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Alternative treatment of psoriasis - is rifampicin a mild immunosupressor?

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VERSITA

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

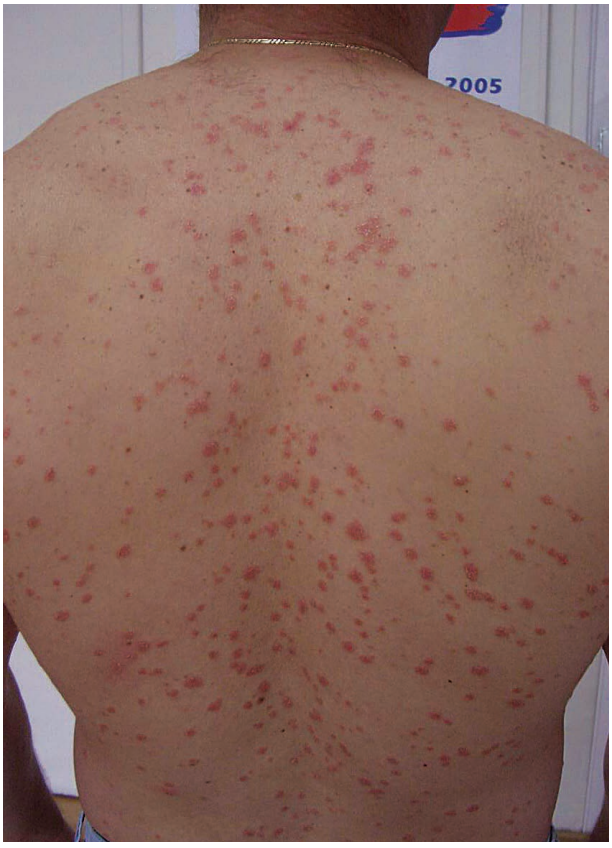

Figure 1. The first patient from the group B: PASI 10.8 score at baseline

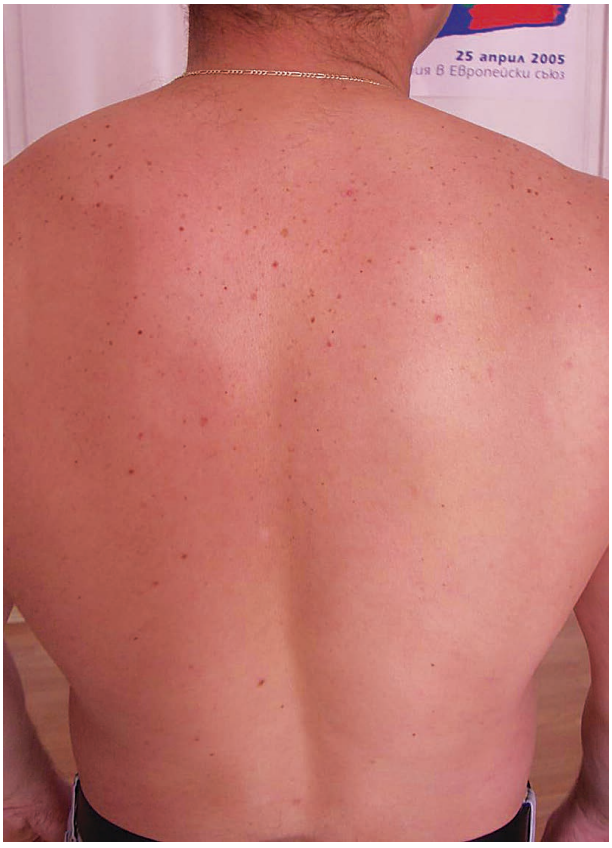

Figure 2. The first patient from the group B: PASI 0.5 score on the 60th day

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

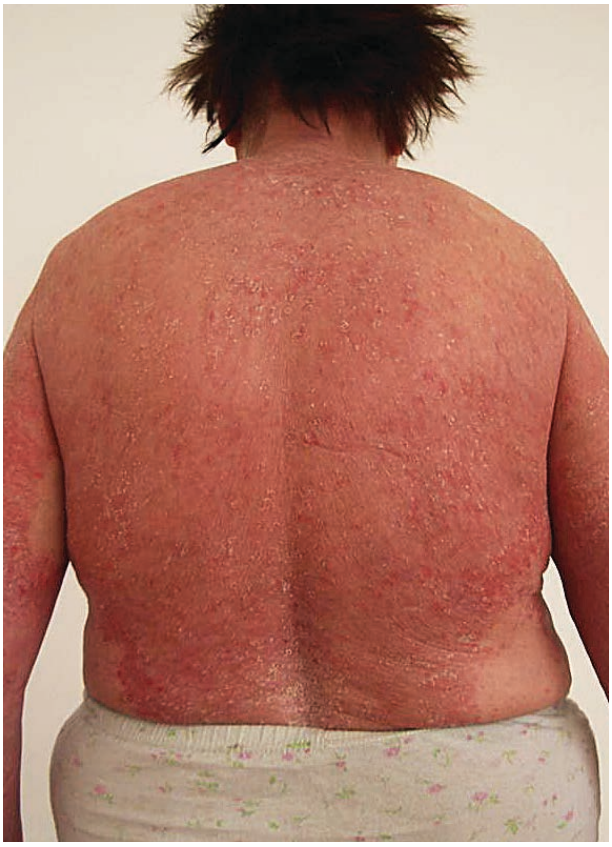

Figure 3. The second patient with chronic plaque psoriasis: PASI 25.1 score at baseline

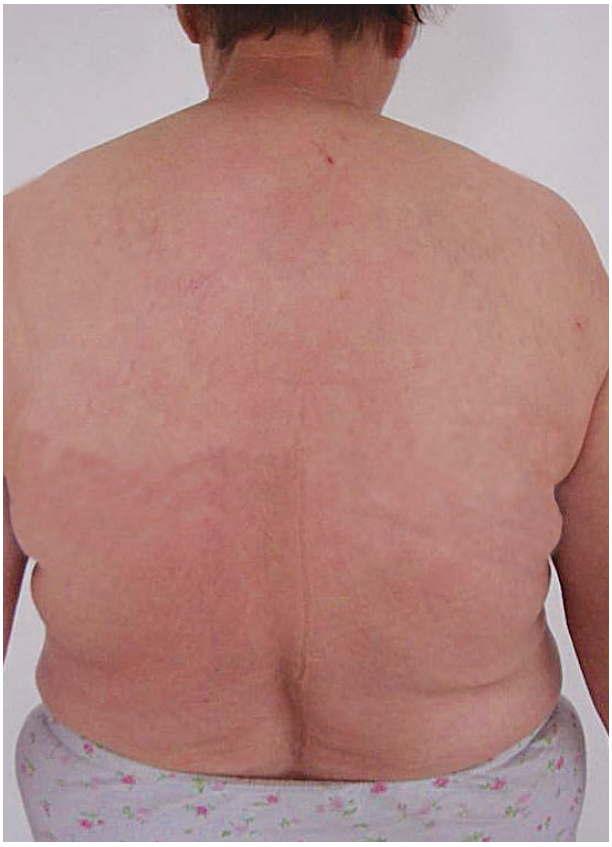

Figure 4. The second patient with chronic plaque psoriasis: PASI 0.8 score on the 6th month

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.