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Systemic Treatments of Acne Vulgaris – 4 Case Series and Review of Literature

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Abstract

Acne vulgaris is a common disease among both adolescents and adults (adult acne). We present four different clinical cases classified as moderate-severe acne vulgaris treated with systemic treatments based on European protocols and review of the literature. Acne vulgaris is a disease that affects a lot the quality of life of the patient and either of the whole family. Treatment with systemic therapies based on the gravity of acne, the conditions of the patient and their preferences and tolerability of the medication have to be taken in consideration for good results.

Keywords: Acne vulgaris, systemic treatments, doxycycline, isotretinoine, oral contraceptive, spironolactone.

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INTRODUCTION

Acne vulgaris is a common disease among adolescents and adults (adult acne). It is a chronic inflammatory disease of pilosebaceous unit. The pathogenesis is complex resulting from increased sebum production induced from androgen, inflammation, and colonization by Corynebacterium (Propionibacterium acnes). (1,2) We present four clinical cases classified as moderate - severe acne vulgaris treated with systemic treatments based on European protocols and review of the literature. Acne vulgaris depending on clinical condition is classified as: mild, moderate, severe. The cases with moderate and severe conditions need systemic treatment combined with local treatment. Trigger factors have to be discussed carefully with the patient in a way to minimize the possibility to exacerbate acne. Oral antibiotics is an option of treatment of papular- pustular acne but always needs to combine oral antibiotics with local treatments to decrease antibiotic-resistant organisms. (1, 2, 3) Another effective therapy option is oral isotretinoin but doctors and patients have to take in consideration side effects and teratogenicity of this medication. Alternatives of systemic acne treatments are oral contraception and spironolactone. Every treatment has to be tailored for every case and for specific needs of the patients. Treatment with systemic therapies based on the gravity of acne, the conditions of the patient and their preferences and tolerability of the drug have to be taken in consideration before the treatment.

In this paper we discuss four different cases and systemic treatment recommended for these patients and we discuss the relevant literature.

Case 1

We present a 17 years old male who has been suffering from acne vulgaris since he was 12 years old. In the clinical examination were noticed papule/ pustular elements, black/white comedones and some acne scars remained from previous acne elements. The elements were localized on forehead, cheeks, chin and the upper part of the trunk. Time after time he was treated locally with salicylic acid washable gels, topical antibiotics (erythromycin and clindamycin) without significant improvement. The condition has affected a lot his quality of life and either the life of his parents. Both parents have had acne vulgaris during their adulthood.

Referring to the acne classification the case was classified as moderate acne vulgaris and the treatment recommended for this situation based on acne guidelines were oral antibiotics.

We started the treatment as follows: a- Doxycycline 200 mg/day, for 10 days, lowering the dose to 100 mg/day for 20 days and maintenance dose 50 mg/day for 2 months.

b- Local treatment with topical benzoic peroxide and retinoid.

c- Salicylic Acid washing gel.

The follow up was done every 4-6 weeks for 4 months.

In every session the clinical condition was significantly improved with the absence of

papules/ pustules and remaining few comedonic elements. The sebum production was significantly lowering.

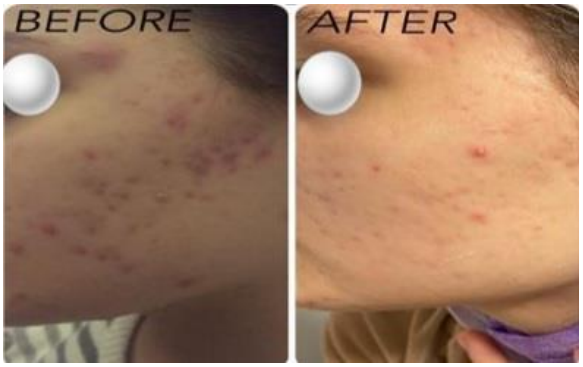

Figure 1. Case 1

Case 2

A girl 22 years old was treated with different local treatments and oral antibiotic (doxycycline) unsuccessfully for four years. The clinical condition was worsening and the stress of the patient and the whole family was at high level. In clinical examination there were evident nodular elements, papule/ pustules on the face and on the trunk. Patient was complaining for pain of the elements, esthetic issue and scars. The weigh was 62 kg.

Referring to the acne classification the case was classified as moderate- severe nodular acne vulgaris and the treatment recommended for this situation based on acne guidelines was systemic retinoid.

We decided to treat the patient with isotretinoin systemic therapy. Before the treatment we performed the blood tests for liver enzymes and lipids profile in the blood. The patient signed a consent paper that she has been informed for the retinoid risks in pregnancy and we decided to explain the contraception procedures.

The treatment at the starting point was:

a. Oral isotretinoin 30 mg/day for 30 days, increasing the dose 60 mg/ day for the next 6 months.

b. Local antimicrobial agent (erythromycin) for 6 weeks

c. Topical benzoic peroxide

d. Salicylic Acid washing gel.

After 8 weeks of treatment the improvement in the reducing number of papules/ pustules and the dimensions of nodules was noticed. One of the evident side effects of the treatment was cheilitis, and for this we recommended a lip balm. The lab tests were re-done after two months of treatment and no any alteration was noticed. We continued the treatment for 7 months with a significant improvement without any other side effects. The result was really good and after this the planning protocol was to treat remaining acne scars.

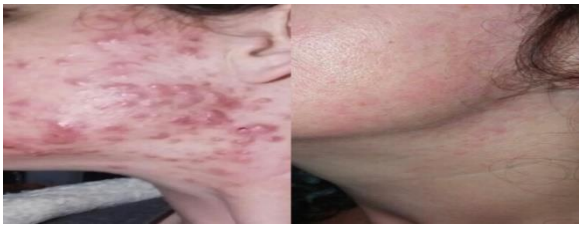

Figure 2. Case 2

Case 3

A.M, 33 years old patient presented in our clinic with acne on face for 1 year. She referred that 4 years ago she was treated for polycystic ovary. She was treated for acne with doxycycline 100 mg-day and topical erythromycin and benzoyl

peroxide for several weeks, but without any improvement. In clinical examination there were evident nodular elements, papule/ pustules on jawline distribution. Referring to the acne classification the case was classified as moderate-severe nodular acne vulgaris. Based on her anamnesis she was recommended to have a gynecological ultrasonography, which resulted in multiple cysts in the ovaries (polycystic ovary). 8 weeks after starting treatment with oral contraceptive (a combined preparation of ethinyl estradiol and drospirenone) patient referred to have considerable improvement of acne. Actually, the patient is in the sixth month of treatment with oral contraception and is being followed up.

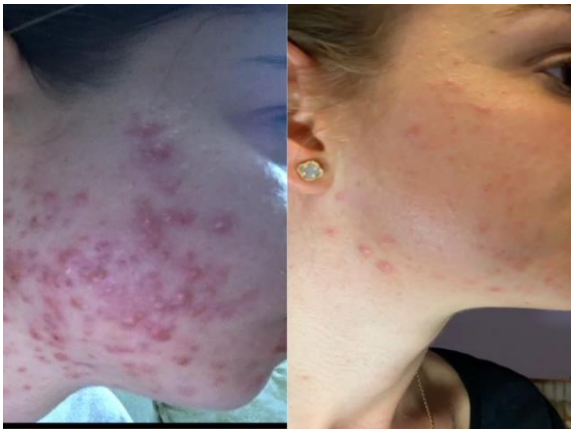

Figure 3. Case 3

Case 4

A female 36 years old has been treated for many years for acne vulgaris but not with a satisfying result. She refers that has used retinoids 10 years before but actually she does not want to use anymore retinoid. The gynecologic structure was not polycyclic structure. In clinical examination there were evident comedonal elements, papule/ pustules on all face. Referring her experience with acne vulgaris, anamnesis and her gynecologic condition we decided to treat the patient with oral spironolactone 50mg / day for the first month and 100mg / day for the next 2 months. Based on the protocol we monitored potassium and creatine levels 1 week after initiation of the therapy and then monthly for 3 months.

Figure 4. Case 4

After the first month there was a noticeable improvement of the condition, and the best results were seen after 3 months of full treatment.

During treatment with spironolactone the patient complained of a slight swelling and breast pain. Now she is in the 6th month of treatment for acne scars and is being followed up.

DISCUSSION

Referring the protocols of Acne treatment, oral antibiotics are prescribed as second-line therapy for patients with mild-to-moderate acne that is not adequately controlled with topical agents alone. Oral antibiotics use is a good choice in the treatment of patients with moderate-to-severe

inflammatory acne. We treat our case 1 with oral antibiotic referring the condition of the patient, his preferences and tolerability. Oral antibiotic treatment is recommended to combine with local treatment to improve the efficacy and either for resistance reason with topical retinoid or benzoyl peroxide if tolerated. (1,2,3) Referring to this protocol the treatment of our case 1 was the choice of antibiotic and local treatment. The results were noticeable improvement after 4 months of treatment. Monotherapy just with oral antibiotics is not recommended referring the last protocols and publications. (4, 5) The global problem of antibiotics resistance emphasizes the fact that the treatment must be recommended to be used for the shortest possible duration, ideally 3-4 months. (5) Local treatment during the use of oral antibiotics and after are strongly recommended. (6, 7, 8,9)

Treatment with antibiotics for limited period use may reduce and minimize the risk of inflammatory bowel disease (for tetracycline's), pharyngitis (for tetracycline's) (10), Candida difficile infection (11) and candida vulvovaginitis. The studies have shown that these side effects during antibiotic use are rare. During pregnancy antibiotics: Penicillin, erythromycin, and cephalosporin have safety profile. (12) The antibiotics that are recommended for treatment of acne vulgaris are: tetracycline class (minocycline, doxycycline, tetracycline), macrolides, azithromycin, Trimethoprim sulfamethoxazole (TMP/SMX), Penicillin and cephalosporin.

First line therapy for moderate- severe inflammatory acne referring the antibiotic use is the group of tetracycline that include: minocycline, doxycycline, and tetracycline. All the drugs within this group have an anti-inflammatory effect. (5) Doctors have to take in consideration some issues before prescribing this group of drugs: allergy, age< 8 years old, and pregnancy. One side effect or phenomenon associated with this group is pseudotumor cerebri. (5) Doxycycline is recommended in the dosage 1.7-2,4 mg/kg dose range (12) but for practical reason it is recommended to be used 50, 100, 200 mg a day. The use of doxycycline in sub antimicrobial dose (20 mg, 40 mg daily) is used successfully for anti-inflammatory effect in patients with moderate acne vulgaris. (13, 14) Doctors have to take in consideration that doxycycline is a photosensitizing medication and is more than minocycline, (5) and either the fact of gastrointestinal disturbances in high doses. (15) To minimize these side effects of the treatment patients should be advised to wear high SPF factor cream every day, to avoid sun baths during the treatment and to take doxycycline after the meal with water. (5) Another oral antibiotic that is recommended to treat acne vulgaris is minocycline that is recommended to be used 1 mg/kg. (5) For practical purposes, minocycline is generally dosed at 50 to 100 mg twice daily. Referring a study by Strauss et al treatment with minocycline was thought to be superior to doxycycline in reducing Proponium acnes. (16) Side effects noticed during the treatment with

minocycline are tinnitus, dizziness, and pigment deposition within the skin, mucous membranes, and teeth. (5) The hyperpigmentation is noticed in patients that use high dose and for long period. (5) In few cases are reported hypersensitivity drug reactions, drug-induced lupus. (17,18,19,20) Oral erythromycin is another oral antibiotic that is used successfully in the treatment of acne vulgaris. Is a medication of choice in pregnant woman? (21,22). It is recommended to be used in the doses 250 to 500 mg twice daily and in combination with local treatment such as Benzoyl peroxide. (23) Doctors have to take in consideration that although erythromycin is largely considered safe for use during pregnancy, some papers reported existence of fetal cardiac malformation (24) and if used for long periods of time, hepatotoxicity is noticed in 10-15% of pregnant patients. (25,26)

Azithromycin is a medication that is tolerated better than erythromycin and is recommended in different dosage. One protocol is 500 mg, once daily for 4 consecutive days per month for 2 consecutive months. (27,28) Referring another study the protocol is 500 mg once daily for 3 days in the first week followed by 500 mg once weekly until week 10. (29) Another group of authors recommend the use of 500 mg once daily for 3 consecutive days each week in month 1 followed by 500 mg once daily for 2 consecutive days each week in month 2 and then 500 mg once daily for 1 day each week in month 3. (30) Referring one study in 2005 it was emphasized that azithromycin is as effective to treat patients with Acne Vulgaris as doxycycline. (30) Another more recent study in 2014 by Ullah et al. that compare the treatment of Acne Vulgaris with azithromycin and doxycycline showed the superiority of doxycycline. (31)

In patients with Acne vulgaris that are recalcitrant to tetracycline and macrolide it is recommended to use Trimethoprim sulfamethoxazole (TMP/SMX). Doctors when switch to this medication have to take in consideration the risk of resistance development. Referring the protocols TMP/SMX should be restricted to patients who are unable to tolerate tetracycline agents or in patients who are treatment-resistant. (5) The usual dose for patients with AV is one double-strength tablet twice daily. Side effects reported are gastrointestinal disturbances, photosensitivity, drug eruptions and Stevens-Johnson syndrome/TEN. (32,33)

Another alternative for the treatment of Acne vulgaris is Penicillin and cephalosporin especially during pregnancy or with allergies to other classes of antibiotic treatments. (5) Side effects include risk of hypersensitivity reactions (drug eruptions, anaphylaxis) and gastrointestinal disturbances (i.e., nausea, diarrhea, and abdominal distention and discomfort). (5) The recommended dosing for amoxicillin is 250 mg twice daily up to 500 mg three times daily. A study published by Fenner et al. showed that cephalexin is effective to treat patients with acne, 78% of patients noticed clinical improvement. (34) Recommended doses of cephalexin are 500 mg twice daily.

Our case 2: based on clinical condition and the anamnesis of the patient we decided to treat the patient with isotretinoin. Isotretinoin is a non-hormonal and non-microbial treatment option for moderate - severe acne vulgaris. (33) It is used successfully to treat recalcitrant resistant Acne Vulgaris or cases that relapses quickly after the antibiotic treatment. (34, 35, 36, 37,38,39) Based in protocols, isotretinoin is indicated for the treatment of patients with moderate- severe inflammatory acne that is either treatment-resistant, produces physical scarring or significant psychosocial distress. (50) Different studies shows that isotretinoin is effective in decreasing sebum production, the number of acne lesions (papules, pustules, nodules) and acne scars. (39,40,41,42,43,44,45,46,47) The starting dose recommended is 0.5 mg/kg/day for the first month and then increased to 1 mg/kg/day as tolerated up to a cumulative dose of between 120 and 150 mg/kg. (46,47,48) Some studies shows that higher cumulative doses up to 200 mg/kg may be more effective to reduce the rates of acne relapse and retreatment, but doctors have to take in consideration side effects of the medication. (50, 49) During the everyday practice in a way to minimize side effects and the medication to be tolerated well by patients are recommended low dose isotretinoin (0.25-0.4 mg/kg/day) and lower cumulative dose regimens. (34,35, 37,38, 40,48,49,50,51,52,53) It is recommended to take isotretinoin with meals, absorption is increased with fatty foods. (54,55)

In adult women, before prescribing isotretinoin it is recommended to take in consideration the contraception methods because of teratogenicity effect. Doctors should counsel women that they should not become pregnant 1 month before, during, or within 1 month after completion of isotretinoin therapy. Other side effects reported include: xerosis, cheilitis, xerophthalmia (most frequently), decreased night vision, vision changes, headache, hepatotoxicity, hypertriglyceridemia, mood changes, bone demineralization, cardiovascular risk factors, possible link to depression/anxiety/mood changes/suicidality, and possible link to inflammatory bowel disease (IBD). (31) A study by Zaenglein et al emphasize that there is insufficient data to support the link between isotretinoin use and IBD. (31) A frequent side effect during the treatment with oral isotretinoin are symptoms that mimic hypervitaminosis. A but these side effects resolve after discontinuation of therapy. (31) There is a debate referring the link between oral isotretinoin use and depression, anxiety, mood changes, or suicidal ideation/suicide is mixed. Some case reports show that isotretinoin has no negative effect on mood, memory, attention, or executive function. (31,55,56,57,58,59,60,61,62,63,64,65,66,67,69)
But in the other hand there are studies that shows that 140 patients treated with isotretinoin have committed suicide while taking this treatment or within a few months of discontinuation of treatment and around 257 patients have been hospitalized for severe depression or attempted

suicide. (70) However, there are authors that argued that the number of reported cases that suffer for depression among isotretinoin users is not greater than people that suffer from depression in the general population. (71) It is recommended for doctors to monitor carefully patients under treatment with isotretinoin for depressive symptoms. The AAD working group recommends that prescribing physicians monitor patients for any indication of depressive symptoms and educate patients on the potential risks of treatment with isotretinoin.

After the first month of treatment, we did laboratory test to monitor the patient health (case 2) during the treatment with oral isotretinoin. Serum lipid profile (serum cholesterol, triglycerides), liver functions tests (transaminases) are known to increase in some patients who take oral isotretinoin (72,73,74). Some practitioners monitor laboratory test results monthly, but others only check at baseline and after dosing changes. Referring Hansen et al. recommendations for lipid panel and liver function tests are indicated to be repeated after two months and if these results are within the parameters, then no more tests are needed. (75) Pregnancy testing is required for female patients of childbearing potential at baseline, monthly during therapy, and 1 month after completion of isotretinoin treatment. The use of isotretinoin during pregnancy is contraindicated.

Our case 3: based on clinical condition and the anamnesis of the patient we decided to treat the patient with birth pill control (combined preparation of ethinyl estradiol and drospirenone). OCPs offer a valuable treatment option of women with acne. Hormonal contraception is used for treating acne vulgaris in the settings of hyperandrogenism, late-onset acne (> 25 years of age), and jawline acne distribution, acne with menstrual flare, comedonal acne with seborrhea, and acne that is resistant to conventional therapies. (78) cOCPs include an estrogen component, usually ethinyl estradiol, and a variant of progestin component. Estrogens are known to decrease sebum production and inhibit production of LH, FSH hormones. Progestin-only contraception is not used to treat acne. Synthetic progestins act at the progesterone receptor but also react with the androgen receptor to varying degrees and thus may even potentiate acne. (80) Newer synthetic generation progestins, have less activity at the androgen receptor and more specificity for the progestin receptor. These modifications were undertaken to reduce the potential risk of thromboembolic events and androgenetic side-effects. In most of the studies analyzed, total acne lesion counts decreased 40% to 60% with cOCP use and inflammatory lesion counts show greater improvement than noninflammatory lesion counts. (80) Cyproterone acetate (2 mg of cyproterone acetate and 0.35 of ethinyloestradiol) has shown variable efficacy outcomes. RadosławSłopień et al in their study emphasized that the results were visibly improved in acne in 40% and noticed a very good cosmetic effect in 26% of patients after 3 months of treatment.

Cypreterone is an analog of 17 OH-progesterone. cOCPs containing chlormadinone acetate or cyproterone acetate seemed to improve acne better than those containing levonorgestrel; however, this was based on limited clinical data. (86) Drosperinone is an analogue of spironolactone also used in the treatment of acne. DRSP 3 mg has been combined with two different doses of EE: 0.030 mg for one type of an oral contraception and 0.020mg for another medication of oral contraception. A drospirenone COC appeared to caused improvement in the facial and trunk acne (improvement > 50%) after 6 months of treatment and to be more effective than norgestimate or nomegestrol acetate plus 17β-estradiol but less effective than cyproterone acetate. (82) Dienogest significantly improved acne in 52%-66% of treated patients. (83-84) Dienogest was more antiandrogenic than both drospirenone and chlormadinone acetate. (85) EE-norgestimate was shown to be efficacious in moderate facial acne treated for 6 months, inflammatory lesions reduced by 56%, non-inflammatory by 41% and 32% achieved excellent improvement. (81) A lot of formulations of oral contraceptive medications exist, but the U.S. Food and Drug Administration (FDA) has only approved three types of OPCs for the treatment of acne vulgaris: norgestimate 0.180 mg/0.215 mg/0.25 mg - ethinyl estradiol 0.035 mg; norethindrone 1 mg- ethinyl estradiol 0.020 mg/0.030 mg/0.035 mg; drospirenone 3 mg -ethinyl estradiol 0.02 mg .(86) Cyproterone acetate is a synthetic derivative of 17-OH progesterone, approved in Europe for the treatment of acne, but is not available in the United States. Before prescribing OCPs should be considered some important contraindications: cardiovascular risk factors, severe hypertension, history of stroke or myocardial infarction, smoking combined with age > 35 years, history of migraine with focal aura, history of migraine combined with age > 35 years, current or past history of breast cancer or endometrial cancer, diabetes with complications, hepatic malignancy, abnormal liver function, hypersensitivity to OCPs, pregnancy. (87) OCPs offer an acne treatment option, but they are overlooked because dermatologists are unfamiliar with their description, their side effects. One study showed that dermatologists prescribed OCPs in only 2% of visits with female patients aged 12 to 55 years who presented for acne treatment. (80) Patients' fear of using a medication for several months/years as well as the possibility of serious side effects are another barrier to the use of OPCs. In conclusion, oral contraceptive pills can be an effective treatment option for women with acne, but understanding the risks and identifying the ideal candidates for therapy is essential.

Our case 4: based on clinical condition and the anamnesis of the patient we decided to treat the patient with spironolactone. Post-adolescent acne primarily affects females and is resistant to conventional treatment in 79-82% of cases (88). 81% of women report failures with systemic antibiotics and failures in response to treatment with isotretinoin ranging from 15 to 30% (89).

Spironolactone is used as a good alternative treatment in this population. It works as an inhibitor of the 5-alpha-reductase receptors at the sebaceous gland and reduces production of luteinizing hormone (LH) production at the pituitary level. Currently, very few studies have been performed in a limited number of patients: the studies showed that at low doses (lower than 200 mg/day over 3 months duration), spironolactone can be effective against acne. (89) P. Vargas-Mora et al 2020 recommend in acne to start dosing at 25 mg/d for 1 week and then to increase to 50 mg/d (and maintain this dose in most patients). In this study authors have not found it necessary to use doses greater than 100 mg/d. The treatment works slowly over several months. Although spironolactone has been around for almost 30 years in the US as a treatment for facial acne, its indication for acne treatment has not yet been approved by the FDA, which limits dermatologists in its description. Common side-effects in pre-menopausal women include breast tenderness/enlargement and irregular menstrual periods. These effects can be avoided by taking spironolactone with oral contraceptive pills in women of childbearing age. This medicine should not be prescribed to women who are pregnant or planning to become pregnant. Spironolactone can cause mild or serious side effects. Mild side effects of Spironolactone can include confusion, headache, itching, menstrual problems, nausea and vomiting, diarrhea, sexual dysfunction, stomach cramps, dizziness. Most of these side effects may go away within a few days or a couple of weeks. Serious side effects can include: allergic reaction, electrolyte imbalance, gynecomastia. Physician should recommend to check frequently the potassium level in women with heart or kidney problems as well as those taking medications that affect potassium levels. (90) Because of its anti-androgenic effects, spironolactone has been hypothesized to be associated with an increased risk of estrogen-sensitive cancers but there is currently no evidence to support this in human subjects (91). The benefits of using spironolactone in the treatment of acne are: Improving the quality of life in women suffering from acne; reduces the risk of developing bacterial resistance by reducing the prescription of antibiotics (92); can be used as an alternative to isotretinoin in patients of childbearing age and the peripheral hyperandrogenia that frequently occurs in women does not respond well to isotretinoin. Patients showed 73.1%, 75.9%, and 77.6% improvements on the face, chest, and back, respectively, which supports that spironolactone is equally effective in treating acne in multiple areas of the body. (91) Based on the study performed by Charny at al (2017) spironolactone has a higher efficacy than minocycline and almost the same as isotretinoin making it an effective treatment for acne in adult women. Although it has shown efficacy, its indication has not yet been approved by the FDA for acne treatment. Studies with larger groups will be needed for spironolactone to gain legitimacy as a systemic acne medication. Thus,

for many dermatologists' spironolactone remains an alternative rather than a mainstay treatment for female patients with acne. (91)

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Conflicts of interest: None declared.

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