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CONTENTS

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Alternative treatment of psoriasis - is rifampicin a mild immunosupressor?

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Abstract

Psoriasis is a common T-cell-mediated autoimmune inflammatory disease. Conventional systemic therapy includes: methotrexate, cyclosporine, retinoids and psoralen ultraviolet A, which are effective, but associated with toxicity and adverse effects which may limit their long-term use. Although effective as well, data on the long-term safety of newly introduced biologic agents are still not available. Herein, we present our clinical experience with rifampicin in the treatment of psoriasis, and review of literature regarding its potential mechanisms of action.

Psoriasis is a T-cell-mediated autoimmune inflammatory disease (1, 2). It significantly affects the quality of life of patients suffering from psoriasis and their families (3). The therapeutic goal is to obtain satisfactory disease control, and improve patients' quality of life. Conventional systemic therapy includes methotrexate, cyclosporine, retinoids and psoralen ultraviolet A, which are used in the treatment of the disease, but they are associated with toxicity and adverse effects, which may limit their long-term use (4). In recent years, new biological agents such as etanercept, efalizumab, alefacept, infliximab, and adalimumab have been introduced (5). Although effects of some of these new agents have been evaluated for longer periods of continuous use, the majority of data concerning their usage have been obtained only for short-term treatment.

We started using rifampicin in the treatment of psoriasis in 1992 (6-8). Kazandjieva et al., reported on four patients with tuberculosis treated with rifampicin (9-10) who suffered from concomitant psoriasis. The authors observed complete clearance of the psoriatic skin lesions during the one-year treatment with rifampicin. Numerous studies have been conducted since then (11-16). Recently, Tsankov et al. hypothesized that rifampicin acts as a mild immunosuppressive agent (17).

Materials and methods

We randomized patients suffering from either guttate or plaque psoriasis. Patients under 18 years of age were not enrolled in the study, as well as patients with a history of liver disease. After an one month-wash-out period rifampicin therapy was initiated. There was no Psoriasis Area and Severity Index (PASI) cut-off for admission into study and no history, or clinical signs of psoriatic arthritis. All patients included in the study underwent examination of total blood cell count and liver enzymes before treatment, once during the treatment, and at the end of rifampicin therapy. All patients were informed about the transient orange-red color of body fluids at the beginning of rifampicin therapy.

Treatment of guttate psoriasis with rifampicin

A group of 82 patients with guttate psoriasis received an oral dose of 600 mg of rifampicin for at least 60 days. Only emollients were used for topical therapy. Psoriasis Area and Severity Index (PASI) was calculated at baseline, and on the 60th day. The primary end-point was the reduction of PASI at the end of the therapy.

Streptococcal infections are well-known triggers of guttate psoriasis (18-21), so guttate psoriasis patients were divided into two groups according to the following criteria:

1. Clinical evidence of dental, ear, nose, throat or genitourinary infection;

2. Bacterial culture from the pharynx or vaginal smear;

3. Positive antistreptolysin titer (>200).

Group A (39 patients; 23 female and 16 male) - *with* evidence of concomitant streptococcal infection.

Group B (43 patients; 21 female and 22 male) - *without* evidence of concomitant streptococcal infection.

The control group included 10 randomly selected patients with guttate psoriasis (4 female and 6 male; 5 patients had a concomitant streptococcal infection, and another 5 were without evidence of streptococcal infection). They were given placebo capsules, labeled as rifampicin, in the same daily dosage for 60 days, and emollients.

The usual two-sample *t*-test was used to compare the difference between the factor levels. The non-parametric Mann-Whitney U-test was also used. The *t*-test was used to compare the average percentage reduction as well.

Treatment of chronic plaque psoriasis with rifampicin

Rifampicin was used in 25 patients with chronic plaque psoriasis and it was administered in the same daily dose as in the group with guttate psoriasis. PASI was calculated at baseline and on the 60th day. The primary endpoint was the reduction of PASI at the end of the therapy.

Extended treatment of psoriasis with rifampicin

Rifampicin therapy was continued in 20 psoriatic patients who achieved at least PASI 50 after 60 days. Thirteen of these patients were from the guttate psoriasis group, and seven were from the group with chronic plaque psoriasis. None of the patients had had previous history of any systemic treatment for their psoriasis, except phototherapy. The daily dose of rifampicin remained 600 mg per day orally. Emollients were given for topical therapy only. The primary endpoint was the reduction of PASI on the 6th month and lack of exacerbation of the disease during this period.

Moreover, three patients on the extended treatment with rifampicin presented with clinical remission after 6th months and continued rifampicin therapy (11 months now).

Results

Guttate psoriasis

Results of therapeutic effectiveness of rifampicin in patients with guttate psoriasis are summarized in Table 1.

Table 1. Rifampicin treatment of patients with guttate psoriasis

	Patients with guttate psoriasis		
	Group A	**Group B**	**Placebo**
Number of patients	39	43	10
Age - years	16 - 68	23 – 71	31 - 59
Gender – female/male	23/16	21/22	4/6
Duration of psoriasis	3 weeks - 13 years	1 – 28 years	2 months – 5 years
Mean PASI at baseline	8.11	8.95	4.82
Mean PASI on the 60th day	2.06	2.57	2.93
Mean PASI reduction	75%	71%	39%
PASI 50 – number of patients (%)	28 (72%)	30 (70%)	3 (30%)
PASI 75 – number of patients (%)	20 (51%)	19 (44%)	0

PASI 50, PASI reduction of 50% at the end of the therapy; PASI 75, PASI reduction of 50% at the end of the therapy

The *t*-test for two independent groups was used to compare differences. The *t*-test did not show statistically significant differences between Groups A and B (p=0.20). This may be due to small samples of patients and the corresponding great variations in the groups. The non-parametric Mann-Whitney U-test also showed no significant differences (p=0.114). Even when changing PASI at baseline and on 60th day, in order to make the distributions normal, the comparison with *t*-test showed no differences once again (p=0.14). The *t*-test was applied to compare the average percentage reduction as well. However, no significant difference (p=0.47) was established. In the group A, the mean PASI decreased from 8.11 (at the beginning of the therapy) to 2.06 on the 60th day. In the group B, the mean PASI decreased from 8.95, at baseline, to 2.57 at the end of the therapy (Figure 1 and Figure 2). Based on the obtained results, it can be concluded that improvements in group A and group B are statistically identical (p<0.001).

Comparing the efficacy of rifampicin with placebo, there is a significant evidence in favor of rifampicin (p < 0.005).

Three patients reported transient nausea and vomiting. There were no patients with abnormal laboratory findings. Blood cell counts and liver enzymes were normal at baseline, during and at the end of rifampicin therapy. All patients reported orange-red urine color, which disappeared after completion of treatment. None of the patients required discontinuation of therapy due to side-effects.

Chronic plaque psoriasis

The results in chronic plaque psoriasis patients are summarized in the Table 2.

It was observed that some of the patients achieved a very good therapeutic response - 12% of them had PASI 75 scores at the end of treatment. However, some patients achieved PASI 30. It should be pointed out that the disease severity index in the chronic plaque

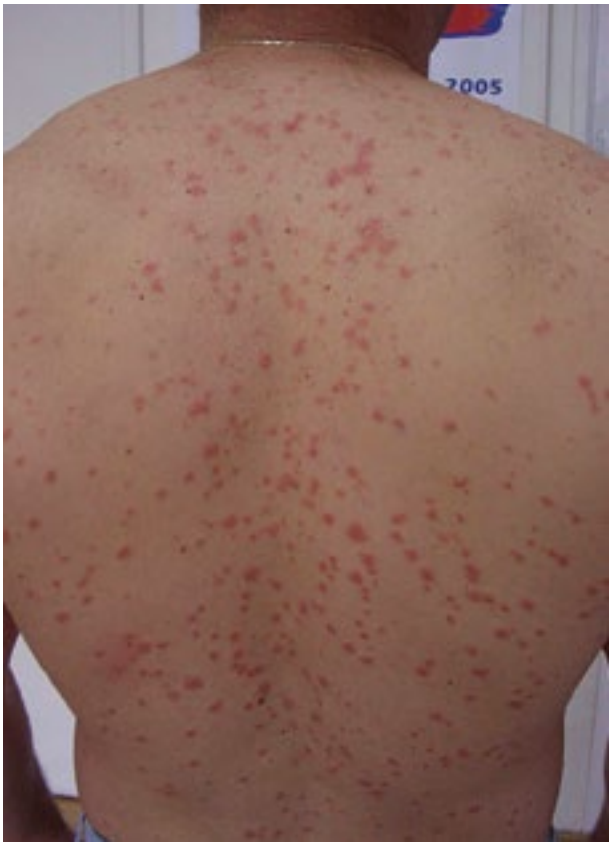

Figure 1. The first patient from the group B: PASI 10.8 score at baseline

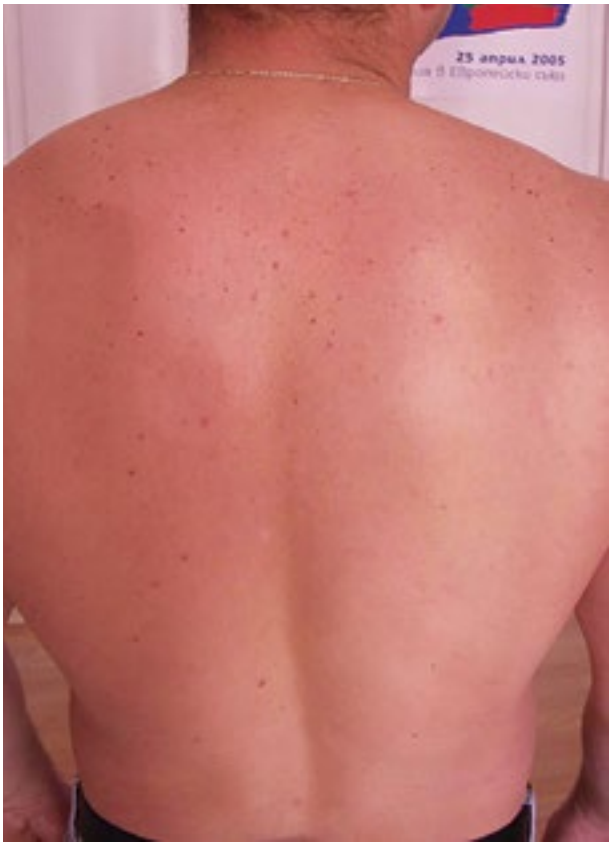

Figure 2. The first patient from the group B: PASI 0.5 score on the 60th day

Table 2. Rifampicin treatment of patients with chronic plaque psoriasis.

Patients with chronic plaque psoriasis	
Number of patients	25
Sex – female/male	14/11
Age - years	29 – 69
Duration of psoriasis - years	1 – 25
Mean PASI at baseline	18.05
Mean PASI on the 60th day	9.02
Mean PASI reduction	50.03%
PASI 50 – number of patients (%)	13 (52%)
PASI 75 – number of patients (%)	3 (12%)

PASI 50, PASI reduction of 50% at the end of the therapy; PASI 75, PASI reduction of 50% at the end of the therapy

psoriasis group was greater (mean PASI at baseline was 18) than the severity index in the guttate psoriasis group (mean PASI at baseline was 8.48).

Extended treatment of psoriasis with rifampicin

The improvement achieved on the 60th day was maintained in those patients who continued receiving rifampicin for 6 months. Ten patients (50%) achieved PASI 90 after 6 months. All patients with guttate psoriasis presented with marked improvement (PASI 75) or remission (PASI 90) at the end of the 6-month period. Three chronic plaque psoriasis patients maintained remission achieved after 6 months, through the whole treatment period (Figure 3 and Figure 4). None of the patients suffered exacerbation of the disease during the 6 month period of rifampicin therapy. Three patients on rifampicin therapy have been followed up for 11 months and they are still without exacerbation of the disease. None of the patients demonstrated any clinical or laboratory side effects during the extended treatment period. The orange-red urine color disappeared soon after drug discontinuation.

Discussion

We began our clinical studies with rifampicin in patients with guttate psoriasis, believing that its antimicrobial properties would be most effective for this form of the disease. However, data suggesting immunosuppressive properties of rifampicin have been available in the literature for more than 30 years. Paunescu et al. suggested that rifampicin exhibits immunosuppressive properties both in vitro and in vivo. Specifically, they found that it affects antibody production and certain cell-mediated forms of immunity. This action of rifampicin is achieved if two or four times the therapeutic human doses are used, and it is reversible in vivo (22). Nilsson et al. found that stimulated human lymphocytes are significantly inhibited by rifampicin (23). Gupta et al. established a considerable T-lymphocyte suppression, 2-3 weeks after the initiation of rifampicin therapy (24). The cellular suppression, evident after a 28-day treatment with rifampicin, is transient when the drug is discontinued. Mlambo et al. reported that at high doses rifampicin moderately suppressed TNF-α, and these findings suggested that rifampicin had

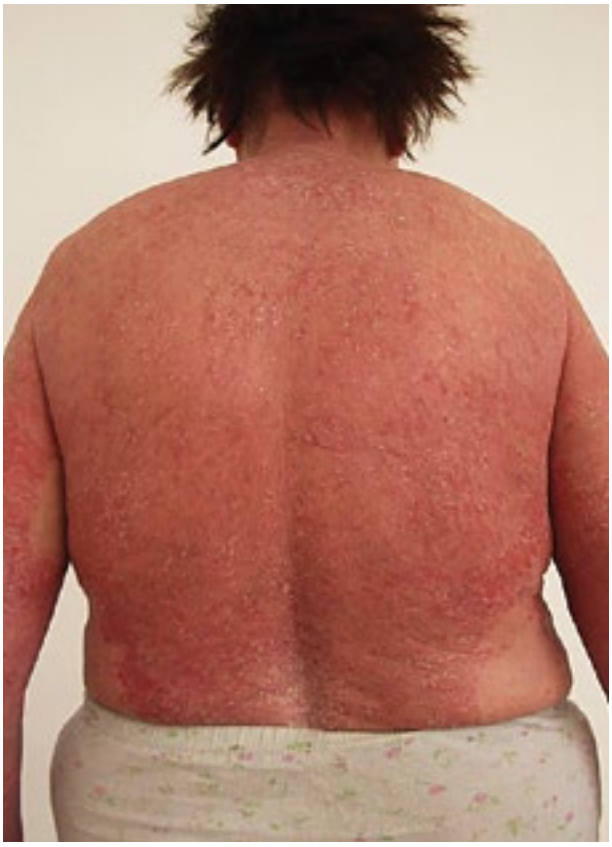

Figure 3. The second patient with chronic plaque psoriasis: PASI 25.1 score at baseline

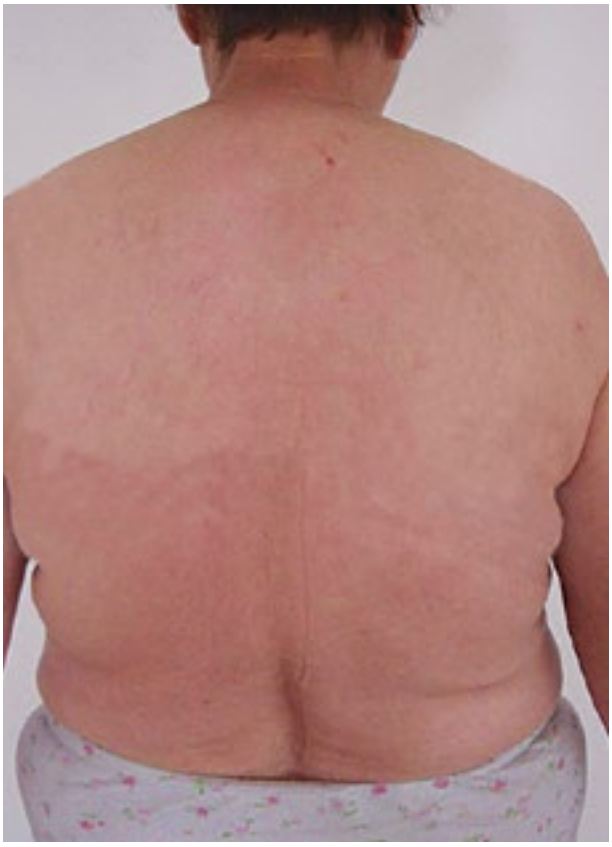

Figure 4. The second patient with chronic plaque psoriasis: PASI 0.8 score on the 6th month

differential immunomodulatory effects on the innate immune mechanisms (25). Rifampicin may also inhibit the secretion of IL-1β and TNF-α (26). Calleja et al. demonstrated that rifampicin both binds to, and activates, the human glucocorticoid receptor, which regulates the expression of many genes, including those encoding interleukins that regulate immune responses (27). Most recently, Dubrac et al. established that pharmacologic activation of pregnane X receptor (PXR) inhibits T-lymphocyte function (28). The authors showed that PXR agonists, such as rifampicin, inhibit the expression of CD25, a T-lymphocyte activation marker, as well as synthesis and production of the Th1 cytokine IFN-gamma by T-lymphocytes in a PXR-dependent manner. Moreover, pharmacologic PXR activation dramatically reduces the ability of T-lymphocytes to proliferate in response to a strong immune stimulation.

Tuberculosis is the main indication for rifampicin, as part of the antituberculotic drug combination where rifampicin is administered for more than a year. Data on its side effects and drug interactions have been reported for more than 35 years of clinical experience (29-32). We used rifampicin in psoriasis patients for 6 months. Our results in plaque type psoriasis are preliminary. The number of patients in this group was too small for statistical significance, and there was no control group for comparison. We believe that there are good-responders and nonresponders to rifampicin. More studies on the use of rifampicin in psoriasis are necessary. However, our current therapeutic results, along with the literature data suggest that rifampicin is a mild immunosuppressive agent which can be used in all types of psoriasis, but it is most effective in the guttate psoriasis patients.

Conclusion

Psoriasis is still an incurable disease. Most patients experience a recurrence after the systemic treatment with rifampicin (15-45 days) is discontinued. This

is evident for all the conventional drugs, even for new biological agents. Our results are promising in the continuous search for alternative therapeutic modalities providing psoriasis patients with periods of remission and better quality of life. However, due to its moderate immunosuppressive effect, we believe that rifampicin can serve as a cheap, effective, and safe alternative to the new biological agents.

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Alternativna terapija psorijaze: da li rifampicin ima blago imunosupresivno dejstvo?

Sažetak

Uvod: Psorijaza je učestala inflamatorna bolest kože koja nastaje usled patološke aktivacije T-ćelija. Konvencionalna sistemska terapija (metotreksat, ciklosporin, retinoidi, PUVA tj. psoralen i UVA) efikasna je, ali usled toksičnosti ovih preparata, njihova dugotrajna primena je isključena. Iako su novi biološki agensi takođe efikasni, nedostaju podaci o njihovoj bezbednosti prilikom duže primene.

Cilj: Zadatak ovog rada je da prikaže kliničko iskustvo u primeni rifampicina kod bolesnika s psorijazom, kao i pregled literature koja se bavi njegovim mogućim mehanizmima delovanja.

Materijal: Ispitivanje je obuhvatilo randomizirani uzorak, koga su činili oboleli od gutatne ili hronične plakozne psorijaze sa različitim PASI (eng. Psoriasis, Area and Severity Index) skorom (predstavlja standardni metod za kvantitativnu ocenu lokalizacije, rasprostranjenosti i težine kliničkog nalaza kod obolelih od psorijaze, usvojen na međunarodnom nivou). Osobe mlađe od 18 godina i osobe koje su davale anamnestičke podatke o bolestima jetre, i artritisu nisu bile uključene u ispitivanje. Svi ispitanici su dali svoj pismeni pristanak. Pre započinjanja lečenja, svima je dato objašnjenje o prestanku narandžasto-crvene prebojenosti urina po prestanku uzimanja leka. Ukupan broj leukocita i jetreni enzimi su određivani u tri navrata: na početku, u toku i na kraju lečenja. Eksperimentalnu grupu su činile 82 osobe sa gutatom psorijazom i 25 osoba sa hroničnom plakoznom psorijazom. Svi ispitanici sa gutatnom psorijazom, podeljeni su u dve grupe: grupa A, oboleli sa streptokoknom infekcijom (39 osoba) i grupa B, oboleli bez streptokokne infekcije (43 osobe). Prisustvo ili odsustvo infekcije je određivano na osnovu sledećih kriterijuma: klinički manifestna orofaringealna ili genitourinarna infekcija; biogram brisa uzetog sa sluzokože orofaringealne ili genitourinarne regije; antistreptollizinski titar >200. Kontrolnu grupu je činio randomizirani uzorak od 10 osoba sa gutatnom psorijazom, od kojih je 5 bilo sa streptokoknom infekcijom.

Metode: Svi ispitanici u eksperimentalnoj grupi su lečeni peroralno kapsulama rifampicina u jednoj pojedinačnoj dnevnoj dozi od 600 mg, tokom 60 dana. Lečenju je predhodio period bez terapije, u trajanju od minimum mesec dana. Isti protokol je primenjen i u kontrolnoj grupi, samo što su ispitanici umesto rifampicina, dobijali placebo kapsule etiketirane kao rifampicin. Svim ispitanicima su lokalno aplikovane indiferentne emolijentne kreme. PASI skor je određivan nultog dana i šezdesetog dana lečenja. Za procenu efikasnosti terapije korišćen je stepen smanjenja PASI skora šezdesetog dana u odnosu na nulti. Šezdesetog dana lečenja, kod 20 osoba, 13 sa gutatnom i 7 sa plakoznom psorijazom, utvrđeno je smanjenje PASI skora za najmanje 50% u odnosu na nulti dan, te je lečenje istim protokolom nastavljeno. Nakon 6 meseci lečenja, određivan je PASI skor. Za procenu efikasnosti terapije korišćen je stepen smanjenja PASI skora u odnosu na nulti dan, kao i odsustvo recidiva bolesti tokom šestomnesečnog perioda lečenja.

Rezultati: Nakon 60 dana lečenja, rezultati ispitivanja efikasnosti terapije sa rifampicinom, dobijeni kod ispitanika sa gutatnom psorijazom i infekcijom i gutatnom psorijazom bez infekcije, prikazani su u Tabeli 1. Rezultati dobijeni u grupi A ispitanika sa gutatnom psorijazom i streptokoknom infekcijom, su poređeni sa istim rezultatima dobijenim u grupi B ispitanika sa gutatnom psorijazom bez streptokokne infekcije. Nije utvrđena statistički značajna razlika između ove dve grupe (*t*-test za dve nezavisne grupe i neparametrijski Mann-Whitney U-test). Takođe, šezdesetog dana lečenja nije utvrđena statistički značajna razlika (pomoću *t*-testa) između dve grupe ni u prosečnom smanjenju PASI skora (p=0.47). U grupi sa infekcijom, prosečan PASI skor je smanjen šezdesetog dana sa 8.11 koliko je iznosio na početku lečenja, na 2.06. U grupi sa gutatnom psorijazom bez infekcije, PASI je snižen sa 8.95 na 2.57 (Slika 1 i 2). Rifampicin je pokazao statistički značajno veći terapijski efekat u lečenju gutatne psorijaze u odnosu na terapijski efekat koji je pokazao placebo ($p < 0.005$). Tokom 60 dana lečenja, samo su 3 ispitanika imala prolaznu muku i povraćanje, niko od ispitivaih nije imao poremećaj laboratorijskih parametara, kod

svih je nestajala promena u boji urina po prestanku terapije, niko od ispitanika nije morao da prekine započeto lečenje. U grupi obolelih sa hroničnom plakoznom psorijazom (Tabela 2), početna prosečna vrednost PASI skora je bila viša (PASI =18) u odnosu na grupu obolelih od gutatne psorijaze (PASI =8.48). Pojedini ispitanici su postigli dobar terapijski efekat,12% je imalo smanjenje PASI skora za 75%, dok su pojedini ispitanici ostvarili smanjenje PASI skora za samo 30%. U grupi od 20 pacijenata koj kojih je lečenje rfampicinom nastavljeno, 50% je postiglo smanjanje PASI skora za 90% nakon 6 meseci lečenja Kod svih ispitanika sa gutatnom psorijazom, nakon 6 meseci lečenja PASI je smanjen za 75% ili 90% u odnosu na nulti dan. Svo vreme dok je trajalo lečenje rifampicinom, ni jedna osoba nije imala recidiv psorijaze kao ni poremećaj laboratorijskih parametara, kod svih je nestajala promena u boji urina po prestanku terapije. Tri ispitanika su postigla kompletnu remisiju i kod njih je lečenje nastavljeno. Do recidiva bolesti nije došlo ni nakon 11 meseci lečenja.

Zaključak: Psorijaza još uvek ostaje u grupi onih oboljenja kod kojih ne postoji radikalna specifična terapija, jednako efikasna kod svih obolelih. Kod većine obolelih koji su lečeni sa rifampicinom, recidiv bolesti je nastupio 15-45 dana nakon prestanka lečenja, što se dešava i nakon prestanka lečenja sa konvencionalnim ali i novim biološlim metodama sistemskog lečenja. Rezultati ovog ispitivanja pokazuju da bi se imunosupresivno dejstvo rifampicina moglo upotrebiti u lečenju obolelih od gutatne psorijaze, kao efikasna i bezbedna jeftina terapijska alternativa novim biološkim agensima. Potrebna su dalja ispitivanja sprovedena na značajno većem broju obolelih, kako bi se precizno evaluirala efikasnost rifampicina i bezbednost njegove primene u terapiji različitih formi psorijaze.

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).

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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.

LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

INOVACIJA TESTIRANA NA KOŽI SKLONOJ AKNAMA

Masna koža s blagim do umerenim aknama

EFFACLAR DUO

Sa termalnom vodom La Roche-Posay

Dvostruko delovanje.
Jedna nega.

Zahvaljujući jedinstvenom spoju aktivnih sastojaka, efikasnost kod oba tipa lezija...

1
- Niacinamid → protiv upala
- Pirokton olamin → deluje protiv bakterija i gljivica

2
- LHA + salicilna kiselina → keratolitičko delovanje
- Linolna kiselina → regulacija keratinizacije

Fiziološki pH 5.8
Bez alkohola
Bez boje
Bez parabena
Bez ulja
Nekomedogeno

...bez efekta isušivanja

24 satna hidratacija

Matirajuća i osvežavajuća nemasna tekstura.
Odlična podloga za šminku.

La Roche-Posay. Posvećen dermatologiji.

THE NOVI SAD DERMATOVENEREOLOGIC MOULAGE COLLECTION,
CLINIC OF DERMATOVENEREOLOGY, CLINICAL CENTER OF VOJVODINA, NOVI SAD, SERBIA
VOJISLAV ŠIKOPARIJA, SCULPTOR DONATES HIS MOULAGES TO THE FACULTY OF MEDICINE IN NOVI SAD, BELGRADE, 1964

Malignant transformation of a chronic leg ulcer: a case report

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Abstract

Squamous cell carcinoma (SCC) is a malignant tumor of epidermal keratinocytes which may arise *de novo,* or at already affected skin areas of different etiology, including chronic vascular ulcers (CVUs). We present a 74-year-old female patient, hospitalized in the Department of Dermatology, with venous ulceration of the lower right leg, 10x5 cm in size, with well-demarcated edges, and the base covered with fibrin and granulation tissue. The ulceration appeared 7 years ago, while 3 years ago it spread rapidly with pain in the right lower leg. In the beginning, the patient was treated with local and systemic antibiotic therapy. Later, hydrocoloid dressings and compressive bandages were applied, and after that hyperoxygenation was performed in the hyperbaric chamber. Although the above-mentioned therapy was applied correctly, it was not efficient. Since malignant alteration was suspected, two biopsies were taken and in both, histopathologic analysis showed granulation tissue without dysplasia. The third biopsy, however, performed a month after the second one, revealed a squamous cell carcinoma. After further investigations, amputation of the right lower leg was suggested. Therefore, in cases with extended CVUs without no adequate therapeutical response during a long period of time, malignant transformation should be considered, and multiple biopsies at various sites should be performed.

Long-lasting chronic leg ulcers (CLUs) of vascular origin are at increased risk for transformation into carcinomas. Malignant transformations are rare, and often misdiagnosed complications of CLU. However, the most common among them are well-differentiated squamous cell carcinomas (2). Clinical sings of malignant CLU include abnormal granulation tissue, the edges of the ulcer well differentiated from the surrounding skin, failure of progress despite accurate diagnosis and treatment, unusual pain and abnormal bleedding. Malignancy in CLU is confirmed by histopathology, taking multiple biopsies from different sites of the ulcer (3). It is necessary to determine the clinical stage of lesions, whereas histopathological differentiation reveals the extention of lesions, important for proper treatment.

Case report

We present a female patient, 74 years of age, admitted to the Department of Dermatology and Venereology of the Military Medical Academy with a lower leg ulceration which appeared 7 years ago. The ulceration increased in depth and width with years until it reached 10x5 cm in size, with intense pain, regardless of time or activity. The patient had no history of diabetes, or other chronic diseases, except for hypertension. It started 3 years ago, and was under good control with antihypertensive therapy. The ulceration was located on the front side of the right lower leg, irregular shaped, with hard edges, while the bottom was filled with granulations and even a slight touch could cause bleeding. The surrounding skin was unchanged, and lymph nodes were not enlarged (Figure 1).

Laboratory findings showed a mild anemia, while the other findings were within normal limits. Ultrasonography of the lower extremities revealed insufficiency of perforating venules in the distal third of the right lower leg, without signs of deep venous thrombosis, but degenerative changes were diagnosed on the arteries. Chest radiography and abdominal ultrasound findings were normal in the beginning, and the patient was treated with local and systemic antibiotic therapy. After that, hydrocolloid dressings and compressive bandages were used, without success, so hyperoxygenation in hyperbaric chamber was performed. None of these therapeutic modalities

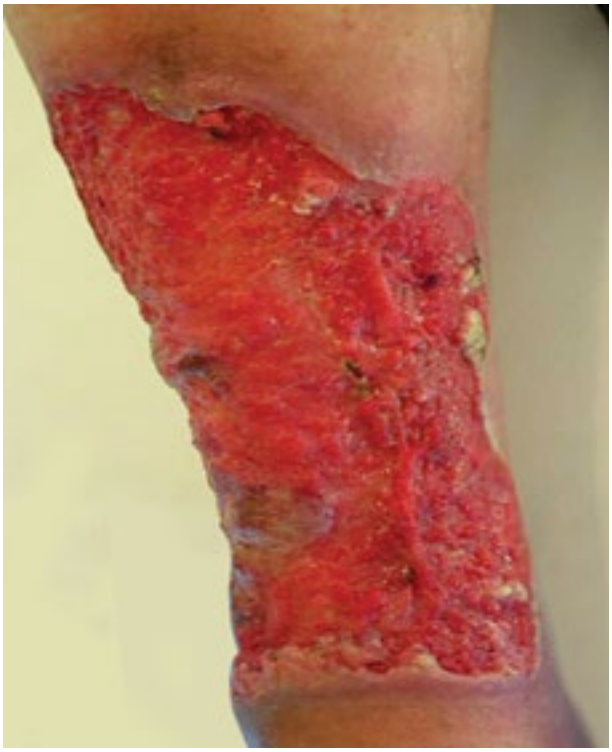

Figure 1. The ulceration on the front side of the right lower leg

were effective. Since the ulcer was refractory to treatment, a malignant alteration was suspected. In short period of time, two biopsies were taken and both histopathological findings revealed granulation tissue without dysplasia. During the following month, conservative therapy (antibiotic, antiseptic and compressive therapy) was continued, but it resulted with increased granulation tissue formation at the bottom and borders of the ulceration.

On the next admission, a sample was taken again for cytologicae examination, and malignant cells were found. The third biopsy was taken from the border of the ulceration, and histopathological analysis revealed a squamous cell carcinoma, grade III (Figure 2). Radiography of the right lower leg showed incipient osteolysis, but neither lymph node involvement, nor visceral metastases were established by ultrasound**.** There was no evidence of malignancy dissemination, and the disease regressed to stage Ib. After consulting plastic, vascular and orthopedic surgeons, amputation of the right lower leg was recommended, and rejected by the patient. She was dismissed with symptomatic therapy.

Discussion:

SCC is the most common type of tumor arising from a chronic leg ulcer (CLU). Malignant transformations of chronic leg ulcers are mainly encountered in elderly patients over 70 years of age, and more often in females (female to male ratio: 2.5:1) (1).

In our patient, the ulceration appeared seven years before the diagnosis of SCC was made. According to the literature, SCC associated with chronic ucerations, the above-mentioned period is not a long one. The study of Combemale et all. performed in 2007 in France, included 85 patients with malignant transformation of CLU. In these patients the transformation lasted 27 years, on average (1). In our case report, the patient presented with all clinical characteristics of malignant transformation: abnormal granulation tissue, well defined peripheral margins, protracted course and spreading of the ulcer despite appropriate treatment, unusual pain and abnormal bleeding. However, the diagnosis could not be established after two biopsies. Hanson et al. pointed to the difficulty of obtaining histological confirmation, even in granulating forms, and recommended (5), similar to Bardursson et al., multiple (up to five) biopsies at several sites of the ulcer, estimating a 25% risk of false-negative results upon a single biopsy (4).

Radiography revealed incipient osteolysis in our patient, while there was neither lymph node involvement, nor visceral metastases**.** In their study Combemale et al. found that 41% of tumors invaded

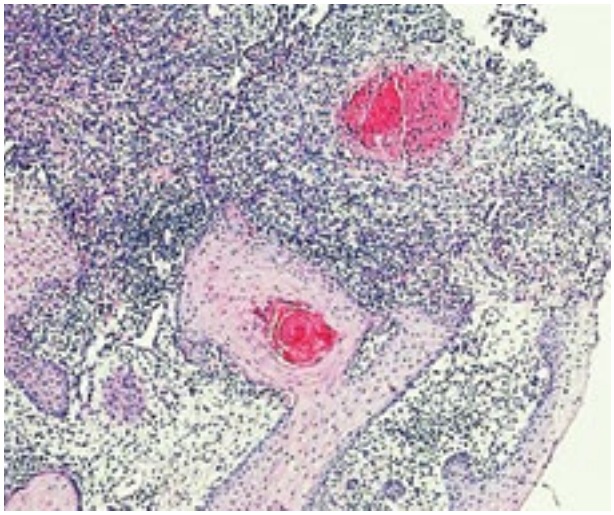

Figure 2. Skin biopsy, exulcerated and infiltrative keratinized squamous cell carcinoma (HE x 100)

the underlying bone, whereas lymph node involvement and visceral metastases occurred rarely (9%) (1).

Histological differentiation is a major prognostic factor. Tumors may be well, moderately or poorly differentiated (6). Treatment depends on the clinical stage of the disease. Amputation shoud be considered for all tumors that are not well differentiated (6). According to Baldursson et al. radiotherapy is only palliative. In our patient, amputiation was recommended as the best therapeutic option, taking into consideration the size and depth of the tumor invasion and grade III SCC, confirmed by histopathological analysis, but it was rejected by the patient.

Conclusion:

In cases of long term CVU and absence of adequate therapeutic response, malignant transformation should be considered and multiple biopsies at various sites of the lesion should be performed.

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Maligna alteracija hronične venske ulceracije na podkolenici: prikaz slučaja

Sažetak

Uvod: Planocelularni karcinom kože je maligni tumor keratinocita koji može da se javi *de novo* ili na već izmenjenoj koži različite etiologije, uključujući i hroničnu vensku ulceraciju.

Prikaz slučaja: Bolesnica starosti 74 godine, hospitalizovana u Klinici za kožne i polne bolesti, VMA sa venskom ulceracijom desne potkolenice promera 10x5 cm, podrivenih i eleviranih ivica, dna prekrivenog obilnim fibrinskim naslagama i granulacionim tkivom. Ulceracija se pojavila pre 7 godina, a od pre 3 godine se izrazitije širila i produbljivala sa bolovima u desnoj potkolenici. Uzet je isečak ivice ulceracije za patohistološku analizu u dva navrata i oba puta viđeno je granulaciono tkivo. Bolesnica je lečena ambulantno i u više navrata hospitalno različitom lokalnom i antibiotskom terapijom, hidrokoloidnim pločama, kompresivnim zavojima, oksigenom terapijom u hiperbaričnoj komori bez zadovoljavajućeg efekta. Zbog dalje sumnje na malignu alteraciju uzet je otisak rane za citološku analizu i viđene su ćelije koje mogu da odgovaraju planocelularnom karcinomu, što je tek trećom biopsijom i dokazano, isptivanjima radi određivanja stadijuma, utvrđeno je da je bolest u IB stadijumu. Uz konsultaciju hirurga-plastičara, vaskularnog hirurga i ortopeda, indikovana je amputacija desne potkolenice.

Zaključak: Ukoliko hronična ulceracija nema adekvatan terapijski odgovor i ne zarasta uprkos terapiji, neophodno je misliti na malignu alteraciju i učiniti nekoliko sukcesivnih biopsija sa više različitih mesta ulceracije radi PH analize.

History of dermatology and venereology in Serbia – part IV/1: Dermatovenereology in Serbia from 1919 – 1945

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UDC 616.97:614.2(091)(497.11)"1919/1945"

Abstract

After the First World War, Serbia was ravaged and in ruins, whereas the Health Care Service was destroyed. Organization and reorganization of the Health Care Service started with a fight against the spread of infectious diseases. Foundation of specialized health institutions was among the first tasks. As early as 1920, an *Outpatient Service for Skin and Venereal Diseases* was established and managed by Prof. Đorđe Đorđević. In 1922, after he was appointed as Associate Professor at the newly established *Faculty of Medicine* in Belgrade, he founded a *Clinic for Skin and Venereal Diseases*, and acted as its first director. In 1928, a *Municipal Outpatient Clinic for Skin and Venereal Diseases* was founded, whereas in 1938 a modern organization of the Service was established in a new building. After a break during the I World War, the *Dermatovenereology Department* of the *General Military Hospital* in Belgrade, founded in 1909, continued working until the Second World War. In Novi Sad, the *City Hospital* was founded in 1909, including a *Dermatovenereology Department*. After the First World War, in 1921, Dr. Jovan Nenadović founded a *Department of Skin and Venereal Diseases* (100 beds) in the *General Public Hospital*, as well as, an independent *Public Outpatient Clinic* for free-of-charge treatment of patients with venereal diseases. In Niš, the first *Organization Unit for Venereal Diseases* was founded in 1912, but the *Department of Venereal Diseases* was founded in 1921, and it was managed by Dr. Petar Davidović, while in 1927 a Department *of Skin and Venereal Diseases* was established within the *General Public Hospital*. In 1920, a *Dermatovenereology Department* of the *Military Hospital* in Niš was established. Apart from these, as early as 1921, there was a total of 7 Outpatient Clinics in Serbia, and in 1923 there were 14 venereal departments, and 1 dermatovenereology department.

After the First World War, the Kingdom of Serbs, Croats and Slovenes was proclaimed in 1918, as well as the first Ministry of Public Health (MPH). Thus, the whole enlarged country was integrated into a unique system of health care delivery, although the initial positions of certain parts were quite different. The seven-year war (1912 – 1918), occupation and epidemics of infectious diseases led to a massive loss of lives and medical personnel in Serbia (1). Out of nearly three million inhabitants of Serbia before the First World War, over 1.200.000 people lost their lives (2), including 35% of physicians (1). The country was ravaged and in ruins (1, 3), whereas the Health Care Service was destroyed. Infectious and venereal diseases spread, and it was necessary to start organization and reorganization of the sanitary service (1). Again, it meant starting from scratch, in somewhat better circumstances than earlier, because some habits and laws have been preserved, and the health care service had had a certain tradition.

Legislation and Organization of the Dermatovenereology Service

Shortly after the war, proper legal regulations were brought, but they were replaced in 1921 by the *Law on the Foundation of Special Institutions for Infectious Diseases and Free-of Charge Health Care Service* (1, 2). Based on this Law, the MPH was responsible for the: detection, eradication and treatment of acute and chronic infectious diseases, keeping strict records of patients and for health education of the population (1). *The Law on the Eradication of Infectious Diseases*,

passed in 1930, included the following guidelines for venereology: foundation of institutions for free-of-charge treatment; employment of professionally educated physicians; foundation of hospital departments for venereal diseases; units for prevention of venereal diseases; institutions for the treatment of children with congenital syphilis; mobile outpatient services; forced treatment, and taking special measures in counties where more than 5% of population were infected by syphilis. Reporting diseases was mandatory in cases where spread of infection was anticipated. In 1931 and 1934, *Laws on Eradication of Endemic Syphilis (1)* and of *Venereal Diseases* were passed, respectively (4). Skin diseases were covered by General Legislation.

Three basic problems were recognized in the organization of public health care: insufficient number of hospitals and physicians, and almost complete lack of bacteriological laboratories (1). The first two problems were directly related to dermatovenereology.

Health Institutions

The Outpatient Service for Skin and Venereal Diseases (OSSVDs) was founded by a special regulation of the MPH in Belgrade in 1920, since it was the Center for organization of Sanitary Services in Serbia (1). Firstly it was situated in Dečanska Street, then in Vidinska Street (today George Washington street), which remained recognized as a location of the first dermatovenereology institutions in Belgrade, but also by a great number of brothels, which were there before and after the First World War (5). Dr. Đorđe Đorđević (Figure 1) was the Head of the OSSVDs, and Dr. Sima Ilić (Figure 2), was the dermatovenereologist-practitioner (6). Both of them were very important for the development of the Serbian dermatovenereology. The Service provided a temporary residence to the newly founded *Clinic for Skin and Venereal Diseases* (see below). When the Clinic was moved in 1925, the OSSVDs continued working as the institution of the MPH, and Dr. Sima Ilić was the Head of the Service (6).

The Clinic for Skin and Venereal Diseases (CSVDs) was founded in 1922, when dr Đorđević was appointed as Associate Professor at the newly established Faculty of Medicine in Belgrade (1920) (7). The Clinic had no capacities for in-patients (8), but all other health and

Figure 1. Prof. Dr. Đorđe Đorđević

educational activities were exercised at the OSSVDs, based on the agreement between the Faculty of Medicine and the MPH (6). Till 1932, the CSVDs has been moved two more times into private residences, unfortunately always in inadequate premises. Hospital departments were founded in 1925, whereas in 1932, the CSVDs was moved to the facilities of the Institute of Anatomy, which had previously been used by the (cancelled) *Clinic of Applied Anatomy* (6) (Figure 3). The working conditions were somewhat better, and apart from hospital departments and laboratories, in 1935 the Clinic possessed a library with 700 books and 450 journals, as well as a moulage collection of 400 exhibits (7). Apart from this, in 1935 a Specialized Outpatient Service was opened for treatment of

Figure 2. Prof. Dr. Sima Ilić

students (9). During the Second World War, the occupation authorities took possession of the Clinic with the entire inventory, so that only the Outpatient Service continued working. After the Germans had left in 1944, part of the library and the moulage collection remained behind (10). The first Head of the CSVDs was Professor Đorđe Đorđević (1922 – 1935), followed by Professor M. Kićevac (1935 – 1940) (7), and Dr. Sava Bugarski (1940 – 1944) (6,11).

The Dermatovenereology Departments of the *General Public Hospita*l (GPH), founded in Belgrade at the end of the XIX century (see part III/1), the first dermatovenereology departments for in-patients in Serbia, continued working after the First World War.

The Municipal Outpatient Clinic for Skin and Venereal Diseases in Belgrade was founded on September 15, 1928. During the following ten-year period, it was housed in inadequate private facilities, with small and disorganized settings (Figure 4). When the economic crisis ended in the 1930s, a new building was built in 1938 in Vidinska Street (17, George Washington Street), and it was called the *City Outpatient Clinic*, today *City Department of Skin and Venereal Diseases*. It was a modern building and it was the first institution of its kind in Central Europe (Figure 5). The Head of the Institution was Dr. Jovan Spasojević who worked with Dr. Mihailo Gačić, both dermatovenereologists. Its significance can easily be seen from the following data: during 1928, a total of 1.072 patients were examined, in 1929, 15.217 patients, and in 1937, 51.194 patients had undergone examination (5).

The Department of Skin and Venereal Diseases (100 beds) of the *General Public Hospital* (GPH) (Figure 6),

Figure 3. The Institute of Anatomy in Belgrade, a temporary residence of the Clinic for Skin and Venereal Diseases in 1932 (indicated by an arrow)

Figure 4. The Municipal Outpatient Clinic for Skin and Venereal Diseases in Belgrade

Figure 5. The City Outpatient Clinic for Skin and Venereal Diseases in Belgrade

and the independent *Public Outpatient Clinic* for free-of-charge treatment of patients with venereal diseases in Novi Sad, were founded in 1921, by Dr. Jovan Nenadović, the first Serbian dermatovenereologist in Vojvodina. He was the director of both institutions (12). We must also note that in 1909, the *City Hospital* with a *Dermatovenereology Department* was founded (13), but after the First World War there was no place for treatment of patients with skin and venereal diseases (12). Apart from that, an *Anti-Venereal Outpatient Department* was founded in 1925 (13). Further development of dermatovenereology in Vojvodina started with these institutions with close cooperation with the Belgrade Dermatology School. Dermatovenereologists, who took part in the development of dermatovenereology, and in the work of institutions of that time, were also members of the *Dermatovenereology Section of the Serbian Medical Association*.

The first *Organization Unit for Venereal Diseases* in Niš was founded in 1912, and in 1920 it was moved into the bungalows of the *City Hospital. The Department for Venereal Diseases* with an Outpatient facility outside the Hospital circle was founded in 1921 and it was managed by Dr. Petar Davidović. *A Department for Skin and Venereal Diseases* of the GPH in Niš was opened in 1927. Its director was Dr. Petar Zurin, a dermatovenereologist (1, 14). After the foundation of the *Faculty of Medicine* in Niš (1960) it had become a teaching hospital for medical students (14) (Figure 7).

In 1921, at the initiative of Prof. Đ. Đorđević, Serbia had complete outpatient health care centers in Niš, Petrovac, Užice, Boljevac County, Subotica, Veliki Bečkerek (Zrenjanin) and Mitrovica (15). As soon as 1923, general hospitals had 14 venereal departments and 1 dermatovenereology department,

Figure 6. The General Public Hospital in Novi Sad with the Department of Skin and Venereal Diseases (Archive of Vojvodina)

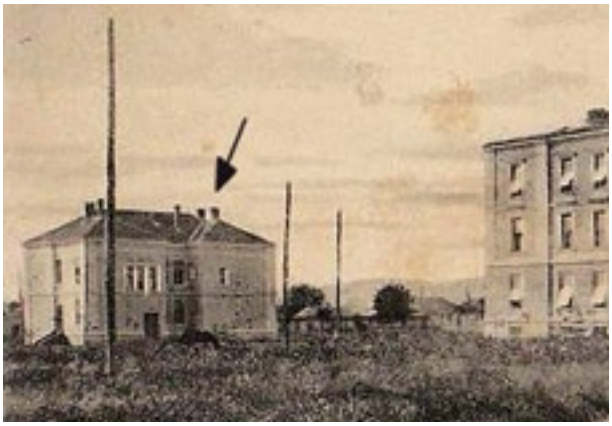

Figure 7. The General Public Hospital in Niš, the present Clinic for Skin and Venereal Diseases (indicated by an arrow)

in Subotica (16). It is noticeable that these departments were called "venereal", just as the physicians were called "venereologists" (1), pointing once again to the fact that venereal diseases were still a major dermatovenereology problem.

The Dermatovenereology Department of the *General Military Hospital* in Belgrade, founded in 1909 (see part III/1), worked until the First World War, when the *General Military Hospital*, under the Austrian occupation, became *"Das K. und K Reservspital Brško"* (17). After the war, the Department continued working till the beginning of the Second World War.

Figure 8. The Main Military Hospital in Belgrade with the Dermatovenereology Department

Figure 9. The Military Hospital in Niš with the Dermatovenereology Department

From 1941 to 1944, the occupation authorities once again used the *General Military Hospital* for their purposes (18). After the war, it continued working as the Main Military Hospital, moreover, the, Dermatovenereology Department continued working as well (19) (Figure 8).

After the First World War, in 1920, new departments were founded in the *Military Hospital* in Niš (Army Military Hospital for the territory of Moravska military district) (Figure 9), including a *Dermatovenereology Department* (20).

The first hospital for the treatment of syphilis in Serbia was founded in 1851 in Knjaževac (see part II), but during time it was transformed into the *County General Hospital* (21). With the archive destroyed, there is no evidence of its work, but it is apparent that patients with syphilis prevailed, because it is well known that at the beginning of the 1950's, this was the most outspread and best known area with endemic syphilis in Serbia (22).

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Abbreviations

CSVDs – Clinic for Skin and Venereal Diseases
GPH – General Public Hospital
MPH – Ministry of Public Health
OSSVDs – Outpatient Service for Skin and Venereal Diseases

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A report on the 11th International Union against Sexually Transmitted Infections World Congress

The International Union against Sexually Transmitted Infections (IUSTIs) was founded in 1923, and it is organized on both global and regional basis. It is the oldest international organisation with the objective of fostering international cooperation in the control of sexually transmitted infections (STIs), including HIV/AIDS. IUSTIs is concerned with the medical, scientific, social and epidemilogical aspects of STIs and their control. It is an Official Non-Government Organization in Consultative Status with the World Health Organization.

The 11th IUSTIs World Congress took place in Cape Town, South Africa, from 9th to 12th Novemeber 2009. This was the first IUSTIs meeting in Africa, which has the highest burden of HIV infection in the world, whereas STIs still play an important role in fuelling the on-going transmission.

During the Congress, there were 7 plenary lectures, 44 symposia in 17 topic symposia, 48 oral presentations and 139 posters.

The plenary sessions covered rapid diagnostic tests for STIs, prevention of mother to child transmission of HIV, biological drivers of the HIV epidemic, sexual networks, male circumcision, HIV vaccines, the use of information technology in novel ways to improve STIs/HIV clinical practice, STIs bacterial typing, updates in STIs, human papilloma viruses (HPV) vaccination and HPV clinical disease, STIs treatment as a component of HIV prevention, and finally, IUSTIs global challenges.

STIs represent a major health problem in both developed and developing countries, reflected by the estimated 300 milion new cases occurring worldwide every year. Although a decline in STIs has been observed since the 1950s, in many countries an increase has been reported during the last few years, especially in syphilis, gonorrhea and some viral infections including HIV. At present, there are drugs which can eradicate bacterial, protozoal and ectoparasitic infections. However, challenges remain in countering genital pathogens even where antibiotics are available, with the increasing incidence of antibacterial resistance in gonococci.

Figure 1. Prof. Dr. Skerlev from Zagreb and Dr. Zoran Golušin from Novi Sad during the Congress in Cape Town

High levels of resistance in gonococci especially against quinolones has now become a worldwide problem and reflects the ability of micro-organisms to escape antibacterial strategies.

The major impact of STIs on public health today derives from viral rather than bacterial infections, and many viral infections still represent a major therapeutic challenge. Hepatitis B and AIDS are a substantial problem in Western Europe and the USA, but represent devastating epidemics in Central and South Africa, certain parts of Asia and Eastern Europe. Antiviral resistance is an ongoing and increasing problem in the treatment of HIV infected individuals.

Pre-exposure vaccination against hepatitis B is recommended for individuals at risk, but vaccination strategies may fail because of the high costs in developing countries and public resistance against vaccination in general.

It has been known that high risk genotypes of

HPV carry the risk of malignancy and lead to invasive carcinoma of the genital tract in women and men. The results of HPV vaccination are promising and give hope that genital cancer can be reduced or even eradicated by large scale vaccination programs.

Two posters from Serbia were presented: „Epidemiological Characteristics of Syphilis in Vojvodina in the Last Three Decades“ by Zoran Golušin, Slobodan Stojanović, Siniša Tasić, Zoran Nedić and „Condylomata acuminata and Buschke-Lowenstein tumor“ by Zoran Nedić and Zoran Golušin.

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2010

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
18-23 March, 2010	7th World Congress of The International Academy of Cosmetic Dermatology (IACD), Cairo, Egypt	30 November, 2009	www.cairoderma.com
26-28 March, 2010	Hair and Scalp Diseases in Clinical Practice. Course and Symposium, Warsaw, Poland	Under construction	www.spederm.eu
7-10 April, 2010	13th World Congress on Cancers of the Skin, Madrid, Spain	15 February, 2010	www.wccs2010.com
8-11 April, 2010	Winter Academy Dermatology, III Congress - St. Moritz-Pontresina, Switzerland	31 January, 2010	www.winteracademy.net
13-15 April, 2010	Dubai World Dermatology & Laser Conference & Exhibition, Dubai, UAE	30 November, 2009	www.dubaiderma.com
13-16 May, 2010	7th EADV Spring Symposium, Cavtat, Croatia	10 January, 2010	www.eadvcavtat2010.com
20-22 May, 2010	10th ESPD (European Society for Pediatric Dermatology) Congress, Lausanne, Switzerland	14 December, 2009	www.espd2010.com
11 June, 2010	Scientific meeting "Diseases of the oral mucosa - what is new? Academy of Medical Sciences of theSerbian Medical Society, Belgrade, Serbia	No abstract submission	www.sld.org.rs
16-19 June, 2010	6th Congress of the European Association of Dermatologic Oncology, Athens, Greece	28 February, 2010	www.eado2010.org
1-4 July, 2010	Congress of the Psoriasis International Network, Paris, France	15 February, 2010	www.pso2010.com
2-4 July, 2010	1st International Summit for Nail Diseases, Athens, Greece	15 March, 2010	www.erasmus.gr/en/congresses/athens
22-24 July, 2010	New Trends in Allergy VII & 6th Georg Rajka Symposium, International Symposium on Atopic Dermatitis, Munich, Germany	31 March, 2010	www.new-trends-allergy.de
4-7 September, 2010	16th Meeting of the European Society for Pigment Cell Research, Hinxton Cambridge, UK	31 May, 2010	www.registration.hinxton.wellcome.ac.uk
9-11 September, 2010	40th Annual ESDR Meeting (European Society for Dermatological Research), Helsinki, Finland	14 May, 2010	www.esdr2010.org
15-18 September, 2010	10th Congress of the European Society of Contact Dermatitis, Strasbourg, France	March, 2010	www.escd-gerda2010.com
6-10 October, 2010	19th EADV Congress Gothenburg, Sweden	3 March, 2010	www.eadvgothenburg2010.org
21-23 October, 2010	XXXI Symposium of The International Society of Dermatopathology, Barcelona, Spain	Under construction	www.isdpbarcelona2010.net
29 October – 01 November, 2010	10th ADI (Ionic Dermatological Association) International Congress, Floriana, Malta	27 August, 2010	www.malta2010.net
4-7 November, 2010	1st World Congress on Controversies in Plastic Surgery and Dermatology, Barcelona, Spain	4 August, 2010	www.comtecmed.com/coplasdy/2010

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AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists.* The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

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1. Editorials *(limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.*

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Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at http://www.bipm.fr/en/si/.

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