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Apremilast

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Abstract

Apremilast is an orally used small-molecule inhibitor of phosphodiesterase-4. It has been approved for the treatment of adult patients with psoriatic arthritis and moderate to severe plaque psoriasis. Clinical studies have reported that it is also effective in hairy skin and nail psoriasis, generalized pustular psoriasis, and palmoplantar pustulosis. In psoriasis vulgaris, a PASI75 response was achieved in 30-70% of the patients in 12-16 weeks. It is generally well-tolerated, and its most common side effects are diarrhea, headache, and nausea, all of which disappear in time.
Keywords: Psoriasis, phosphodiesterase inhibitor, apremilast

Öz

Apremilast, oral olarak kullanılan, küçük moleküllü fosfodiesteraz-4 inhibitörüdür. Psoriatik artritli ve orta/şiddetli plak psoriasisli yetişkin hastaların tedavisinde onaylıdır. Yapılan klinik çalışmalarda saçlı deri, tırnak psoriasisi, jeneralize püstüler psoriasis ve palmoplantar püstülosiste de etkili olduğu bildirilmiştir. Psoriasis vulgariste PAŞİ75 cevabı hastaların %30-70'inde 12-16 haftada alınmıştır. Genel olarak iyi tolere edilir, diyare, baş ağrısı ve bulantı en sık görülen yan etkiler olup zamanla geriler.
Anahtar Kelimeler: Psoriasis, fosfodiesteraz inhibitörü, apremilast

Introduction

Apremilast is an orally used small-molecule inhibitor of phosphodiesterase 4 (PDE4). It received FDA approval in 2014 to be used for the treatment of active psoriatic arthritis first and then for the treatment of moderate to severe plaque psoriasis in adult patients[1,2].

Mechanism of action

Through what mechanisms apremilast shows its action in psoriasis and psoriatic arthritis is not fully explained, but it is believed to prevent degradation of cyclic adenosine monophosphate (cAMP) by inhibiting PDE4, and the increased cAMP levels as a result of this reduce the secretion of proinflammatory cytokines such as TNF-α, IL-2, IL-12, IL-23 and IFN while increasing the secretion of anti-inflammatory cytokines such as IL-10, and in this way, apremilast shows its action by stopping intracellular inflammatory cascade at an early stage[1-5]. Although it inhibits production of Th1, Th2 and Th17 cytokines, it does not affect clonal expression of T or B-cells and antibody response. This explains its low risk of serious infection and favourable safety profile[5].

Indications

Apremilast is indicated in patients with moderate to severe plaque psoriasis who do not respond to, have a contraindication for, or cannot tolerate phototherapy or other conventional systemic therapies[1,2,4,6,7,10-12,15-21]. Clinical studies

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have reported that it is also effective in hairy skin and nail psoriasis, generalized pustular psoriasis, and palmoplantar pustulosis[4,11,16,17]. Table 1 shows approved indications of apremilast.

Table 1. Indications of apremilast
1) Psoriatic arthritis (FDA approval PsA 21 March 2014)
2) Psoriasis vulgaris (FDA approval 23 September 2014) Apremilast is indicated in patients with moderate to severe plaque psoriasis who do not respond to, have a contraindication for, or cannot tolerate phototherapy or systemic therapies
3) Behçet's disease (FDA approval 19 July 2019)

Contraindications

The contraindications of apremilast are shown in Table 2.

Table 2. Contraindications of apremilast[7-15,19-21]
1) Known hypersensitivity to apremilast or any of its ingredients
2) Severe acute infections
3) Pregnancy, lactation
4) Galactose intolerance, lactase deficiency or glucose glactose malabsorption
5) Malignancy or lymphoproliferative diseases
6) Depression
7) Due to lack of a safety profile for the use of apremilast in patients with a neurological disease and its potential to interact with other drugs, it can be used in this group of patients after considering its benefit-harm status

Dosage and treatment scheme

Table 3 shows a treatment scheme for apremilast in the treatment of psoriasis and psoriatic arthritis.

Efficacy

In the treatment of psoriasis vulgaris with apremilast, 30-70% of patients are reported to achieve a PASI75 response within 12-16 weeks[1,4,7,16]. Its efficacy in psoriatic arthritis is stated to be higher than in plaque psoriasis[4].

Duration of treatment

A maximum length of usage has not been established for patients who respond to apremilast. Psoriasis rebound has been reported in 3% of the patients who discontinued the therapy. There are no studies on the efficacy/loss of efficacy in an intermittent apremilast therapy[7-9].

Side effects

Apremilast is generally well tolerated. Diarrhoea, headache and nausea are the most common side effects, which usually appear at week 2. With the continuation of the dose, they decrease in time and disappear. The frequency and severity of side effects have been shown to not increase in long-term treatment with no new side effects emerging[1-4,7,8]. Possible side effects of an apremilast therapy and recommendations to control them are shown in Table 4.

Use in special cases

Use of apremilast in special cases is shown in Table 5.

Use of apremilast in the presence of comorbidities

Use of apremilast in the presence of comorbidities is shown in Table 6.

Drug interactions with apremilast

The drug interaction potential of apremilast is lower compared to other conventional medications.
When used in combination with drugs that make cytochrome p450 induction (rifampin, phenobarbital, carbamezapine, phenytoin) Apremilastın loses some of its efficacy[3,4].

Laboratory follow-up

Treatment with apremilast is fairly easier than with other conventional systemic treatment agents as it involves no organ toxicity; it does not require hepatitis virus or tuberculosis screening. There are no recommendations on the requirement of routine laboratory testing at the beginning of an apremilast therapy and during follow-up or on the

Table 3. Therapeutic dosing regimen for apremilast

Apremilast (Otezla® tablet)
A 10 mg pink tablet (APR written on one side and the number 10 on the other side)
A 20 mg brown tablet (APR written on one side and the number 20 on the other side)
A 30 mg beige tablet (APR written on one side and the number 30 on the other side)

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 and thereafter	
Morning	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening	Morning	Evening
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

In psoriasis and psoriatic arthritis, it is given in increasing doses during the first 5 days and will be continued with 2x30 mg after day 6. The purpose of this titration scheme is to reduce the gastrointestinal symptoms that may arise at the beginning of the treatment.

The tablets may be taken independent of meals, they should be swallowed without breaking, crushing or chewing[3,4,7,8]

Table 4. Possible side effects of an apremilast therapy and recommendations to control them[2]	
Gastrointestinal	Diarrhoea, nausea, increased bowel movements, dyspepsia, reflux, abdominal pain, vomiting For nausea, taking the drug with meals, having frequent and small amounts of meal, restricting liquid intake during meals, and using antiemetics may be recommended For diarrhoea, taking the drug with meals, restricting caffeine, and in the case of severe diarrhoea and vomiting, decreasing the dose, hydration, and using antidiarrhoeal drugs are recommended; in severe cases, discontinuation of the therapy may be necessary Care should be taken in older patients as diarrhoea and vomiting may cause loss of volume and hypotension
Respiratory system	Upper respiratory tract infection, bronchitis, coughing
Neurological	Tension headache, migraine
Psychiatric	Depression, insomnia Patients who have a history of depression, suicidal ideation or behaviour should be informed about the risks and benefits of the therapy before starting the treatment[20]
Metabolism	Loss of appetite, weight loss (in long-term treatment, loss of about 5-10% of body weight, 2 kg on the average, irrespective of gastrointestinal side effects, has been reported)
Skin	Psoriasis rebound in 03% of the patients who discontinued the therapy
Other	Backache

Table 5. Use of apremilast in special cases	
Use in pregnancy and lactation	The pregnancy category of apremilast is C. It is not to be used during pregnancy as sufficient and well controlled studies on its use in pregnant women are not available. Discontinuation of it 2 days prior to conception is recommended. Since it is not known whether or not apremilast or its metabolites are present in human milk, it should not be used during lactation[16,22,23].
Use in paediatric patients	Since safety and efficacy of apremilast in minor patients are not evidenced, it should not be used in children and adolescents[22,23].
Use in geriatric patients	Care should be taken in older patients using apremilast as diarrhoea and vomiting may cause loss of volume and hypotension. In cases of severe diarrhoea and vomiting, the dose should be decreased, and if symptoms persist, the treatment should be discontinued[22,23].
Use in liver and kidney dysfunctions	The pharmacokinetics of apremilast is not affected by moderate or severe liver failure; dose adjustment will not be necessary in liver diseases. In the case of a serious renal disorder, dose adjustment will be necessary in an apremilast therapy. In patients with severe renal failure (creatinin clearance less than 30 mL/minute), the dose should be reduced to 30 mg once daily. In this group of patients, the titration doses for the first 5 days will be reduced to the morning dose alone, omitting the evening dose[3,22,23].
Use of apremilast in chronic infections	**HBV: HbsAg+ and anti-HBc+ patients:** No data is available for this. **Anti HCV+ patients:** Despite limited data on this, apremilast has a preferable safety profile. Since there is no evidence-based suggestion on the effects of apremilast on HBV and HCV replication or a requirement for a hepatitis screening in its product characteristics, it is deemed unnecessary to perform a hepatitis B and C serology screening at the beginning of the treatment[7,8,12-14,22,23]. **Tuberculosis infection:** Since apremilast does not increase the risk of tuberculosis, a tuberculosis screening is not necessary[7,8,12-14,22,23]. **HIV:** There is no data on treatment with apremilast in HIV-infected psoriasis patients. If these patients have no other treatment alternative, this treatment should be planned in collaboration with an infectious diseases specialist[22-24].
Use during COVID-19 pandemic	It is safe[25-27]

frequency of follow-up procedures[1,4-20,21]. However, since leukopenia, neutropenia, thrombocytopenia, anemia, and elevations in creatinin and liver enzymes have been reported and dose adjustment is required in renal failure, these parameters should be monitored at the beginning, and when necessary during maintenance. The S3 guideline also recommends whole blood count, and monitoring of liver enzymes and serum creatinin before the treatment and at 3-month intervals[21]. Laboratory follow-up for apremilast treatment is shown in Table 7.

Therapies in combination with apremilast

No data is available on the combinations of apremilast with phototherapy, conventional systemic and biological agents, but since there are studies reporting that its use is effective and safe in such combinations, it can be used together with other therapies when necessary. A pharmacokinetic study on the use of apremilast in combination with methotrexate has shown that these two medications are not affected by the pharmacokinetics of each other; thus, it can be

Table 6. Use of apremilast in the presence of comorbidities[21-23]	
Psoriatic arthritis	Apremilast is indicated for psoriatic arthritis.
Obesity	No data is available on the advantages or disadvantages of using apremilast in obese patients. However, since it causes a 5-10% loss (average 2 kg) of the body weight, it may be preferable for this patient group.
Diabetes mellitus	There is no evidence showing that apremilast has an effect on insulin resistance. Diabetes mellitus is not a contraindication for the use of apremilast.
Inflammatory bowel disease	No data is available on the advantages or disadvantages of using apremilast in psoriasis patients with inflammatory bowel disease.
Coronary heart disease/ atherosclerosis	No data is available on the advantages or disadvantages of using apremilast in patients with coronary heart disease/atherosclerosis.
Congestive heart failure	Congestive heart failure is not a contraindication for the use of apremilast. An apremilast therapy seems safe in these patients.
Malignancy	There is limited data on the carcinogenic potential of apremilast; it has a relative contraindication in those with a malignancy or lymphoproliferative disease.
Depression	Apremilast should be given to patients with a psychiatric disease or depression taking into consideration any drug interactions and benefit/harm status and only after giving information to the patient. If any depression/ suicidal ideation or behaviour is observed, the treatment should be discontinued.
Multiple sclerosis and Lupus vulgaris	Sufficient data on these are not available; any worsening of these conditions has not been reported in studies.

used in combination with methotrexate. A transition from apremilast to phototherapy, conventional and biological medications may be made without a need for a waiting period[18].

Table 7. Laboratory follow-up for apremilast[20]		
	Pre-treatment	**Every 3 months**
Whole blood count	+	+
ALT, AST, GGT	+	+
S Cre	+	+
Pregnancy test	+	+
No testing is recommended in the product characteristics of apremilast. However, laboratory follow-up may be performed for individual patients (depending on the clinical progress, dose adjustments in renal failure, and any impairment in liver functions).		
Safety monitoring (clinical and laboratory) of patients who use apremilast in combination with a conventional systemic or biological agent should be performed in line with the optimal safety monitoring of each drug in the combination		

Apremilast-vaccines

There is no recommendation or information on vaccination during the use of apremilast. Randomized, controlled studies have allowed administration of live vaccines. Whenever possible, completion of live vaccines before the therapy or postponing them until after the therapy is recommended[7,8,12].

Apremilast - surgery

There is no information as to what the approach would be in patients being treated with apremilast and for whom a surgery is planned. However, it is believed that there is no need to suspend the treatment. Decision should be made for each individual patient[25].

SUGGESTIONS

- Apremilast may be used in patients with acute and chronic infections, serious renal dysfunction (GFR below 30), patients whose body weight is low, patients with depression, suicidal ideation or behaviour, and patients using drugs that make cytochrome p450 enzyme induction, taking into consideration benefit-harm status/making dose adjustments/informing and carefully monitoring the patient.

1) Since sufficient well controlled studies on the use of apremilast in pregnancy are not available, it should not be used during pregnancy; contraception should be used throughout the treatment, and if pregnancy occurs, the treatment should be discontinued. Its pregnancy category is C.
2) Since it is not known whether or not apremilast or its metabolites are present in human milk, it should not be used during lactation.
3) Benefit-harm ratio should be considered when deciding on the treatment in patients who have psychiatric symptoms or use drugs that may cause psychiatric symptoms. The treatment should be discontinued if new psychiatric symptoms emerge or current symptoms exacerbate, or there is suicidal ideation or attempt.
4) Care should be taken in older patients using apremilast as diarrhoea and vomiting may cause loss of volume and hypotension.
5) Body weight should be noted before the treatment and patients whose body mass index is below 18.5 should be monitored for body weight[21].

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