CHOINKA, Martyna, KOMARÓW, Małgorzata, WDOWIAK, Natalia, LISSAK, Karina, SZCZEPANIAK, Zuzanna, KONOPKA, Agata, KALISIAK, Jakub and KARASIŃSKA, Dominika. Novel methods of treating atopic dermatitis. Quality in Sport. 2024;22:54315. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54315
https://apcz.umk.pl/QS/article/view/54315

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 15.08.2024. Revised: 25.08.2024. Accepted: 10.09.2024. Published: 11.09.2024.

Novel methods of treating atopic dermatitis

Martyna Choinka[1,*]; ORCID ID: 0009-0005-0951-3368;
m.choinka@op.pl

Małgorzata Komarów[2]; ORCID ID: 0009-0005-8293-5030;
gosiakomarow7@gmail.com

Natalia Wdowiak[3]; ORCID ID: 0009-0004-3894-9921;
natalia.wdowiak5@gmail.com

Karina Lissak[2]; ORCID ID: 0009-0000-9084-4060;
karina.lis2323@gmail.com

Zuzanna Szczepaniak[3]; ORCID ID: 0009-0004-8025-6037;
zuzanna.a.szczepaniak@gmail.com

Agata Konopka[4]; ORCID ID: 0009-0000-1004-0629;
agatakonopka21@gmail.com

Jakub Kalisiak[5]; ORCID ID: 0009-0000-2472-3148;
kubakalisiak@gmail.com

Dominika Karasińska[6]; ORCID ID: 0009-0003-1215-5165;
dakarasinska@gmail.com

1. University Clinical Hospital in Poznan, Przybyszewskiego Str. 49, 60-355 Poznan, Poland

2. Lower Silesian Oncology Center in Wroclaw, Hirszfelda Square 12, 53-413 Wrocław, Poland

3. Provincial Specialist Hospital in Wroclaw, H. Kamieńskiego Str. 73a, 51-124 Wrocław, Poland

4. A. Falkiewicz Specialist Hospital in Wroclaw, Warszawska Str. 2, 52-114 Wrocław, Poland

5. Independent Public Complex of Health Care Facilities of the Ministry of Interior and Administration in Poznan, Dojazd Str. 34, 60-631 Poznan, Poland

6. University Clinical Hospital in Wroclaw, Borowska Str. 213, 50-556 Wroclaw, Poland

* Correspondence: m.choinka@op.pl

Abstract

Atopic dermatitis is a long-term inflammatory skin disease caused by factors such as skin barrier dysfunction and immune system dysregulation . Currently, the first-line treatment for atopic dermatitis involves the use of topical glucocorticosteroids; however, this treatment is associated with many side effects. Therefore the need of finding new methods of treatment arises.

Objective: The objective of this study is to gather and analyze literature on new methods of treating atopic dermatitis.

Materials and methods: The review was based on the analysis of materials collected in the database, PubMed, Google Scholar, Web of Science, Embaseand, Scopus, books and other scientific articles.

Keywords: „atopic dermatitis", „AD treatment", „Janus kinase (JAK) inhibitors", „Phosphodiesterase Inhibitors"

Introduction

Atopic dermatitis (AD) is an eczematous, inflammatory skin disease. This chronic condition often begins in the first few years of life and may persist into adulthood and often occurs in people with a personal or family history of asthma and allergic rhinitis [1,4]. AD affects up to 20% of children in the United States, and prevalence may be increasing [2]. Currently, the first-line treatment for atopic dermatitis is the use of topical glucocorticosteroids, but this treatment is associated with many side effects such as: skin atrophy, the formation of permanent telangiectasia, striae or dyspigmentation. Due to local suppression of the immune system, bacterial or fungal superinfections of skin lesions may also occur [5]. When using glucocorticosteroids, it is also important to remember about the withdrawal effect, i.e. exacerbation of skin lesions after discontinuation of the drug, and tachyphylaxis, i.e. reduced effectiveness during prolonged therapy. These symptoms not only reduce the quality of life of patients, but also contribute to their own discontinuation of treatment [6,7]. All these negative effects have become a reason to look for new, safer therapies. In our article, we will describe the latest methods of treating AD.

Pathogenesis

The pathogenesis of Atopic Inflammation is complex. It is compounded by factors such as skin barrier dysfunction and a dysregulated immune system. The Th2-cell system becomes overactive, and as a result, excessive production of cytokines such as IL-4, IL-13 and those secreted by Th1, Th17, Th22 and Il-33, TSLP, Il-25, originating from damaged epidermis [8,9,10,11].

Scales assessing the severity of the disease

The three most popular scales for assessing the severity of the disease are SCORAD (Scoring Atopic Dermatitis Index), EASI (Eczema Area And Severity Index) and IGA (Investigator's Global Assessment scale).

The SCORAD scale takes into account objective symptoms, such as: the affected area (A) and the intensity of changes (B) and subjective symptoms, itching reported by the patient within 72 hours, or sleep disorders (C). The first component (A) is most often assessed using the

"rule of nines", in which the head constitutes - 9% of the affected surface and, respectively: upper limbs - 2 times 9%, chest - 9%, abdomen - 9%, posterior part of the torso - 18%, lower limbs - 2 times 18%, and perineum 1%. The result obtained is divided by 5.

The second component (B) takes into account the presence of erythema, swelling/lumps, crusts/oozing, erosions, lichenification, dry skin and assigns points: 0 – no changes, 1 – slight changes, 2 – moderate intensity, 3 – very severe changes.

The last component is assessed using a visual analogue scale with values from 1 to 10.

On this scale, the minimum number of points is 0, where there are currently no symptoms of the disease, and the maximum value to be obtained is 103 points. There are 3 degrees of severity of AD: mild (<25 points), moderate (25–50 points) and severe (>50 points) [12,13].

The EASI scale also takes into account the extent and intensity of skin lesions. It takes into account four symptoms: erythema, infiltration, excoriation and lichenification in four locations: upper limbs, lower limbs, trunk and head. Points are awarded on a scale from 0 (no changes) to 3 (very severe changes). The surface area in the above-mentioned areas is also assessed, where from 0 (no changes) to 6 points (90-100% of the affected surface area) is awarded. The maximum score on the scale is 72 points [14,15].

The IGA scale can be used to clinically assess the severity of atopic dermatitis. It is a 5-point scale, where the severity of the lesions is taken into account: 0 – clear skin, 1 – almost clear, 2 – mild, 3 – moderate, 4 – severe [16].

Phosphodiesterase-4 inhibitors

Phosphodiesterase-4 inhibitors (PDE-4 inhibitors) block the degradation of cAMP in the cells of the lungs, causing bronchodilation, as well as decrease inflammatory mediators. They can be administered orally, topically or in the form of injections [17,18].

Roflumilast

Roflumilast is a highly selective phosphodiesterase-4 inhibitor. Melinda Gooderham et al published the results of a phase 2 randomized, double-blind study to evaluate the efficacy and

safety of Roflumilast 0.15% and 0.05% ointment. It included 136 patients with mild to moderate AD aged ≥12 years, divided into 3 groups. They applied roflumilast 0.15% cream, roflumilast 0.05% cream, or vehicle cream once daily for 4 weeks. The endpoint was the absolute change in the Eczema Area and Severity Index (EASI) from baseline to week 4 of treatment, percentage change and responder rates, Validated Investigator Global Assessment-AD (vIGA-AD). The absolute change in EASI scores was -6.4 (P=0.097 vs placebo) for roflumilast 0.15%, -6.0 (P=0.356) for roflumilast 0.05%, and -4.8 for placebo, there was also an improvement in vIGA-AD outcome "clear" or "almost clear.". Treatment-related adverse events (AEs) of mild rash and moderate application site pain occurred in 2 patients receiving roflumilast, and 1 patient receiving roflumilast discontinued the study due to an AE [19,20].

Difamilast

Another phosphodiesterase 4 inhibitor is difamilast. Hidehisa Saeki et al. conducted a randomized, double-blind, phase 3 study of 364 patients aged 15 to 70 years with an IGA score of 2 or 3, half of whom received topical difamilast ointment 1% and half the vehicle. After 4 weeks, the IGA was reassessed and showed a score of 0 or 1 with a 2-fold improvement for diflamast (38.46% vs 12.64%, respectively, P < .0001). Adverse events occurring during the study were mostly mild or moderate and occurred less frequently with difamilast [21].

It appears that ointments are effective and well tolerated for treating AD [22,23,24]

Janus kinase (JAK) inhibitors

JAK inhibitors stop the Janus kinase activity by competitively binding to it and as a result interfering with the JAK-STAT pathway. That leads to a suppression in signaling of inflammatory cytokines such as IL-6 or IL-23 and modifies the immune response of the cells. JAK inhibitors can be found in oral or topical forms [25,26].

Ruksolitynib

Kim Papp et al pooled the results of 2 double-blind, phase 3 studies (NCT03745638/NCT03745651) that assessed the safety and efficacy of ruxolitinib cream for more than 8 weeks. They included 1,249 patients aged ≥12 years. They were randomly

assigned to twice-daily treatment with 0.75% ruxolitinib cream, 1.5% ruxolitinib cream, or vehicle cream in a 2:2:1 ratio. Patients who used ruxolitinib cream had significant improvement in IGA (IGA score of 0/1 with ≥2-point improvement from baseline). They also achieved ≥50% reduction in disease area and ≥2-point reduction in itch score. Ruxolitinib cream was well tolerated during the 52-week study in this patient population [27].

Delgocytynib

Hidemi Nakagawa et al conducted a double-blind study in Japanese patients aged ≥ 16 years with moderate to severe AD. The first part of the study, which lasted 4 weeks, included 158 patients who were randomly assigned to receive delgocitinib 0.5% ointment or vehicle ointment in a 2:1 ratio. Of the 106 patients in the delgocitinib group, 98 (92.5%), 52 in the placebo group, 29 (55.8%) completed part 1, and 3 (5.8%) discontinued the study. A total of 154 patients started part 2, and 138 (89.6%) patients completed part 2, in which patients received delgocitinib 0.5% ointment for 24 weeks. At the end of treatment in part 1, the mean percent change from baseline in the modified Eczema Area and Severity Index score was significantly greater in the delgocitinib group than in the vehicle group (-44.3% vs 1.7%, P < .001). Improvement in the modified Eczema Area and Severity Index score was maintained in part 2. Most adverse events were mild and unrelated to delgocitinib during the study periods. Delgocitinib ointment was effective and well tolerated [28].

A similar double-blind study was conducted in pediatric patients aged 2 to 15 years who were randomized 1:1 to delgocitinib 0.25% ointment or vehicle ointment for 4 weeks in Part 1. Part 2 was a 52-week extension period in which patients received delgocitinib 0.25% or 0.5% ointment. At the end of treatment in Part 1, the mean percent change from baseline in the modified Eczema Area and Severity Index score was significantly greater in the delgocitinib group than in the vehicle group (-39.3% vs +10.9%, P < .001). Improvement in AD was also observed through week 56 in Part 2. Most adverse events were mild and unrelated to delgocitinib during the study periods [29].

Tofacitinib

Tofacitinib interacts with cytokines such as IL-2, IL-4, IL-6, IL-7, IL-9 or IL-21 and inhibits transduction of their signals. It was firstly registered for the treatment of rheumatoid and psoriatic arthritis.

R.Bissonnette et al. conducted a phase IIa, double-blind, randomized study (NCT02001181) involving 69 adults with mild-to moderate AD (with four patients discontinued from the study) who received 2% tifacitinib or vehicle ointment twice daily in 1:1 ratio for 4 weeks, the primary point of the study being percentage change from baseline in Eczema Area and Severity Index (EASI) score. At the end of the study the mean change in EASI total score was significantly greater in the tofacitinib group vs. the vehicle group (-81,7% vs. -29,9%, P< 0,001), as it was also at weeks 1 and 2. Treatment-emergent AE (TEAE) occurred in 44% of patients with a great majority of them (89%) being mild - the most frequent were infections. No severe or serious AEs were recorded [30].

A Case Report by S. Berbert Ferreira and coauthors described a 63-year-old male patient with a chronic severe AD (SCORAD-66,7%, DLQI-22) and multiple systemic therapy failures (including topical and oral corticosteroids, methotrexate, azathioprine, cyclosporine, ustekinumab and phototherapy). The patient was administered tofacitinib citrate 5mg BID with gradually decreasing doses of prednisone (until total suspension) and only topical moisturizers. After 3 months an almost complete clearance of face, trunk, upper and lower extremities (SCORAD-10,1%, DLQI-3) was reported with a sustained response at 16 months visit. One episode of uncomplicated herpes simplex infection has been reported with no abnormal laboratory findings [31].

Upadacytynib

Upadacitinib has the greatest potency for JAK1 and is administered orally. There were two multicentered phase 3 trials conducted by Emma Guttman-Yassky and coauthors. In the Measure Up 1 study, 847 patients were randomly assigned to receive either upadacitinib 15 mg (n=281), upadacitinib 30 mg (n=285), or a placebo (n=281). Similarly, in the Measure Up 2 study, 836 patients were randomly assigned to upadacitinib 15 mg (n=276), upadacitinib 30 mg (n=282), or a placebo (n=278). By week 16, both studies met their coprimary endpoints (all $p<0.0001$). In Measure Up 1, the percentage of patients who achieved EASI-75 at week 16 was significantly higher in the upadacitinib 15 mg group (196 out of 281 patients, or 70%) and the upadacitinib 30 mg group (227 out of 285 patients, or 80%) compared to the placebo group (46 out of 281 patients, or 16%). In the Measure Up 2 study, 60% of patients in the upadacitinib 15 mg group (166 out of 276 patients) and 73% of patients in the upadacitinib 30

mg group (206 out of 282 patients) achieved the endpoint, compared to just 13% of patients in the placebo group (37 out of 278 patients). Considering the results of those trials Upadacitinib monotherapy could be a promising treatment option with a favorable benefit-risk profile for patients with moderate-to-severe atopic dermatitis [32,33].

Aryl hydrocarbon receptor modulators

Aryl hydrocarbon receptor is a ligand-activated protein, a transcription factor, that when activated results in immunosuppression. It plays an important role in differentiating of hepatocytes, T-cells or neurons, as well as regulating xenobiotic metabolism [34].

Tapinarof

Through binding to topical aryl hydrocarbon receptors (AhR), tapinarof suppresses cytokines (such as IL-17, IL-4, IL-13) and induces expression of skin barrier proteins, including filaggrin and loricrin. It was the first FDA-approved topical substance in this class, in a form of 1% cream, used in a treatment of plaque psoriasis in adults, that is being investigated for the use in atopic dermatitis as well.

Amy S. Paller et al. published the result of a phase IIb, double-blind study (NCT02564055), where 247 randomized patients received tapinarof cream 0,5%, 1% or vehicle once or twice a day. At the end point of 12 weeks the patients receiving cream 1% twice daily showed IGA response of 53%, cream 1% once daily of 46%, cream 0,5% twice daily of 37%, cream 0,5% once daily of 34% vs. receiving vehicle twice daily of 24% and once daily of 28% . 191 of 247 patients that completed the study were also able to maintain the effect for 4 weeks after the end of the study. The treatment was well tolerated, with AEs being mostly mild to moderate [35].

Biologics

Biologics are a diverse group of treatment options that play an increasing role for AD patients and are the object of continuously expanding research. Through targeting specific molecules,

they show noticeably better risk-benefit ratios than some of the conventional treatment options [36].

Lebrikizumab

Lebrikizumab is a high-affinity IgG4 monoclonal antibody that selectively binds to interleukin (IL)-13, which prevents the formation of the interleukin-4Rα–interleukin-13Rα1 receptor signaling complex. Amy S Paller and coauthors pooled the results of three studies, ADvocate1 (NCT04146363), ADvocate2 (NCT04178967), and ADhere (NCT04250337), in patients with moderate-to-severe atopic dermatitis. A total of 206 adolescent patients (≥ 12 to < 18 years, weighing ≥ 40 kg) received subcutaneous loading doses of lebrikizumab 500 mg at baseline and week 2, followed by 250 mg every 2 weeks. 172 patients completed the treatment period. A total of 62.6% achieved IGA 0/1 with ≥ 2-point improvement from baseline, and 81.9% achieved EASI-75 by week 52. The mean percent EASI improvement from baseline to week 52 was 86.0%. 5 patients discontinued treatment. A total of 134 patients (65%) reported at least one treatment-emergent AE, most of which were mild or moderate in intensity [37].

Nemolizumab

Nemolizumab is a humanized monoclonal antibody that blocks the A receptor for IL-31, currently under investigation for a treatment of pruritus, one of the symptoms of atopic dermatitis.

K. Kabashima et al. conducted a two phase III, long-term study of patients with a score of min. 3 out of 5 on an itch scale and VAS score of min. 50, uncontrollable by antihistamines or topical treatments. In the first study (Study-JP01 (JapicCTI-173740)), in part A 215 patients received subcutaneously nemolizumab (60mg) or placebo in ratio 2:1 for 16 weeks, resulting in the mean change of -42,8% in the VAS score in the nemolizumab group, while the change in the placebo group was -21,4% ($P<0.001$). After completion, the 52-week part B started where 206 patients were to be administered nemolizumab (60mg) up to week 64 with a decrease of 65,9% (the mean change in the VAS score) in a nemolizumab group after 68 weeks. A similar outcome was observed in the second study (Study-JP02 (JapicCTI-183894)), where 88 patients received nemolizumab (60mg, Q4W) for 48 weeks. Over 90% of patients reported TEAEs, with the great majority mild in severity (nasopharyngitis being the most common) [38,39].

Dupilumab

Dupilumab is an antibody that binds to the subunits of the IL-4 and IL-13 cytokine receptors, and inhibits the IL-4 and IL-13 signaling pathways. This binding also inhibits downstream signaling through the JAK-STAT pathway, a critical pathway for the transcription of genes involved in inflammatory responses.

Eric L. Simpson et al. conducted two phase 3 trials (SOLO 1 and SOLO 2) involving 1,379 patients. Dupilumab was administered subcutaneously for 16 weeks to patients who had been randomized into three groups: the first group received 300 mg of dupilumab weekly, the second group every other week and the third group was given a placebo.

In the combined SOLO 1 and SOLO 2 trials, a total of 169 patients receiving dupilumab every other week, 170 patients receiving it weekly, and 43 patients receiving a placebo achieved the primary outcome ($P<0.001$ for both comparisons with placebo). Additionally, significantly more patients who received any regimen of dupilumab achieved at least a 75% improvement from baseline to week 16 on the EASI-75 compared to those who received a placebo ($P<0.001$ for all comparisons) [40].

Another phase 3 trial, known as CHRONOS, conducted by Andrew Blauvelt et al., evaluated the long-term management of moderate-to-severe atopic dermatitis using dupilumab in combination with topical corticosteroids (TCS). This study involved 740 participants. Of these, 106 patients received both dupilumab and topical corticosteroids, while the remaining 315 patients were given a placebo alongside TCS. The results showed that both IGA and EASI scores improved significantly more in patients treated with both dupilumab and TCS [41].

Tralokinumab

Tralokinumab is a human antibody that binds to and neutralizes IL-13, preventing it from binding to its receptor, IL-13Rα1. To test its effectiveness, three phase 3 trials named ECZTRA 1, 2, and 3 were conducted. The identically designed ECZTRA 1 and 2 trials involved a total of 1,596 patients. Participants were initially randomized in a 3:1 ratio, with the first group receiving a 600 mg dose on day 0, followed by 300 mg of tralokinumab every other week for 16 weeks, while the second group received a placebo.

After this initial period, patients treated with tralokinumab who achieved a clinical response were rerandomized into three groups with proportions of 2:2:1. Group one received 300 mg every 2 weeks, group two received 300 mg every 4 weeks, and group three received a placebo for 36 weeks. In both studies, significantly more patients reached an IGA score of 0 or 1 and EASI 75 at week 16 with tralokinumab compared to placebo. In ECZTRA 1, IGA 0/1 was achieved by 15.7% of patients receiving tralokinumab (compared to 7.1% of patients receiving placebo) ($P = 0.002$), and EASI 75 was achieved by 25% of patients treated with tralokinumab and 12.7% with placebo ($P < 0.001$). In ECZTRA 2, the IGA endpoint was achieved by 22.2% of patients treated with the antibody, compared to 10.9% treated with placebo ($P < 0.001$), and the EASI 75 endpoint was reached by 33.2% of the tralokinumab group and 11.4% of the placebo group ($P < 0.001$). Among patients who reached an IGA score of 0 or 1 with tralokinumab at week 16, this score was maintained through week 52 without the need for rescue medication (including TCS) in 51% of those receiving tralokinumab every 2 weeks (Q2W) and in 47% of those rerandomized from tralokinumab to placebo ($P = 0.68$) in ECZTRA 1, versus 59% receiving tralokinumab Q2W and 25% rerandomized from tralokinumab to placebo ($P = 0.004$) in ECZTRA 2. The proportion of patients who continued to maintain an IGA score of 0 or 1 at week 52 after being rerandomized to tralokinumab every 4 weeks was 39% in the ECZTRA 1 trial and 45% in the ECZTRA 2 trial. The conclusion is that tralokinumab as a standalone treatment was more effective than placebo at 16 weeks and was well tolerated for up to 52 weeks of therapy [42].

ECZTRA 3 evaluated the efficacy and safety of tralokinumab in combination with topical corticosteroids (TCS). A total of 380 patients underwent 16 weeks of therapy with 300 mg of tralokinumab (253 patients) or placebo (127 patients) every 2 weeks, with additional use of topical corticosteroids as needed. The patients who achieved endpoints were rerandomized 1:1 to tralokinumab Q2W or Q4W, with TCS as needed, for another 16 weeks. At week 16, an IGA score of 0/1 was reached by 38.9% of patients receiving the antibody compared to 26.2% receiving placebo ($P < 0.001$), and EASI 75 was achieved by 56% versus 35.7% ($P < 0.001$) for tralokinumab and placebo, respectively. After the rerandomization, at week 32, an IGA 0/1 response was maintained without any rescue therapy in 89.6% (Q2W) and 77.6% (Q4W), and EASI 75 was maintained in 92.5% (Q2W) and 90.8% (Q4W). This leads to the conclusion that tralokinumab 300 mg in combination with TCS as needed was effective and well tolerated in patients [43,44].

Other mechanisms of action

Brepocitinib

Combining inhibitory activity on TYK2 and JAK1, small-molecule brepocitinib impacts the IL-12 and IL-23 pathways and presents promising results administered orally in plaque psoriasis or alopecia areata.

Megan N. Landis et al. conducted a phase IIb, double-blind, dose-ranging study (NCT03903822) of 292 patients aged 12-75 in 10 countries with the clinical diagnosis of AD for ≥ 3 months, IGA score of 2 or 3 and EASI total score of 3 to 21 at the baseline, that were randomized to eight group receiving topical brepocitinib 0,1%,0,3%, 1,%, 3% or vehicle once a day and brepocitinib 0,3%, 1% or vehicle twice a day. At the end point of 6 weeks the greatest mean percentage reduction in EASI score was visible in participants administering brepocitinib 1% twice daily (-75,1) and once daily (-70,1), brepocitinib 3% (-67,9) and 0,3% (-64,6) applied once daily following behind. Of six groups receiving active treatment, five responded with a significant reduction in IGA score vs. respective vehicle. Most adverse events and discontinuations were recorded in vehicle groups, worsening of AD being the most common [45].

Asivatrep

Asivatrep is a potent and selective antagonist of the transient receptor potential vanilloid subfamily V member 1 (TRPV1). Chun Wook Park and coauthors conducted a double-blind, phase 3 study in 240 patients aged ≥12 years with mild to moderate AD who received 1.0% asivatrep or vehicle twice daily in a 2:1 ratio for 8 weeks. The study was designed to assess the efficacy and safety of the drug. IGA scores of 0 or 1 were achieved by 36.0% of patients in the asivatrep group and 12.8% in the placebo group, and ≥2 points of improvement in IGA from baseline were achieved by 20.3% vs 7.7%, respectively. The mean percentage decrease in EASI area was 44.3% in the asivatrep group and 21.4% in the placebo group. No significant safety issues were reported [46].

Summary

Atopic dermatitis is a common disease. The current gold standard is the use of topical glucocorticosteroids. Due to their adverse effects such as: skin atrophy, the formation of permanent telangiectasia, striae or dyspigmentation and including their limitations in the anogenital area, new drugs are needed. The drugs we described have different mechanisms of action: biologics (Lebrikizumab, Nemolizumab, Dupilumab, Tralokinumab), phosphodiseterase-4 inhibitors (Roflumilast, Difamilast), janus kinase inhibitors (Ruksolitynib, Delgocytynib, Tofacitinib, Upadacytynib), aryl hydrocarbon receptor modulator (Tapinarof) and others (Brepocitinib, Asivatrep). They are well tolerated and no serious adverse effects were noted during their use. It seems that in the future they will be able to be used instead of glucocorticosteroid for people with atopic dermatitis. However, many of them require a longer period of study and verification of their safety in other groups of patients, including pediatric patients.

Disclosure:

Authors' contribution:

Conceptualization: Martyna Choinka

Methodology: Małgorzata Komarów

Software: Natalia Wdowiak

Check: Agata Konopka

Formal Analysis: Dominika Karasińska

Investigation: Zuzanna Szczepaniak

Resources: Jakub Kalisiak

Data Curation: Karina Lissak

Writing-Rough Preparation: Martyna Choinka

Writing-Review and Editing: Małgorzata Komarów

Visualization: Karina Lissak

Supervision: Dominika Karasińska

Project Administration: Agata Konopka

All authors have read and agreed with the published version of the manuscript.

Funding statement:

The study did not receive special funding.

Institutional review board statement:

Not applicable.

Informed consent statement:

Not applicable.

Data availability statement:

Not applicable.

Conflict of interest:

The authors declare no conflict of interest

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