotoxic. It is used as a monotherapy or in combination with phototherapy in various clinical forms of psoriasis. Due to its teratogenicity, its use in women of reproductive age is not recommended unless there is no alternative. Studies of this drug show that acitretin monotherapy is less effective in plaque psoriasis than other conventional systemic therapies but is superior to them in generalized, palmoplantar, pustular, and hyperkeratotic variants.

Keywords: Psoriasis, acitretin, treatment

Öz

Asitretin etretinatın aktif metaboliti olan sentetik bir retinoiddir. Psoriasis tedavisinde keratinositlerin proliferasyonunu baskılayıp, diferansiyasyonunu artırarak etki gösterir. Diğer sistemik antipsoriatik ajanlardan farkı immünosüpresif ve sitotoksik olmamasıdır. Psoriasisin farklı klinik formlarında monoterapi ya da fototerapi ile birlikte kombine olarak kullanılmaktadır. Teratojenitesi nedeniyle alternatifi olduğu sürece doğurganlık çağındaki kadınlarda kullanılması önerilmez. İlaçla ilgili çalışmalar asitretin monoterapisinin plak tip psoriasiste diğer geleneksel sistemik tedavilerden daha az etkili olduğunu, jeneralize, palmoplanter püstüler ve hiperkeratotik varyantlarda diğer geleneksel sistemik tedavilere göre daha üstün olduğunu göstermektedir.

Anahtar Kelimeler: Psoriasis, asitretin, tedavi

Introduction

Acitretin, pharmacologically an active metabolite of etretinate, is a second-generation synthetic retinoid and due to its superior pharmacokinetic properties replaced etretinate in late 1980s. Supposing that alcohol present in daily food and beverages and in some drugs would convert its acitretin into etretinate, acitretin can be evaluated in the same way as etretinate in terms of its half-life[1-5,8,9].

Mechanism of action

Contrary to other systemic antipsoriatic agents, acitretin is not immunosuppressive or cytotoxic. It shows its action in psoriasis by suppressing keratinocyte proliferation, enhancing keratinocyte differentiation, and suppressing production of vascular endotelial growth factor, chemotactic response and activation, and induction of Th17 cells by interleukin-6[1,2,4,5,8,9].

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E-mail: nihalkundakci@hotmail.com **Received/Geliş Tarihi:** 07.02.2022 **Accepted/Kabul Tarihi:** 11.02.2022
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Cite this article as: Kundakçı N. Acitretin. Turkderm-Turk Arch Dermatol Venereol 2022;56(Suppl 1):21-5

Turkderm - Turk Arch Dermatol Venereol
2022;56(Suppl 1):21-5

Indication

Table 1 shows indications of acitretin for use in psoriasis. It is used for these indications as a monotherapy or in combination with topical therapies, UVB, PUVA, cyclosporine, and biological therapies. Acitretin should not be considered as a first line treatment in female patients at a reproductive age unless there is no alternative treatment for these indications[3-5,9-11].

Table 1. Indications of acitretin for use in psoriasis

1. Moderate to severe plaque psoriasis that does not respond to, or is not suitable for topical therapies and phototherapy
2. Generalized pustular psoriasis
3. Localized pustular psoriasis

Contraindication

Acitretin is teratogenic and should not be used in pregnant women, those planning to get pregnant or in women at their productive age who are unable to secure contraception for 3 years and during lactation. Table 2 shows the absolute and relative contraindications of acitretin[1-3,5,8-11].

Table 2. Contraindications of acitretin

Absolute contraindications	Relative contraindications
Pregnancy and lactation	Diabetes mellitus
Those sensitive to acitretin, other retinoids or the ingredients of these	Hyperlipidemia/ hypertriglyceridemia
Moderate to severe liver dysfunction	Atherosclerosis
Moderate to severe renal failure	Concurrent use of hepatotoxic drugs
Alcoholism	Impaired patient compliance
Blood donation	Heavy alcohol consumption
Use of drugs contraindicated for simultaneous use	Use of contact lenses

Dose

Since absorption and metabolic rate of acitretin as well as therapeutic and toxic responses depend on the dose and thus may vary from person to person, the dose should be adjusted individually for each patient. Dosage and schema recommendations for an acitretin therapy are given in Table 3[1-3,5,8-11].

Table 3. Dosage and schema recommendations for an acitretin therapy

Start/dose of an acitretin therapy
Acitretin 10 mg and 25 mg are in stern capsules in the doses
In female patients, a pregnancy test should be carried out, contraception should be started 1 month in advance and the therapy should start after waiting for day 2 and day 3 of the cycle, the patient should be informed about abstaining from pregnancy 3 years following the treatment, a written consent should be obtained, and if the patient's compliance is poor, the therapy should not be started
Alcohol use should be restricted/banned (banned for female patients during and until 2 months after the treatment; with alcohol, hepatotoxicity also increases)
Its bioavailability increases with greasy foods. The capsules are taken as a single dose with greasy food or milk. The daily dose may be taken as a whole, or in high doses, divided into 2 or 3 doses
Acitretin is used in doses between 0.25 and 1 mg/kg/day, and when used as a monotherapy, its effective dose has been reported to be 25-50 mg/day; it is generally used in doses of 10-50 mg/day. Higher doses (0.75-1 mg/kg/day) are used in pustular psoriasis and lower doses (0.25 mg/kg/day) in erythrodermic psoriasis. The most accepted and recommended approach is gradual dose increase which is more convenient to tolerate side effects[1-3,5-7]
Starting dose: It is started with 20-30 mg/day (0.3-0.5 mg/kg/day) for 2-4 weeks and continued with 25-50 mg/day (maximum: 75 mg/day, 3x25 mg) (0.5-0.8 mg/kg/day, maximum: 1 mg/kg/day) for 6-8 weeks. Response is slow and it takes 3-6 months to obtain the maximum response
Maintenance dose: The dose for maintenance is also adjusted based on clinical efficacy and tolerability. In patients requiring long-term treatment, the lowest effective dose (often 10 mg/day or 25 mg/every other day, not to exceed 50 mg/day) may be used for maintenance
Duration of treatment/maintenance treatment: There is no total dose restriction that limits the duration of an acitretin therapy. The treatment may be discontinued in patients giving adequate response; the treatment is planned in the same manner for relapses. A maintenance therapy with acitretin is effective and safe. In patients requiring long-term treatment, the treatment is continued with the lowest effective dose (often 10 mg/day or 25 mg/every other day, not to exceed 50 mg/day)

Efficacy

The clinical studies made with acitretin in psoriasis had different clinical types and used different doses and combined therapies. There are a few randomized controlled studies with much differing reports of clinical responses. Studies show that acitretin monotherapy is less effective in plaque psoriasis than the other traditional systemic therapies but is superior to them in generalized, palmoplantar pustular and hyperkeratotic variants. Clinical response to an acitretin therapy is slow, showing its first signs in 4-8 weeks and an apparent recovery in 3-6 months. Clinical effect should be assessed at week 12[3,7].

Usage in special patient groups

Side effects

Side effects occur in most of the patients receiving an acitretin therapy. These side effects usually disappear when the dose is decreased or

the drug is discontinued. Sometimes, an exacerbation of psoriatic symptoms may be observed at the beginning of the therapy[1,5,8-11]. The side effects of acitretin are shown in Table 4.

Table 4. Acitretin side effects

Teratogenity: Retinoid embryopathy.
Mucocutaneous side effects: Dry skin and mucosa, weakening and thinning of hair, thinning and fragility in nails, paronychia, pyogenic granuloma, photosensitivity, bullous eruptions, retinoid dermatitis.
Hepatotoxicity: Elevated liver enzymes, which is often reversible, severe hepatotoxic reaction, cirrhosis (alcohol use, diabetes and obecity increase this risk).
Hyperlipidemia: Hypertriglyceridemia, elevated VLDL, hypercholesterolemia, increase in VLDL/LDL, low HDL, pancreatitis (diabetes, obesity, alcohol consumption and a family history of hypertriglyceridemia increase the risk).
Skeletal anomalies: Pain in muscles and bones, ligament calcification, diffuse idiopathic skeletal hyperostosis (DISH)-like involvement, early closure of epiphyses in children.
Depression: Depression, aggressive behaviour, suicidality.
Other side effects: Benign intracranial hypertension, blurry vision, impaired night vision, candida vulvovaginitis, increased insulin sensitivity/hypoglycemia in those taking antibiotics, acute myocardial infarction, thromboembolism, hypersensitivity (urticaria, angioedema), myopathy, myalgia, rhabdomyolysis, peripheral neuropathy.

Acitretin use in the presence of comorbidities

Due to many comorbidities involved in psoriasis, restriction of many systemic treatment options is sometimes necessary, whereas some options may become advantageous to treat both conditions. Table 5, 6. shows the place of acitretin in treatment in the presence of common comorbidities of psoriasis[14,15].

Table 5. Recommendations for using acitretin in special patient groups

Use in pregnancy Pregnancy category X.	As long as there is an alternative for it, acitretin should not be given to women at productive age. Pregnancy test should be negative 2 weeks prior to the treatment, it should be started at day 2 or 3 of the menstrual cycle, contraception should be in place 4 weeks before and during the treatment, and until 3 years from the discontinuation of the acitretin therapy. Female patients using acitretin must definitely avoid consuming alcohol during and until 2 months after the treatment. No risk has been shown in the reproduction safety of males receiving acitretin therapy[1-3,5,13,15].
Use during lactation	It has been shown that 1.5% of acitretin's plasma concentration passes into milk. Acitretin should also be avoided in breastfeeding mothers[1-3,13-15].
Use in paediatric patients	Considering the benefit/harm ratio, it may be used in children as intermittent rescue treatment for generalized pustular flare-ups, or as a monotherapy or in combination with topical therapies and narrow-band UVB in erythrodermic or severe plaque psoriasis. The treatment will be started with a 0.5-1 mg/kg/day dose, when there is a considerable recovery, the dose will be lowered down to 0.2 mg/kg/day, and the treatment will be continued for another 2 months after remission. Radiological assessment is recommended in paediatric patients due to the risk of early closure of epiphyses and hyperostosis. As it is teratogenic, adolescent girls should use oral contraceptive during its use and until 3 years after its discontinuation[5,12,13,15].
Use in geriatric patients	Since the cardiovascular risk associated with hypertriglyceridemia emerges after many years, older people are at lower risk; therefore, it is a reasonable option for the treatment of psoriasis in the geriatric age group, but in addition to senile xerosis, the dryness and itching caused by asitretin may turn out to be a major issue[13,15].
In liver and kidney disease	It is contraindicated for moderate to severe liver and kidney failure.
Use during chronic infections	HBV: HBsAg+ and anti-HBc+ and anti-HCV+ patients: It is not generally recommended for its hepatotoxicity, but if it is to be used, liver functions should be monitored closely. It is a conventional treatment agent preferred in tuberculosis infections and HIV+ patients[13].
Use during COVID-19 pandemic	It is a safe conventional therap[18,19].

Table 6. Use of acitretin in the presence of psoriasis comorbidities

Arthropathic psoriasis	Acitretin is moderately effective when there is joint involvement; it cannot be used as a monotherapy in psoriatic arthritis.
Inflammatory bowel disease (IBD)/Crohn's disease	Acitretin is not effective in IBD; no evidenced association between acitretin use and IBD development has been shown.
Malignancy	Systemic retinoids prevent or delay the development of non-melanoma skin cancers. Systemic retinoids are appropriate treatment options in patients with systemic malignancies.
Obesity	Due to the hyperlipidemic side effects of acitretin, obese patients need higher doses and this leads to an increase in side effects.
Atherosclerosis	Although acitretin causes hyperlipidemia, no increase in the risk of major cardiovascular event has been shown with the use of etretinate in patients with psoriasis.

Table 6 Continued	
Congestive heart failure (CHF)	No newly emerging CHF or exacerbation has been reported with the use of acitretin.
Multiple sclerosis (MS)	No data is available on the use of acitretin in MS patients.
Lupus erythematosus	Acitretin has been used in the treatment of LE with success.
Depression	Depression, aggressive and suicidal behaviours have been reported with the use of acitretin. This should be taken into consideration in the presence of comorbid depression, and when such behaviours emerge, the therapy should be discontinued.

Laboratory follow-up

Before starting the treatment with acitretin, a pregnancy test should be conducted in female patients at the reproductive age 2 weeks before the treatment to rule out possible pregnancy; current or past history of liver disease, extensive alcohol consumption and hepatotoxic drug use, current or past history of kidney disease, nephrotoxic drug use, current or past lipid profile disorders, obesity, diabetes mellitus, and antidiabetic drug use should be questioned; and the tests shown in Table 7 should be performed before and during the treatment[3,5,8-11].

Table 7. Laboratory tests to be performed before and during acitretin therapy[10]

Test	Pre-treatment	After 4 weeks	After 8 weeks	After 12 weeks	Every 3 months
Whole blood count	+	+	+	+	+
ALT, AST	+	+	+	+	+
S Cre, BUN	+	+	+	+	+
Lipid profile	+	+	+	+	+
FBS	+		+		
Pregnancy test	+	+	Monthly		

ALT: Alanine aminotransferase, AST: Aspartate transaminase, BUN: Blood-urea nitrogen. The number and frequency of laboratory tests may change depending on the clinical status, the patient and the risk status, and during dose increases.

1. If there are abnormal results in transaminases, weekly monitoring will be carried out and the acitretin dose will be adjusted accordingly. If transaminases are elevated by 3 times the normal limit and the billirubin level is above 50 Imol/L or ALT is above 200 IU/L, a gastroenterology consultation should be made. Monitoring of liver functions for at least 3 months is recommended in these patients. In patients whose disease is very severe and acitretin therapy cannot be discontinued due to other treatments being unsuccessful, continuation of the therapy with a gastroenterologist, and if necessary, making a liver biopsy are recommended.
2. If the therapeutic response to acitretin is good but there is persistent lipid elevation, first diet, and if necessary, lipid lowering agents (gemfibrozil) may be prescribed. In the presence of hypertriglyceridemia, close monitoring will be needed if the triglyceride level is above 5 mmol/L and the treatment should be discontinued if it goes above 10 mmol/L due to the risk of pancreatitis.
3. In patients with diabetes mellitus, blood sugar measurements should be done more often at the beginning of the treatment.
4. In relation to the effects of acitretin on the skeletal system, routine radilological examinations are not recommended in asymptomatic patients, but they may be necessary in patients showing symptoms.

Therapies in combination with acitretin

Transition from acitretin therapy to other therapies

When a therapy change is to be made for safety reasons, a run-in period may be needed until the safety parameters return to normal. When replacing a therapy due to inefficacy, a direct change of the therapy or a transition to a period where two therapies are administered at the same time may be considered. When switching from methotrexate to acitretin, monitoring for possible hepatotoxicity and keeping the initial dose of acitretin low is recommended. When switching from cyclosporine to acitretin, the goal is to phase out the cyclosporine dose and continue with acitretin for maintenance. Although concurrent use of these two agents is unfavourable due to hyperlipidemia, the malignancy preventing property of acitretin constitutes the favourable side of such rotation. A transition from acitretin to a biological agent may be made without any washout period or through a period where the two therapies are used at the same time.

Table 8. Therapies in combination with acitretin[1-3,5,8-11]

	Result
Calcipotriol	Possibility to reduce treatment dose and duration, additive and synergic effect
Phototherapy (nb UVB, PUVA)	Increased efficacy, lower total UV dose (decrease in the risk of carcinogenicity). The therapy that is most commonly combined with acitretin is phototherapy. In this combination, it is recommended to start asitretin 25 mg/day 2 weeks before the phototherapy, which should also be started with a lower UV dose, and if acitretin is to be given to a patient who had received prior phototherapy, the UV dose needs to be lowered by 3-50% a week after starting acitretin
Methotrexate	Risk of hepatotoxicity?
Cyclosporine	Increase in efficacy? Hyperlipidemia, short-term combinations between transitions
Other biological agents	Since it is not immunosuppressive, its combination with biologicals may be appropriate

Drug interactions with acitretin[3,5,8-11]

Acitretin and vaccines

There is no vaccination restriction for patients treated with acitretin[16].

Table 9. Drug interactions with acitretin

Drug	Type of interaction
Methotrexate	Increases liver toxicity
Tetracycline, doxycycline, minocycline	Pseudotumour cerebri, concurrent use is contraindicated
Oral contraceptives	While an acitretin therapy has no effect on combined oral contraceptives, it reduces the anovulatory action of oral contraceptives that contain low progesterone or solely progestin
Antidiabetic drugs	Increases hypoglicemia risk
Phenytoin	Acitretin reduces protein-binding ability of phenytoin; clinical significance of this is unknown
Corticosteroids	Risk of hyperlipidemia increases
Vitamin A	Vitamin A supplements should not be taken together Exceeding 2400-3000 IU/day should be avoided

Table 9 Continued	
Lipid-lowering agents	Risk of myotoxicity
Antifungal imidazoles	Liver toxicity
Sirolimus	Sirolimus levels rise, sirolimus also leads to hypertriglyceridemia

Acitretin and surgery

Acitretin is agreed to not have any effect on wound site infections or wound healing. Therefore, there is no need to discontinue an acitretin therapy during ordinary surgeries such as urgent orthopaedic procedures[17].

SUGGESTIONS

- It has been shown that acitretin monotherapy is less effective in plaque psoriasis compared to the other traditional systemic therapies but is superior to them in generalized, palmoplantar, pustular and hyperkeratotic variants.
- Unless there is no alternative to it, acitretin should not be prescribed to women at their reproductive age, but can be used in postmenopausal female and male patients. In male patients, the amount passing into the semen has not been found clinically significant.
- A pregnancy test should be conducted in female patients at the reproductive age 2 weeks before starting the acitretin therapy to rule out possible pregnancy; the drug should be started at day 2 or 3 of the menstrual cycle. An effective contraception method should be started 4 weeks before starting the treatment and contraception should continue with two effective methods during the treatment and until 3 years after the treatment.
- Since acitretin decreases the effect of oral contraceptives, preparations with low-dose progesterone should be used.
- Although the amount passing into milk is low, it should not be used during lactation.
- Patients should avoid donating blood during the treatment and until 3 years after the treatment.
- Due to its effects on the skeletal system, acitretin should be used with caution in child patients considering its benefits/harms and the bone development and growth parameters of these children should be monitored.
- Daily vitamin A intake should not exceed 2400-3000 IU/day in patients using acitretin.
- Alcohol consumption should be questioned before starting the treatment and female patients should not be allowed to use alcohol also for another 2 months after the treatment.
- As acitretin will increase insulin sensitivity, patients using antidiabetics are at risk of hypoglycemia; therefore, blood sugar levels should be monitored more closely at the beginning of the treatment.
- Patients with diabetes, alcoholism and obesity should be monitored even more closely for the risk of hypertriglyceridemia.
- Patients receiving an acitretin therapy should be reminded of avoiding intense ultraviolet exposure (i.e. sunlight, solarium).
- Since acitretin causes thinning of the skin and increased skin fragility, patients should be warned to not use epilating wax to eliminate undesired hair.

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