The efficacy and safety of the new drug apremilast for the treatment of psoriasis and psoriatic arthritis

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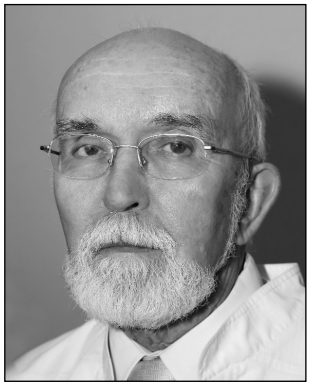

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Apremilast (AP) is a new phosphodiesterase 4 inhibitor for the treatment of psoriasis and psoriatic arthritis (PsA). Treatment with AP reduces the level of proinflammatory cytokines and the activity of inflammatory changes.
The positive impact of AP treatment on the course of psoriasis has been proven in a number of clinical trials, for example ESTEEM 1 (Efficacy and Safety Trial Evaluating the Effects of apreMilast in psoriasis), in which the treatment with AP has led to a decrease in PASI scores in patients with moderate and severe psoriasis en plaque: after 16 weeks, a 75% PASI improvement was significantly more common in patients taking AP 30 mg twice daily (33%) than in those who used placebo (PL) (5%) ($p = 0.0001$). In the PALACE 1 trial, the PsA patients were given AP at a dose of 20 or 10 mg twice daily. At 16 weeks, the patients who used AP at doses 20 and 30 mg twice daily, more frequently showed a 20% improvement according to the American College of Rheumatology (ACR) response criteria (ACR20) than those who received PL (in 30.4, 38.1, and 19% of cases; $p = 0.0166$ and $p = 0.0001$, respectively). Following 52 weeks of AP treatment, ACR20 was achieved by 63.0% of the patients who took the drug at 20 mg twice daily, and by 54.6% of those who used 30 mg twice daily. The PALACE 1, PALACE 2, and PALACE 3 trials demonstrated that the most common adverse events (AE) were diarrhea, nausea, headache, upper respiratory tract infections, and nasopharyngitis. Most AE were mild and moderate; and the rate of therapy discontinuation due to AE was low.
These PALACE trials covering 1493 patients have provided evidence for the efficacy and safety of AP in treating moderate PsA activity.

Key words: ampremilast; phosphodiesterase 4 inhibitor; psoriasis; psoriatic arthritis.
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Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting joints, spine, and entheses, associated with psoriasis of the skin and nail plates [1]. PsA symptoms are found in almost 40% of psoriasis patients [2]. Highly sensitive and specific CASPAR (Classification of Psoriatic Arthritis) criteria are now widely used to diagnose PsA [3].

PsA treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), intraarticular glucocorticoids (GCs), disease-modifying anti-rheumatic drugs (DMARDs) and genetically engineered biologic agents, or biologic medications. Methotrexate (MT), leflunomide, sulfasalazine, and cyclosporine are among DMARDs most frequently used for psoriasis and PsA treatment [4P8].

Prescription of TNFα inhibitors has become the standard treatment for patients with inflammatory joint diseases in cases, where inefficiency and/or intolerance to NSAIDs and DMARDs is present. However, in some PsA patients, TNFα inhibitors do not allow controlling the disease activity [9-11]. Moreover, the use of biologic medications is associated with the risk of developing severe infections, reactivation of latent tuberculo-

sis, worsening of the course of demyelinating diseases and congestive heart failure. In addition, with parenteral administration of biopahrmaceuticals postinfusion adverse events (AE) and AEs at the injection site are observed. The use of biologic medications can be accompanied by the production of autoantibodies, and in some cases of neutralizing antibodies that can reduce the efficacy of the drug [12]. Therefore, such therapy requires careful monitoring for timely detection of infectious complications, reactivation of latent tuberculosis and hypersensitivity.

Thus, although there is no doubt about the efficacy of biologic medciations, they still have significant limitations. Therefore, there remains a need to create new effective and safe medicinal products and use them.

Apremilast (AP) is a new small molecule (chemical formula: N-{2-[(1S)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}acetamide, C22H24N2O7S, trade name Otezla), Specifically inhibiting type 4 phosphodiesterase (PDEase 4). 73% bioavailability, 6-9 h half-life, excreted in the urine (58%) and faeces (39%).

PDEase 4 is one of the major phosphodiesterases expressed in leukocytes. It has four subtypes (A, B, C, D) and is found in epithelial cells of the respiratory tract, in skin cells, unstriated muscles, vascular endothelium and chondrocytes [13, 14]. In addition, PDEase 4 is expressed by immune cells, including dendritic cells (DCs), T cells, macrophages and monocytes [15-17]. PDEase 4 inhibitors cause the accumulation of intracellular cyclic adenosine monophosphate (cAMP), which leads to inhibition of proinflammatory cytokines transcription and other cellular reactions such as neutrophil degranulation, chemotaxis, and adhesion to endothelial cells [18].

AP affects the activity of cells and the content of mediators involved in many pathophysiological processes; reduces in vitro TNFα expression by human peripheral blood mononuclear cells (PBMCs), synoviocytes of patients with rheumatoid arthritis (RA), plasmacytoid DCs, T cells, and keratinocytes. In addition, AP reduces the expression of interleukins (IL) 23 and 12 and increases the in vitro production of IL10 by PBMCs [19]. Given the presence of PDEase 4 in various inflammatory cells and the role of this enzyme in the development of inflammation, PDEase 4 inhibitors can exert an anti-inflammatory effect in almost all inflamed tissues [20].

Targeted inhibition of PDEase 4 results in partial suppression of the production of proinflammatory mediators, such as TNFα, interferon γ, and IL23; and increases the production of anti-inflammatory mediators, including IL10 [18, 19], which in turn leads to a decrease in cellular infiltration of skin and synovial membrane of the joints [19, 21, 22]. In vitro AP significantly reduces the expression of TNFα, IL7, and matrix metalloproteinases 1, 3, 13 and 14 in the synoviocytes of RA patients [21, 22, 23]. In patients with severe psoriasis en plaque, AP reduced infiltration of skin and epidermis with myeloid DCs, resulting in an approximate 20% reduction of epidermis thickness within 29 days [22]. Subsequent studies in psoriasis patients have shown that AP reduces epidermal and dermal infiltrate consisting of myeloid DCs, T cells and natural killers and suppresses the expression of Th1, Th17 and Th22 gene pathogens in psoriatic plaques, resulting in decreased production of IL12 / 23 p40, IL23 p19, IL17A and IL22 [24].

Therefore, the results of preclinical and clinical studies of AP allow one to assume its positive effect in many inflammatory diseases. In the last few years, the efficacy and tolerability of AP have been studied in ankylosing spondylitis [25], RA [26], Behcet's disease [27], psoriasis and PsA [28-36].

844 patients with psoriasis participated in the randomized controlled trial (RCT) ESTEEM 1 (**E**fficacy and **S**afety **T**rial **E**valuating the **E**ffects of apre**M**ilast in psoriasis), 282 of whom received placebo (PL) up to week 16, followed by transfer to AP 30 mg twice daily, the other 562 took AP. The AP treatment has led to a decrease in PASI scores (Psoriasis Area and Severity Index) in patients with moderate and severe psoriasis en plaque after 16 weeks. A 75% PASI improvement was significantly more common in patients taking AP 30 mg twice daily (33%) than in those who used placebo (PL) (5%) ($p = 0.0001$). [28, 29]. In RCT ESTEEM 1 and 2 [30], 66.1% and 64.7% of patients had psoriasis of the nail, respectively, and 66.7% and 65.5% had moderate to severe psoriasis of the scalp. At week 16, a significantly better improvement in the state of psoriatic nails, which was assessed using the NAPSI (Nail Psoriasis Severity Index) index, was observed in patients taking AP, compared to the PL group: the mean value of NAPSI in the main group decreased by 22.5%, And in the PL group it increased by 6.5% (ESTEEM 1, $p <0.0001$); in ESTEEM 2 study, the NAPSI index decreased by 29.0% and 7.1%, respectively ($p <0.0052$). Scalp Physician Global Assessment (ScPGA) at baseline in both groups was i3. After 16 weeks, the ScPGA value equal to 0 (pure skin) or 1 (the minimum manifestations of psoriasis) in patients who took AP was significantly more frequent than in the PL group (46.5% and 17.5% in ESTEEM 1; 40.9% and 17.2% in ESTEEM 2 respectively; p<0,0001 for both RCTs) [31]. RCT LIBERATE (Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis) compared the efficacy and safety of AP therapy at a dose of 30 mg twice daily, PL and Etanercept (ETC) therapy at a dose of 50 mg, subcutaneous, once a week [32]. After 16 weeks, PASI75 in patients receiving ETC and AP was significantly more common than in the PL group: in 48.2% ($p<0.01$), 39.8% ($p<0.01$) and 11.9% cases respectively. After 32 weeks, the patients who continued treatment with ETC and AP demonstrated PASI75 in 61.4% and 53.0% of cases respectively, and in 45.2% of cases after PL was replaced by AP. Differences in the AP and ETC groups were insignificant ($p = 0.26$).

The efficacy of AP has been studied in several studies of PsA patients. In the Phase II study, AP at a dose of 20 mg and 40 mg twice daily demonstrated a much more pronounced effect compared to PL. At week 12 of treatment, a 20% improvement in the criteria of the American College of Rheumatology (ACR20) was achieved in 43.5%, 35.8% and 11.8% of patients respectively [33].

The results of four Phase III RCTs named PALACE (**P**soriatic **A**rthritis **L**ongterm **A**ssessment of **C**linical **E**fficacy) 1, 2, 3 and 4 were published recently.

PALACE 1 was conducted with the participation of 83 research centers in 13 countries [34]. The RCT included patients with active PsA,who met the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria[3], with at least three tender and three swollen joints, who had previously taken various DMARDs (Нь'I25 mg/week, or Leflunomide ⩽20 mg/day, or Sulfasalazine I2 g/day) and/or maximum one biologic medication. The study did not include patients who showed inefficacy of more than three DMARDs or more than one TNF-alpha inhibitor. 504 patients with active PsA were randomized at a 1:1:1 ratio to the PL group and the two AP groups receiving 20 mg and 30 mg twice daily. AP was administered at 10 mg daily with escalation of the dose by 10 mg daily until the appropriate level. If after 16 weeks there was no decrease in the tender joint count (TJC) and swollen joint count (SJC) of 20% or more, AP

was discontinued, and the patients taking PL were randomized at a 1:1 ratio between the two groups receiving AP 20 mg and 30 mg twice daily.

At week 16 in patients who took AP 20 mg and 30 mg twice daily the ACR20 improvement was significantly more frequent than in the PL group: in 30.4% (p = 0.0166), 38.1% (p = 0.0001) and 19% of cases respectively. Patients who had not previously received biologic medications reached ACR20 more often than those who had previous experience of such treatment. AP of 30 mg twice daily provided ACR20 a little more often than a dose of 20 mg twice daily, but this difference was not statistically significant.

After 24 weeks AP in doses of 30 mg twice a day and 20 mg twice a day significantly exceeded the effectiveness of PL (Table 1): ACR20 was achieved in 36.6%, 26.4% and 13.3% of patients, respectively. There was a decrease in the severity of enthesites and dactylytes, as well as a decrease in the PASI index.

RCT PALACE 1 [34], after 52 weeks of treatment, demonstrated an increase in the positive effect of AP on the main PsA symptoms; ACR20 was achieved in 63.0% and 54.6% of patients receiving AP, respectively, at 20 mg and 30 mg twice daily (Table 2).

Most AEs were detected within the first 24 weeks of observation: In the PL group, one or more AEs were observed in 50% of the patients, in the AP groups - in 60% of the patients. Diarrhoea and nausea were observed mainly in the first 2 weeks of treatment and were usually resolved by week 4 without additional therapy. AEs were regarded as serious (SAE) in two patients who received AP 20 mg twice daily. In the first 2 weeks of treatment, they developed a myocardial infarction. Both were smokers, they had hyperlipidemia and hereditary cardiovascular diseases.

The patients who received AP from the very beginning of the study, between week 24 and week 52, developed 5 SAEs: Endometriosis and appendicitis in one patient (20 mg twice daily), gastroenteritis, myocardial infarction and osteoarthritis in one patient (30 mg twice daily).

Of the five cases of infection regarded as a SAE, two were observed in the first 24 weeks: one pneumonia and one GI-clostridial infection in the course of AP 30 mg twice daily treatment; three cases were identified between week 24 and 52: pneumonia and appendicitis in one patient who received AP 20 mg twice daily; gastroenteritis in one patient who took AP 30 mg twice daily).

In addition, in one case squamous cell carcinoma was detected. Six patients were excluded from the study due to the development of SAEs: Two from the PL group (weight loss and prostate cancer); one from the group that received AP 20 mg twice daily (acute myocardial infarction); and three patients receiving AP 30 mg twice daily (deep vein thrombosis and acute hypotension, hypertensive crisis, gastrointestinal clostridial infection). One case was fatal: a 52-year-old woman who took AP 20 mg twice daily and MT. The cause of death was multiorgan failure on the background of a previously existing vitamin B12 deficiency, not associated with the study drug. A small number of patients demonstrated weight loss. It was > 5% in 15.8% of patients who received AP 20 mg twice daily, and 17.2% in patients taking AP 30 mg twice daily.

RCT PALACE 3 studied the efficacy and safety of AP in 505 patients with PsA who had arthritic activity (TJC i 3, SJCi3), despite the DMARD and/or biologic medication therapy [36]. Patients were randomized into three groups (1:1:1): PL, AP 20 mg twice daily and AP 30 mg twice daily. If at Week 16 of the treatment the PL patients did not demonstrate a 20% reduction in TJC and SJC, AP was administered to them. The remaining patients from the PL group were transferred to AP 20 mg twice daily and AP 30 mg twice daily at Week 24.

After 16 weeks of treatment ACR20 was achieved in 28% of patients who received AP 20 mg twice daily; in 41% of patients who received AP 30 mg twice daily; and in 18% of the PL patients (p = 0.0295 and p <0.0001, respectively). Reduction of the HAQ index with AP 30 mg twice daily treatment (M = -0.20) is more evident than in the PL group (M = -0.07, p = 0.0073). In addition, at Week 16 patients with advanced psoriasis who received AP 30 mg twice daily the PASI index improvement by 50% is much more common (in 41% of patients) than in the PL group (24%; p = 0.0098). After 52 weeks of AP treatment, there was a steady improvement of the above-mentioned indicators [36].

In the PALACE 4 study 58% of the patients achieved ACR20 at Week 52, while the positive effect on skin manifestations of psoriasis was modest [37]. In general, the patients tolerated AP well; the impact on laboratory performance was minimal.

In RCTs PALACE 1, 2, 3 and 4, the most frequent AEs included diarrhea, nausea, headache, upper respiratory tract infections and nasopharyngitis [38]. Most AE were mild and moderate; and the rate of therapy discontinuation due to AE was low.

RCTs PALACE 2, 3 and 4 confirmed the efficacy of AP in patients with active PsA, and they did not receive any new data on the safety of AP therapy compared to the results of Phase II studies [39].

Table 1 Efficacy assessment of AP treatment after 24 weeks (n=489)

Index	PL	Apremiplast			
		20 mg 2 times per day	p*	30 mg 2 times per day	p*
ACR20, n (%)	22 (13.3)	43 (26.4)	0.0032	59 (36.6)	<0.0001
ACR50, n (%)	7 (4.2)	24 (14.7)	0.0013	32 (19.9)	<0.0001
ACR70, n (%)	1 (0.6)	9 (5.5)	0.0102	17 (10.6)	0.0001
DAS28 CRP <2.6, n (%)	4 (2.4)	19 (11.7)	0.0011	30 (18.6)	<0.0001
MASES (0P13)	-0.8 (0.31)	-1.6 (0.30)	0.0678	-1.7 (0.29)	0.0334
Dactylitis severity index (0P20)	-1.3 (0.27)	-2.0 (0.30)	0.0710	-1.8 (0.27)	0.1753
PASI50, n (%)	12 (18.5)	25 (33.8)	0.0439	41 (50.6)	0.0001
PASI75, n (%)	3 (4.6)	13 (17.6)	0.018	17 (21.0)	0.004

Note. MASES P Maastricht Ankylosing Spondylitis Enthesitis Score, the change was assessed in patients who had at least one enthesitis prior to the treatment. Dactylitis severity index and its change was assessed in patients who had at least one dactylitis prior to the treatment. PASI was evaluated in patients with advanced psoriasis (i3% of body area), PASI50/75 – improvement in PASI by 50% and 75%; ACR20/50/70 – 20%, 50%, 70% improvement according to the ACR criteria; * – in comparison with the PL.

Table 2 Efficacy assessment of AP treatment after 52 weeks

Index	PL/AP 20 mg twice daily	PL/AP 30 mg twice daily	AP 20 mg twice daily	AP 30 mg twice daily
ACR20	34/64 (53.1)	30/60 (50.0)	75/119 (63.0)	71/130 (54.6)
ACR50	16/63 (25.4)	17/61 (27.9)	29/117 (24.8)	32/130 (13.8)
ACR70	3/62 (4.8)	9/61 (14.8)	18/117 (15.4)	18/130 (13.8)
DAS28-CRP<2.6, n	17/65 (26.2)	11/60 (18.3)	39/120 (32.5)	30/129 (23.3)
MASES (0P13), Нь, %	-50.0	-40.0	-100.0	-66.7
Dactylitis severity index dynamics (0P20), Нь, %	-100.0	-100.0	-100.0	-100.0
PASI50	11/25 (44.0)	11/27 (40.7)	28/53 (52.8)	41/68 (60.3)
PASI75	4/25 (16.0)	6/27 (22.2)	13/53 (24.5)	25/68 (36.8)

Note. n/m – number of responders/number of patients with sufficient data for evaluation. M – mean value. The number in brackets gives the percentage of patients.

In the completed studies, a small number of deviations in the laboratory results were classified as an AE. Most of them were resolved on their own and were not considered to be related to the study drug. The vast majority of such deviations were not considered clinically significant and did not require medical intervention. Among patients who experienced an increase in hepatic transaminase levels, there was no increase in bilirubin level, a decrease in albumin level, or an increase in prothrombin time. With an increase in the dose of AP, there were no trends towards more frequent and more serious deviations in laboratory parameters. The changes in laboratory tests were not of a regular nature and did not allow one to suspect a toxic effect, the development of vasculitis or other subclinical inflammatory process.

AP treatment can be accompanied by increased incidence of depression. Therefore, it should be used with caution in patients with a history of depression and/or suicidal thoughts or attempts [40]. Patients taking AP should monitor their body weight. When it decreases, which cannot be explained by other causes, they should stop taking the drug. AP interacts with inducers of cytochrome P450 enzymes, such as rifampin, phenobarbital, carbamazepine, and phenytoin. Patients should not take these drugs during AP treatment [41].

To reduce the risk of developing an AE in the gastrointestinal tract, the following scheme is recommended to achieve the recommended treatment dose (30 mg twice daily):

- Day 1: 10 mg in the morning
- Day 2: 10 mg in the morning and in the evening
- Day 3: 10 mg in the morning and 20 mg in the evening
- Day 4: 20 mg in the morning and 20 mg in the evening
- Day 5: 20 mg in the morning and 30 mg in the evening
- Day 6: 30 mg in the morning and 30 mg in the evening

For the patients with severe renal failure (creatinine clearance <30 ml/min), the dose is reduced to 30 mg orally once a day. Dose adjustment is not required in patients with mild to moderate renal failure or with impaired hepatic function.

AP efficacy for psoriasis is comparable to that of MT: PASI75, according to RCT, is observed in 30-42% of patients receiving AP treatment, and on average in 40% of patients receiving MT [42].

Based on AP therapy efficacy and safety data in PALACE studies with participation of 1493 patients, in 2014 this drug was approved by the US Food and Drug Administration (FDA) for PsA treatment at a dose of 30 mg twice daily.

Taking into account the results of RCTs, AP may be recommended for PsA treatment, especially in patients with moderate disease activity, especially as the drug is characterized by a good safety profile.

Study transparency

This article is a review of the literature data on the efficacy and tolerability of apremilast.

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Statement of financial and other relations

All the authors took part in the development of the concept and design of the article and in writing the manuscript. All authors approved the final version of the manuscript. The authors did not receive a fee for the article, lectures or grants on the research topic.

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