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Pharmacotherapy of acne: an overview of current therapies

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The review summarized and systematized the existing international data on the pharmacotherapy of acne and recommendations on the patient surveillance.

Keywords: acne, pathophysiologic mechanisms, clinical manifestations, recurrent acne, recommendations on pharmacotherapy.

Improvement of treatment and prevention of acne is one of the priorities of dermatology and cosmetology in connection with chronic relapsing course of the disease and significant decrease in the quality of life regardless of the area type of rash. The process is often accompanied by the development of psychological and social maladjustment, depression, anxiety, and dysmorphophobia [1, 2].

Psychological and social consequences of this disease are sometimes underestimated by both dermatologists and other medical specialists [3].

According to several epidemiological studies, 50—95% of adolescents in the developed countries suffer from acne. Of these, about 70% have mild to moderate acne. Acne is an inflammatory skin disease caused by changes in the pilosebaceous structures. The social significance of acne is characterized not only by its prevalence in the world, but also formation of secondary skin lesions, postacne, associated with scarring [4].

In recent decades, various researchers reported numerous data on the role of *Propionibacterium acnes* in the pathogenesis of acne. The following effects were reliably established and studied: stimulation of proliferative activity of the cells of sebaceous follicle ostium due to increased level of abnormal keratins; epidermal cell differentiation disorders, increase in their adhesion; stimulation of sebum production processes, where sebocytes are affected in the retention phase. They also studied the immune mechanisms of the formation of acne. In particular, *P. acnes* cause activation of the toll-like receptors TLR-2 and TLR-4, antimicrobial peptides, matrix metalloproteinases, activation of the synthesis of proinflammatory cytokines interleukin-1α, interleukin-1β, interleukin-6, interleukin-8, interleukin-12, and tumor necrosis factor-α by immunocompetent skin cells and epidermal cells. This results in formation of local inflammatory process, its persistence and destruction of the dermal matrix [5,6]. Proinflammatory cytokines IL-8 and TNF-α play a key role in the maintenance of inflammatory reactions [7].

Follicular hyperproliferation and blockage, increased sebum secretion, activity of *P. acnes*, and inflammation are the main stages of the development of acne [8].

According to modern classification of acne, there are the following main forms of the disease:

- comedonal form is mainly represented by local non-inflammatory elements (closed comedones) mostly localized on the central part of the face;
- papulopustular form is represented by both open and closed comedones mostly localized on the central part of the face and cheeks; along with comedones, there is a small number of pustules;
- nodular form is mostly represented by inflammatory elements (pustules), up to 25 pieces, sometimes along with a small amount of comedones;
- acne conglobata is a severe form of the disease, where pustules merge to form nodes, cause inflammation of the surrounding skin areas; this form is associated with high risk of scarring [9].

Formation of comedonal acne is the first clinical sign of the onset of the disease [10].

Non-inflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, or nodules) are the major manifestations of acne [11]. Currently, acne is treated taking into account a number of clinical factors, such as severity of the disease, morphology of rash elements, their number and extent, the results of previous treatment, as well as data about the adverse effects of previously used drugs [1].

According to many researchers, antibiotic resistance of acne is one of the significant potential causes of treatment failure. This is further complicated by the fact that neither European nor Russian modern clinical guidelines mention the possibility of monotherapy for acne with antibiotics. The data on the increase in the number of *P. acnes* strains resistant to many broad-spectrum antimicrobials have been reported at the end of the 20th century [12]. The resistance was typically detected in patients with moderate to severe acne. The researchers attribute the development and spread of antibiotic resistance to

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iatrogenic causes, in particular, incorrect regimen of pharmacotherapy, deviations from the recommended treatment regimen in the form of reduced antibiotic dose, frequent courses of treatment with these drugs, prolonged courses of antibiotic therapy, and free availability of drugs to patients due to OTC sales in some countries [1].

The use of the coformulated drugs is the most effective treatment in terms of improvement of clinical efficacy of the therapy, reduced risk of antibiotic resistance of *P. acnes*, and increase in compliance [13]. The use of coformulated drugs with complementary mechanisms of action is believed to be the most effective. Combinations of drugs or active substances in a drug product increase the number of affected pathogenetic elements of acne, in particular follicular hyperkeratosis, colonization by *P. acnes,* and inflammatory skin reaction [14].

Severe forms of acne necessitate administration of systemic antibiotics. A number of methods, whose efficacy was not fully proved, were previously used. These methods include autohaemotherapy, antistaphylococcal gamma globulin, vitamin A, and estrogens [9]. Apart from vitamin A, administration of polyunsaturated fatty acids, such as omega-3, is effective [9].

Combined estrogen-progestin preparations are Also effective. Hormonal therapies are relevant not only in patients with laboratory-confirmed hyperandrogenism, but in the case of severe, treatment-resistant acne with high recurrence rate [15].

In combined estrogen-progestin formulations, estrogen is usually represented by ethinylestradiol and, more rarely, by mestranol. Chlormadinone, drospirenone, and 19-nortestosterone derivatives are the most commonly used progestines. These components interact with testosterone receptors. Testosterone derivatives have androgen-like action. They contribute to the development of acne, cause irritability and fatigue [15].

High doses of estrogen have sebosupressive effect, but isolated administration and high doses are associated with a high risk of adverse effects. Marketed combined oral contraceptives (COCs), as a rule, contain low doses of estrogen. These COCs have no sebosupressive effect, but compensate for hyperandrogenism in other ways:

- inhibit production of pituitary gonadotropic hormones, inhibit ovulation, thereby reducing production of androgens by the ovaries;
- block androgen receptors;
- stimulate hepatic secretion of the globulin binding sex hormones and reduce testosterone secretion;
- progestins included in the formulation inhibit 5α-reductase activity, thereby inhibiting formation of active androgens [16].

The effectiveness of oral contraceptives in treatment of acne was confirmed by numerous studies [17]. Furthermore, these effects may be "masked" by intake of these drugs for other indications, while preventing the development of acne. However, it is important to note that previous studies have shown that formulations containing only progestin, etonogestrel, and levonorgestrel may worsen the symptoms of acne [18].

Spironolactone can be used as a potential sebogenesis inhibitor and antiandrogen, which is a possible alternative to oral isotretinoin and COC and reduces the risk of side effects associated with intake of these drugs [18]. Several studies demonstrated the efficacy of oral spironolactone in the treatment of acne in middle-aged females [19].

To date, the data of about 10 randomized controlled trials on the effectiveness of spironolactone in patients with recurrent acne are available and there are three published articles about side effects of spironolactone in treatment of acne in females [20,21]. However, there are no summarized data on long-term outcomes.

All 10 studies were single-site and were carried out in Canada, Bangladesh, Thailand, Israel, and China (one study), the UK (two), and India (three). The severity of acne varied from mild to severe and was not specified in four studies [20]. In seven studies, acne elements were localized only on the face. [22]

Funding sources of six studies are unknown, one study was funded by the manufacturer of spironolactone, two studies were funded by other organizations [22] not related to the manufacturer, and one study was not supported by pharmaceutical companies [20]. Information about the absence of conflict of interests has been provided in two studies [20, 22].

No cases of increased blood potassium level in females were observed in seven studies that assessed changes in blood potassium level (due to the risk of hyperkalemia) [20, 22]. Similar data were obtained by Plovanovich M. et al., who carried out a retrospective analysis of blood potassium level in 974 females aged 18—45 years, who received spironolactone at a dose of 50—200 mg/day as the therapy for acne. The study was carried out in two research centers in the United States within the period from December 2000 to March 2014 [21].

Based on these data, the researchers concluded that no regular monitoring of blood potassium level is required in females taking spironolactone to treat acne [21]. In the study by Saint-Jean M. et al., the efficacy of spironolactone (75—150 mg/day) in the treatment of acne was observed in 14 females [23].

When comparing the effectiveness of anti-androgens flutamide, finasteride, cimetidine, ketoconazole, and various COCs with that of spironolactone, no significant differences were found, except for COCs with unidentified anti-acne efficacy [24, 25].

The effectiveness of spironolactone monotherapy against non-inflammatory acne was not determined. Expert opinions, comments, as well as guidelines for the treatment of acne with spironolactone (e.g. in the USA) provide no information on this issue [19, 26, 27].

Side effects of spironolactone were dose dependent and occurred at a daily dose exceeding 200 mg. Irregular

menstruation was the most common side effect. Many experts recommend concomitant administration of COCs, which can significantly reduce the incidence and severity of side effects [19, 26]. However, there are experts who, paradoxically, recommend to increase the dose of the drug when it is ineffective [19,26,28]. It is important to note that some current clinical guidelines include spironolactone [27,29,30].

Despite this data, there is no evidence of benefits of oral spironolactone in treatment of acne in females, no reliable data about side effects and long-term results. However, a statistically significant reduction of inflammation was demonstrated in patients with acne who received the drug at a dose of 200 mg/day [21].

The cases of patients with severe inflammation associated with acne, who were administered with systemic glucocorticoids, have been reported. In this situation, side effects of prednisone should be taken into account, in particular, osteoporosis and elevated blood glucose level. The use of these drugs for more than 6 months is not recommended due to suppression of adrenal function [15].

Low-dose prednisolone (2.5—5 mg) or dexamethasone (0.25—0.75 mg) once a day (nocte) inhibit androgen production caused by adrenocorticotropic hormone (ACTH). This evening dose suppresses the morning peak of ACTH and thus reduces androgen level [31].

Oral administration of high doses of hormones can be effective in patients with severe inflammation with underlying acne regardless of hormonal disorders, since low doses of glucocorticoids suppress adrenal function in the case of hyperfunction. Excessive adrenal function can be evidenced by increase in the level of dehydroepiandrosterone, 17-hydroxyprogesterone, and androstenedione [28].

The European guidelines recommend hormone therapy as an alternative to isotretinoin for severe pustular and moderate nodular cystic acne. In the case of nodular acne and acne conglobata, the combination of antibiotics and hormonal therapy is the treatment of choice. Comedonal acne is an absolute contraindication for systemic hormonal therapy [1].

The combination of oral isotretinoin and corticosteroids is the first line treatment for fulminant acne. However, the relapse rate is high, especially with low dose of corticosteroids [32]. To date, there is only one published study describing good response to combination therapy with isotretinoin and prednisolone in patients with fulminant acne [33].

The main effects of systemic administration of hormonal drugs include inhibition of androgen production in the ovaries, adrenal and pituitary glands (tropic hormones), as well as inhibition of androgen receptors in pilosebaceous structures [34].

The following groups of hormonal drugs are mostly used in the treatment of acne:

- androgen receptor blockers;
- COCs inhibiting the androgen production by the ovaries;
- corticosteroids, suppressing androgen production by the adrenal glands;
- 5α-reductase inhibitors [35].

Therapy with hormonal agents is typically used in the combination treatment, rather than as monotherapy. Most often, these drugs are used in combination with antibiotics, benzoyl peroxide, azelaic acid, and, more rarely, retinoids. Administration of hormonal drugs for at least 3 months is usually required to achieve significant clinical improvement [36].

The risk of adverse effects, in particular, vascular thrombosis, should be considered before administration of COCs in the treatment of acne. Administration of these preparations results in threefold higher risk of thrombosis. However, these risks are significantly lower in the case of new generation products containing low doses of estrogens, as well as in non-smoking females under 35 years of age. The highest risk of venous thromboembolism was observed during the 1st year of the use of COCs [37].

There are some data on the use of flutamide in the treatment of acne. This preparation is primarily used for the treatment of prostate cancer, as well as in therapy of hirsutism and androgenic alopecia. The drug inhibits DHT binding to its receptors and enhances degradation of the active form of testosterone to inactive metabolites. The doses of the drug range from 62.5 to 500 mg [25].

There are also scarce data on the use of gonadotropin-releasing factor. These drugs are produced in the form of nasal sprays, subcutaneous and intramuscular injections. To date, there are no unambiguous results of the studies of the efficacy of these preparations for acne, since there are some restrictions on the use of these agents (e.g., bleeding, osteoporosis, hot flushes) [39].

Since insulin resistance may be involved in the pathogenesis of acne, the drugs that increase insulin sensitivity can be used in therapy. For example, metformin can be used in patients with acne in combination with polycystic ovary syndrome, HAIR-AN-syndrome, obesity, or laboratory confirmed hyperinsulinemia. At the same time, the drug does not cause hypoglycemia. Therapy is started with a dose of 500 mg/day, which can be further increased to 2000 mg/day. In the absence of positive dynamics within 6 months from the date of administration, it is advisable to withdraw the drug. Side effects of metformin are dose-dependent. Nausea and vomiting are the most common side effects, which can be avoided by taking the medication after meal and reducing the starting dose to 250 mg/day [40].

In the case of severe and drug-resistant acne, administration of systemic retinoids is indicated. However, oral administration of isotretinoin, which is a very effective drug for the treatment of acne, typically causes xerosis, cheilitis, and photosensitization [38]. According to many authors, systemic retinoids are the most effective drugs

for the treatment of acne. They are mainly indicated in patients with nodular cystic acne, recurrent inflammatory acne, ineffective antibiotic therapy, and the tendency to formation of hypertrophic scars at the site of resolved acne elements. Isotretinoin acts on pathological follicular hyperkeratosis, reduces sebum production, and has anti-inflammatory and anti-chemotactic properties. Isotretinoin acts on chemotaxis of phagocytes and thus has indirect antibacterial effect against *P. acnes* [44].

Decrease in sebum production is observed after about 2 weeks of therapy. There is also decrease in microbial colonization and concentration of inflammation mediators in the lesions. This occurs due to the interaction between isotretinoin and nuclear receptors, thereby reducing the differentiation of sebocytes and, as a result, sebum synthesis [45].

Systemic antibiotics are administered in the case of severe symptoms dominated with inflammatory component. There are a number of limitations to the antibiotic therapy. Furthermore, it is associated with significant side effects. For example, amoxicillin affects the gastrointestinal organs, causing, for example, nausea and vomiting [41]. Macrolide antibiotics, for example erythromycin, demonstrate good clinical efficacy against acne [42]. Monotherapy with oral antibiotics is ineffective in the case of fulminant acne [32].

The frequent and unreasonable use of antibiotics for acne may provoke the development of antibiotic resistance. These preparations have only antibacterial effect and no effect on sebum synthesis [43].

Enzyme preparations with anti-inflammatory and immunomodulating effect can be used for therapy and prevention of acne. These drug products may contain pancreatin, papain, rutoside, bromelain, trypsin, lipase, amylase, and chymotrypsin.

Dolzhikova E.M. et al. (2011) evaluated the effectiveness and pathogenetically validated the use of systemic enzyme therapy in various dermatoses, including acne. The therapeutic efficacy of these drugs in patients with acne is based on anti-inflammatory and immunomodulating effects, as well as the ability to increase the concentration of antimicrobial drugs in the lesion. Systemic enzyme therapy is accompanied by positive clinical effect in the form of reduced erythema and itching, reduced number of rash elements, enhanced repair and epithelialization processes. Furthermore, this lowers the risk of the development of acne conglobata and hypertrophic scars after healing and significantly prolongs remission [46].

Clinical efficacy of systemic enzyme therapy was also observed in the following diseases: atopic dermatitis, eczema, scleroderma, psoriasis, porphyria cutanea tarda, alopecia [46].

Convincing data were obtained by S. Wilson et al., who used local injections of phytogenous acidic peptidoglycan as a primary therapeutic method for papulo-pustular acne, which resulted in significant clinical effect. Immunological effect included increase in the level of various leukocyte subclasses, their activation, and increase in their phagocytic activity. Moreover, no significant increase in the concentration of proinflammatory cytokines was observed with this form of administration of the drug [47].

In summary, acne is a serious medical and social problem, while the repertoire of systemic therapies is limited. Only a small number of therapies have high clinical efficacy in most patients. This situation necessitates the discovery of new therapies and in-depth study of the effectiveness of existing ones.

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