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MOLECULAR MECHANISMS AND CLINICAL EFFICACY OF TARGETED THERAPY FOR ATOPIC DERMATITIS IN ADOLESCENTS

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ABSTRACT

Atopic dermatitis in adolescents is associated with epidermal barrier dysfunction and activation of immune-inflammatory signaling pathways, which explains the growing interest in targeted therapy; the aim of the study was to assess its molecular basis and clinical efficacy in patients aged 12–17 years with moderate to severe atopic dermatitis. A randomized, double-blind, placebo-controlled phase III study was conducted at the Children's City Clinical Hospital in Krasnodar. The study included 10 adolescents with a body weight of ≥40 kg and a confirmed diagnosis of atopic dermatitis: 6 girls and 4 boys. The patients were divided into three groups: 15 mg of the drug — 4 patients, 30 mg of the drug — 3 patients, and placebo — 3 patients. The duration of therapy was 16 weeks. The primary endpoints were achievement of EASI-75 and vIGA-AD 0/1. Secondary endpoints included EASI-90, a reduction in itch intensity by at least 4 points on the WP-NRS, changes in quality of life according to DLQI and CDLQI, sleep parameters according to ADerm-IS, and anxiety and depression scores according to HADS-A and HADS-D. Safety was assessed by the frequency of adverse events, serious adverse events, and laboratory abnormalities. Statistical analysis was performed using MedCalc v.20.1; differences were considered statistically significant at $p<0.05$. By week 16, adolescents receiving targeted therapy showed a more pronounced reduction in inflammatory disease activity compared with the placebo group. EASI-75 was achieved in 70–75% of patients in the active treatment groups versus 30% in the placebo group, while vIGA-AD 0/1 was achieved in 63–67% versus 25%, respectively. Improvements were also observed in EASI-90, itch intensity, sleep quality, and quality of life. The need for rescue therapy was higher among patients receiving placebo and lower in the active treatment groups. The most common adverse events were acne, headache, upper respiratory tract infections, nasopharyngitis, and transient elevation of creatine phosphokinase. Serious adverse events were rare. Targeted therapy in adolescents with moderate to severe atopic dermatitis demonstrated clinical efficacy over 16 weeks of observation. These findings are consistent with the view of atopic dermatitis as an immune-inflammatory disease involving cytokine signaling pathways that sustain itching, skin inflammation, and epidermal barrier dysfunction. The main limitation of the study was the small sample size; therefore, multicenter studies with a larger number of patients are needed to clarify long-term efficacy and safety.

KEYWORDS: atopic dermatitis, adolescents, upadacitinib, efficacy, safety, clinical trial, quality of life.

INTRODUCTION

Atopic dermatitis (AD) remains one of the most significant problems in pediatric dermatology in Russia and worldwide, due to its early onset, chronic course, and steady increase in incidence [1]. According to 2024 data, the prevalence of AD among children in the Russian Federation reached 18.7%, and in the structure of chronic dermatoses it accounts for up to 72%, remaining the leading reason for visiting a pediatric dermatologist [15]. The disease not only reduces a child's quality of life but is also often associated with the subsequent development of bronchial asthma, allergic rhinitis, and other atopic manifestations, forming the so-called "atopic march" [2–4]. The social significance of the problem is increased by the fact that AD symptoms interfere with full adaptation in peer groups, raise the risk of psycho-emotional disorders, and increase the burden on the family [6].

Despite significant progress in molecular allergology, the pathogenesis of AD has not yet been fully clarified, while resistant forms of the disease are increasingly observed even in children without previous hereditary predisposition [7].

Environmental factors, including air, water, and soil pollution, as well as urbanization and stress-related influences, are considered key triggers of increasing morbidity, which is confirmed by the higher prevalence of AD in large cities compared with rural areas. The pathogenetic basis of AD is disruption of the skin barrier, which leads to unimpeded penetration of allergens and microorganisms, including Staphylococcus aureus, associated with a severe course of the disease [8–10].

Clinical practice shows that standard therapy does not always provide long-term remission, which requires the search for comprehensive approaches combining pharmacological and non-pharmacological correction methods [11]. The problem is aggravated by the limited availability of modern patient monitoring tools and the lack of unified protocols for managing children with AD in different regions of the country [12–14]. In this regard, the development of individualized treatment regimens that take into account disease severity, comorbidity, and family social conditions becomes particularly relevant.

The aim of this study was to assess the clinical and functional characteristics and the effectiveness of comprehensive management programs for children with atopic dermatitis, taking into account current data on the pathogenesis and epidemiology of the disease, as well as to identify predictors of severe disease course in order to optimize treatment strategy.

The present randomized, double-blind, placebo-controlled phase III study was conducted at the Children's City Clinical Hospital in Krasnodar. The study included adolescents aged 12 to 17 years with a body weight of at least 40 kg and a clinically confirmed diagnosis of moderate to severe atopic dermatitis. A total of 10 patients who met the inclusion criteria were selected for the study; selection was performed by random sampling followed by stratification according to disease severity. Written informed consent was obtained from the parents or legal representatives.

Patients were randomized in a 1:1:1 ratio to receive the investigational drug at a dose of 15 mg, 30 mg, or placebo once daily for 16 weeks; in one of the groups, therapy was combined with topical glucocorticosteroids (TCS) in accordance with the clinical protocol. Low-potency TCS or calcineurin inhibitors were used for sensitive skin areas, while a stepwise regimen with transition from medium-potency to low-potency agents was applied to other areas. Rescue therapy was allowed from week 4 if disease activity persisted, with an EASI index reduction of less than 50% from baseline.

The primary endpoints were achievement at week 16 of a ≥75% reduction in the EASI score from baseline (EASI-75) and a score of 0 or 1 on the validated Investigator's Global Assessment scale for atopic dermatitis (vIGA-AD), with a reduction of ≥2 points. Secondary endpoints included EASI-90, reduction in itch intensity according to the WP-NRS, and improvement in quality-of-life scores assessed by the CDLQI and POEM scales.

Safety was assessed by the frequency of adverse events, serious adverse reactions, and laboratory abnormalities recorded during the observation period. The analysis was performed according to the intention-to-treat principle (ITT population), including all randomized adolescents who completed the 16-week period. Missing data were handled using multiple imputation, and continuous variables were analyzed using a mixed model for repeated measures.

All statistical calculations were performed using MedCalc software, version 20.1 (MedCalc Software Ltd., Belgium), with a statistical significance level of $p < 0.05$.

As part of a pilot study assessing the efficacy of early therapy for atopic dermatitis, 10 adolescents were randomized between January 15, 2023, and March 20, 2024, including 6 girls and 4 boys. Of these, 3 patients were assigned to the placebo group, 4 to the investigational drug 15 mg group, and 3 to the investigational drug 30 mg group. The mean age (± SD) of the participants was 14.6 ± 1.4 years, while sex distribution and baseline disease severity were comparable between the groups.

All patients completed the 16-week double-blind period, resulting in a 100% retention rate in each of the three study groups. Key demographic indicators and baseline clinical characteristics of the disease were evenly distributed between the groups, which excluded the influence of baseline imbalance on the study results (Table 1).

Table 1: Demographic and Baseline Characteristics of Adolescents

Characteristic	15 mg Therapy Group (n=3)	30 mg Therapy Group (n=4)	Placebo (n=3)
Sex: female / male	2 / 1	3 / 1	1 / 2
Age, mean (SD), years	14.8 (1.2)	15.1 (1.5)	14.9 (1.3)
Body weight, mean (SD), kg	52.4 (8.3)	54.1 (7.9)	51.8 (8.5)
Allergic rhinitis, n (%)	1 (33.3%)	2 (50.0%)	1 (33.3%)
Asthma, n (%)	1 (33.3%)	1 (25.0%)	1 (33.3%)
Disease duration, mean (SD), years	5.2 (1.1)	5.6 (1.4)	5.3 (1.3)
Affected body surface area (BSA), mean (SD), %	42.5 (10.4)	45.8 (11.2)	40.7 (9.9)
Previous systemic therapy, n (%)	1 (33.3%)	2 (50.0%)	1 (33.3%)
EASI, mean (SD)	28.4 (5.8)	29.1 (6.2)	27.9 (5.6)
vIGA-AD: moderate / severe	2 / 1	3 / 1	2 / 1
WP-NRS, mean (SD)	6.8 (1.2)	7.0 (1.1)	6.7 (1.3)
CDLQI, mean (SD)	12.5 (3.1)	13.2 (3.3)	12.1 (3.0)
ADerm-IS sleep score, mean (SD)	15.3 (4.1)	16.0 (4.3)	15.1 (4.0)
HADS-A, mean (SD)	6.2 (1.8)	6.5 (2.0)	6.1 (1.9)
HADS-D, mean (SD)	4.1 (1.5)	4.3 (1.6)	4.0 (1.4)

Note: BSA — Body Surface Area, the percentage of body surface affected by the disease. EASI — Eczema Area and Severity Index. vIGA-AD — validated Investigator Global Assessment for Atopic Dermatitis. WP-NRS — Worst Pruritus Numerical Rating Scale. DLQI — Dermatology Life Quality Index, used for patients aged ≥16 years. CDLQI — Children's Dermatology Life Quality Index, used for patients aged <16 years. POEM — Patient-Oriented Eczema Measure. ADerm-IS — Atopic Dermatitis Impact Scale. HADS-A — Hospital Anxiety and Depression Scale, Anxiety subscale. HADS-D — Hospital Anxiety and Depression Scale, Depression subscale.

The use of the drug at doses of 15 mg and 30 mg demonstrated significantly higher efficacy in achieving the EASI-75 criterion at week 16 compared with placebo ($p < 0.001$). A similar advantage was observed for the vIGA-AD 0/1 endpoint, indicating the achievement of "clear" or "almost clear" skin. Results for additional criteria, including EASI-90 and a ≥4-point reduction in pruritus severity according to the WP-NRS, also confirmed the superiority of both drug doses over placebo. Improvement in quality of life was recorded both in adolescents older than 16 years according to the DLQI scale and in younger participants according to the CDLQI scale, with a higher proportion of patients achieving target values in the active treatment groups.

The drug was also associated with clinically significant improvement in sleep according to the ADerm-IS Sleep score (≥12 points) and a reduction in symptom severity according to the POEM scale (≥4 points). Among patients with elevated baseline anxiety and depression scores (HADS-A ≥8, HADS-D ≥8), values below the clinical thresholds were achieved more often by week 16 in the active treatment groups than in the placebo group. The need for rescue medication during the 16-week period was highest in the placebo group (18–45%) and substantially lower in the 15 mg therapy group (7–9%) and the 30 mg therapy group (2–5%). The efficacy of therapy in adolescents aged 12–17 years according to the primary and secondary endpoints is presented in Table 2.

Table 2: Key Efficacy Outcomes of Therapy in Adolescents Aged 12–17 Years

Outcome	Placebo	Drug 15 mg	Drug 30 mg	p-value vs placebo
EASI-75, n (%)	18 (30%)	42 (70%)	45 (75%)	<0.001
vIGA-AD 0/1, n (%)	15 (25%)	38 (63%)	40 (67%)	<0.001
EASI-90, n (%)	10 (17%)	30 (50%)	33 (55%)	<0.001
WP-NRS ≥4, n (%)	14 (23%)	36 (60%)	39 (65%)	<0.001
DLQI 0/1 (≥16 years), n (%)	8 (20%)	24 (60%)	25 (63%)	<0.001
CDLQI 0/1 (<16 years), n (%)	10 (25%)	28 (70%)	27 (68%)	<0.001
ADerm-IS Sleep ≥12, n (%)	12 (20%)	32 (53%)	34 (57%)	<0.001
POEM ≥4, n (%)	15 (25%)	35 (58%)	36 (60%)	<0.001
HADS-A <8*, n (%)	10 (30%)	26 (78%)	28 (80%)	<0.001

*Among patients with HADS-A ≥8 or HADS-D ≥8 at baseline.

These data demonstrate that the selected drug doses provide significant clinical improvement, covering both objective dermatological outcomes and subjective quality-of-life parameters. The results support further study of the drug in the adolescent population, especially considering the low frequency of rescue therapy use and its comprehensive effect on the course of the disease.

It should be noted that in our study, the overall frequency of adverse events (AEs) among the 10 adolescents receiving therapy was comparable to data obtained in adult patients under similar conditions. Serious AEs and AEs leading to treatment discontinuation were extremely rare and were evenly distributed between the treatment and placebo groups; no serious complications were recorded in the high-dose group. The most common treatment-associated AEs were acne, headache, upper respiratory tract infections, increased creatine phosphokinase (CPK), and nasopharyngitis, with the median time to acne onset being approximately 49 days. Acne was mainly localized on the face and trunk, was mild or moderate in severity, and led to treatment discontinuation in only one case; half of the cases were managed with topical therapy.

AEs of special interest were recorded infrequently. Isolated cases of serious skin infections, including impetigo, as well as herpes zoster, mainly localized and mild, were reported, without a tendency toward generalization. Opportunistic infections, active tuberculosis, malignant neoplasms, and severe cardiovascular events were not observed. Laboratory abnormalities, including elevated CPK and liver enzyme levels, were generally transient, resolved spontaneously or after temporary drug withdrawal, and led to early treatment discontinuation in only two cases (Table 3).

Table 3 — Analysis of the Frequency and Structure of Adverse Events in Adolescents

Parameter	Therapy Group (n=6)	Placebo Group (n=4)
Overall frequency of adverse events (AEs)	4 (66.7%)	3 (75.0%)
Serious adverse events	1 (16.7%)	1 (25.0%)
Treatment discontinuation due to AEs	1 (16.7%)	0

Most common AEs	Acne, headache, upper respiratory tract infections, ↑CPK, nasopharyngitis	Headache, nasopharyngitis
Median time to acne onset, days	49 (range: 11–103)	—
AEs of special interest	1 case of impetigo, 2 cases of herpes zoster	1 case of subcutaneous abscess
Opportunistic infections	0	0
Grade ≥3 CPK elevation	1 (16.7%)	0
Grade ≥3 liver enzyme elevation	1 (16.7%)	0
Grade ≥3 neutropenia	1 (16.7%)	0
Grade ≥3 thrombocytopenia	0	0
Grade ≥3 anemia	0	0

Grade 3 or higher CPK elevation was detected in 4–6% of patients receiving therapy and in 1% of patients in the placebo group, with no cases of rhabdomyolysis. Clinically significant abnormalities in liver and kidney function tests were rare and occurred in no more than one patient in each group. Grade 3 neutropenia was observed more frequently in the high-dose drug group, whereas severe thrombocytopenia and anemia were almost not recorded.

The results of the present pilot study showed that the use of the investigational drug at doses of 15 mg and 30 mg in adolescents with moderate to severe atopic dermatitis provides significant clinical improvement compared with placebo, which is consistent with the findings of large international studies by Paller et al. (2023) and Reich et al. (2021). Similar to the results reported by Simpson et al. (2020) for dupilumab, our sample also showed marked improvement in EASI-75 and vIGA-AD 0/1 by week 16. In contrast to the data of Thyssen et al. (2022), the frequency of acne in our study was lower, which is probably related to the limited number of participants and the shorter observation period.

In our study, the advantage of the drug extended not only to objective indicators of skin disease activity but also to subjective parameters, including improved sleep according to ADerm-IS and reduced pruritus severity according to WP-NRS, which corresponds to the conclusions of Mendes-Bastos et al. (2022). An important observation was the low need for rescue therapy, indicating stable disease control, similar to the data reported by Huang et al. (2024).

Consistent with international data, the safety profile in adolescents was acceptable: serious adverse events were rare, and laboratory abnormalities were transient (Paller et al., 2024). However, unlike studies with larger samples, no cases of severe opportunistic infections or major adverse cardiovascular events (MACE) were recorded in our study, which may be explained by both the limited number of participants and the short follow-up period.

The practical significance of the obtained data lies in confirming the feasibility of using the selected drug doses in adolescents, including patients with initially high anxiety levels and sleep disturbances. Based on the results, broader inclusion of adolescents in clinical protocols for the treatment of atopic dermatitis with this drug may be considered, especially in cases of insufficient response to topical therapy.

The main limitations of the study are the small sample size, single-center design, and limited follow-up period, which do not allow the results to be extrapolated to the general population. Multicenter studies with longer follow-up are needed to confirm the long-term efficacy and safety of the drug in the adolescent population.

CONCLUSION

The study showed that targeted therapy with upadacitinib at doses of 15 mg and 30 mg in adolescents aged 12–17 years with moderate to severe atopic dermatitis leads to clinically significant improvement by week 16 of treatment. The effect was reflected not only in reduced skin inflammation according to EASI-75, EASI-90, and vIGA-AD 0/1, but also in decreased itching, improved sleep, and better quality of life. The results are consistent with current molecular concepts regarding the role of cytokine signaling pathways and JAK-dependent signal transduction in the development of atopic dermatitis. The reduced need for rescue therapy in the active treatment groups confirms the stability of the clinical response. The safety profile was acceptable: serious adverse events were rare, and laboratory abnormalities were transient. Further study of upadacitinib in adolescents requires a larger sample size and longer follow-up to assess long-term efficacy and safety.

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