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Evaluation of nanoliposomal forms of retinoids' efficiency in treatment of acne

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Abstract. The study aimed to determine the clinical efficacy and tolerability profile of the nanoliposomal form of tretinoin in patients with moderate acne. The study was conducted as a randomised controlled trial involving 120 patients with moderate acne at the Department of Dermatovenereology, Allergology, Clinical and Laboratory Immunology of the Shupyk National Healthcare University of Ukraine; over 12 weeks, clinical dynamics, subjective assessment of efficacy and the incidence of adverse reactions were compared with nanoliposomal and traditional forms of tretinoin. Patients treated with nanoliposomal tretinoin showed a 58.8% reduction in clinical acne severity, which indicated a higher therapeutic efficacy compared to the traditional formulation, where the reduction was only 41.7%. In this group, the number of inflammatory elements decreased by 64% and non-inflammatory elements by 53.7%, while in the control group, the corresponding figures were 42% and 34.6%, which confirmed the ability of the nanoform to affect both comedogenesis and inflammatory processes. Complete disappearance of inflammatory lesions was achieved in 28.3% of patients in the main group, which was more than twice as high as in the group of traditional tretinoin. The subjective assessment of treatment effectiveness was significantly higher among nanoform users (8.1 vs 6.3 points), indicating better satisfaction with the result. Adverse reactions occurred in less than 12% of participants in the main group, while in the comparison group, their frequency exceeded 25%, indicating a higher dermatological tolerance of the nanoliposomal drug. The results obtained can be used by dermatologists to make an informed choice of topical acne therapy, in particular when prescribing modern forms of tretinoin to patients with hypersensitivity of the skin or low tolerance to traditional drugs

Keywords: skin; comedones; inflammation; tretinoin; peeling; adverse reaction; intolerance

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous skin units, accompanied by the formation of comedones, pustules, infiltrative elements and post-inflammatory changes, including scars and hyperpigmentation. Clinical practice is dominated by persistent and recurrent forms of the disease, which are characterised by reduced sensitivity to standard topical therapy, in particular to antibacterial agents. Therapeutic approaches are based on the use of systemic and topical retinoids, but classical dosage forms often demonstrate limited efficacy due to the instability of active substances, insufficient penetration through the stratum corneum of the epidermis and a high incidence of local adverse reactions. In dermatology, there is a growing scientific interest in the use of nanotechnology platforms to ensure targeted and controlled transdermal delivery of active compounds. The research relevance is determined by the need to evaluate the efficacy and safety of nanoliposomal forms of retinoids as a potential means of increasing bioavailability, reducing toxicity and optimising clinical effect in the treatment of acne.

The pathogenetic basis of acne is the interrelated processes of follicular hyperkeratosis, seborrhoea, colonisation by *Cutibacterium acnes* and initiation of the inflammatory cascade, which are implemented through hormone-receptor and immune regulation. The study by S. Bharti & H.C. Vadlamudi [1] analysed the molecular

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relationships between the retinoic acid receptor, retinoid X receptor, transcription factors, and hormones that activated sebocytes and contributed to the persistence of inflammation. This review formed the theoretical basis for the determination of retinoids as multifunctional modulators of genetic activity that act at several levels of pathogenesis. The analysis proposed by M.C. Marchitto *et al.* [2] analysed the differences between retinoid molecules in the context of clinical forms of acne and the phase of the inflammatory process. The authors not only classified drugs by mechanism of action but also raised the problem of insufficient individualisation of retinoid therapy, which limited its use in difficult cases. L.A. Bolotna [3] summarised the clinical evidence of the effectiveness of retinoids in different acne phenotypes, emphasising the need for a combined assessment of their comedolytic, anti-inflammatory and keratolytic effects when choosing a drug. In addition, the study highlighted the insufficient correspondence between the pathogenetic effect of retinoids and the practice of their use, which led to a loss of effectiveness in real life. Such a critical analysis was used to interpret retinoids not only as a standard of care, but also as a means of targeted pathogenetic intervention, the potential of which remained far from being exhausted.

Traditional dosage forms of topical retinoids, including tretinoin and adapalene, are limited in clinical use due to the instability of active ingredients, limited penetration through the stratum corneum of the epidermis and a high risk of irritation. The clinical and pharmacological review by A.C. Narsa *et al.* [4] demonstrated that the photophilicity of retinoids and their surface activity caused a high incidence of local adverse reactions, which directly affected patient compliance. The study highlighted the need to develop modified-release and barrier-neutral formulations. A significant complication of the use of traditional retinoids in patients with a dark phototype was described by V. Callender *et al.* [5], emphasising the link between epidermal irritation and post-inflammatory hyperpigmentation. Therefore, the study concluded that there is a critical need for forms with reduced irritation potential for sensitive skin. I.O. Doroshkevych *et al.* [6] revealed another systemic problem: limited implementation of retinoid therapy in primary care due to low clinical awareness of doctors and patients' cautious attitude to side effects. These studies outlined the range of disadvantages of classical topical forms, which justified the need to search for new delivery platforms with improved pharmacological characteristics.

The development of nanoliposomal forms of retinoids is a promising way to overcome the pharmacokinetic limitations of classical drugs and optimise their safety profile. In the clinical experiment by A. Samadi *et al.* [7], the use of tretinoin in nanolipid carriers provided significantly higher clinical efficacy compared to standard forms, which was manifested in a decrease in the number of inflammatory elements and the acne severity index. At the same time, a decrease in the frequency of local side effects was recorded, which confirmed the better tolerability of nanostructured systems. In the publication by N. Dragicevic & H.I. Maibach [8], liposomal platforms were considered as a means of stabilising retinoids and regulating the rate of their transdermal transport, which contributed to more accurate dose control in the microenvironment of the follicular apparatus. The review also revealed significant advantages of such systems in terms of reducing the irritant effect of the active substance. Another innovative approach was the proliposomal nanofibres described by S. Tort *et al.* [9], which combined the delivery of retinoic acid with the effect of inhibiting the *Cutibacterium* acnes biofilm. The study demonstrated the effectiveness of this technology in a model of microbiological resistance, indicating its potential in the treatment of complex forms of acne. Another example of the technological implementation of the nanoliposomal strategy was the study by A. Arooj *et al.* [10], in which a gel form of adapalene encapsulated in liposomes was created. Based on the results of the evaluation of the physicochemical properties and *in vitro* activity of the gel, the study noted an improved drug release, enhanced skin penetration and prospects for further clinical trials.

Despite the growing number of studies in the field of transdermal delivery of retinoids, there are no data on the clinical efficacy of nanoliposomal forms of retinoids based on direct comparison with traditional drugs under standardised conditions of observation. The study aimed to evaluate the therapeutic effect and tolerability of nanoliposomal tretinoin in the treatment of patients with moderate acne. The objectives included: analysis of the dynamics of clinical parameters during therapy, assessment of the frequency and nature of side effects, and comparison of the efficacy of the study form with the reference standard form of tretinoin.

MATERIALS AND METHODS

The study was conducted in the format of a randomised controlled trial during June-August 2024 at the clinical base of the Department of Dermatovenereology, Allergology, Clinical and Laboratory Immunology of Shupyk National Healthcare University of Ukraine. The chosen period ensured a full 12-week treatment course followed by short-term follow-up to assess the durability of the clinical effect and the incidence of adverse reactions. The study included 120 patients aged 18 to 35 years with a clinically confirmed diagnosis of moderate acne, established by a dermatologist based on examination and history. The severity of acne was assessed using the Global Acne Grading System (GAGS) scale, which is recommended for standardised assessment of the clinical course of the disease following European guidelines for the treatment of acne [11]. This age range is justified by the high prevalence of persistent acne in young adults, which is characterised by a persistent clinical course and reduced efficacy of standard topical retinoid therapy. Participants were randomly divided into two equal groups of 60 people each. The allocation was carried out by stratified randomisation using a computer-generated sequence that ensured the groups were balanced by age and gender (30 men and 30 women in each group).

Group A was treated with an experimental topical nanoliposomal form of tretinoin (0.05%, gel base). The preparation contained tretinoin, phosphatidylcholine (liposome backbone), cholesterol (membrane stabiliser), ethanol, ethylenediaminetetraacetic acid dinitrate salt (Trilon B), purified water and Carbopol 934P (gelating agent). Liposomes were prepared by lipid film hydration followed by ultrasonic homogenisation (10 min, 60% amplitude) at 40°C. Gelation was performed at pH (hydrogen potential) 6-6.5. The average hydrodynamic diameter of the particles was

182 ± 15 nm (determined by dynamic light scattering), and the polydispersity index was 0.21. Physicochemical stability was assessed by centrifugation and temperature cycling. The tretinoin content was determined by high-performance liquid chromatography; the pH of the drug was 6.2 ± 0.3; the viscosity was 8,700 centipoise. The technology was developed based on patent WO1998/030215A1 [12]. Group B (control, with active comparison) used the traditional form of tretinoin Airol 0.05% cream (Pierre Fabre, France).

Participants in both groups received written instructions for the use of the products: apply once a day (in the evening, after cleansing the skin), applying a thin layer to the affected areas of the face, avoiding the area around the eyes, lips and mucous membranes. Do not wash or use other products for 6 hours after application. For hygienic care, Obagi Nu-Derm Foaming Gel (pH 5.5) (Obagi Cosmeceuticals LLC, USA) was recommended twice daily. The use of aggressive cosmetics (alcohol-containing tonics, scrubs) was prohibited. For the prevention of photosensitisation, all patients used La Roche-Posay Anthelios SPF 50+ (Sun Protection Factor) (La Roche-Posay Laboratoire Dermatologique, France) daily with reapplication in case of sun exposure; it was also recommended to avoid insolation, tanning beds and thermal procedures. No additional topical or systemic acne medications were used during the treatment period. A combined approach was used to monitor compliance with the therapeutic protocol. All patients kept self-observation diaries, which were checked at each follow-up visit (weeks 2, 6, and 12). In addition, a visual skin examination and standardised photographic recording of the skin condition were performed at the same control points under constant lighting conditions, distance (50 cm) and angle. Images were captured using a Canon EOS 90D digital SLR camera (24.2 MP, EF-S 18-55 mm lens) in manual mode. Assessment of the residual amount of the drug in individually dispensed tubes was used as an auxiliary indicator of therapeutic adherence.

The study included patients who met the following criteria: age 18-35 years, clinically confirmed moderate acne, no treatment with systemic retinoids or antibiotics for at least 3 months before enrolment, and no concomitant diseases that could affect the course of acne. Patients with severe or conglomerate forms of acne, dermatoses that make diagnosis difficult (rosacea, seborrhoeic or oral dermatitis), allergies to drug components, as well as pregnant or lactating women or participants in other clinical trials within the previous 6 months, were excluded. The clinical effectiveness of the treatment was assessed based on the dynamics of the GAGS score, a standardised scale that addresses the number and type of lesions in different anatomical areas (forehead, cheeks, nose, chin) with appropriate correction factors. The total score on the GAGS scale (0-44) was used to classify the severity of acne as follows: 1-18 points – mild, 19-30 points – moderate, 31-38 points – severe, 39-44 points – extreme. Assessment was performed at three control points: at the beginning of treatment (day 0), after 6 weeks, and at the end of the course (week 12). The primary efficacy endpoint was a reduction in the total GAGS score of ⩾50% from baseline, which was interpreted as a clinically significant improvement. Secondary outcome measures were absolute reduction in the number of inflammatory (pustules, papules, nodules) and non-inflammatory elements (comedones), as well as an overall assessment of improvement in the clinical condition of the skin using the Visual Analog Scale (VAS) (0-10), where 0 corresponded to no positive dynamics and 10 to complete clinical recovery. An additional criterion for evaluating efficacy was the presence of clinical remission, which was defined as the complete absence of inflammatory elements and a decrease in the number of non-inflammatory elements of ⩾90% of the baseline. Clinical dynamics were assessed by two independent researchers with a higher medical education in dermatovenereology and more than 10 years of clinical experience. Both had experience in clinical trials (at least 5 years). Visual skin examination was performed in the dynamics (week 0, 6, 12) and was accompanied by standardised photographic recording of the skin condition, the conditions of which have already been described in the previous subsection. All assessments were performed in a blinded mode concerning the group Affiliation of the patients.

The safety and tolerability of the therapy were assessed through systematic monitoring of the most common local adverse reactions typical of topical tretinoin use. The frequency and intensity of such symptoms as erythema, flaking, burning, itching, dry skin and the appearance of new inflammatory elements as signs of a possible reactive exacerbation were studied. The assessment was conducted by a dermatologist at each follow-up visit using a standardised 4-point severity scale (0 – absent, 1 – mild, 2 – moderate, 3 – severe). The first control was performed at week 2 of treatment, which corresponded to the early induction phase of the drug. Additionally, the number of patients who discontinued treatment due to intolerance was recorded.

The data were analysed using IBM SPSS Statistics, version 26.0. The Shapiro-Wilk test was used to check the normality of the distribution. Quantitative indicators are presented as mean with standard deviation (M±SD) or median with interquartile range (Me [Q1-Q3]), depending on the nature of the distribution. Comparisons between groups were performed using Student's t-test or Mann-Whitney test; for dynamic changes within groups, paired t-test or Wilcoxon test. Frequency data were analysed using the χ^2 test or Fisher's test. The level of statistical significance was set at $p < 0.05$. The clinical trial complied with the ethical and legal requirements set out in the Declaration of Helsinki [13], the International Council for Harmonisation Good Clinical Practice guidelines [14], and Order of the Ministry of Health of Ukraine No. 690 [15]. All participants provided written informed consent after receiving full information about the purpose, procedures, and potential risks.

RESULTS

Dynamics of changes in acne severity per the GAGS scale. In the dynamics of the 12-week treatment, a statistically significant decrease in the mean GAGS score was recorded in both study groups. At baseline (day 0), the mean GAGS score in group A was 27.4 ± 2.8 points, which corresponded to the average severity of acne. In group B, the baseline score was 27.1 ± 2.6 points. There was no statistically significant difference between the groups at the start of the study ($p = 0.64$), which confirmed the baseline homogeneity of the sample according to the main efficacy assessment criterion. After 6 weeks of therapy, group A showed

a decrease in the GAGS index to 17.2 ± 2.4 points, which corresponded to an average decrease of 37.2% compared to baseline ($p < 0.001$ compared to baseline). In group B, at the same stage of treatment, the index decreased to 20.3 ± 2.9 points, which was only a 25.1% decrease ($p < 0.001$). At the same time, the intergroup difference in favour of the nanoliposomal drug reached high statistical significance ($p < 0.001$), indicating a faster therapeutic effect in patients treated with the nanostructured form of tretinoin. After completion of the full course of treatment (week 12) in group A, the mean GAGS score decreased to 11.3 ± 2.1 points, which corresponded to an absolute decrease of 16.1 points (58.8% relative to baseline). In group B, the score decreased to 15.8 ± 2.3 points, which was a 41.7% improvement. Both groups demonstrated intra-group statistically significant dynamics ($p < 0.001$), but comparative analysis confirmed the advantage of the nanoliposomal form of tretinoin ($p < 0.001$, including at week 12). Table 1 showed the dynamics of the mean values of the GAGS index in groups A and B during the treatment period.

Table 1. Dynamics of the GAGS index in groups A and B during treatment (M ± SD)

Time point	Group A (nano-gel)	Group B (Airol cream)
Day 0	27.4 ± 2.8	27.1 ± 2.6
Week 6	17.2 ± 2.4	20.3 ± 2.9
Week 12	11.3 ± 2.1	15.8 ± 2.3

Source: compiled by the author

The use of the nanoliposomal delivery system not only contributed to a more pronounced clinical effect but also ensured its earlier realisation. By week 6, more than half of the patients in group A achieved a reduction in GAGS of ⩾50%, which met the primary endpoint of clinical improvement. In group B, this result was recorded mainly at the final stage of treatment, with a statistically lower proportion of patients achieving a ⩾50% reduction ($\chi^2 = 11.47$; $p = 0.0007$). The nanoliposomal form of tretinoin was characterised not only by greater efficacy but also by faster achievement of the therapeutic response threshold. The decrease in the mean GAGS score in group A was also accompanied by a smaller interindividual variation: the standard deviation at week 12 was 2.1 points, while in group B it was 2.3 points. This indicated a more uniform clinical effect and better reproducibility of results in the population. The reduction in variability may indicate greater bioavailability and stability of the active substance in the conditions of nanostructured delivery.

In an additional stratified analysis, it was found that among patients with a baseline GAGS score of ⩾30 (upper limit of moderate), 76.7% of participants in group A achieved a reduction in score to ⩽18 (mild) by week 12. In group B, this result was observed only in 41.6% of cases ($p = 0.002$), which confirmed the effectiveness of the nanoliposomal form of tretinoin even in clinically more severe cases. A comparative analysis of the dynamics of the mean GAGS index values by group demonstrated a stable advantage of the nanoliposomal drug from week 6 of treatment, which persisted until the end of the study. In group A, the rate of reduction of the GAGS index was higher during the first 6 weeks of treatment, after which a gradual slowdown in clinical dynamics was observed, indicating an approach to a therapeutic plateau. In group B, the improvement was slower and less pronounced, with no clear signs of reaching a clinically stable level by the end of the study.

The results confirmed the significant advantage of the nanoliposomal form of tretinoin over the traditional form in the treatment of moderate acne. The use of the nanostructured delivery system provided not only a more pronounced reduction in the GAGS index, but also a faster achievement of the therapeutic effect, a higher frequency of clinically significant improvement (⩾50% reduction in the GAGS score), and lower variability of results, which indicated better reproducibility of the effect in real clinical practice. The stratified analysis further demonstrated the efficacy of the drug even in patients with a higher initial severity, which expands the potential indications for the use of the nanoliposomal form of retinoid in dermatological practice.

Dynamics of changes in the number of inflammatory and non-inflammatory elements of the skin rash. The assessment of the quantitative dynamics of clinical manifestations of acne expanded the insight into the effectiveness of the used dosage forms of tretinoin in the study groups. A comparative analysis of the number of inflammatory (pustules, papules, nodules) and non-inflammatory elements (open and closed comedones) at three control points (day 0, week 6, week 12) revealed differences in the therapeutic effect between nanoliposomal and traditional forms of tretinoin.

At the beginning of the study, both groups demonstrated a comparable profile of clinical lesions. In group A, the average number of inflammatory elements was 22.8 ± 3.9, and 29.4 ± 4.6 non-inflammatory elements. In group B, the corresponding figures were 23.1 ± 3.7 and 28.9 ± 4.3. The intergroup differences did not reach statistical significance ($p > 0.05$), which indicated the initial clinical homogeneity of the sample. At week 6 of therapy in group A, a significant reduction in inflammatory elements was recorded to 13.6 ± 3.2, which corresponded to an average reduction of 40.3% ($p < 0.001$). Non-inflammatory elements decreased to 18.5 ± 3.9 (37.1% decrease; $p < 0.001$). In group B, the number of inflammatory elements decreased to 17.5 ± 3.6 (24.2% decrease) and non-inflammatory elements to 22.6 ± 4.1 (21.7% decrease), which was also statistically significant compared to the baseline ($p < 0.001$), but significantly lower compared to group A ($p < 0.01$). At week 12 of treatment in group A, the mean number of inflammatory elements was 8.2 ± 2.7, which corresponded to an overall decrease of 64% from baseline. Non-inflammatory elements decreased to 13.6 ± 3.4 (53.7% reduction). In group B, the values were 13.4 ± 2.9 (42% decrease) and 18.9 ± 3.6 (34.6% decrease), respectively. Comparative analysis confirmed a statistically significant predominance of the effect of the nanoliposomal form in both inflammatory ($p = 0.0003$) and non-inflammatory elements ($p = 0.0009$). The data are summarised in Table 2.

Table 2. The average number of inflammatory and non-inflammatory elements (pcs.) in patients of both groups in the dynamics of treatment (M ± SD)

Metric	Group	Day 0	Week 6	Week 12
Inflammation elements (number)	A	22.8 ± 3.9	13.6 ± 3.2	8.2 ± 2.7
	B	23.1 ± 3.7	17.5 ± 3.6	13.4 ± 2.9
Non-inflammation elements (number)	A	29.4 ± 4.6	18.5 ± 3.9	13.6 ± 3.4
	B	28.9 ± 4.3	22.6 ± 4.1	18.9 ± 3.6

Source: compiled by the author

The analysis of the dynamics of the number of clinical skin lesions showed a significant therapeutic advantage of the nanoliposomal form of tretinoin over the traditional one. The most pronounced effect in group A was observed already at the intermediate stage of treatment, indicating early suppression of the inflammatory process and activation of the comedonolytic mechanism. Such dynamics were clinically significant, as early reduction of inflammatory elements helps to reduce the risk of post-inflammatory hyperpigmentation and scarring. At the same time, the gradual, less pronounced reduction of rashes in group B indicated a limited permeability of the traditional dosage form and a slower rate of realisation of the therapeutic effect.

The rate of reduction of papulopustular elements, which are key markers of active inflammation, should be noted separately. In group A, more than 62% of patients demonstrated a >50% reduction in the number of inflammatory elements by week 6, whereas in group B, the corresponding figure was only 38% ($p = 0.0017$). This indicated a faster anti-inflammatory effect of the nanoliposomal form of tretinoin. The reduction in the number of comedones in group A was also statistically significant and more pronounced. The proportion of patients in whom the number of non-inflammatory elements decreased by ⩾50% was 54.2% in group A versus 31.7% in group B ($p = 0.0031$). This difference indicated a more effective comedonolytic and keratolytic elimination of follicular mouth hyperkeratosis with the use of a nanoliposomal preparation. In addition to quantitative changes, the distribution of elements in different anatomical zones was analysed. The most pronounced decrease in inflammatory elements in group A was recorded in the forehead (71.3%) and cheeks (68.4%), while in group B these figures were 48.2% and 46.9%, respectively. A similar trend was observed for non-inflammatory elements: in group A, the most pronounced improvement was in the chin area, which confirmed the systemic clinical response to the use of the nanoliposomal preparation.

Additional analysis revealed that at week 12, complete disappearance of inflammatory elements (0-1 residual lesions) was achieved in 28.3% of patients in group A, while in group B, this result was recorded in only 13.3% of cases ($p = 0.0095$). This indicator was considered an indicator of clinical remission, which is directly relevant to improving the quality of life of patients. Stratification analysis revealed that in patients with predominantly comedonal acne (more than 60% of lesions at baseline), clinical improvement at week 12 was significantly better in group A, where 67.9% achieved a ⩾50% reduction in the number of non-inflammatory elements, compared to 39.4% in group B ($p = 0.0024$). This led to the conclusion that the use of the nanoliposomal form of tretinoin is particularly appropriate for comedonal and mixed forms of acne. The comparative dynamics of achieving clinically significant changes in groups A and B were conducted based on four key parameters: reduction of inflammatory and non-inflammatory elements, achievement of clinical remission and efficacy in patients with comedonal acne (Fig. 1).

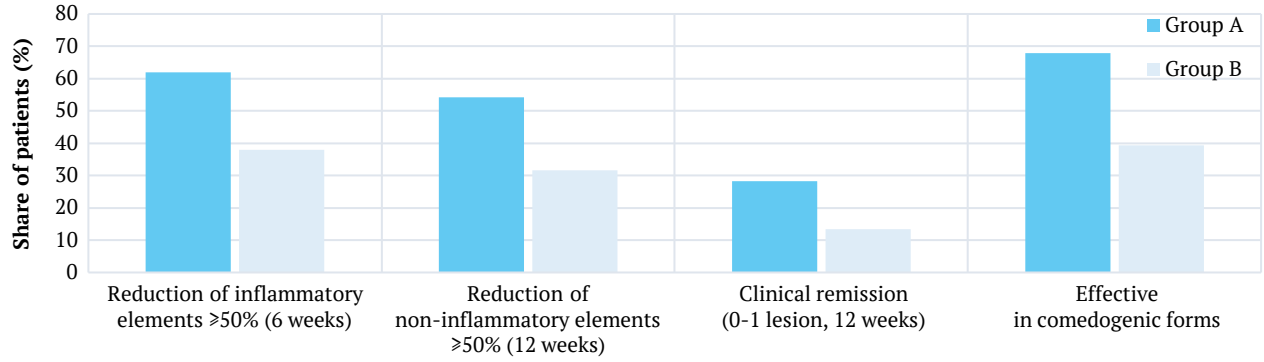

Figure 1. Comparative efficacy of nanoliposomal and traditional forms of tretinoin on key clinical indicators
Source: compiled by the author

Figure 1 illustrated the differentiated nature of the therapeutic response to nanoliposomal and traditional forms of tretinoin according to the main clinical criteria. The visible structural superiority of the nanostructured drug in all segments of the graph confirms its ability to provide rapid reduction of both inflammatory and non-inflammatory elements, achievement of remission and effectiveness in comedonal acne. Based on these features, it is possible to consider this formulation as more targeted in the context of heterogeneous manifestations of the disease. The analysed data confirmed that the nanoliposomal form of tretinoin provides not only a quantitative improvement in the main clinical parameters but also demonstrates the prognostic stability of the effect in different groups of

patients. Such pharmacodynamic stability is a key factor in the development of long-term strategies for the management of patients with acne, especially in cases of resistance to standard therapy or when it is necessary to minimise the systemic burden.

Subjective assessment of clinical improvement using the VAS scale. The subjective perception of the effectiveness of therapy was analysed based on the VAS scale at three time points. The initial scores were the same in both groups, but significant differences were found in the dynamics, which were used to compare the level of patient satisfaction with the use of different dosage forms of tretinoin.

At the baseline, both study groups demonstrated comparable levels of subjective self-esteem. In group A, the average value of the VAS scale was 2.1 ± 0.8 points, in group B – 2 ± 0.9 points, which did not indicate a statistically significant difference between them ($p > 0.05$). This indicated the homogeneity of the sample in terms of the initial level of satisfaction and confirmed the objective severity of acne as perceived by the patients themselves. At week 6 of therapy, there was a significant improvement in subjective scores in both groups, but the intensity of these dynamics varied significantly depending on the form of tretinoin. In group A, the mean VAS score increased to 6.4 ± 1.1 (change + 4.3 points; $p < 0.001$), while in group B it was only 4.9 ± 1.3 (change + 2.9 points; $p < 0.001$), which revealed a significant between-group difference ($p = 0.002$). This indicated a higher early satisfaction with treatment when using the nanoliposomal formulation. The analysis of the proportion of patients who rated the therapeutic effect at ⩾7 points (the threshold for subjective therapeutic satisfaction) also showed a significant advantage of group A, 51.7% versus 29.2% in group B ($p = 0.0034$). This indicator is especially relevant in clinical practice, as it is a marker of high patient motivation to continue to comply with prescriptions. At the final, 12th week of treatment, the level of subjective satisfaction reached its maximum values in both groups, but the gap between them remained. In group A, the mean VAS score was 8.1 ± 1, while in group B it was 6.3 ± 1.4 ($p = 0.0007$) (Fig. 2). The proportion of patients who reported a satisfaction level of ⩾7 points in group A was 78.3%, in group B, only 49.2% ($p = 0.0012$). Thus, in group A, almost twice as many participants achieved a high level of subjective efficacy of therapy.

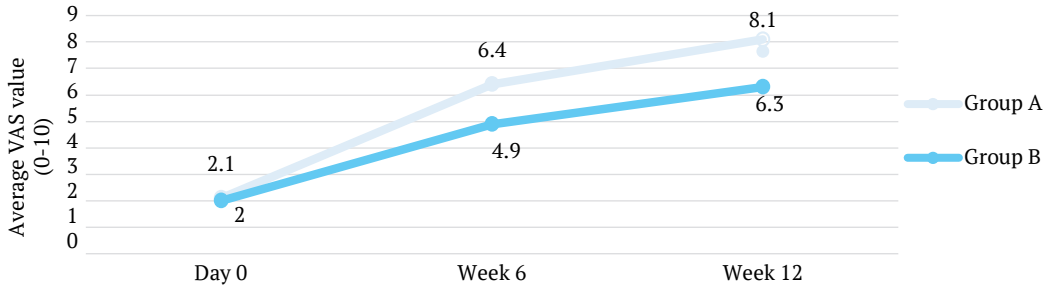

Figure 2. Dynamics of mean VAS values in groups A and B during treatment
Source: compiled by the author

Figure 2 illustrated a gradual increase in satisfaction scores in both study groups, but the curves have different steepness, indicating a faster subjective response in the case of nanoliposomal preparation. Visualisation of the dynamics also reveals the presence of a clinical plateau in group A after 6 weeks of treatment, while in group B, the growth is slower and without clear signs of reaching maximum efficacy. In addition to the main quantitative changes, additional stratified analyses were performed depending on the severity of acne at the start of treatment. In the subgroup of patients with moderate disease (GAGS 19-30) in group A, 82.4% of respondents reported satisfaction ⩾7 points at week 12, while in group B this figure was 53.6% ($p = 0.0018$). In the subgroup with severe acne (GAGS >30), treatment satisfaction was expressed in 71.9% of cases in group A versus 41.2% in group B ($p = 0.0027$). The superiority of the nanoliposomal formulation in terms of patient experience was demonstrated in both clinical subtypes. To summarise the results, it is worth noting that emotional perception of therapy was closely related to its clinical effectiveness, especially in the nanoliposomal group. The high satisfaction scores recorded regardless of acne severity indicate the potential of this formulation as a first-line strategy to increase patient adherence and long-term stability of results.

Assessment of tolerability and frequency of adverse reactions. Throughout the entire observation period, no cases of medication non-compliance or premature discontinuation without medical reasons were recorded in either group. All patients adhered to the prescribed therapeutic recommendations, which were confirmed by regular checking of self-observation diaries, standardised photographic recording of skin conditions, and examination during follow-up visits. Treatment tolerability was assessed based on the frequency and severity of localised adverse reactions that occurred in response to tretinoin. The most common symptoms were erythema, flaking, burning, itching, dry skin and the appearance of new inflammatory elements.

During the second week of therapy, the highest frequency of side effects was observed in both groups, which is typical for the induction phase of tretinoin treatment. In group B (traditional formulation), moderate or severe erythema was recorded in 47.5% of participants, while in group A (nanoliposomal formulation), this figure was only 31.7%. The incidence of complaints of dry skin reached 39.2% in group B versus 28.3% in group A. A similar picture was observed for other irritation symptoms: burning (36.7% vs 21.7%), peeling (42.5% vs 26.7%) and itching (24.2% vs 13.3%). In the subsequent dynamics (6 and 12 weeks), a gradual decrease in the intensity of side effects

was observed in both groups, but the level of symptom reduction was significantly higher in the nanoliposomal group. Thus, at the 12th week of treatment, the incidence of any side effects in group A did not exceed 12%, while in group B it remained at the level of 25-30%. The most persistent symptoms were dryness and peeling, indicating a cumulative and dose-dependent effect of tretinoin, but in group A, they were characterised by a predominantly mild degree of severity.

The intensity of adverse reactions, assessed on a 4-point scale, also confirmed the superiority of the nanoliposomal formulation. In group B, at week 2, more than 40% of patients scored ⩾2 for at least two symptoms (erythema, dryness), while in group A, the proportion of such patients was only 17%. By week 12, both groups showed a decrease in symptom intensity, but the mean score in group B remained higher for all indicators (e.g., mean value for peeling 1.6 ± 0.7 in group B vs. 0.8 ± 0.5 in group A). The emergence of new acne lesions as a form of reactive exacerbation was observed mainly in the early stages of treatment. In group B, such episodes were observed in 18.3% of cases, while in group A, only in 10%, and had a short duration. Such dynamics can be explained by the less aggressive keratolytic effect of the nanoliposomal formulation, which provided a more controlled release of the active substance. The frequency of discontinuation due to side effects was also lower in group A. In total, 2 patients (3.3%) in group A discontinued treatment prematurely, while 6 patients (10%) in group B discontinued treatment, mainly due to persistent irritation that could not be corrected by adjunctive emollient therapy. To compare the severity of local adverse reactions in the course of therapy in groups A (nanoliposomal tretinoin) and B (traditional form of tretinoin), an analysis was performed using a standardised 4-point scale. The results of the assessment are shown in Table 3.

Table 3. Severity of side effects in the dynamics of treatment (groups A and B)

Adverse reaction	Group	Week 2	Week 6	Week 12
Erythema	A	31.7	18.3	8.3
	B	47.5	35	22.5
Peeling	A	26.7	14.2	5
	B	42.5	31.7	15
Burning sensation	A	21.7	10.8	3.3
	B	36.7	24.2	10.8
Itching	A	13.3	5.8	1.7
	B	24.2	15.8	6.7
Dry skin	A	28.3	12.5	4.2
	B	39.2	25.8	12.5
New inflammations	A	10	4.2	0.8
	B	18.3	9.2	3.3

Source: compiled by the author

The analysis showed a higher tolerability of the nanoliposomal form of tretinoin, which is possibly related to its pharmaceutical structure: liposomal encapsulation reduced direct contact of the active substance with the skin, modulated its release and reduced the risk of local irritation. This was of key importance for the chronic course of the disease, when the duration of treatment and the need for good tolerability become crucial factors in the success of therapy. Thus, the nanoliposomal form of tretinoin provided an improved safety profile in terms of both the frequency and severity of side effects. Reduction in the number of intolerable reactions, less need for additional symptomatic correction and higher completion rate of the full course of treatment define this formulation as clinically preferable in the treatment of mild to moderate acne.

DISCUSSION

The interpretation of the data obtained can be used to compare the observed effects of the nanoliposomal form of tretinoin with the existing ideas about the pathogenesis of acne and the peculiarities of the action of topical retinoids. The analysis in comparison with the literature can be used to assess the degree of compliance of the results with the available evidence and to outline the potential benefits of the investigated drug for practical use. The study determined that the average GAGS score decreased in group A from 27.4 ± 2.8 to 11.3 ± 2.1 points, while in group B from 27.1 ± 2.6 to 15.8 ± 2.3 points during 12 weeks of treatment. In patients with a baseline GAGS level ⩾30, the achievement of mild acne was observed in 76.7% of patients in group A versus 41.6% in group B, which showed the effectiveness of the nanoliposomal form of tretinoin even in clinically burdened cases. A similar dynamic of the effectiveness of nanoliposomal systems was observed by V. Singh *et al.* [16], who showed that nanotechnological platforms increased the permeability of retinoids and provided an earlier clinical effect in patients with papulopustular acne. The study by J. Lalrengpuii *et al.* [17] found that retinoid nanoparticles reduced the time to achieve a therapeutic effect by about 30% compared to the standard form, which was qualitatively consistent with a faster reduction in GAGS in group A in this study. Z.M. Dos Santos *et al.* [18] demonstrated that long-term use of lipid nanotherapeutic systems led to a more stable remission in patients with moderate acne, which correlated with the lower variability of clinical response found in patients treated with nanoliposomal tretinoin. In addition, M.J. Tsai *et al.* [19] reported that liposomal forms of retinoic acid inhibited keratinocyte proliferation and destroyed the *Cutibacterium acnes* biofilm, which could be an additional mechanism for reducing the severity of acne observed in group A.

In the study, the number of inflammatory elements in group A decreased by 64% and non-inflammatory elements by 53.7%, which was significantly higher than in group B (42% and 34.6%). The proportion of patients with a reduction in inflammatory lesions of ⩾50% was 62% in group A versus 38% in group B, while a reduction in the number of non-inflammatory elements of ⩾50% was achieved in 54.2% of cases in group A and 31.7% in group B. Complete disappearance of inflammatory elements at week 12 was recorded in 28.3% of patients in group A compared with 13.3% in the control group. The obtained results correlated with the results of N. Mohsin *et al.* [20], who noted that nanostructured delivery systems demonstrated an earlier reduction of papulopustular elements in patients with moderate acne. A decrease in the effectiveness of traditional tretinoin on non-inflammatory elements was also noted by A.M. Bilovol & M.V. Kropivnyi [21], which corresponded to lower comedone reduction rates in group B in this study. As shown by H. Baldwin *et al.* [22], classical forms of retinoids provided slow dynamics of changes in mixed forms of acne, without achieving a high proportion of clinical remission, which contrasted with 28.3% complete disappearance of elements in group A. In turn, J. Zhong *et al.* [23] demonstrated that the inclusion of tretinoin in nanolipid carriers significantly increased comedonolytic activity due to improved penetration and reduced surface irritation, which could explain the significantly higher frequency of reduction of non-inflammatory elements in group A. The established superiority of nanoliposomal tretinoin was confirmed both quantitatively and anatomically, with the most pronounced effect in the forehead and cheeks, indicating a uniform transdermal distribution of the active substance.

In the dynamics of treatment, a significantly higher level of subjective satisfaction with therapy was found in the group of nanoliposomal tretinoin. At week 12, the mean VAS score was 8.1 ± 1 in group A, which was significantly higher than 6.3 ± 1.4 in group B ($p = 0.0007$). The proportion of patients who scored ⩾7 points for the treatment result was 78.3% in group A and only 49.2% in group B, and even in the subgroup with severe acne, satisfaction with therapy was achieved significantly more often in cases of using the nanoform (71.9% vs 41.2%). The positive subjective response of patients could be due to several factors, among which the reduced frequency of local side effects played a key role. The review by J.H. Saurat *et al.* [24] emphasised that the level of skin irritation directly affected the perception of the effectiveness of topical therapy, even with the same clinical dynamics. The lower intensity of erythema, burning and dryness in group A found in this study could explain the advantage of subjective assessment, especially in the early stages of treatment. Consistent with this, D.Z. Eichenfield *et al.* [25] reported that forms of retinoids with improved tolerability provided higher patient satisfaction already at 4-6 weeks of therapy, which is fully consistent with the results obtained in group A. According to M. Kassir *et al.* [26], selective retinoic acid receptor agonists demonstrated a better subjective tolerance profile, which emphasised the importance of receptor-specific and pharmacokinetic characteristics of the molecule for the formation of a positive patient experience. N. Wagner *et al.* [27] demonstrated that it was the reduction in the frequency of irritation reactions that was a leading factor in the formation of adherence to therapy and an increase in patient confidence, which is fully consistent with the high VAS scores in group A, even in patients with severe clinical forms of acne.

In the group treated with nanoliposomal tretinoin, a significantly lower frequency and intensity of local adverse reactions were recorded compared to the traditional formulation. Already at 2 weeks of treatment, the incidence of erythema, burning, dryness and peeling was 12-20% lower in group A, and at the final stage of therapy, side effects were recorded in less than 12% of patients compared to 25-30% in the control group. The mean value of peeling severity in group B was twice as high as in group A (1.6 ± 0.7 vs 0.8 ± 0.5), which was accompanied by a higher frequency of early discontinuation of therapy (10% vs 3.3%). A similar reduction in the irritant potential of nanostructured retinoids was demonstrated by A. Otlewska *et al.* [28], who reported that encapsulation of the active substance in liposomes reduced contact toxicity and provided a gradual release without peak concentrations on the skin surface. A systematic review by J. Kapała *et al.* [29] noted that a reduction in the incidence of side effects to <15% was associated with a better adherence profile, which was consistent with fewer treatment discontinuations in group A. The positive effect of lipid carriers on reducing irritation was also confirmed by the study by M. Pawłowska *et al.* [30], which showed that liposomal systems with retinol and peptides mitigated transepidermal stress and maintained physiological pH, which increased tolerability even with prolonged use. In addition, İ. Eroğlu *et al.* [31] showed that the combination of liposomes with moisturising components further neutralised cumulative dryness, which potentially explains the lower severity of this symptom in group A in the present study.

The efficacy of the nanoliposomal form of tretinoin observed in the study could be due not only to the physicochemical advantages of the delivery platform but also to its effect on key pathogenic mechanisms of acne. As noted by C. Mias *et al.* [32], chronic inflammation in acne lesions was mediated by the activation of Th17 lymphocytes, with intensive involvement of the IL-17-dependent pathway. Controlled delivery of tretinoin in the follicular zone could modulate this response by reducing the local expression of proinflammatory genes. In addition, the study by I. Cavallo *et al.* [33] demonstrated that Cutibacterium acnes biofilms, characteristic of recurrent acne, increased microbial resistance and reduced the effectiveness of standard topical agents. Liposomal carriers, due to their ability to penetrate the extracellular matrix of biofilms, provided targeted drug delivery and increased antimicrobial activity. According to M. Deng *et al.* [34], disruptions in intercellular interaction in the inflammatory microenvironment were important, due to overexpression of inflammatory regulatory genes in keratinocytes. Nanostructured platforms could potentially compensate for these mechanisms by prolonging the release of the active substance and avoiding local concentration peaks. A. Sedighidarijani *et al.* [35] additionally confirmed that lipid carriers with retinoids demonstrated efficacy in experimental acne modelling both *in vitro* and *in vivo*, which confirmed the universality of the mechanisms underlying the clinical results.

The results of the study confirmed the clinical feasibility of using the nanoliposomal form of tretinoin in patients with moderate acne. Convincing evidence of its advantages over the traditional formulation was obtained both in terms of objective efficacy (reduction of GAGS scores, reduction of inflammatory and non-inflammatory elements) and subjective assessment of patients. Reduced frequency and intensity of local adverse reactions resulted in better tolerance and higher adherence to treatment. Given the stable dynamics of the therapeutic response, especially in subgroups with more severe disease, nanoliposomal tretinoin can be considered an effective and safe alternative for long-term topical acne therapy with a high potential for widespread clinical use.

CONCLUSIONS

During 12 weeks of treatment, both forms of tretinoin demonstrated a reduction in the clinical severity of acne, but the nanoliposomal form provided a significantly more pronounced effect. A 58.8% reduction in GAGS scores in group A was accompanied by less variability in response and a higher frequency of mild acne, especially in the subgroup of patients with more severe initial courses. This indicates the increased therapeutic activity of the nanostructured form and its ability to provide a clinical response even in difficult clinical cases. Both forms of tretinoin helped to reduce the number of inflammatory and non-inflammatory lesions, but in patients of group A, the reduction was significantly higher. This was true for both inflammatory elements (64% vs 42%) and non-inflammatory elements (53.7% vs 34.6%), indicating the universal efficacy of the nanoliposomal formulation. The frequency of achieving a reduction of ⩾50% was higher in group A, and the complete disappearance of inflammatory elements was recorded almost twice as often. Such dynamics indicate the simultaneous effect of the nanoparticle form on the key pathogenetic links of comedogenesis and inflammation.

The VAS score confirmed high subjective satisfaction with nanoliposomal tretinoin treatment. In the dynamics of therapy, this formulation was consistently associated with higher scores (8.1 ± 1 vs 6.3 ± 1.4 at week 12) and with a higher proportion of patients who perceived the results positively (78.3% with VAS ⩾7 in group A). This was especially noticeable in patients with severe disease, where satisfaction scores were 30% higher. This indicates a close relationship between clinical improvement, tolerability and positive patient assessment of therapy when using the nanoformulation. The safety profile of the nanoliposomal formulation of tretinoin was significantly better than that of the traditional formulation. A reduction in the incidence of side effects such as erythema, flaking, burning and dryness was evident already at week 2 of treatment. By the end of the course of therapy, adverse reactions in group A were observed in less than 12% of patients, which is almost twice as low as in group B. The average severity of peeling was two times lower, and the frequency of treatment discontinuation due to intolerance was three times lower. Such indicators indicate better dermatological tolerance and potentially higher adherence to long-term therapy when using the nanoformulation. The main limitation of the study is the limited period of observation (12 weeks), which excludes conclusions on the duration of clinical remission, the frequency of relapse and the long-term safety of the nanoliposomal form of tretinoin in chronic acne. Further studies should include long-term prospective follow-up to assess the durability of the therapeutic effect, the inclusion of inflammatory and microbiota biomarkers to better determine the mechanisms of action, and the expansion of the sample by age and acne phenotypes to increase the extrapolation value of the results.

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CONFLICT OF INTEREST

None.

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Оцінка ефективності наноліпосомальних форм ретиноїдів у лікуванні акне

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Анотація. Метою дослідження було визначення клінічної ефективності та профілю переносимості наноліпосомальної форми третиноїну у пацієнтів з акне середнього ступеня. Дослідження проводилося як рандомізоване контрольоване дослідження за участю 120 пацієнтів з акне середнього ступеня на кафедрі дерматовенерології, алергології, клінічної та лабораторної імунології Національного університету охорони здоров'я України імені П. Л. Шупика; протягом 12 тижнів порівнювали клінічну динаміку, суб'єктивну оцінку ефективності та частоту побічних реакцій з наноліпосомальною та традиційною формами третиноїну. У пацієнтів, які отримували наноліпосомальний третиноїн, спостерігалося зниження тяжкості клінічного акне на 58,8 %, що свідчить про вищу терапевтичну ефективність порівняно з традиційною формою, де зниження становило лише 41,7 %. У цій групі кількість запальних елементів зменшилася на 64 %, а незапальних елементів – на 53,7 %, тоді як у контрольній групі відповідні показники становили 42 % та 34,6 %, що підтверджує здатність наноформи впливати як на комедогенез, так і на запальні процеси. Повного зникнення запальних уражень було досягнуто у 28,3 % пацієнтів основної групи, що більш ніж удвічі перевищувало показники групи традиційного третиноїну. Суб'єктивна оцінка ефективності лікування була значно вищою серед користувачів наноформ (8,1 проти 6,3 балів), що свідчить про кращу задоволеність результатом. Побічні реакції виникали менш ніж у 12 % учасників основної групи, тоді як у групі порівняння їх частота перевищувала 25 %, що свідчить про вищу дерматологічну переносимість наноліпосомального препарату. Отримані результати можуть бути використані дерматологами для обґрунтованого вибору місцевої терапії акне, зокрема при призначенні сучасних форм третиноїну пацієнтам з гіперчутливістю шкіри або низькою переносимістю до традиційних препаратів

Ключові слова: шкіра; комедони; запалення; третиноїн; лущення; побічна реакція; непереносимість