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Treatment of acne vulgaris: a literature review

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Abstract

Acne vulgaris is a common skin disease, which affects individuals of all races and ages. In Caucasians, almost 85% of individuals between 12 and 25 years, as well as 25% of adults, are affected with some forms of acne. The pathophysiology of acne is multifactorial, and thus, the treatment must cover all the possible causes of acne. For this reason, acne therapy is mostly a combination therapy, with the main goal to achieve clinical improvement, without scarring and residuals, as much as possible. The treatment should be planned individually, depending on the clinical appearance, severity and psychological profile of the patient. The treatment usually takes time and requires dedication and patience of both the patient and the physician.

Acne vulgaris is a chronic inflammatory disease of pilosebaceous unit, which is characterized by noninflammatory (opened or closed comedones) and inflammatory (papules, pustules, nodules) skin lesions. The lesions generally affect the face, chest and back, skin regions with greatest density of sebaceous glands. The prevalence of facial acne in adolescent population ranges from 81% to 95% in boys, and 79% to 82% in girls (1). The peak incidence is between 14 and 17 years in girls, and 16 and 19 years in boys.

At least four factors are important in the development of acne: plugging of the hair follicle with abnormally cohesive desquamated cells, genetically predisposed sebaceous gland hyperactivity, colonization of the sebaceous follicles with bacteria (especially *Propionibacterium acnes - P. acnes*), inflammation and immune response (2). The first pathological change is comedo formation. If a closed comedo or microcomedo erupts, an inflammatory reaction ensues, resulting in the formation of papules, pustules, nodules and pseudocysts. Furthermore, *P. acnes* contribute to the inflammatory response and release of proinflammatory mediators. Although acne is not an inherited condition, obviously there is a genetic predisposition to acne. Several genes are believed to be involved, of which only cytochrome P-450-1A1 gene, and the steroid 21-hydroxylase gene are documented (3). Positive family history of acne is obtained in 40% of patients and correlates with more severe forms (4). Scarring may also occur, but it is not in direct correlation with the severity of inflamed acne. There are different types of scars and it can be associated with loss of collagen fibers which causes ice pick scars and atrophic macular scars, while with collagen increase, hypertrophic scars develop.

Acne and acne scarring, especially on the face, may be the reason of psychological and social disability in some patients. Anxiety, depression, social withdrawal, decreased self-esteem, embarrassment, frustration are reported in many patients (5, 6, 7). For this reason, assessment of the degree of psychosocial disturbances is important in planning acne treatment.

The treatment choice for acne depends on several important factors: severity of acne; type of acne lesions; presence of scarring; psychological and social impact of the disease on the individual. Acne assessment using the *Leeds Acne Grading Scale* is very useful, practical, easy to use (8). Generally, acne can be classified into three categories: mild (mainly non-inflammatory lesions); moderate (non-inflammatory and inflammatory lesions, such as papule, pustule, small nodules) and severe (nodules and pseudocysts). Presence of scarring and significant psychological and social disability can be the reason to use aggressive therapy depending on the acne grade (9).

Topical treatment

Topical treatment is the first choice in acne treatment: as monotherapy in mild forms of acne, or in combination with systemic agents in moderate and severe cases. Topical medications are active only where and when they are applied, whereas their main action is prevention of new lesions.

Topical retinoids

Topical retinoids represent a mainstay of acne treatment because of theirs effects: they reduce microcomedone formation and number (precursors of lesions), resolve mature comedones, reduce inflammatory lesions, promote normal desquamation of follicular epithelium, they have anti-inflammatory activity, enhancing increased penetration of other drugs (such as topical antibiotics, resulting in synergistic effects), and maintain remission of acne by inhibiting comedo formation, and thus preventing new lesions.

Retinoids used for acne treatment include: tretinoin and isotretinoin (first generation retinoids); monoaromatic retinoids, such as motretinide, a second generation monoaromatic retinoid; and adapalene and tazarotene, a third generation retinoids. Retinol and retinaldehyde are also used (10).

Tretinoin

Tretinoin (all-trans retinoic acid), the first topical retinoid developed for acne treatment is available in cream: 0.025%, 0.01%, 0.05%, 0.1%; in gel 0.1%, 0.025%; in liquid form: 0.05%; 0.1% and 0.2%; a 0.05% ointment; in 0.05% compresses, in 0.1% gel microsphere and in form of a 0,025% polymer cream. This agent is known to bind to and activate all three retinoic acid receptors, (RAR) subtypes, and the cellular retinoic acid binding protein (CRABP). It acts by increasing the turnover of follicular epithelial cells and by accelerating the shedding of corneocytes, and thus, normalizes keratinization. In this way, it causes significant reduction of noninflammatory and inflammatory acne lesions. Skin irritation, its commonest side-effect, can be diminished with new, liposomal encapsulated tretinoin formulation (gel or cream formulation, which contains polyoprepolymer-2), a large polymer compound that delays absorption of tretinoin in epidermis (11, 12).

Isotretinoin

Isotretinoin (13-cis retinoic acid) is available as 0.05% gel, and 0.05% and 0.01% cream. Topically applied, it has similar effectiveness as tretinoin, but with less skin irritation. In contrast with the oral formulation, it neither reduces the size of sebaceous glands nor suppresses sebum production.

Adapalene

Adapalene is a third-generation naphthoic acid derivative of retinoic acid, that selectively binds to RAR-beta and-gamma subtypes, and activates gene expression through all three RARs. It is available as a 0.1% and 0.3% gel, and as a 0.1% cream (13, 14). Adapalene shares some of the biological characteristics of tretinoin, but has different physicochemical properties, including increased chemical and light stability (for this reason it can be used during the day) and high lipophilicity. It modulates cellular keratinization and inflammatory processes, and inhibits lipoxygenase activity and oxidative metabolism of arachidonic acid. This drug is the FDA pregnancy category C, and should be used with caution in pregnant women. Some studies have shown that a major congenital malformation rate of 1.9% occurred in mothers who used topical retinoid during the first trimester of pregnancy, versus 2.6% in mothers who were not exposed to retinoid (15).

Tazarotene

Tazarotene (also belongs to the third-generation of retinoids) is an acetylenic retinoid, which penetrates the skin and it is converted to an active metabolite, tazarotenic acid, which has a high affinity for RAR-beta and RAR-gamma. The mechanisms of its action are extensively studied on psoriatic skin lesions, and they enhanced normalization of keratinocyte proliferation and differentiation, as well as reduction in keratinocyte-expressed markers that attract inflammatory cells (16). Similar to other topical retinoid, the main side-effects are skin peeling, dryness and redness, burning, and itching. The recommended short term therapy (between 30 seconds and 5 minutes) showed good tolerability and acne improvement (17). Tazarotene is in the FDA pregnancy category X, so it should not be used during pregnancy and breastfeeding. It proved to be teratogenic in animals, after systemic

administration of high doses, but not after topical exposure.

Motretinide

Mortified is a second-generation monoaromatic retinoid which is slightly less effective than retinoid, but it is also less irritant. This agent is available as a 0.1% cream and solution in Switzerland (18).

Retinaldehyde

Retinaldehyde, a key intermediate molecule in the metabolism of natural retinol by keratinocytes, has mild comedolytic effects and antibacterial activity against Gram-positive bacteria, including *P. acnes*. On the market, it is available as *Diacneal*® (0.1% retinaldehyde, 6% glycolic acid) for cosmetic therapy, and for clinical trials as a 0.5-1% cream.

After achieving positive results in acne treatment, retinoids are very important and suitable for maintenance therapy. It is well known that comedo formation occurs 2-6 weeks after cessation of treatment. For this reason, long-term application (of several years duration) of retinoids is recommended to prevent microcomedone formation.

Topical antibiotics

Topical antibiotics are used in the treatment of mild inflammatory acne. The most widely used agents are: *clindamycin* (available as a 1% gel, solution and lotion) and *erythromycin* (available as a 1% and 2% solution; as a 2% ointment and 2% and 4% gel) (18, 19, 20). The primary action of these agents is to reduce the *P. acnes* population on the skin surface, especially within follicles. They also exhibit a mild comedolytic effect, reducing *P. acnes* and interleukin-1 production. They demonstrate a mild anti-inflammatory effect by suppressing leukocyte chemotaxis. However, these agents should not be used as monotherapy; if monotherapy is necessary, it should be used for a short (3-4 weeks) period. This is due to a dramatic increase in bacterial resistance during the past 20 years (21,22), and unsatisfactory results, especially of *erythromycin*, and *clindamycin*. The reason why the efficacy of topical *clindamycin* has remained stable, despite an increased resistance of *P. acnes,* may be due to nonbacterial effects of this local antibiotic, such as inhibition of leukocyte chemotaxis or inhibition of extracellular lipase production by *Propionibacteria* (23). The topical antibiotic therapy should be discontinued after the resolution of inflammatory lesions or, if there is no improvement after 6-8 weeks of treatment, alternative therapy should be considered.

Benzoyl peroxide

Benzoyl peroxide is one of the most commonly used topical agents in acne treatment. It has strong anti-inflammatory, anti-microbial, and anti-comedogenic effects, so it is frequently used as first-line therapy for mild to moderate acne. It is available as gel, cream, lotion and solution at different concentrations (2.5%, 3%, 4%, 5%, 10%) (24). The main side-effects, erythema, scaling and itching, can be controlled by less frequent application. Long-term administration of this agent causes no skin damage and there is no evidence of acquired bacterial resistance.

Azelaic acid

Azelaic acid, naturally occurring saturated dicarboxylic acid, inhibits DNA synthesis of keratinocytes, has some comedolytic activity and antimicrobial effects on *Staphylococcus epidermidis* and *P. acnes*. On the market, it is available as 20% cream and 15% gel (25). However, it shows less effective results when compared to antibiotics; it can also be used in the treatment of postinflammatory hyperpigmentation.

Dapsone gel 5%

Dapsone is a sulfone with anti-inflammatory and antimicrobial properties (26). It has been available for over 60 years and proved effective in the treatment of acne, including inflammatory, nodulocystic acne. However, systemic administration of dapsone in acne treatment has never been widely accepted because of its toxicity and influence on dose-induced hemolytic anemia, due to production of hydroxylamine metabolite. Individuals with glucose-6-phosphate dehyrdogenase (G6PD) deficiency are more susceptible to developing hemolytic anemia (especially male patients, because G6PD enzyme is located on the X chromosome). Administration of dapsone as a 5% aqueous gel is a clinically-effective dose, with minimal systemic absorption, and approved safety (25, 26). Local irritation is minimal. New anti acne agents may be used to prevent the increasing prevalence of antibiotic-resistant strains of *P. acnes*.

Topical hormone therapy

Knowing that increased sebum production is due to androgens acting at the genetically predisposed sebaceous follicle, attempts to include hormones in acne treatment have been promoted. Hormone therapy may include of antiandrogens (cyproterone acetate, spironolactone) and enzyme inhibitors that are involved in androgen metabolism in the skin.

Topical administration of cyproterone acetate showed the same effectiveness as oral antiandrogen medications, with reduced risk of adverse effects, avoiding high serum cyproterone acetate levels (29).

Other topical treatment modalities

Phototherapy

Phototherapy includes visible light and photodynamic therapy. *P. acnes* are Gram-positive anaerobic bacteria that produce and accumulate porphyrins. Irradiation of bacterial colonies with blue visible light (peak irradiation at 415 nm) and mixed blue and red light (peaks of irradiation at 415 and 660 nm) leads to photoexcitation of bacterial porphyrins, singlet oxygen formation, and bacterial destruction (30,31). Addition of delta-aminolevulinic acid (ALA) enhances intracellular porphyrin synthesis. Significant adverse effects, such as discomfort during the treatment, transient hyperpigmentation, superficial exfoliation, erythema, crust formation, duration of treatment (45 minutes per session for truncal acne) are reasons why this therapeutic modality is not yet widely accepted (32).

Administration of coherent *LASER* light (infrared 1450 nm diode laser) may be useful in acne treatment, as a safe and effective method. However, this laser causes thermal coagulation of the sebaceous lobule and associated hair follicule, reducing both sebaceous gland secretion and inflammation (33).

Chemical peel

Three types of chemical peels are used: superficial (Jessner peels, glycolic acid and lactic acid peels 35 - 50%, trichloroacetic acid (TCA) 10 - 30%); intermediate (TCA 30 - 50%); deep (phenol) peels. Superficial peels show the best benefit-risk ratio in all anti-acne scar treatments, by reducing postinflammatory hyperpigmentation, macular erythematous scars and size of dilated pores. The extent of peeling depends on the anatomic site of application, presence or absence of seborrhea, integrity of epidermis, agent concentration, number and duration of applications. Erythema, desqumation, crusting, folliculitis, hyper or hypopigmentation and flare of acne lesions may be consequences of peeling (34).

Skin surgery

Mechanical removal of lesions (open and closed comedones) with comedo extractor can also be helpful. Punch excision and elevation, skin grafting and subcision are surgical methods which can be applied depending on the type of acne residues. Injections of steroids and liquid nitrogen can be initial steps in treatment of hypertrhopic and keloid scars (35).

Systemic treatment

Oral antibiotics

Systemic antibiotic therapy is primarily used in moderate-to-severe inflammatory acne, acne resistant to topical treatment, and in acne affecting large body surface. *Tetracyclines* and their derivatives *(doxycycline, minocycline)*, are the most widely used antibiotics, as well as macrolides *(erythromycin)* and *trimethoprim/sulfamethoxazole*. When choosing antibacterial agents, one should take into account the efficacy, cost-effectiveness, benefit-risk ratio, patients' acceptability and potential development of resistance (36).

Tetracycline is a safe and efficient agent for acne vulgaris. The initial dose is 500 mg twice a day for an average time of 6 weeks, and after the decrease of inflammation, the dose should be reduced to 500 mg per day. The main side-effects are gastrointestinal symptoms, such as diarrhea, vomiting, dyspepsia, and vaginal candidiasis in women. Tetracycline causes enamel hypoplasia and yellowish teeth in children.

Doxycycline, a second generation tetracycline, shows excellent penetration in to the pilosebaceous unit. The initial dose is 100 mg twice a day. It exhibits the same side-effects as tetracycline, but photosensitivity is the most prominent (also photo-onycholysis).

Minocycline is considered to be the most effective tetracycline, with the lowest rate of resistance to *P. acnes* (also in cases of cross-resistance to other tetracyclines) (37). The initial dose is 50-100 mg twice

a day, while the maintenance dose is 50-100 mg a day. The main side-effects are skin discoloration (especially parts of the skin with inflammatory lesions and scars) and more pronounced CNS adverse effects, such as vertigo, dizziness and ataxia. Minocycline is also associated with serious adverse effects, which were first reported in 1992, (case of minocyclin-induced lupus) (38). Other drug-induced syndromes associated with this agent are autoimmune hepatitis, serum sickness and vasculitis.

Erythromycin is a macrolide antibiotic, which is effective in inflammatory lesions, but it is frequently associated with resistant strains. The initial dose is 500 mg twice a day. It causes gastrointestinal side-effects (vomiting, diarrhea, flatulence), but it can be used during pregnancy.

Trimethoprim/sulfamethoxazole is effective and inexpensive, but it is used as a third-line antibacterial agent in acne treatment, due to potential serious adverse effects, such as: Stevens-Johnson syndrome, toxic epidermal necrolysis and bone-marrow suppression.

Azithromycin (500 mg three times a week during 8 weeks) has recently been added to the list of systemic antibiotics; it shows good bacteriostatic activity, no reported bacterial resistance, good tolerance, and few gastrointestinal disturbances, such as heartburning and nausea; it can be used during the summer, because no photosensitivity reactions have been reported (39).

The arising problem in acne treatment is development of resistant strains of *P. acnes*, which has increased from 20% in 1988, to around 25% in 1990, 43% in 1993, and 62% in 1996 (23). In order to prevent this increasing problem, antibacterials should be prescribed for 6 months on average; if retreatment is required, the same antibiotic should be used; concomitant use of oral and topical, chemically-different antibiotics, should be avoided.

Isotretinoin

Isotretinoin is an oral retinoid used to treat severe nodulo-cystic acne, moderate or severe acne not responding to conventional oral and topical therapies, acne with marked scarring and acne patients with psychological problems, such as severe depression or dysmorphophobia (40, 41). It is also used in gram-negative folliculitis, pyoderma faciale and severe acne rosacea. Isotretinoin targets all pathogenic elements of acne: by decreasing the size and secretion of sebaceous glands, it normalizes follicular keratinization and prevents formation of new comedones; it indirectly inhibits *P. acnes* growth, by changing the follicular milieu, and shows anti-inflammatory effects (42). The oral dose ranges from 0.1 to 2 mg/kg (the average initial dose is 0.5 mg/kg; maximal 1 mg/kg; total cumulative dose of 120-150 mg/kg).

Isotretinoin is commonly used as monotherapy, except in cases of acne fulminans or pyoderma faciale, when it is used with oral corticosteroids and nontetracycline antibiotics. Common side-effects are dry and fragile skin, dry or cracked lips, nosebleeds, and rarely headache. Last reports from December 2009, (43), indicated that isotretinon can cause severe side-effects, such as erythema multiform, Steven-Jones syndrome and toxic epidermal necrolysis. Routinely, serum lipids and standard liver function tests should be regularly monitored. However, it should be used with great caution in women of child-bearing age, due to its potential teratogenic effects, and they should start therapy only after negative pregnancy test results. Adequate contraception is essential before, during and 2 month after therapy. Depression, which is usually reported in association with isotretinoin therapy, is considered as an idiosyncratic side-effect in 1% of cases (44).

On the other hand, treatment of severe acne with isotretinoin has shown to reduce anxiety and depression in patients (45).

After one course of isotretinoin therapy, 38% of patients had no acne; acne was controlled with topical therapy in 17%, and with topical therapy and oral antibiotics in 25% of patients. A second course of isotretinoin was necessary in 20% of patients (46).

Hormonal therapy

Hormonal therapy for acne is an option for women who need oral contraception for gynecologic reasons (contraception, menstrual disturbances), and for female patients with severe seborrhea, acne, hirsutism and female androgenic alopecia. Reduction of sebum secretion is the main effect of hormonal therapy, which is, one of the multiple events in acne pathogenesis. Because of that, this therapy is not a first-line choice, and it is often combined with other anti-acne agents.

Hormonal therapy includes several different

antiandrogens: *androgen receptor blockers* (cyproterone acetate, spironolactone, flutamide), *ovarian or adrenal androgen production inhibitors* (estrogens, oral contraceptives, cyproterone acetate, low-dose corticosteroids) and *5-alpha reductase inhibitors* (2).

Cyproterone acetate is a progestational anti-androgen, which is combined with ethinyl estradiol in oral contraceptive formulations, which is widely used in Europe. This agent causes several side-effects, such as leg edema, breast tenderness, fluid and sodium retention, headache, fatigue, liver dysfunction and blood clotting disorders (47).

Spironolactone is an androgen receptor blocker and an inhibitor of 5-alpha reductase; 50 or 100 mg twice a day may improve inflammatory acne. It may cause hyperkalemia, irregular menstrual periods, fatigue, breast tenderness and headache (48).

Estrogens combined with progestin (to avoid the risk of endometrial cancers associated with unopposed estrogens) are commonly used as antiacne agents. Ovarian production of androgens is suppressed by direct gonadotropin suppression and prevention of ovulation. An important side-effect of this therapy is venous thromboembolism, and can be resolved with reduced doses of estrogens. Other side-effects are transient, including nausea/vomiting, breast tenderness, leg edema and weight gain.

Glucocorticoids can suppress adrenal androgen production when administrated in low doses. They can be helpful in the treatment of patients (of both sexes) with elevated serum level of testosterone and dehydroepiandrosterone. Moreover, they can be used orally in combination with isotretinoin in the treatment of acne fulminans and pyoderma faciale.

Inhibitors of 5-alpha reductase (Flutamide) are currently not available for acne treatment. They are registrated in the treatment of prostate cancer, and there are some attempts to treat acne and androgenic alopecia in menopausal women (49).

Zileuton

Zileuton, a 5-lipoxygenase inhibitor, reduces the number of inflammatory lesions in moderate acne and inhibits the synthesis of sebaceous lipids (50). Metabolism of arachidonic acid (AA) via the 5-lipoxygenase pathway enchases leukotriene-B4 (LTB4) synthesis, interleukin-6 (IL-6) release and increases intracellular neutral lipids in human sebocytes (51). Zouboulis et al. (52) investigated the role of zileuton (a drug which is widely used in the treatment of chronic asthma) on moderate inflammatory acne (4x 600 mg/day, orally, for 3 months) and found that zileuton directly inhibits sebum synthesis in a transient manner with a potency similar to low-dose isotretinoin.

Future of acne treatment

The analysis of the genome sequence and of *P. acnes* bacteriophage (53), is the basis for genetic manipulation with the host bacterium. Such therapy would overcome the problems with resistance of *P. acnes*, which results from long-term use of antibiotics. An inactivated *P. acnes* vaccine, targeted the whole bacterium, has been successfully tested in mice. It showed improvement in inflammatory acne. Because the induction of cytokines, chemokines and metalloproteinases by *P. acnes* occurs via Toll-like receptor 2 (TLR2)-dependent pathway, development of vaccines or other immune therapies targeting TLR2, and other TLRs, may provide other alternatives to conventional therapy (54). Agents that modulate the TLR response and downregulate TLR2 expression and function, indicate that vaccine with potent anti-TLR immunity might be the promising antiacne therapy (55).

References

1. Lello J, Pearl A, Arroll B. Prevalence of acne vulgaris in Auckland senior high school students. N Z Med J 1995;08:287-9.
2. Gollnick H,Cunliffe W, Berson D, et al. Management of acne: a report from Global Alliance to Improve Outcomes in Acne. J Am Acad Dermatol 2003;49(1 Suppl):S1-37.
3. Kubba R, Ajaj AK, Thappa DM, et al. Acne in India: guidelines for management-IAA consensus document. Genetics in acne. Indian J Dermatol Venereol Leprol 2009;75(Suppl 1):S4.
4. Cunliffe WJ, Gollnick HPM. Acne: diagnosis and management. London: Martin Dunitz; 2001.p.1-46.
5. Yazici K, Baz K, Yazici AE, Kokturk A, Tot S, Demirseren D, et al. Disease-specific quality of life associated with anxiety and depression in patients with acne. J Eur Acad Dermatol Venerol 2004;18:435-9.
6. Dreno B. Assessing quality of life in patients with acne vulgaris. Am J Clin Dermatol 2006;7(2):99-106.
7. Ahmed S, Ahmed I. Frequency and magnitude of anxiety and depression among acne patients: a study of 100 cases. J Liaquat Uni Med Health Sci 2007;6(1):25-9.
8. Burke BM, Cunliffe WJ. The assessment of acne vulgaris: leeds technique. Br J Dermatol 1984;111:83-92.

9. Baldwin H. Tricks for improving compliance with acne therapy. Dermatol Ther 2006;19:224-36.
10. Thielitz A, Gollnick H. Topical retinoids in acne vulgaris. Am J Clin Dermatol 2008;9(6):369-81.
11. Webster GF. Topical tretinoin in acne therapy. J Am Acad Dermatol 1998;39: S38-44.
12. Lucky AW, Cullen SI, Jarratt MT, et al. Comparative efficacy and safety of two 0.0025% tretinoin gels: results from multicenter double-blind, parallel study. J Am Acad Dermatol 1998;38(4):S17-23.
13. Irby CE, Yentzer BA, Feldman SR. A review of adapalene in the treatment of acne vulgaris. J Adolesc Health 2008;43:421-4.
14. Laboratories, Differin (adapalene) 0.3% gel product insert information, United States (online). Available from: URL:http://www.differin.com/AboutDifferin/ProductInsert_Gel 0,3. aspx [Accessed 2010 Jan 28].
15. Jick SS, Terris BZ, Jick H. First trimester topical tretinoin and congenital disorders. Lancet 1993;341:1181-2.
16. Chandraratna RA. Tazarotene: the first receptor-selective topical retinoid for the treatment of psoriasis. J Am Acad Dermatol 1997;37(Suppl 2 Pt 1):S12-7.
17. Bershad S, Kranjac, Singer G, Parente J, Tan MH, Sherer D, Persuad AN, et al. Successful treatment of acne vulgaris using a new method. Arch Dermatol 2002;38:481-9.
18. Krautheim A, Gollnick H. Acne: topical treatment. Clin Dermatol 2004;22:398-407.
19. Simonart T, Dramaix M. Treatment of acne with topical antibiotics: lessons from clinical studies. Br J Dermatol 2005;153:395-403.
20. Poljački M, Subotić M, Đuran V, Matic M, Ivkov M. Terapija vulgarnih akni lokalnom elektroforetskom primenom klindamicina. U: II Kongres pedijatara Jugoslavije: zbornik sažetaka; 1998 sept. 20-26; Novi Sad, Jugoslavija. Novi Sad: Udruženje pedijatara Jugoslavije; 1998. str. 303-5.
21. Coates P, Vyakrnam S, Eady EA, Jones CE, Cove JH, Cunliffe WJ. Prevalence of antibiotic-resistant propionibacteria on the skin of acne patients:10-year surveillance data and snapshot distribution study. Br J Dermatol 2002;146:840-8.
22. Ross JI, Snelling AM, Carnegie E, Coates P, Cunliffe WJ, Bettoli V, et al. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003;148:467-78.
23. Cooper AJ. Systemic review of Propionibacterium acnes resistance to systemic antibiotics. Med J Aust 1998;169:259-61.
24. Lookingbill DP, Chalker DK, Lindholm JS. Treatment of acne with combination of clindamycin/bezoylperoxyd gel compared with clindamycin gel, benzoylpreoxyde gel and combined results of two double blind investigations. J Am Acad Dermatol 1997;37:590-5.
25. Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Derm Venereol Suppl (Stockh) 1989;143:35-9.
26. Zhu YI, Stiller MJ. Dapsone and sulphones in dermatology: overview and update. J Am Acad Dermatol 2001;45:420-34.
27. Draelos ZD, Carter E, Maloney MJ, Elewski B, Poulin Y, Lynde C, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. J Am Acad Dermatol 2007;439:e1-10.
28. Piette W, Taylor S, Pariser D, Jarratt M, Pranav S, Wilson D. hematologic safety of dapsone gel 5%, for topical treatment of acne vulgaris. Arch Dermatol 2008;144:1564-70.
29. Gruber D, Sator M, Joura E, Kokoschka EM, Heinze G, Huber J. Topical cyproterone acetate treatment in women with acne. Arch Dermatol 1998;134:459-63.
30. Papageorgiou P, Kartsambas A, Chu A. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. Br J Dermatol 2000;142:973-8.
31. Charakida A, Seaton E, Charakida M, Mouser P, Avgerinos A, Chu A. Phototherapy in the treatment of acne vulgaris. Am J Clin Dermatol 2004;5(4):211-6.
32. Morton CA, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002;146:552-67.
33. Friedman P, Ming J, Kimyai-Asadi A, Goldberg L. Treatment of inflammatory facial acne vulgaris with the 1450-nm diode laser: a pilot study. Dermatol Surg 2004;30:147-51.
34. Goodman GJ. Management of post-acne scarring. What are the options for treatment? Am J Clin Dermatol 2000;1:3-17.
35. Dreno B. Acne: physical treatment. Clin Dermatol 2004;22:429-33.
36. Tan HH. Antibacterial therapy for acne. Am J Clin Dermatol 2003;4(5):307-14.
37. Garner SE, Eady EA, Popescu C, et al. Minocycline for acne vulgaris: efficacy and safety. Cochrane Database Syst Rev 2000;(2):CD002086.
38. Sturkenboom MC, Meier CR, Jick H, et al. Minocyclin and lupus-like syndrome in acne patients. Arch Intern Med 1999;28:392-7.
39. Bardazzi F, et al. Azitromycin: a new therapeutical strategy for acne in adolescents. Dermatol Online J 2008;13(4):4.
40. Cooper AJ. Treatment of acne with isotretinoin: recommendations based on Australian experience. Aust J Dermatol 2003;44:97-105.
41. Poljački M, Gajinov Z, Subotić M, Đuran V, Matić M. Izotretinoin u dermatoloskoj praksi. Med Pregl 1996;49(5-6):199-202.
42. Blomhoff R, Blomhoff HK. Overview of retinoid metabolism and function. Int J Neurobiol 2006;66:606-30.
43. Reactive Holding Statement for postmarketing reports of severe skin reactions with use of isotretinoin. Basel: Roche; 2009.
44. Chee Hong Ng, Schweitzer I. The association between depression and isotretinoin use in acne. Ausst N Z J Psychiatry 2003;37(1):78-84.
45. Rubinow DR, Peck GL, Squillace KM, et al. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. J Am Acad Dermatol 1987;17:25-32.
46. White GM, Chen W, Yao J, et al. Recurrence rate after first course of isotretinoin. Arch Dermatol 1998;134:376-8.
47. Huber J, Walch K. Treating acne with oral contraceptives: use of lower doses. Contraception 2006;73:23-9.
48. Muhlemann MF, Carter GD, Cream JJ, Wise P. Oral spironolactone: an effective treatment for acne vulgaris in women. Br J Dermatol 1988;115:227-32.
49. Thilboutot D. Acne: hormonal concepts and therapy. Clin Dermatol 2004;22:419-28.
50. Zouboulis C, Nestoris S, Adler YD, et al. A new concept for acne therapy: a pilot study with zileuton, an oral 5-lipooxygenase inhibitor. Arch Dermatol 2003;139:668-70.

51. Zouboulis CC, Seltmann H, Alestas T. Zileuton prevents the activation of the leukotriene pathway and reduces sebaceous lipogenesis. Exp Dermatol 2010;19:148-50.
52. Zouboulis CCh, Saborowski A, Boschnakow A. Zileuton, an Oral 5-lipoxygenase inhibitor, directly reduces sebum production. Dermatology 2005;210:36-8.
53. Farrar M, Howson K, Bojar R, et al. Genome sequence and analysis of a Propionibacterium acnes bacteriophage. J Bacteriol 2007;189(11):4161-7.
54. Nakatsuji T, Liu YT, Huang CP, Gallo R, Huang CM. antibodies elicited by inactivated Propionibacterium acnes-based vaccines exert protective immunity and attenuate the IL-8 production in human sebocytes: prevalence to therapy for acne vulgaris. J Invest Dermatol 2008;128:2451-7.
55. Kim J. Acne vaccines: therapeutic option for the treatment of acne vulgaris? J Invest Dermatol 2008;128:2451-7.

Lečenje običnih akni (*acne vulgaris*) – pregled literature

Sažetak

Definicija: Obične akne (lat. acne vulgaris) predstavljaju hronično inflamatorno oboljenje pilosebacealne jedinice, koje se učestalo javlja u doba puberteta.
Epidemiologija: Smatra se da oko 85-100% adolescenata i mlađih odraslih u uzrastu 12-24 godine, boluje od ovog oboljenja godinama (bar povremeno). U grupi adolescenata, učestalost i težina kliničke slike, kao i sklonost ožiljavanju je veća kod muškaraca, dok je sklonost ka perzistiranju promena i nakon puberteta više izražena kod osoba ženskog pola.
Patofiziologija: U nastajanju akni učestvuje više faktora. Rane karakteristike oboljenja, kao što su seboreja i formiranje komedona, posledica su androgene sekrecije adrenalnog porekla. Sa postepenim razvojem gonadalne aktivnosti, androgeni poreklom iz testita i ovarijuma, dovode, na nivou genetski predisponiranih folikula, do više izražene seboreje i komedogeneze. Drugi faktori koji su odgovorni za formiranje komedona su iritantni efekat lipidnih sastojaka sebuma, aktivnost lokalnih citokina, naročito interleukin 1- alfa i kolonizacija mikroorganizmima, naročito *Propionibacterium acnes.*
Kliničke varijante: Prvi klinički znaci oboljenja su seboreja i komedoni (otvoreni i zatvoreni). Tokom sledećih nekoliko meseci, javljaju se upalne promene, koje se sastoje od papula i površno lokalizovanih pustula, veličine do 5 mm. Mogu da se jave i dublje lokalizovane upalne promene, kao što su nodulusi, pustule veće od 5 mm i pseudociste. Posledica upalnih promena je stvaranje ožiljaka, koje može biti udruženo sa gubitkom kolagena, u vidu atrofičnih makularnih i *„icepick"* ožiljaka, ili se, zbog izražene fibrozne reakcije ispoljava u vidu hipertrofičnih ožiljaka.
Terapijski principi: S obzirom na multifaktorsku patofiziologiju akni, lečenje se mora usmeriti protiv, što je moguće više činilaca koji učestvuju u njihovom nastajanju i prilagoditi kliničkoj slici.
Cilj terapije podrazumeva uglavnom kombinovanu terapiju, a najvažnije je postizanje kliničkog poboljšanja, sa što je manje moguće izraženim ožiljavanjem i reziduama.
Neupalne akne: Koriste se topikalni lekovi koji deluju antiseboroično, npr. spironolakton i antikomedogeno, npr. retinoidi i azelaična kiselina.
Upalne akne: Za lečenje blažih i srednje teških oblika upalnih akni, potrebno je primeniti benzoil-peroksid, klindamicin, azelaičnu kiselinu. Za srednje teške upalne oblike, koji zahvataju veće površine kože, lečenje se sprovodi sistemskom primenom antibiotika, najčešće tetraciklina, eritromicina i azitromicina.
Nodulo-cistične akne, kao i srednje teški oblici koji ne daju zadovoljavajući odgovor na primenjenu konvencionalnu lokalnu i sistemsku terapiju, akne sa izraženim ožiljavanjem, kao i pacijenti sa psihološkim problemima, predstavljaju indikaciju za sistemsku primenu isotretinoina.
Zaključak: Lečenje se planira individualno, u odnosu na kliničku sliku i težinu oboljenja, kao i psihološki profil obolelog. Lečenje je dugotrajno i zahteva obostranu predanost i istrajnost i obolelih i lekara.