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Current issues of acne treatment

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Abstract

Purpose of the study: to analyze isotretinoin (Verocutan®) efficacy and safety in patients with moderate-to-severe juvenile and adult acne with various administration regimens. Materials and methods. 83 patients aged 12-43 with acne of variable severity were chosen for the study. Depending on the degree of severity (clinical form of the disease) and daily isotretinoin (Verocutan®) dose, the patients were divided into 4 groups. Efficacy was evaluated based on IGA and DQoL indices; special methods included corneometry and sebumetry; safety monitoring included blood biochemistry test, pregnancy test in females of child-bearing age, and adverse events. Study results: isotretinoin (Verocutan®) in different doses decreases sebum production on average by 50% in 3 months (according to sebumetric data), which promotes the achievement of IGA 0 and quality of life increase more than in 90% patients. Conclusion: 0.5 mg/kg Verocutan® is recommended for administration in moderately severe juvenile and adult acne with treatment duration of 8-10 months (during the first month, isotretinoin 20 mg may be administered to decrease the severity of predictable side effects). 0.8-1.0 mg/kg Verocutan® is recommended for administration in severe acne; if persistent clinical effect (IGA 1) is achieved during one month, isotretinoin dose can be decreased by 10 mg (in daily equivalent) every 2-3 months. Recommended treatment duration is 12 months. Low-dose regimen is recommended for patients with excoriated acne (0.2-0.3 mg/kg during the whole treatment cycle of 6 months).

Key words: juvenile acne, adult acne, excoriated acne, isotretinoin, sebumetry, corneometry, IGA, DQoL index.

Acne is one of the most common chronic dermatological inflammatory diseases, which is detected in 85% adolescents and sometimes in adults (approximately 10% population) [1].

According to modern theories of acne development, the main pathogenetic events include inflammation, sebum hyperproduction, follicular hyperkeratosis, P. acnes colonization. The point of inflammatory process application in acne are sebaceous glands. The sebaceous gland is currently considered not only a skin derivative producing sebum, but also an important regulatory organ with endocrine functions, providing for thermostatic and barrier skin functions. Besides, the sebaceous gland indirectly affects the organization of superficial skin lipids and follicular differentiation [2]. Sebaceous glands are hormone-dependent structures. As currently known, sebocyte membrane contains several types of nuclear receptors: steroid and thyroid receptors; receptors to retinoic acid, vitamin D, peroxisome proliferation activator, liver X-receptor [3]. Sebaceous glands are mostly regulated by androgens, specifically free testosterone. But 90% testosterone circulating in blood is bound with sex-steroid binding globulin (SSBG). Only in sebocytes angrogens are metabolized into free testosterone with the help of 17β- and 3β-hydroxysteroid dehydrogenase enzymes; type I 5α-reductase converts free testosterone into dehydrotestosterone (DHT). DHT stimulates sebum production and sebocyte maturation. Thus, it is safe to conclude that increased activity of 5α-reductase enzyme, increased amount of DH-receptors, or decreased SBBG synthesis (with subsequent increase of free testosterone level in blood) lead to increased function of sebaceous glands [4]. According to observations, the majority of acne patients do not demonstrate increased total testosterone level, but testosterone conversion into DHT increases 20-30-fold [5].

The majority of authors share the view that increased sebaceous gland function and sebum hyperproduction are main pathogenetic factors of acne development [6]. As sebocytes produce free fatty acids that damage sebaceous gland walls even without P. acnes action, inflammation of sebaceous glands theoretically can be aseptic, so the value of bacterial factor in acne development is somewhat overestimated.

A large number of studies performed indicate that quality of sebum is also altered in conditions of increased sebaceous gland activity and increased sebum amount [7]. When sebum is diluted, linoleic acid concentration decreases, which shifts pH to alkaine values and enables increased epidermal permeability. As one of α-linoleic acid functions is suppression of transglutaminase enzyme that regulates keratinocyte differentiation, decreased concentration of this unsaturated fatty acid in sebum ethers leads to predominance of keratinization over desquamation, retention hyperkeratosis in the follicular ostium, and sebaceous gland obstruction [8].

Jeremy A.H., Holland D. et al. demonstrated that α-linoleic acid deficiency was associated with production of IL-1α, which is an important pro-inflammatory factor [9]. Besides, decreased linoleic acid concentration increases permeability of sebaceous & hair follicles for inflammatory factors. Thus, subclinical inflammation which may precede comedone formation should be

considered primary. Congenital immunity activation in acne is accompanied with increased expression of TLRs (toll-like receptors) located on immune competent and epithelial cells of the skin; skin CD4+ lymphocytes and macrophages are activated, with subsequent increased synthesis of cytokines (interleukin (IL)-1α, IL-6, IL-8, IL-12), which in turn cause inflammatory response; antibodies are also synthesized (delayed-type hypersensitivity pattern) [10]. These changes play an important role not only in the development of inflammatory process, but also in stimulation of sebaceous glands and comedone formation [11].

Yamamoto A. and Takenouchi K. detected increased transepidermal water loss (TEWL) and corneal layer dehydration in all patients with acne. Besides, decreased total ceramides and free sphyngosine were also detected, which confirmed impaired function and structure of the intercellular lipid membrane [12]. This means that impaired skin barrier is more likely a consequence rather than the cause of the disease, being a result of increased sebaceous gland function.

Thus, acne pathology is multifactorial, including hormonal androgen impact, along with excessive sebum production, impaired keratinization, inflammation, and stimulation of congenital immune system with several pathways, including hypercolonization with P. Acnes.

Following the modern concept of acne development, the treatment should primarily target the elimination of inflammation, follicular hyperkeratosis, sebum production regulation, and elimination of P. Acnes. In 2018, the following Practical Guidelines for clinicians were published regarding acne treatment: International Consensus of the Global Alliance for Acne Treatment Result Improvement [13]. These recommendations contain the most up-to-date information on patient management. One of the main provisions in these guidelines regards the limited use of systemic and topical antibiotics due to the increasing antibiotic resistance issue [14]. According to recommendations, oral isotretinoin is the first-line drug for severe acne (cystic and conglobate acne). The experience confirms that isotretinoin can also be administered in severe papulopustular acne and in those cases where antibiotic and topical therapy is ineffective.

Issues of dose cumulation and systemic retinoid treatment duration are still being discussed. The majority of authors recommend treatment for at least 4-6 months, with achievement of complete acne resolution, though achievement of the cumulative dose (120-150 mg/kg) does not always correlate with the absence of relapses. At the same time, in patients with moderately severe and severe acne, long-term administration of daily doses less than 0.5-1.0 mg/kg can provide reliable results, as well as the use of the first-line drug without previous failed topical or systemic antibiotic therapy [15-17].

Thus, the current drug of choice for systemic acne treatment is isotretinoin, which has proven its efficacy and safety. High treatment cycle cost is considered one of the disadvantages of systemic isotretinoin. It is important to note that pharmacoeconomy has a significant impact on the treatment compliance of patients. High drug cost, especially in long-term treatment, negatively affects compliance - cases of therapy interruption or discontinuation are not so rare. In 2015, a new Russian isotretinoin drug - Verocutan® (MA No. LP-002988 dated May 07, 2015) was registered; it is manufactured in 10 and 20 mg capsules. The cost of Verocutane treatment cycle is 1.5-2 times lower than analogous drugs. An open randomized crossover study of comparative pharmacokinetics and bioequivalence was performed with drugs Vero-isotretinoin (20 mg capsules, Verofarm OJSC, Russia) and Roaccutane (20 mg capsules, R.P. Sherer, Germany). The comparison showed that pharmacokinetic parameters of those drugs did not differ significantly. According to formal criteria, drugs are bioequivalent, which allows to recommend Verocutan® for acne treatment [18].

Purpose of the study: to analyze isotretinoin (Verocutan®) efficacy and safety in patients with moderate-to-severe juvenile and adult acne with various administration regimens.

Materials and methods

83 patients with variable acne severity participated in the study. This included 49 (59.03%) females and 34 (40.97%) males. Patients' age varied from 12 to 43. Juvenile acne (moderate and severe papulopustular acne) were diagnosed in 46 (55.4%) patients, while adult acne (including excoriated acne) - in 37 (44.6%) patients. Depending on the degree of severity (clinical form of the disease) and daily isotretinoin (Verocutan®) dose, patients were divided into 4 groups (Table 1).

Patients from Groups 1 and 3 were administered low isotretinoin (Verocutan® 20 mg) doses (daily dose 0.3-0.4 mg/kg) to decrease predicted side effects that appear during the 1st month of administration to the largest extent; subsequently, patients were administered the drug in the 0.5 mg/kg dose. In Group 2, patients with severe acne were administered 0.8-1.0 mg/kg doses; when persistent clinical effect (IGA 1-0) was achieved during the final month, isotretinoin dose was decreased by 10 mg (in daily equivalent) every 2-3 months. In Group 4 (patients with excoriated acne), low-dose regimen (0.2-0.3 mg/kg) was used during the whole treatment cycle (6 months) (Table 1). All patients used basic therapy - special cosmetics, including skin cleansing and moisturizing agents.

Table 1

Clinical characteristics of patients and Verocutan® administration regimens

Group	Age (years) *M±m*	Severity/ clinical form of acne	Isotretinoin dose during the 1st month	Isotretinoin dose since the 2nd month	Duration of treatment
Group 1 n=25	15,3±1,7	Moderately severe (IGA 3) juvenile acne	20 mg	0,5 mg/kg	8 months
Group 2 n=21	16,2±0,6	Severe (IGA 4) juvenile acne	0,8-1,0 mg/kg	0,8-1,0 mg/kg	12 months
Group 3 n=20	32,1±2,8	Moderately severe (IGA 3) adult acne	20 mg	0,5 mg/kg	10 months
Group 4 n=17	34,5±1,5	Excoriated acne (IGA 2-3)	0,2 – 0,3 mg/kg	0,2 – 0,3 mg/kg	6 months

Efficacy was evaluated using clinical examination methods: IGA (Investigators Global Assessment) index, DQoL (Dermatological Quality of Life) index; and special methods: corneometry (Corneometer® CM 825, Courage & Khazaka), sebumetry (Sebumeter® SM 815, Courage & Khazaka). Parameter values in persons age-matched with study participants, but without skin lesions were taken as normal values.

The study endpoints included 1, 2, 3 months of treatment and end of treatment (6 or 12 months depending on the study group).

Safety monitoring included blood biochemistry test (before treatment, 2 and 6 months after treatment onset) - levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, triglycerides, cholesterol profile; pregnancy test in females of child-bearing age (contraceptive period duration after treatment - 1 month); adverse events (xerosis, cheilitis, mucosal dryness, retinoid dermatitis, conjunctivitis, musculoskeletal complaints).

Digital data for clinical and special investigation methods were input into Excel tables and processed using Statistica 10 software (MS Office Excel 2010). Quantitative values are presented as M ± m, where M is selected mean arithmetic, and m is standard error of mean. Qualitative values are presented as frequencies and percent. Student t-test is used to compare samples with normal distribution.

Study results

Efficacy was evaluated by inflammatory elements (papules, pustules, nodules, cysts) and retention elements (open and closed comedones). Proportion of patients with achieved IGA 0 effect in Group 1 (n=25) in 6 months was 76%, and in 8 months - 92% (Figure 1).

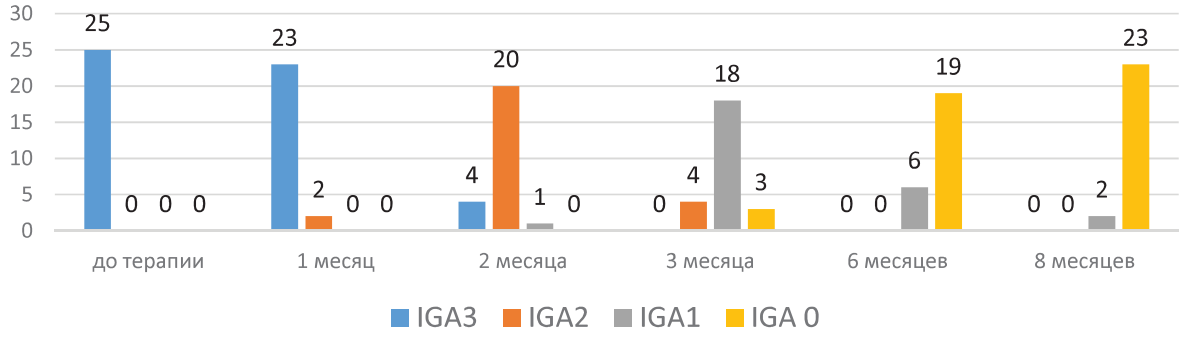

Figure 1. Details of clinical symptom changes (IGA) in Group 1 patients against the background of Verocutan® administration.

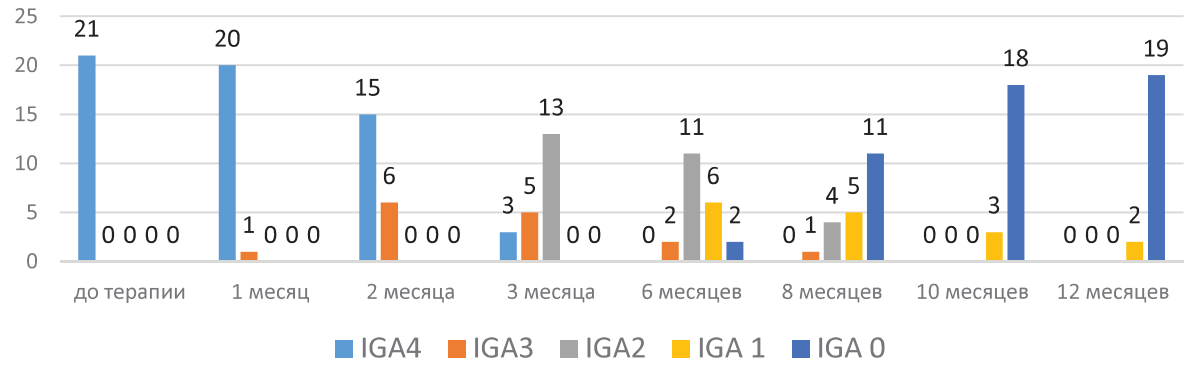

Figure 2. Details of clinical symptom changes (IGA) in Group 2 patients against the background of Verocutan® administration.

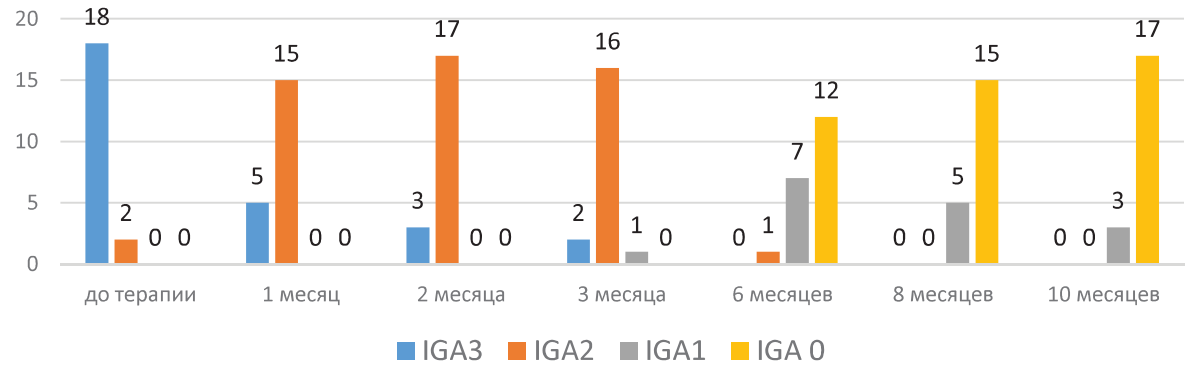

Figure 3. Details of clinical symptom changes (IGA) in Group 3 patients against the background of Verocutan® administration.

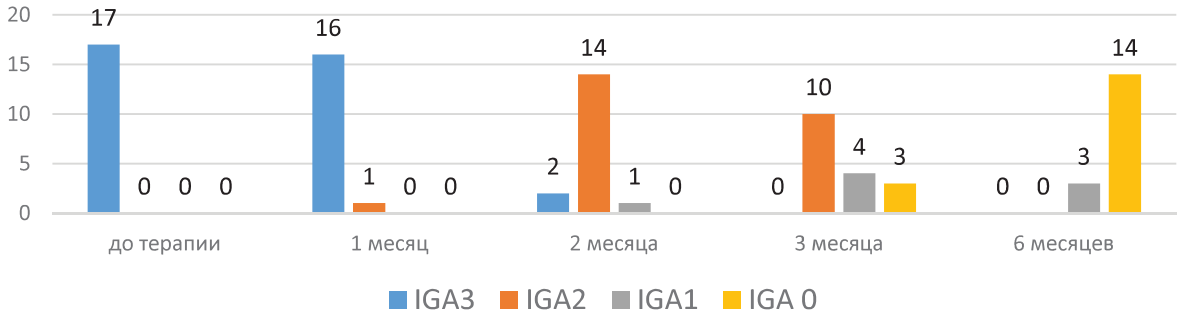

Figure 4. Details of clinical symptom changes (IGA) in Group 4 patients against the background of Verocutan® administration.

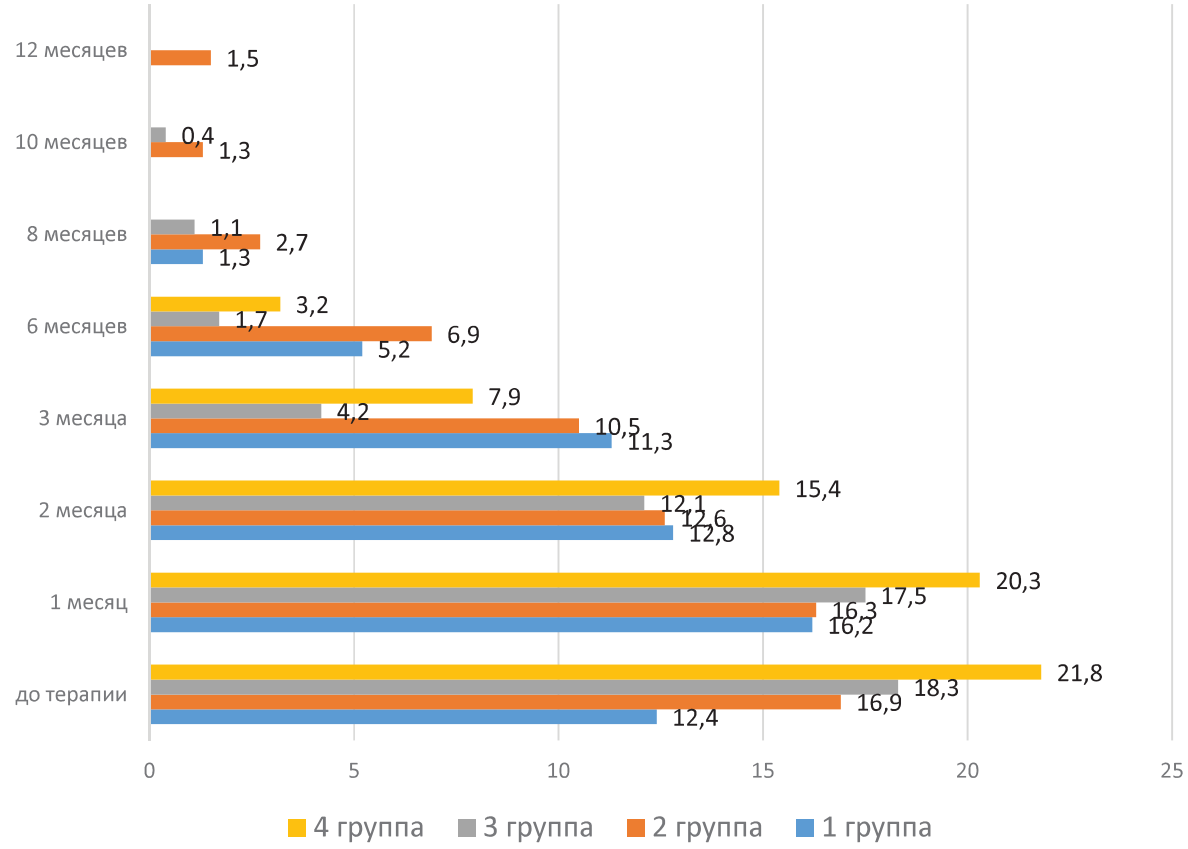

Figure 5. Details of DQoL index (point) changes in patients with acne against the background of Verocutan® administration.

Proportion of patients with achieved IGA 0 effect in Group 1 (n=21) in 6 months was 9.5%, in 8 months - 52.4%, in 10 months - 85.7%, and in 12 months - 90.5% (Figure 2). Thus, in patients with severe acne, "clear" skin (IGA 0) and "almost clear" skin (IGA 1) achievement was comparable with Group 1 patients, but developed later, which justifies the necessity of long-term cycles (>6 months) in this patient category.

Proportion of patients with achieved IGA 0 effect in Group 3 (n=20) in 6 months was 60.0%, in 8 months - 75.0%, in 10 months - 85.0% (Figure 3). Thus, in patients with moderately severe acne, "clear" skin (IGA 0) and "almost clear" skin (IGA 1) achievement was comparable with Group 1 patients.

Proportion of patients with achieved IGA 0 effect in Group 4 (n=17) in 6 months was 82.4% (Figure 4). Thus, in patients with excoriated acne, "clear" skin (IGA 0) and "almost clear" skin (IGA 1) achievement was comparable with Group 1 patients.

Changes of QoL index depended on the patient's age and disease severity (Figure 5). Before treatment, the most significant negative disease impact on quality of life was detected in the group of patients with excoriated acne (Group 4) - 21.8±1.3 points; in patients with moderately severe adult acne, parameters were worse (18.3±1.1) than in juvenile acne (12.4±2.3). According to changes of DQoL index in Group 1, deterioration was detected 1 month later - the index increased by 30.6%, which was likely related to overestimated effect expectancy or development of predictable side effects, although changes were positive in both groups. At the end of treatment cycle, the index decreased in Group 1 by 89.5%, in Group 2 – by 91.1%, in Group 3 – by 97.8%, in Group 4 – by 85.3% (Figure 5).

The main pathological event in acne is sebum hyperproduction. The study analyzed the evaluation of sebumetric values in patients depending on isotretinoin administration regimens (Table 2). Statistically significant changes in Groups 1, 3, 4 were obtained already after a single month of treatment ($p<0.05$). After 3 months of treatment, changes in all groups exceeded 50%, and the values were normal.

Skin moisture before treatment was decreased, mainly in patients with adult acne ($p<0.05$). After 1 month of treatment, despite regular use of specialized cosmetics, the parameter significantly decreased by 26.1-36.9% ($p<0.05$). Moisture recovery was detected from the 3rd month of treatment, and at end of treatment it was either normal or increased (Group 4) (Table 3).

During safety monitoring, which included blood biochemistry test (before treatment, 2 and 6 months after the onset of treatment), AST, ALT, alkaline phosphatase, triglyceride parameters tended to increase in 3-6 months in several (20.0%) Group 2 patients, but baseline values were exceeded by maximum 20%, which confirms dose-dependent direct correlation (in this group, patients were administered 0.8-1.0 mg/kg isotretinoin for 2-6 months, with subsequent dose decrease). These negative changes did not require drug discontinuation.

The following adverse events were detected during months 1-2: xerosis (45.8%), cheilitis (22.9%), mucosal dryness (13.3%), retinoid dermatitis (9.6%); they were infrequently observed due to low doses during the 1st month (Groups 1, 3, 4) and the use of specialized cosmetics, being predominantly registered in Group 2 patients (0.8-1.0 mg/kg dose).

Table 2

Changes of sebumetric parameters against the background of Verocutan® administration in various doses

Group/ age-specific normal values	Before treatment	1 month / changes	2 month / changes	3 month / changes	End of treatment (6-12 months) / changes
Group 1/49.6±5.7	89.6±10.2*	70.3±5.1**/21.5%	61.3±8.2**/31.6%	41.5±10.7**/53.7%	40.6±6.3**/54.7%
Group 2/49.6±5.7	92.3±7.8*	85.5±8.2/7.4%	70.3±5.4**/23.8%	40.8±11.4**/55.8%	41.8±5.7**/54.7%
Group 3/38.4±6.9	78.4±10.7*	55.2±11.6**/29.2%	40.1±8.2**/48.6%	32.4±5.9**/58.5%	30.6±2.4**/60.8%
Group 4/38.4±6.9	80.6±9.5*	65.6±8.7**/17.9%	42.4±5.8**/46.9%	33.6±5.1**/58.3%	31.3±4.9**/61.2%

Note: * compared with normal values, $p<0.05$ ** compared with values before treatment, $p<0.05$.

Table 3

Changes of corneometric parameters against the background of Verocutan® administration in various doses

Group/ age-specific normal values	Before treatment	1 month / changes	2 month / changes	3 month / changes	End of treatment (6-12 months) / changes
Group 1/ 66.7±8.9	65.1±2.3	41.0±2.6**/ -36.9%	40.3±2.5**/ - 38.1%	57.8±3.6**/ -11.2%	64.1±3.7/ -
Group 2/ 66.7±8.9	60.2±1.7	44.5±2.9**/ -26.1%	43.3±2.9**/ -28.1%	51.0±2.6**/ -15.3%	56.3±3.8/ -6.6%
Group 3/ 57.6±3.4	50.5±2.1*	31.4 ±2.5**/ -37.8%	29.5±2.3**/ -41.6%	33.7±2.5**/ -33.3%	51.7±4.1/ -
Group 4/ 57.6±3.4	49.4±2.1*	33.6±2.4**/ -31.9%	29.7±3.1**/ -39.9%	41.4±5.8/ -15.5%	54.4±3.5/ +9.2

Note: * compared with normal values, $p<0.05$ ** compared with values before treatment, $p<0.05$.

Conclusions

1. Isotretinoin (Verocutan®) administered in various doses decreases sebum production (according to sebumetric data) on average by 50% in 3 months. Low isotretinoin doses (0.2-0.3 mg/kg) during the first month in patients with moderately severe acne and during the whole therapy cycle in patients with excoriated acne, as well as the use of specialized cosmetics allow to decrease the frequency and severity of predictable side effects (xerosis, cheilitis, retinoid dermatitis).

2. 0.5 mg/kg Verocutan® is recommended for administration in moderately severe juvenile and adult acne, with treatment duration of 8-10 months (during the first month, isotretinoin 20 mg may be administered to decrease the severity of predictable side effects).

3. 0.8-1.0 mg/kg Verocutan® is recommended for administration in severe acne; if persistent clinical effect (IGA 1) is achieved during one month, isotretinoin dose can be decreased by 10 mg (in daily equivalent) every 2-3 months. Recommended treatment duration is 12 months.

4. Low-dose regimen is recommended for patients with excoriated acne (0.2-0.3 mg/kg during the whole treatment cycle of 6 months).

5. Verocutan® in patients with moderate-to-severe acne is well tolerated and can be considered safe. Skin and mucosal adverse events are quite frequent, but transient (their severity significantly decreases when using low doses (0.2-0.3 mg/kg) during the 1st month of treatment in patients with moderately severe acne); they can be well-controlled with topical moisturizers and do not require drug discontinuation.

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