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-
sion, worsening of the course of denervating diseases and con-
gestive heart failure. In addition, with parenteral administr-
ition of biopharmaceuticals 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 effica-
cy 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 bio-
logic medications, 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 forma-
la: N-[2-[(1S)-1-[(3-Ethoxy-4-methoxyphenyl)-2-[(4-methy-
lonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-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, includ-
ing dendritic cells (DCs), T cells, macrophages and monocytes
[15-17]. PDEase 4 inhibitors cause the accumulation of intra-
cellular 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 media-
tors involved in many pathophysiological processes; reduces in
vitro TNFα expression by human peripheral blood mononu-
clear cells (PBMCs), synoviocytes of patients with rheumatoid
arthritis (RA), plasmaid 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 suppres-
sion 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 syn-
ovidial membrane of the joints [19, 21, 22]. In vitro AP signifi-
cantly reduces the expression of TNFα, IL7, and matrix metal-
lopainases 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 thick-
ness 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 sup-
presses 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 inflammato-
ry 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 (Efficacy and Safety Trial
Evaluating the Effects of apreMilast 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 signifi-
cantly 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 respec-
tively; 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 treat-
ment 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
"reported" in 43.5%, 35.8% and 11.8% of patients
"reported" in the ESTEEM 1, ESTEEM 2 and 3 studies
respectively, while in the PL group it increased by 6.5%.

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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 enthesitis and dactylitis, 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 G1-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 multigang 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)

<table>
<thead>
<tr>
<th>Index</th>
<th>PL</th>
<th>20 mg 2 times per day</th>
<th>p*</th>
<th>30 mg 2 times per day</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20, n (%)</td>
<td>22 (13.3)</td>
<td>43 (26.4)</td>
<td>0.0032</td>
<td>59 (36.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACR50, n (%)</td>
<td>7 (4.2)</td>
<td>24 (14.7)</td>
<td>0.0013</td>
<td>32 (19.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACR70, n (%)</td>
<td>1 (0.6)</td>
<td>9 (5.5)</td>
<td>0.0120</td>
<td>7 (4.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>DAS28 CRP &lt;2.6, n (%)</td>
<td>2 (3.4)</td>
<td>19 (11.7)</td>
<td>0.0011</td>
<td>30 (18.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MASES (OP13)</td>
<td>0.8 (0.81)</td>
<td>1.6 (0.83)</td>
<td>0.0678</td>
<td>1.7 (0.92)</td>
<td>0.0334</td>
</tr>
<tr>
<td>Dactylitis severity index (DP20)</td>
<td>-1.3 (0.17)</td>
<td>-2.0 (0.30)</td>
<td>0.0710</td>
<td>-1.8 (0.27)</td>
<td>0.1753</td>
</tr>
<tr>
<td>PASI50, n (%)</td>
<td>12 (18.5)</td>
<td>25 (33.8)</td>
<td>0.0439</td>
<td>41 (50.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PASI75, n (%)</td>
<td>3 (4.6)</td>
<td>13 (17.6)</td>
<td>0.018</td>
<td>17 (21.0)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**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 (33% 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.
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.

References


