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- Zmanjšuje povnetno hiperpigmentacijo
- Izenačuje površinski mikrobiom kože

6 učinkov v 1 nanosu

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BREZ PARABENA
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Editorial

Acta Dermatovenerologica Alpina, Pannonica et Adriatica accepted for coverage in Thomson Reuters' Emerging Sources Citation Index (ESCI)

Mario Poljak[1,2] ✉, Jovan Miljković[3], Tina Triglav[1,4]

Abstract

Acta Dermatovenerologica Alpina, Pannonica et Adriatica (Acta Dermatovenerol APA) is the leading journal in dermatology and sexually transmitted infections in the region. Several important steps were taken during the last 25 years to improve the journal's quality, global visibility, and international impact. After a 1-year trial period, Thomson Reuters recently informed the editorial office that they had accepted *Acta Dermatovenerol APA* for coverage in Thomson Reuters' new index in the Web of Science Core Collection called the Emerging Sources Citation Index (ESCI). The coverage of *Acta Dermatovenerol APA* begins with the journal content published online in 2016; that is, from volume 25 onwards.

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The journal *Acta Dermatovenerologica Alpina, Pannonica et Adriatica* (*Acta Dermatovenerol APA*) was founded in 1992 in Ljubljana by Aleksej Kansky, who was also the journal's first editor-in-chief (1). Over the last 25 years, the journal and its editors experienced many challenges, as described in detail previously (2). In order to improve the journal's quality and establish its international recognition, several crucial steps were taken. The international profile of the journal significantly increased after 2000, when the journal implemented an online open access policy in addition to the printed version. Since then, the entire content of *Acta Dermatovenerol APA* has been freely available at the journal's website, http://www.acta-apa.org/.

A major accomplishment occurred in 2005, when the journal achieved full indexing status in Index Medicus / MEDLINE in addition to Biomedicina Slovenica and EMBASE / Excerpta Medica. Thus, from volume 14 onwards, the entire content of the journal has been included in PubMed, one of the most important bibliographic databases for medical journals. Coverage of the journal in PubMed significantly improved its international recognition and substantially boosted its citation rate (2).

After identifying several cases of plagiarism and duplicate publications leading to subsequent retractions (3), another major achievement was compulsory checking of the scientific integrity of all material submitted from June 2008 onward using the plagiarism-detection software Ithenticate (http://ithenticate.com/). In the last decade, plagiarism-detection software has allowed us to identify several cases of scientific misconduct. Unfortunately, we are still receiving manuscripts with an unacceptably high plagiarism score, leading to immediate rejection of more than one-fifth of the manuscripts submitted.

In 2012, we significantly redesigned the journal's structure and appearance in line with modern standards for a European journal. During 2014, we also fundamentally redesigned the journal's website, including digitization of all 699 contributions published since 1992, which are now freely available in full text format on the journal's archive website (http://www.acta-apa.org/journals/acta-dermatovenerol-apa/archive).

Recently, several steps were taken to further increase the journal's quality, including regular citation analyses (3), to attain the next important goal in the journal's development: official indexing of the journal in one of the three Thomson Reuters' Web of Science Core Collection flagship citation indexes, such as Science Citation Index Expanded (SCIE), and subsequently achieving the journal's first official impact factor. After a 1-year trial period, Thomson Reuters informed the editorial office in July 2016 that they had accepted *Acta Dermatovenerol APA* for coverage in Thomson Reuters' new index in the Web of Science Core Collection called the Emerging Sources Citation Index (ESCI). The coverage of *Acta Dermatovenerol APA* begins with the journal content published online in 2016; that is, from volume 25 onwards.

ESCI is a new edition in the Web of Science Core Collection launched in November 2015 (http://wokinfo.com/essays/journal-selection-process/). This is a multidisciplinary citation index covering all areas of scholarly literature. The selection process for ESCI is related to the process applied to three Thomson Reuters' Web of Science Core Collection flagship citation indexes: SCIE, the Social Sciences Citation Index (SSCI), and the Arts & Humanities Citation Index (AHCI). Journals accepted for coverage in ESCI must be peer reviewed, follow ethical publishing practices, meet Thomson Reuters' technical requirements, have English-language bibliographic information, and be recommended or requested by a scholarly audience of Web of Science users. Although some journals are selected directly into one or more Thomson Reuters' flagship citation indexes (SCIE, SSCI, AHCI), many other eligible journals are now being initially covered in ESCI. Journals initially covered in ESCI may be evaluated later for coverage in SCIE; however, coverage in ESCI does not guarantee eventual acceptance into SCIE. It is important to note that coverage in ESCI is entirely separate from coverage in SCIE and is never duplicated. Differently from journals indexed in SCIE, SSCI, and/or AHCI, Thomson Reuters does not calculate journal impact factor metrics for journals covered in ESCI. However, because ESCI is a true citation index, it is possible for users to track citation activity at the article and publication levels, and the citation activity for journals covered in ESCI will be used in the selection process for SCIE, SSCI, and AHCI.

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Thus, although we are not where we initially headed, we are proud that Thomson Reuters has accepted *Acta Dermatovenerol APA* for coverage in ESCI. In a year or two, when Thomson Reuters evaluates the latest Journal Citation Report data for our journal, the data may warrant the evaluation of the *Acta Dermatovenerol APA* for the desired SCIE. Thus, at this point, *Acta Dermatovenerol APA*'s destiny is completely in our hands: authors submitting their manuscripts to us as well as the journal's editors and reviewers. We ask all of our readers to strongly consider submitting their best original manuscripts, case reports, and reviews to *Acta Dermatovenerol APA*.

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3. Poljak M. Editorial: Acta Dermatovenerologica Alpina, Pannonica et Adriatica and scientific misconduct. Acta Dermatovenerol Alp Pannonica Adriat. 2009; 18:91-3.

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Efficacy and safety of 5% minoxidil topical foam in male pattern hair loss treatment and patient satisfaction

Hournaz Hasanzadeh[1], Saman Ahmad Nasrollahi[1], Nader Halavati[2], Maryam Saberi[3] ✉, Alireza Firooz[1,2]

Abstract

Introduction: Male pattern hair loss is widespread around the world. Its prevalence indicates the importance of finding the best treatment modalities. This study evaluates the efficacy and safety of minoxidil 5% topical foam in male pattern hair loss treatment and patient satisfaction.
Methods: This study was a before-and-after trial on 17 male patients with male pattern hair loss. Subjects were instructed to apply one capful (1 ml) of minoxidil 5% topical foam on the scalp daily for 6 months. Efficacy was assessed through hair counts, subject assessment, and global photographic review.
Results: Seventeen male volunteers were recruited, and three volunteers were withdrawn; 14 participated in the trial for 16 weeks, and 12 continued up to 24 weeks. The average hair count with a camera at week 16 (181.87 ± 52.42) and week 24 (194.58 ± 62.82) and with an eye count at week 16 (62.57 ± 15.28) and week 24 (69.91 ± 15.61) increased significantly compared to the baseline after intervention.
Conclusion: This study confirmed that minoxidil 5% topical foam is a safe and effective treatment for MPHL. The effect of it is evident after 24 weeks of use.

Keywords: minoxidil, foam, hair loss, alopecia

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Background

Male pattern hair loss (MPHL), or androgenic alopecia, is the most prevalent type of hair loss in men. It affects 30 to 50% of men by age 50 (1). The prevalence of hair loss type III or greater in men 18 to 49 years old has been estimated to be at least 42%. Within the age range of 40 to 49 years, 53% of men have moderate to extensive hair loss (2).

MPHL is often regarded as a relatively minor medical condition, but it may result in anxiety and depression in some men because it impacts self-image (1). MPHL caused low self-esteem, depression, and dissatisfaction with body appearance in a multinational study. The result of the study showed that 96% of men in the United States, France, Germany, Spain, Japan, and Korea 25 to 49 years old reported concerns about their hair loss, and 75% mentioned they were extremely concerned. Only 16% of men reported they had not attempted any treatment, whereas 34% of men had tried one or two treatments before the study, 24% tried three or four, and 26% tried five or more self-treatments. A total of 24.4% of men in this study said that they were dissatisfied with their physician consultations, and most of them indicated that their dissatisfaction was a result of a specific treatment recommendation, remaining unanswered questions, or physician discomfort or disinterest in discussing hair loss (3).

Most treatment modalities for MPHL are not FDA-approved and overall are not significantly effective. Minoxidil 5% topical solution (MTS) is FDA-approved for men with MPHL. Substituting for MTS, a foam vehicle has been developed to deliver minoxidil. Consumer use studies have shown that the foam formula was rated significantly higher on several aesthetic attributes compared to MTS (4–6).

Our study assessed the efficacy and safety of a 5% minoxidil topical formulation in a propylene glycol–free foam vehicle in men with androgenic alopecia.

Patients and methods

Design: A phase 2 before-and-after trial was carried out on 17 patients with MPHL for 6 months at the Pharmaceutical, Cosmeceutical, and Hygienic Evaluation Lab (Derma Lab) of the Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences (TUMS) in Tehran, Iran. Inclusion criteria were men with MPHL between 18 and 49 years old, Hamilton–Norwood pattern III–V, with normal health status, and providing written informed consent. Exclusion criteria were sensitivity to minoxidil, using any topical OTC or prescription medication for hair growth within the past 3 months, using 5α-reductase inhibitors within the past year, using isotretinoin within the past year, radiation to the scalp within the past year, chemotherapy within the past year, using botanicals/nutraceuticals for hair regrowth for the past 3 months, using systemic steroids for more than 14 days within the past 2 months prior to enrollment in the study, uncontrolled hypertension, history of hypotension, any chronic active scalp inflammation or infection, any untreated cancer excluding basal cell carcinoma and squamous cell carcinoma of non-scalp areas, scalp reduction, and use of hair weaves.

The subjects were instructed to apply one capful (1 ml) of minoxidil 5% topical foam (Delta Darou, Iran) to the scalp and then massage it into the vertex and frontal balding scalp once a day and not wash it for at least 6 hours.

Efficacy assessment: The following assessments were made at baseline and at 16 and 24 weeks after treatment:

[1]Pharmaceutical, Cosmeceutical, and Hygienic Skin Products Clinical Evaluation Lab (DermaLab), Center for Research & Training in Skin Diseases & Leprosy (CRTSDL), Tehran University of Medical Sciences (TUMS), Tehran, Iran. [2]Clinical Trial Center (CTC); Tehran University of Medical Sciences (TUMS), Tehran, Iran. [3]Community-Based Participatory Research Center, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences (TUMS), Tehran, Iran. ✉ **Corresponding author: marsabery@yahoo.com, saberinamin@razi.tums.ac.ir**

1) Target area hair counts:
   A) A semi-permanent ink-dot tattoo was placed for precise localization of the target area.
   B) A camera was used to take photographs of the target area and the entire scalp in precisely fixed situations.
   C) All visible hairs were dot-mapped and counted by a technician trained in the procedure and blinded to the intervention.
2) Subject assessment:
   Subjects were asked to fill out a questionnaire that rated their overall hair-loss condition in the vertex region compared to baseline. They rated their perception of their hair-loss condition compared to the baseline using a five-point scale, on which −2 = moderately worse, −1 = minimally worse, 0 = no change, +1 = minimally improved, +2 = moderately improved.
3) Global photographic review (GPR):
   GPR was carried out at baseline and at 6 months after treatment. The baseline and post-treatment pictures were shown in a side-by-side presentation and were rated independently by a blinded dermatologist using the same five-point scale as above.

Safety assessment: The patients were asked and examined for possible side effects, including signs of scalp irritation such as dryness/scaling, folliculitis, and erythema.

Data collection and analysis: A specific case report form was prepared and completed for each patient to collect data. Percentage and frequency were used to describe qualitative data, and mean and standard deviation were used for description of quantitative data. The comparison of quantitative data before and after the test was performed by non-parametric equivalent. Estimation of all the tests was performed at a significance level of 5%.

Ethics: All patients signed an informed consent form prior to inclusion. The Ethics Committee approved the project and the Declaration of Helsinki was followed throughout the study.

Results

Seventeen volunteers were enrolled in this study. One of them was excluded due to irregular use of the drug despite satisfaction with the treatment. Another one left the study due to lack of satisfaction with the drug. One patient reported desquamation and further hair loss after 2 months of use and was excluded. In the end, 14 patients participated in the study for 16 weeks, and 12 continued up to 24 weeks. The mean (± SD) age of the participants was 30.35 (± 8.4), range 18 to 44 years. The characteristics of the participants and hair-loss features at the baseline are shown in Table 1.

Upon assessment of hair loss at weeks 16 and 24, 64.3% and 75.0% of the volunteers, respectively, confirmed that their hair-loss condition had improved after using the drug (Table 2).

As Table 3 shows, the average hair count with a camera at week 16 (181.87 ± 52.42) and week 24 (194.58 ± 62.82), and with an eye count at week 16 (62. 57 ±15.28) and week 24 (69.91 ±15.61) increased significantly compared to the baseline after intervention. Figure 1 confirms this improvement in the hair count for two volunteers after 24 weeks.

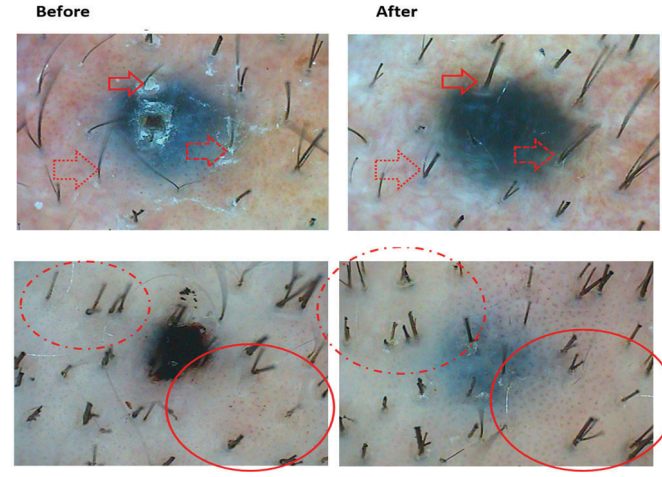

Figure 1 | Two volunteers with moderate improvement in average hair growth at week 24 (before, after).

The global photographic review by an expert after intervention indicated that 21.4% showed no change, 28.6% showed minimal improvement, and 50.0% showed moderate improvement (Table 4 and Fig. 2). The satisfaction with efficacy (reduction in the amount of hair loss, new hair growth, or increase in hair thickness) at weeks 16 and 24 showed that 50.2% and 75.0% of the participants were very satisfied, respectively. Regarding the drug dosage form and ease of use at weeks 16 and 24, 85.7% and 91.6% of the participants were very satisfied, respectively (Table 5).

Among the participants that regularly took the drug for at least 4 months, two people reported mild itching on the neck. No serious side effects were seen during the treatment.

Table 1 | Characteristics of participants and hair-loss features at baseline.

Characteristic	Grade	*n*	Percent
Male pattern hair-loss grade based on the Hamilton–Norwood scale	3	5	35.7
	4	5	35.7
	5	4	28.6
Use of drug	Completely regular	11	78.6
	Regular	3	21.4

Table 2 | Subject assessment of hair-loss condition at weeks 16 and 24.

Scale	Week 16, *N* = 14 *n* (%)	Week 24, *N* = 12 *n* (%)
−2 Moderately worse	0	0
−1 Minimally worse	0	0
0 No change	5 (35.7)	3 (25.0)
+1 Minimally improved	6 (42.9)	6 (50.0)
+2 Moderately improved	3 (21.4)	3 (25.0)

Table 3 | Week 16 and 24 changes from baseline hair count.

Variable	Before intervention *N* = 14 Mean (SD)	After intervention week 16, *N* = 14 Mean (SD)	*p* value (weeks 0 and 16)	After intervention week 24, *N* = 12 Mean (SD)	*p* value (weeks 0 and 24)
Target area hair count (camera)	162.85 (45.93)	181.87 (52.42)	.015	194.58 (62.82)	.019
Target area hair count (eye)	54. 92 (14.06)	62.57 (15.28)	.003	69.91 (15.61)	.002

Discussion

Androgenic alopecia is the prevalent cause of baldness occurring through progressive hair loss (7). Because the prevalence rates are so high in the Asian studies mentioned above, a more standardized protocol is necessary. The different types of hair loss and family histories of Asian patients with androgenic alopecia may affect treatment response (8).

This study was conducted to evaluate the efficacy of minoxidil 5% topical foam in Iranian men.

The results showed that the average hair count (with camera and eye) increased at weeks 16 and 24 compared to the baseline with a significant difference (Table 3 and Fig. 1).

A study by Olsen et al. comparing 5% minoxidil foam with a placebo in androgenic alopecia showed that the mean target

Table 4 | **Global photographic review after intervention.**

Scale	Results, *N* = 14	
	n	%
−2 Moderately worse	0	0
−1 Minimally worse	0	0
0 No change	3	21.4
+1 Minimally improved	4	28.6
+2 Moderately improved	7	50.0

Table 5 | **VAS score of drug effect, form, and ease of use at weeks 16 and 24.**

VAS scores	Drug effect		Dosage form and ease of use	
	Week 16 *N* = 14 *n* (%)	Week 24 *N* = 12 *n* (%)	Week 16 *N* = 14 *n* (%)	Week 24 *N* = 12 *n* (%)
0–2.5	2 (14.3)	0	0	0
2.5–5	4 (28.6)	3 (25.0)	2 (14.3)	1 (8.3)
5–7.5	4 (28.6)	6 (50.0)	1 (7.1)	1 (8.3)
7.5–10	4 (28.6)	3 (25.0)	11(78.6)	10 (83.3)

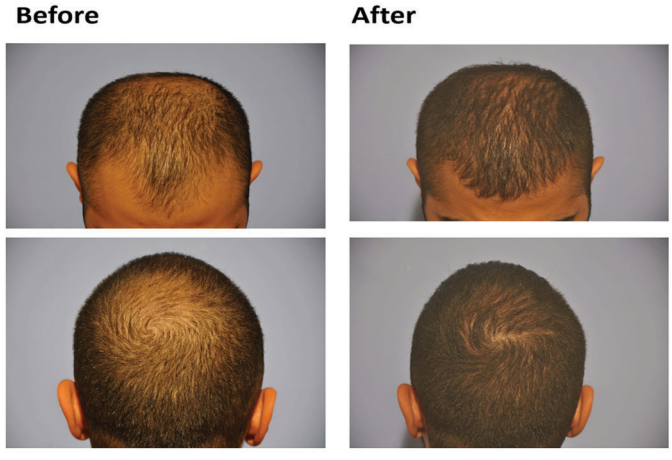

Figure 2 | A subject, 32 years old, with moderate improvement in hair growth as rated by an expert panel at week 24 (before, after).

area hair count increased significantly compared to the baseline (20.9% vs. 4.7%) (5).

In another study, Hillmann et al. reported that application of minoxidil 5% topical foam improved the front temporal and vertex target area hair count and width compared to the baseline up to week 16. At 24 weeks, significant improvement in scalp coverage for the target area was reported (9). A placebo control assessment of minoxidil 5% topical foam in hair density, width, and scalp coverage in the vertex and front temporal areas showed that minoxidil 5% topical foam is effective in the target area of men in 104 weeks (10).

In our study, an expert panel review of global photographic assessment, which is a useful follow-up tool and a way to assess treatment response, showed a 78.6% improvement in treatment response (Fig. 2). This outcome confirms the result by Mirmirani et al. Their study of 16 men demonstrated that minoxidil topical foam induced hair growth on the vertex and frontal scalp of patients with androgenic alopecia (11). Further studies on the efficacy of minoxidil 5% topical foam for treating female pattern hair loss have shown that this kind of formulation can be attractive (12, 13).

All of the studies above mentioned greater effectiveness of minoxidil 5% topical foam in improving hair growth in men and woman. However, some studies compared minoxidil topical foam and minoxidil topical solution. Preclinical studies comparing the efficacy of 5% foam versus 5% solution vehicles on hamster ears showed a greater uptake of minoxidil 5% topical foam (14). Another study, in which six macaques were treated topically with the two formulations above, demonstrated increased hair weight of 12.4 mg with minoxidil 5% topical foam versus 9.27 mg with minoxidil 5% topical solution from the baseline (15). More studies are needed on the effects on hair growth with minoxidil 5% topical foam versus minoxidil 5% topical solution.

Assessment of the condition of volunteers at weeks 16 and 24 revealed that hair loss after using the 5% minoxidil topical foam improved (64.3% and 75.0% improvement, respectively). This outcome is similar to the results reported by Olsen et al., which showed that 70.6% of participants stated that their hair loss had improved from the baseline and only 6.2% were not satisfied (5).

Our results showed that the participants were satisfied with the drug efficacy at week 16 (50.2%) and week 24 (75.0%) and with the drug form and ease of use at week 16 (85.7%) and week 24 (91.6%). This is comparable to a consumer use study that reported similar satisfaction regarding application such as lack of dripping and quick absorption and drying (5, 16).

None of the participants experienced any skin burning, itching, erythema, swelling, or scaling after applying minoxidil 5% topical foam. Adverse effects after the use of minoxidil 2% topical solution on the scalp (such as itching, dryness, and redness) were observed in 7% of patients. These complications are higher after the use of minoxidil 5% topical solution because the concentration of propylene glycol is a key factor in the sensitivity of irritated skin and is known as a factor in allergic contact dermatitis. Because the foam is free of propylene glycol, the side effects are therefore less than with the solution (16). Our research results showed that the tolerability profile was high and the low rate of irritant contact dermatitis was the same as in the results reported in the study by Kanti et al. (10).

Conclusion

Androgenic alopecia is one of the most prevalent dermatological illnesses that causes patients to seek treatment. There are limited options for treating it effectively. This is why androgenic alopecia remains an important area for further research to obtain more information regarding its pathogenesis and newer therapeutic options that are now being developed. Our study indicates that minoxidil 5% topical solution is a safe and effective treatment for MPHL and increasing hair count.

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Evaluation of hygiene habits: cross-sectional study

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Abstract

Introduction: It is well known that adequate hygiene is important for health. Even though this topic has drawn the attention of the media, little or no scientific investigation has been done.
Methods: We performed a comparative questionnaire-based cross-sectional study in three groups: patients attending a dermatology outpatient clinic, patients attending an internal medicine consultation, and community members.
Results: We analyzed a total of 446 questionnaires (249 from dermatology patients, 98 from internal medicine patients, and 99 from the community group). The three groups did not differ statistically in sex and age (p = 0.070). The patients from the dermatology department had a higher education level. The number of weekly baths did not differ among the three groups (p = 0.417). Hair hygiene did not differ between the three groups. The dermatology and internal medicine groups washed their hands more frequently than the community group (p = 0.028).
Conclusion: Comparing our results to the limited data available, we find that the population surveyed has better hygiene habits than those previously reported. We believe that hygiene habits should be discussed during office visits.

Keywords: cross-sectional study, epidemiology, hygiene habits, dermatology

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Introduction

The skin is the body's largest and most visible organ. It reflects a person's general health and performs many important functions (1). It is well known that adequate hygiene is important for good health. Poor hygiene can be associated with individual or community health problems, especially infectious diseases. On the other hand, excessive hygiene can aggravate skin conditions such as atopic dermatitis (2). Although this topic has drawn media attention, little to no scientific investigation has been carried out on worldwide population hygiene habits, except for hand hygiene as part of the prevention of iatrogenic or hospital-acquired infections.

No study evaluating skin hygiene was found in PubMed and the only information retrieved was based on internet surveys of the general population. A French internet survey (3), with a sample population of 566 individuals, stated that 70% of women and 60% of men do not shower every day. An English internet survey (4), with a sample population of 2,021 women, stated that 4 out of 5 women admit they do not shower every day and 33% said they could go for three days without washing their body. The most common reason given for showering so little was time constraints. Despite these results, 92% of the women stated that they understood the importance of a proper skin care regime.

In our dermatology practice we have patients from all kinds of social and economic levels with different hygiene habits. Dermatology patients are said to have better skin and body hygiene than patients from other departments, although no study has evaluated this premise. Common knowledge suggests that individuals that undergo regular medical follow-ups have better health/hygiene practices than individuals with no medical follow-up, even though there are no studies that support this hypothesis.

The primary objective of this study was to determine if there were differences in hygiene habits in three different groups of individuals (dermatology patients vs internal medicine patients vs community members).

Secondary aims included: (1) Determine if there were differences in hygiene habits in each group (2) Describe hygiene habits in the different groups of individuals; and (3) Identify poor hygiene behaviors that should be addressed and discussed during future consultations.

Methods

Construction and validation of the questionnaire

A 20-item questionnaire was created using input from seven dermatologists. We applied the questionnaire experimentally to 100 patients and observed response rates. After repeating this procedure twice, the final version of the questionnaire was composed of 16 items divided into five dimensions: 1) Sociodemographics, 2) Body hygiene, 3) Hair hygiene, 4) Hand hygiene, and 5) Other aspects (see Table 1).

Study design

The study was a comparative questionnaire-based cross-sectional study of three groups of individuals: patients attending the dermatology outpatient clinic, patients attending internal medicine consultation, and community members. The study was approved by the local ethics committee.

Subject selection

Copies of the questionnaire were distributed to patients attending consultations at the Department of Dermatology of the Vila Nova de Gaia e Espinho Central Hospital (CHVNGE), at the CHVNGE Department of Internal Medicine, and to community members

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(shopping malls and community parks). Inclusion criteria included patients more than 18 years old and exclusion criteria included illiteracy and incomplete questionnaires. A cover letter described the purpose of the study and invited individuals to participate on a voluntary basis. Participation in this study was anonymous and no identifying data was collected. The study met the criteria of "Good Clinical Practice" and the principles of the Declaration of Helsinki as reflected in the approval by our institution's human research review committee.

Only questionnaires with 100% response rates were analyzed. This criterion was selected after all questionnaires were collected, but before data analysis.

The study began in November 2014 and ended in March 2015.

Statistical analysis

SPSS version 22 (SPSS IBM, New York, U.S.A) was used to perform the statistical analysis of the data. Chi-square was used to study the association between groups. One-way ANOVA was used to compare means between groups. A significance level (alpha) of 0.05 was used.

Results

We analyzed a total of 446 questionnaires (249 from dermatology patients (55.8% female and 44.2% male), 98 from internal medicine patients (67.3% female and 32.7% male) and 99 from the com-

Table 1 | **Comparison between groups: results and questionnaire analysis.**

			Dermatology group	Internal medicine group	Community group	p
		Number (n)	249	98	99	
Socio-Demographics	Sex	Female (%) Male (%)	139 (51.5) 110 (62.5)	66 (24.4) 32 (18.2)	65 (24.1) 34 (19.3)	p = 0.070
	Age	Mean age (years)	47.65 (±20.78)	53.63 (±19.13)	43.74 (±13.16)	p < 0.001 (ANOVA)
	Education	Did not attend school High school University	7 (100%) 197 (51.3%) 45 (81.8%)	0 90 (23.4%) 8 (14.6%)	0 97 (25.3%) 2 (3.6%)	
	Work status	Employed Unemployed Retired Student	97 (46.2%) 31 (47.0%) 81 (65.3%) 40 (87.0%)	42 (20.0%) 16 (24.2%) 38 (30.6%) 2 (4.3%)	71 (33.8%) 19 (28.8%) 5 (4.0%) 4 (8.7%)	p < 0.001
	Do you have any skin disease?	No Yes	114 (39.0%) 135 (87.7%)	94 (32.2%) 4 (2.6%)	84 (28.8%) 15 (9.7%)	p < 0.001
Body Hygiene	How often do you take a bath per week?	1–2 3–4 Every day More than once a day	38 (55.9%) 79 (51.3%) 125 (58.4%) 7 (70.0%)	18 (26.5%) 36 (23.4%) 44 (20.6%) 0	12 (17.6%) 39 (25.3%) 45 (21.0%) 3 (30.0%)	p = 0.417
	Reason for showering so little	Yes No	36 (72.0%) 213 (53.8%)	4 (8.0%) 94 (27.7%)	10 (20.0%) 89 (22.5%)	p = 0.021
	When you bathe, you use:	Soap Bar soap ("lye soap") Shower gel Shampoo Other	55 (47.4%) 25 (46.3%) 158 (62.0%) 10 (50.0%) 1 (100%)	32 (27.6%) 20 (37.0%) 38 (14.9%) 8 (40.0%) 0	29 (25.0%) 9 (16.7%) 59 (23.1%) 2 (10.0%) 0	p = 0.003
	How do you bathe?	Shower Immersion	239 (55.8%) 10 (55.6%)	96 (22.4%) 2 (11.1%)	93 (21.7%) 6 (33.3%)	p = 0.358
	Have you reduced the number of baths in the last 2 years?	No Yes	236 (55.0%) 13 (76.5%)	98 (22.8%) 0	95 (22.1%) 4 (23.5%)	p = 0.073
Hair Hygiene	How often do you wash your hair per week?	1–2 › 3–4	72 (50.3%) 174 (58.0%)	38 (26.6%) 60 (20.0%)	33 (23.1%) 66 (22.0%)	p = 0.227
	Where do you wash your head?	At home At hairdresser At home and hairdresser	173 (53.4%) 5 (38.5%) 71 (65.1%)	76 (23.5%) 2 (15.4%) 20 (18.3%)	75 (23.1%) 6 (46.2%) 18 (16.5%)	p = 0.060
	When you wash your hair, you use:	Over-the-counter Shampoo / conditioner Shampoo / conditioner from pharmacy Shampoo / conditioner from hairdresser Soap Other	167 (57.6%) 43 (64.2%) 24 (41.4%) 10 (40.0%) 5 (83.3%)	58 (20.0%) 14 (20.9%) 12 (20.7%) 14 (56.0%) 0	65 (22.4%) 10 (14.9%) 22 (37.9%) 1 (4.0%) 1 (16.7%)	p < 0.001
Hand Hygiene	How often do you wash your hands per day?	1–2 3–4 ›5	12 (54.5%) 54 (50.0%) 183 (57.9%)	6 (27.3%) 18 (16.7%) 74 (23.4%)	4 (18.2%) 36 (33.3%) 59 (18.7%)	p = 0.028
	When you wash your hands you use:	Solid soap Liquid soap Bar soap ("lye soap") Shower gel Water Other	70 (63.3%) 129 (58.9%) 35 (44.9%) 9 (60.0%) 5 (21.7%) 1 (100.0%)	20 (18.2%) 40 (18.3%) 32 (41.0%) 2 (13.3%) 4 (17.4%) 0	20 (18.2%) 50 (22.8%) 11 (14.1%) 4 (26.7%) 14 (60.9%) 0	p < 0.001
Other	Do you use beauty products?	No Yes	99 (54.1%) 150 (57.0%)	46 (25.1%) 52 (19.8%)	38 (20.8%) 61 (23.2%)	p = 0.393

munity group (65.7% female and 34.3% male). The three groups did not differ statistically in sex ($p = 0.070$). Individuals from the internal medicine group were older than the dermatology and community group individuals (mean age of 53.6 y vs. 47.7 y vs. 43.7 y; $p < 0.001$). The patients from the dermatology department had a higher education level (197 patients completed high school and 45 patients completed university). The dermatology group had the biggest percentage of individuals in all professional statuses ($p < 0.001$). The patients from the dermatology group had more diagnosed skin diseases ($p < 0.001$). It is important to note that although patients from the dermatology group are followed for skin problems, 114 patients stated they had no skin disease.

The number of weekly baths did not differ in the three groups ($p = 0.417$). 125 patients of the dermatology group, 44 patients of internal medicine group, and 45 individuals of the community group showered every day.

The dermatology group gave various reasons for showering less often. 30.5% of the dermatology group said that showering too often is bad for your skin, and 22.2% stated they do not shower more because of lack of time. In the community group, 60% of individuals stated that time constraints were their principal reason for not showering more often. In the three groups, shower gel was the most frequently used body cleanser. Twenty individuals from the internal medicine group, 25 from the dermatology group, and 9 from the community group stated they use bar soap ("lye soap") as body cleanser. Of the three groups, the dermatology group used bar soap more frequently ($p = 0.003$). In all groups showering was the most frequent type of bath. Almost every individual from the three groups said they had not reduced their number of baths in the last 2 years.

Hair hygiene did not differ between the three groups in terms of frequency ($p = 0.227$). The majority of individuals in the three groups (174 individuals from the dermatology group, 60 from the Internal medicine group, and 66 from the community group) washed their hair more than 3 or 4 times per week. The majority wash their hair at home and use over-the-counter shampoo and conditioner.

The dermatology and internal medicine groups washed their hands more frequently than the community group ($p = 0.028$). Liquid soap was the most frequently used hand cleanser. Thirty-five individuals from the dermatology group, 32 from the internal medicine group, and 11 from the community group stated they washed their hands with bar soap.

The majority of individuals from the three groups stated they use beauty products and there was no statistical difference between groups ($p = 0.393$).

We analyzed each group of individuals separately and did not find significant differences in hygiene habits between sexes. Individuals younger than 65 years shower more frequently, and 60.5% of the dermatology patients that only shower once a week were older than 65 ($p < 0.001$). Of the individuals that stated they only wash their hair once to twice a week, 47.2% of individuals belonged to the age group older than 65. In the dermatology group and internal medicine group individuals younger than 65 years use beauty products more frequently ($p < 0.001$).

Discussion

To our knowledge this is the first scientific study that describes and compares hygiene habits in three groups of individuals (a dermatology group, internal medicine group and community group). We believe this study should be used as a starting point for characterization of hygiene habits in population groups with different geographic, cultural, and economic profiles. The publication of these studies will offer epidemiologic data about hygiene habits and ultimately establish practical recommendations in terms of body hygiene for our patients and the general population.

We are aware that our study has some limitations. Because there are no comparative scientific studies, we cannot conclude objectively if the hygiene habits of our population groups are more adequate than other groups. Our sample size is small and we did not estimate sample size previously. We used a non-random sampling technique because it was the most practical and accessible way of sampling our participants. We used opportunity sampling, and thus we are aware our data cannot be generalized to all dermatology or internal medicine or community populations. Due to difficulties in subject selection, the internal medicine and community groups were smaller than the dermatology group. We did not estimate sample size and made every effort to include the maximum number of subjects in each group.

Common knowledge frequently suggests that women have more adequate hygiene than men. Surprisingly, our study revealed no gender differences between the three groups in terms of hygiene habits. Although one French internet survey (3) stated that 70% of women and 60% of men do not shower every day, our study demonstrated that 50.2% of the dermatology group, 44.9% of the internal medicine group and 45.5% of the community group shower every day, and less than 18.4% of all individuals shower only once or twice a week. An English internet survey (4) declared that the most common reason given for showering so little was time constraints. In our study, 60% of internal medicine group individuals and 22.2% of the dermatology group also referred to time constraints as the reason for not showering more often. Interestingly, 30.5% of the dermatology group stated that they do not shower more often because it is bad for your skin. Although some diseases may be aggravated by dehydration of the stratum corneum during frequent, hot, long-lasting baths, many other diseases may result from or be aggravated if there is inadequate hygiene. Our study identified the use of bar soap as a poor hygiene habit that should be discouraged. Bar soap (or "lye soap") is abrasive by promoting protein denaturation, has a high pH and should not be used for body/hair/handwashing. 20.4% and 32.7% of individuals from the internal medicine group, 10.0% and 14.1% from the dermatology group, and 9.1% and 11.1% from the community group used bar soap as body and hand cleanser, respectively. In an attempt to establish a correlation between the economic crisis and reduction in hygiene habits we asked: "Have you reduced your number of baths in the last 2 years?" Our study failed to corroborate this assumption and almost all individuals from the three groups had not changed their hygiene habits in the last 2 years.

It is commonly believed that, because women have longer hair, that they wash their hair less frequently than men. It is also believed that women have their hair washed more frequently at the hairdresser. Ours study demonstrated that there were no gender differences in terms of hair hygiene.

Although the dermatology and internal medicine groups washed their hands more frequently than the community group, all groups can be considered as having adequate hand hygiene. At least 60% of all individuals wash their hands more than 5 times per day and less than 6% stated that they washed their hands only once or twice a day.

It is known that individuals that are professionally and socially active and practice sports might tend to shower more frequently. As expected, individuals older than 65 years were identified as showering and washing their hair less often. Although it is acceptable that with age and the resultant decrease in physical activity there may be a decrease in hygiene habits, it is also true that the skin barrier properties of the stratum corneum are modified with age. We consider that some individuals older than 65 years may not have the need to shower every day, but we believe that 1 to 2 showers a week may be insufficient, especially in the summer.

Conclusion

When we compare our results with the limited available data, we find that the surveyed population has better hygiene habits than those previously reported. Our study demonstrated a relatively large number of subjects that use bar soap ("lye soap"). We believe that hygiene habits should be discussed during office visits.

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Hepatitis D virus infection in Slovenian patients with chronic hepatitis B virus infection: a national prevalence study and literature review

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Abstract

Introduction: Of the 350 million individuals chronically infected with hepatitis B virus (HBV) worldwide, approximately 15 to 20 million have been exposed to hepatitis D virus (HDV). This study determined for the first time the HDV prevalence in Slovenian patients with chronic HBV infection. In addition, a literature search was performed to identify all HDV prevalence studies from European countries.

Methods: A total of 1,305 HBsAg-positive serum samples, obtained from the same number of patients, were randomly selected from 2,337 patients referred to the Slovenian national reference laboratory for viral hepatitis between 1998 and 2015. All samples were retrospectively tested for the presence of total anti-HDV antibodies. Anti-HDV-positive patients were additionally tested for the presence of anti-HDV IgM antibodies, HDV antigen, and HDV RNA.

Results: Total anti-HDV antibodies were detected in three of the 1,305 patients tested (0.23%; 95% CI: 0.08–0.67%), of whom one patient had recovered from the past HDV infection and two patients had an ongoing chronic HDV infection. The literature search identified 36 peer-reviewed HDV prevalence studies published between 1983 and 2016 and originating from 21 European countries.

Conclusion: The observed prevalence of HDV infection in Slovenia was among the lowest reported in Europe and worldwide. Due to the observed low prevalence of HDV infection, routine diagnostic testing for HDV should not be considered in differential diagnosis of exacerbation of liver disease in Slovenian patients with chronic HBV infection.

Keywords: hepatitis D virus, prevalence, acute HDV infection, chronic HDV infection, Slovenia, Europe

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Introduction

Hepatitis D virus (HDV), the only representative of the family *Deltaviridae*, is one of the five primary etiological agents of viral hepatitis. HDV is an incomplete satellite virus that can replicate only in cells concomitantly infected with hepatitis B virus (HBV) because its envelope consists of HBV surface antigens (HBsAg) and lipids from the host cell (1). HDV is mostly transmitted parenterally, with the highest transmission rates in injecting drug users and individuals exposed to infected blood or blood products (2–4). In addition, intra-familiar transmission in hyper-endemic regions (4) and sexual transmission are also described (5, 6). Upon co-infection with HBV and HDV, acute hepatitis is usually followed by a resolution of both HBV and HDV infections. However, super-infection with HDV usually results in chronic hepatitis caused by both viruses. In comparison to patients with chronic hepatitis B, patients with chronic hepatitis B and D are significantly more likely to develop cirrhosis, liver decompensation, and hepatocellular carcinoma (4, 7, 8).

Of the 350 million individuals chronically infected with HBV worldwide, approximately 15 to 20 million have been exposed to HDV infection (9, 10). Interestingly, the prevalence of HDV infection varies greatly across different geographic regions and does not exactly match the distribution of patients with chronic HBV infection (11, 12). As a result of vaccination against HBV, mandatory testing of blood donors, improvements in sanitation, and behavioral changes, HDV prevalence has decreased in the last 20 years in the majority of European countries, especially in southern Europe (13). However, it has recently begun rising again in some European countries, such as France, Germany, Spain, and the United Kingdom, due to immigration from endemic areas (mainly from Africa, eastern Europe, and Turkey) (2, 14–19).

Slovenia is a country with a population of approximately two million and an estimated HBV prevalence of less than 5%. To the best of our knowledge, no reports on HDV prevalence in Slovenia have been published to date in the peer-reviewed literature. Thus, the main aim of our study was to determine the HDV prevalence in Slovenian patients with chronic HBV infection. In addition, to compare our results with existing published data, a literature search was performed to identify all HDV prevalence studies originating from European countries. A literature search was performed on June 10th, 2016. Eligible peer-reviewed studies, with no bias toward articles written in English, published between 1983 and 2016 were searched through the MEDLINE/PubMed, Web of Science, Scopus, and Google Scholar databases using a combination of the following terms: *hepatitis D virus*, *HDV*, *HDV antibodies*, *prevalence*, and *Europe*.

Material and methods

This study included 1,305 HBsAg-positive serum samples obtained from the same number of patients randomly selected from all 2,337 patients with chronic hepatitis B referred to the Slovenian national reference laboratory for viral hepatitis at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, between February 1998 and December 2015 (Fig. 1). Information on sex, age, and place of residence was available for all 1,305 patients tested; our study group comprised 792 men (60.7%)

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and 513 women (39.3%). The mean age for men and women at diagnosis of chronic hepatitis B was 45.5 and 43.3 years, respectively. Considering the 95% confidence interval and 2.5% margin of error, our sample size was representative for all patients with chronic HBV infection in Slovenia.

The selected HBsAg-positive serum samples were retrospectively tested for the presence of total anti-HDV antibodies using the commercially available enzyme-linked immunosorbent assay ETI-AB-DELTAK-2 (DiaSorin, Saluggia, Italy) with 99.0% (95% confidence interval; CI: 97.8–99.6%) clinical specificity and 99.4% (95% CI: 96.8–100%) clinical sensitivity for detection of total anti-HDV antibodies, as declared by the manufacturer. Additional serum samples were retrieved from all anti-HDV-positive individuals and retrospectively tested for the presence of anti-HDV IgM and HDV-Ag using the commercially available enzyme immunoassays ETI-DELTA-IGMK-2 (DiaSorin) and ETI-DELTAK-2 (DiaSorin), respectively. According to the manufacturer, ETI-DELTA-IGMK-2 (DiaSorin) and ETI-DELTAK-2 (DiaSorin) have a clinical specificity of 99.0% (95% CI: 97.9–99.6%) and 99.0% (95% CI: 98.0–99.6%), respectively, and a clinical sensitivity of 99.5% (95% CI: 97.4–100%) and 100% (95% CI: 87.2–100%), respectively. All serology-based methods were performed strictly following the manufacturer's instructions.

For detecting HDV viremia, total nucleic acids were extracted from all anti-HDV-positive serum samples using the commercially available MagNA Pure Compact Nucleic Acid Isolation Kit I (Roche Diagnostics, Mannheim, Germany) on the MagNA Pure Compact Instrument (Roche Diagnostics), following our in-house protocol. Briefly, prior to automatic extraction of nucleic acids using a Total_NA_Plasma_external_lysis protocol, an external lysis of each serum sample (200 µl) was performed using 300 µl of MagNA Pure LC Total Nucleic Acid Isolation Kit – Lysis/Binding Buffer Refill (Roche Diagnostics) and 30-minute incubation at 25 °C and 350 rpm. Total nucleic acids were eluted in 100 µl of elution buffer and stored (in 10 µl aliquots) at –20 °C. In all samples, the quality/integrity of the extracted RNA was verified by amplification of the 85-bp fragment of human ribosomal RNA (rRNA), encoding the S9 protein, using primers (RibPS9-F and RibPS9-R) and a probe (RibPS9-Probe) previously published (20). The RibPS9 reverse-transcription real-time PCR was conducted using LightCycler 480 RNA Master Hydrolysis Probes (Roche Diagnostics) in a 25 µl reaction mixture, consisting of 5 µl of template RNA, 7.4 µl of 2.7 × LightCycler 480 RNA Master Hydrolysis Probes, 1.3 µl of Activator (50 mM), 1 µl of 20 × Enhancer, 0.5 µM of each primer, 0.2 µM of the TaqMan probe, and water. The test was performed on the LightCycler 480 II RT-PCR Instrument (Roche Diagnostics) under the following conditions: 3 min at 63 °C (4.4 °C/s), 30 s at 95 °C (4.4 °C/s), followed by 45 cycles of 15 s at 95 °C (4.4 °C/s), 1 min at 60 °C (2.2 °C/s), and 1 s at 72 °C (4.4 °C/s), and a final 10 s cooling of the reaction mixture at 40 °C (2.2 °C/s). Only RibPS9-positive samples were used in downstream determination of the presence of HDV RNA. The in-house HDV reverse-transcription real-time PCR (HDV rt-RT-PCR), enabling amplification of a 71-bp fragment of the conserved genomic region encoding HDV-Ag, was performed using primers (HDV-F1, HDV-F2, and HDV-R) and a probe (HDV-probe) (21, 22) previously published, following the same protocol as described above, with the exception of annealing temperature, which was set to 55 °C. Based on the testing of HDV-RNA-positive clinical samples with known concentrations of viral RNA (300-11,000,000 viral copies/ml), the analytical sensitivity of the HDV rt-RT-PCR was estimated to be at least 300 viral copies/ml.

Information on HBV viral load was retrieved from the database of the Slovenian national reference laboratory for viral hepatitis.

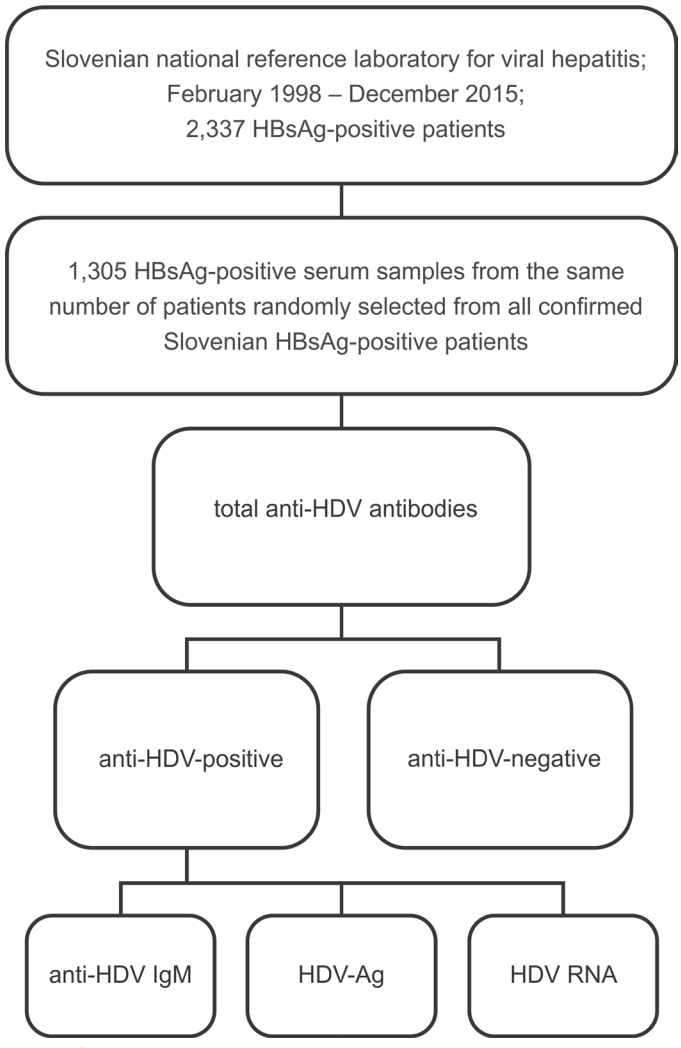

Figure 1 | Overview of the study protocol. Between February 1998 and December 2015, 2,337 HBsAg-positive patients were followed by the Slovenian reference laboratory for viral hepatitis. Among all HBsAg-positive patients, 1,305 patients were randomly selected for total anti-HDV antibody testing. All anti-HDV-positive patients were further tested for the presence of anti-HDV IgM antibodies (anti-HDV IgM), hepatitis D antigen (HDV-Ag) and HDV RNA.

Results

Total anti-HDV antibodies were detected in three of 1,305 patients with chronic HBV infection (0.23%; 95% CI: 0.08–0.67%). In a 48-year-old male patient, except for total anti-HDV antibodies, no other HDV infection markers were detected in any of the samples tested, suggesting resolved HDV infection in this patient (patient 1, Table 1). In contrast, anti-HDV IgM antibodies and HDV RNA were detected in all samples tested obtained from a 28-year-old female patient and a 60-year-old male patient (patients 2 and 3, Table 1) suggesting ongoing chronic HDV infection in both patients. Interestingly, HDV-Ag could not be detected in any serum samples from both patients with ongoing HDV infection. All three anti-HDV antibody-positive patients tested negative for the presence of human immunodeficiency virus (HIV) infection and were generally considered to be immunocompetent.

Discussion

A literature search on HDV prevalence studies from European countries, performed on July 10th, 2016, resulted in 36 peer-reviewed studies from 21 European countries (Table 2). According to this search, Slovenia was one of the few remaining European

countries with no reports on HDV prevalence published in the peer-reviewed literature. In this study, total anti-HDV antibodies were detected in 3/1,305 (0.23%; 95% CI: 0.08–0.67%) Slovenian patients with chronic HBV infection. Our results could be considered representative for all patients with chronic HBV infection in Slovenia, considering the 95% confidence interval and 2.5% margin of error. Even though information on sex, age, and place of residence was available for all patients in the study, the low rate of HDV positivity prevented the analysis of a possible relationship between anti-HDV positivity and patients' characteristics.

As a result of vaccination against HBV, mandatory testing of blood donors, improvements in sanitation, and behavioral changes, HDV prevalence has decreased in the last 20 years in the majority of European countries, especially in southern Europe (13). In several cross-sectional studies, which included hundreds of HBsAg-positive individuals with liver disease, the HDV prevalence in Italy was estimated at 24.7% in 1981, 23.4% in 1987, 14.4% in 1992, 8.3% in 1997, and 8.1% in 2007 (23–27). However, since 2007 no further decrease in HDV prevalence was recorded in Italy, with steady prevalence rates of 8.4% among HBsAg carriers (28). Of note, the reported prevalence of HDV infection was lower, ranging from 1.3 to 5.0% in Italians and from 4.7 to 7.9% in immigrants, in studies providing data from limited geographic regions (29, 30). Unlike several HDV prevalence studies in Italy, the data on HDV prevalence in the other three countries bordering Slovenia are scant and outdated because they date back to 1985, 1993, and 1994, respectively (31–33). Thus, the prevalence of HDV infection in Austria, Croatia, and Hungary was estimated at 2.9% (HBsAg carriers), 19.0% (chronic HBsAg carriers), and 13.6% (chronic HBsAg carriers), respectively (31–33). Even though a more thorough comparison of HDV prevalence is hampered due to outdated information from the majority of countries bordering Slovenia and the use of HDV diagnostic tests with different analytical characteristics in prevalence surveys in different countries, it seems that the HDV prevalence in Slovenian patients with chronic HBV infection is among the lowest in southern Europe. The low prevalence of HDV infection may be attributable to the low HBV burden in Slovenia, which reflects broad HBV vaccination coverage and mandatory testing of blood donors, pregnant women, and family members and partners of HBsAg-positive individuals. It is noteworthy that in Slovenia the national HBV vaccination program started in 1983 and continued to expand until 1998, when HBV vaccination of preschool children was added to the national vaccination schedule. Interestingly, Italy's incidence of acute HBV (1 per 100,000) is similar to that of Slovenia (0.8 per 100,000) and Italy established a HBV vaccination program for neonates and 12-year-olds in 1991 (34, 35); however, in comparison to Slovenia, the prevalence of HDV infection in still significantly higher in Italy. It appears that in Europe HDV is sustained by two different residual pools of HDV-infected patients: (i) young individuals that are migrating from HDV endemic areas and (ii) older individuals that were infected with HDV during the 1980s epidemics (also referred to as the domestic pool) (2, 8, 36). Without accurate epidemiologic data, one can only speculate that the observed difference in HDV prevalence between Slovenia and Italy is a consequence of an existing reservoir of HDV-positive individuals that were infected during the 1980s epidemics in Italy. Moreover, the higher HDV prevalence in Italy could also be attributable to differences in risky behavior among HDV-positive individuals in both countries, such as drug abuse or promiscuous sexual practices.

In contrast to southern Europe, HDV prevalence has recently begun to rise again in other European countries, such as France, Germany, Spain, and the United Kingdom, due to immigration from endemic areas (mainly from Africa, eastern Europe, and Turkey) (2, 14–19). With on-going globalization and the influx of immigrants from less-developed endemic countries, where HBV is not controlled through vaccination and screening, regular epidemiological surveillance of HDV prevalence in Slovenia is also recommended in the near future.

To evaluate whether differences in HDV prevalence across European countries could be at least partially attributed to the use of anti-HDV antibody tests with different analytical characteristics (mainly different analytical specificity), the material and methods sections of published studies (Table 2) were carefully analyzed. Out of 36 eligible studies, the commercially available enzyme-linked immunosorbent assay ETI-AB-DELTAK-2 (DiaSorin) was used in nine studies (14, 16, 19, 30, 37–41) and the Abbott anti-HD radioimmunoassay (Abbott Laboratories, Chicago, IL) and Radim anti-HDVAb (Radim Iberica, Barcelona, Spain) were used in one study each (17, 29). Unfortunately, tests used for detecting anti-HDV antibodies were not specified in the majority of eligible studies. In addition, due to the wide timespan of eligible studies (published from 1983 to 2016), we were unable to associate reported HDV prevalence rates with the use of specific diagnostic test(s) for detecting anti-HDV antibodies.

Table 1 | Characteristics of three anti-HDV-positive patients: one patient with past HDV infection (patient 1) and two patients with ongoing chronic HDV infection (patients 2 and 3).

					HBV infection markers			HDV infection markers		
Patient no.	Sex	Age at diagnosis	Place of residence	Sample no. (date: mm/dd/yyyy)	HBsAg	HBV DNA (IU/ml)	Total anti-HDV Ab	HDV-Ag	anti-HDV IgM	HDV RNA
1	M	48	Ljubljana	1 (03/14/2000)	positive	N/A	positive	negative	negative	negative
				2 (03/23/2000)	positive	N/A	positive	negative	negative	negative
				3 (12/17/2001)	positive	353	positive	negative	negative	negative
2	F	28	Kranj	1 (11/07/2008)	positive	N/A	positive	negative	positive	positive
				2 (11/11/2008)	positive	232	positive	negative	positive	positive
				3 (02/03/2009)	positive	1,020	positive	negative	positive	positive
				4 (12/08/2009)	positive	< 6	positive	negative	positive	positive
3	M	60	Postojna	1 (10/10/2007)	positive	65	positive	negative	positive	positive
				2 (09/17/2008)	positive	34	positive	negative	positive	positive
				3 (10/20/2009)	positive	58	positive	negative	positive	positive
				4 (02/01/2011)	positive	370	positive	negative	positive	positive
				5 (05/24/2011)	positive	68,452	positive	negative	positive	positive
				6 (09/05/2011)	positive	646	positive	negative	positive	positive
				7 (12/06/2011)	positive	< 15	positive	negative	positive	positive

Note: total anti-HDV Ab = total anti-HDV antibodies, anti-HDV IgM = anti-HDV IgM antibodies, HDV-Ag = hepatitis D antigen, N/A = not analyzed

Table 2 | **Prevalence of HDV infection in European countries (1983–2016) according to a literature search performed on July 10th, 2016.**

Country	Tested population (time period)	HDV infection marker(s) tested	HDV prevalence; number of positives / samples tested (% positives)	Reference
Albania	patients with chronic viral and/or alcohol-induced liver disease (1995 and 2005)	total anti-HDV Ab	1995: 10/106 (9.4%); 2005: 7/99 (7.1%)	Kondili et al., 2010 (43)
Austria	HBsAg carriers (N/a)	total anti-HDV Ab	4/138 (2.9%)	Frisch-Niggemeyer and Kunz, 1985 (31)
Belgium	chronic HBsAg carriers (2008–2009)	total anti-HDV Ab	44/800 (5.5%)	Ho et al., 2013 (39)
Bulgaria	chronic HBsAg carriers (N/a)	HDV-Ag	9/105 (8.6%)	Naoumov et al., 1986 (44)
Croatia	chronic HBsAg carriers (N/a)	N/a	19/100 (19.0%)	Jelić and Jelić, 1994 (33)
Denmark	chronic HBV patients (1970–1985)	N/a	29/100 (29.0%)	Krogsgaard et al., 1988 (45)
Finland	HBsAg carriers (1983–1984)	total anti-HDV Ab	1/121 (0.8%)	Pohjanpelto et al., 1985 (46)
France	HBsAg-positive blood donors (1997–2011)	total anti-HDV Ab, HDV RNA	1997–2011: 89/4,492 (2.0%); 1997–2005: 33/2,831 (1.2%); 2010: 13/200 (6.5%); 2011: 2/234 (0.9%)	Servant-Delmas et al., 2014 (14)
Germany	HBsAg carriers in Hannover (1992–2006)	total anti-HDV Ab	266/2,354 (11.3%)	Wedemeyer et al., 2007 (15)
	chronic HBsAg carriers in Frankfurt (2000–2011)	total anti-HDV Ab	210/2,844 (7.4%)	Rehnheimer et al., 2012 (16)
Greece	HBsAg carriers (1997–2010)	total anti-HDV Ab	1997–2010: 90/2,137 (4.2%); 1997–2003: 1,280/2,244 (57.0%); 2004–2010: 857/2,429 (35.3%)	Manesis et al., 2013 (47)
Hungary	chronic HBsAg carriers (N/a)	N/a	16/118 (13.6%)	Horváth et al., 1992–1993 (32)
Italy	HBV-infected patients (1978–1981)	total anti-HDV Ab	494/2,001 (24.7%)	Smedile et al., 1983 (23)
	chronic HBsAg carriers (1987 onward)	total anti-HDV Ab	364/1,556 (23.4%)	Sagnelli et al., 1992 (24)
	chronic HBsAg carriers (1992)	total anti-HDV Ab	143/996 (14.4%)	Sagnelli et al., 1997 (25)
	HBsAg carriers (1997)	total anti-HDV Ab	69/834 (8.3%)	Gaeta et al., 2000 (26)
	chronic HBsAg carriers (2006–2007)	total anti-HDV Ab	112/1,386 (8.1%)	Stroffolini et al., 2009 (27)
	chronic HBsAg carriers in Ferrara (1997–2009)	total anti-HDV Ab	Italians: 1/78 (1.3%); immigrants: 6/76 (7.9%)	Contini et al., 2012 (29)
	HBsAg carriers in Milan (2007–2008)	total anti-HDV Ab	Italians: 19/381 (5.0%); immigrants: 5/107 (4.7%)	De Paschale et al., 2012 (30)
	HBsAg carriers (N/a)	total anti-HDV Ab	Italians: 53/716 (7.4%); immigrants: 34/295 (11.5%)	Brancaccio et al., 2014 (28)
Kosovo	general population (healthcare workers, pregnant women, blood donors, patients included in routine blood testing) (2005)	anti-HDV IgG	1/1,287 (0.08%)	Quaglio et al., 2008 (38)
Poland	chronic HBV patients (N/a)	total anti-HDV Ab	4/102 (3.9%)	Chlabicz et al., 2003 (48)
	chronic HBsAg carriers in the northern part of the country (2002–2004)	total anti-HDV Ab, HDV RNA	total anti-HDV Ab: 3/63 (4.8%); HDV RNA: 5/63 (7.9%)	Bielawski et al., 2006 (37)
Portugal	chronic HBsAg carriers (N/a)	N/a	N/a (17.3%)	Ramalho et al., 1987 (49)
Romania	chronic HBsAg carriers (2005)	anti-HDV IgG, HDV RNA	223/1,094 (20.4%)	Popescu et al., 2013 (50)
Serbia and Montenegro	HBsAg carriers (N/a)	total anti-HDV Ab	69/614 (11.2%)	Delić et al., 1993 (51)
Spain	immigrants (HBsAg carriers) from Equatorial Guinea (2002–2008)	total anti-HDV Ab	249/1,220 (20.4%)	Rivas et al., 2013 (17)
	HIV-positive patients (2004 onward)	total anti-HDV Ab	17/1,147 (1.5%)	Fernández-Montero et al., 2014 (52)
	African immigrants (HBsAg carriers) treated by specialists (N/a)	total anti-HDV Ab	1,984/2,518 (78.8%)	Cuenza-Gómez et al., 2016 (18)
Sweden	chronic HBsAg carriers (1997–2008)	N/a	650/9,160 (7.1%)	Ji et al., 2012 (53)
Switzerland	chronic HBV patients (mostly immigrants) (N/a)	total anti-HDV Ab/ anti-HDV IgM/ anti-HDV IgG/ HDV-Ag/ HDV RNA	101/1,699 (5.9%)	Genné and Rossi, 2011 (3)
	HBsAg carriers (2002–2013)	total anti-HDV Ab	15/338 (4.4%)	Hirzel et al., 2015 (41)
United Kingdom	HBsAg carriers (1970–1989) in Northern Ireland	total anti-HDV Ab	9/401 (2.2%)	Curran et al., 1989 (54)
	chronic HBV patients (mostly immigrants) (2000–2006) in London	total anti-HDV Ab	82/962 (8.5%)	Cross et al., 2008 (2)
	HBsAg carriers (2008–2012) in London	total anti-HDV Ab, anti-HDV IgM, HDV RNA	22/1,048 (2.1%)	William Tong et al., 2013 (40)
	HBsAg carriers (mostly immigrants) (2005–2012) in London	total anti-HDV Ab	162/3,610 (4.5%)	El Bouzidi et al., 2015 (19)

Note: total anti-HDV Ab = total anti-HDV antibodies, anti-HDV IgM = anti-HDV IgM antibodies, anti-HDV IgG = anti-HDV IgG antibodies, HDV-Ag = hepatitis D antigen, N/a = not available

In this study, total anti-HDV antibodies were detected in only three patients: in one patient that recovered from a past HDV infection and in two patients with an ongoing chronic HDV infection. Interestingly, HDV-Ag could not be detected in any serum samples of both patients with ongoing HDV infection (Table 1). This is in accordance with previously published studies reporting that in immunocompetent individuals HDV-Ag is frequently neutralized by anti-HDV antibodies and thus not detectable (10, 42). In contrast, HDV-Ag is usually detected in serum samples obtained from immunocompromised patients chronically infected with HDV (10, 42).

In conclusion, in the first Slovenian national prevalence study the observed prevalence of HDV infection was among the lowest reported in Europe and worldwide. The low HDV prevalence in Slovenia is most likely a result of successful prevention of HBV infection with mandatory testing of blood donors, pregnant women, and family members and partners of HBsAg-positive individuals and universal vaccination against hepatitis B. Due to the observed low prevalence of HDV infection, routine diagnostic testing for HDV should not be considered in differential diagnosis of exacerbation of liver disease in Slovenian patients with chronic HBV infection. However, regular epidemiological surveillance of HDV prevalence in Slovenia is still recommended.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Surgical treatment of pyoderma gangrenosum following deep inferior epigastric perforator flap breast reconstruction

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Abstract

Pyoderma gangrenosum is a chronic inflammatory disease characterized by painful cutaneous ulcers. The etiology remains unknown; however, pyoderma gangrenousm can be triggered by surgery. Here we report the case of a 34-year-old Caucasian female that developed pyoderma gangrenosum following deep inferior epigastric perforator flap breast reconstruction. The patient was successfully treated with systemic immunosuppressive therapy and primary closure.

Keywords: Pyoderma gangrenosum, surgery

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Introduction

Pyoderma gangrenosum (PG) is a rare noninfectious neutrophilic dermatosis characterized by recurrent cutaneous ulcerations (1). The disease often appears on the pretibial area. However, it can affect the head and neck region, trunk, breast, hand, and peristomal skin (2). The diagnosis of PG is usually made by excluding other causes of cutaneous ulcers (3). Pyoderma gangrenosum may present with some systemic diseases including ulcerative colitis, Crohn's disease, hepatitis C, seronegative rheumatoid arthritis, spondylitis, monoclonal gammopathies, leukemia, lymphoma, and myelodysplastic syndrome. Therefore, patients should be evaluated for any underlying disease (4). Pyoderma gangrenosum may occur after trauma or injury to the skin. This condition is called pathergy. Pathergy phenomenon is positive in 30% of patients with PG. Therefore, PG can be triggered by many surgical procedures (5).

Case report

A 34-year-old Caucasian female complaining of cutaneous ulcers was admitted to our dermatology department. She had a past medical history of breast cancer treated with total mastectomy of the right breast. Therefore she underwent deep inferior epigastric perforator flap breast reconstruction at the department of plastic and reconstructive surgery. One week after surgery, she had evident erythema, seropurulent drainage, and pain in the area around the incision for the reconstructed breast and the abdomen. Wound and blood culture were both negative. On dermatological examination, there was erythema on the right breast surrounding an open wound with fibrinous debris and limited granulation tissue. We also examined ulceration with mucopurulent and hemorrhagic exudate at the abdominal incision site. The ulcer borders were undermined, bluish, and surrounded by erythema (Figs. 1a–b). Histological examination of the lesions on the patient's right breast and abdomen revealed a dermal-epidermal neutrophilic infiltrate with abscess, ulcer formation, and superficial vessels with fibrin deposition (Fig. 1c). The diagnosis of PG was made based on the appearance of skin lesions, negative wound culture, and histopathology report. The patient was started on a course of high-dose methylprednisolone (64 mg/day p.o.). After 8 weeks of steroid therapy, the treatment was still unsatisfactory. Therefore, cyclosporine (5 mg/kg/day p.o.) was added to the treatment regimen and the steroid dose was gradually reduced. The patient achieved a partial response despite receiving cyclosporine for 4 months. Thus she underwent primary repair at the plastic surgery department (Figs. 2a–b).

Her postoperative period was uneventful. The ulcerative lesions almost completely healed through scar formation over a period of 8 months. Therefore the corticosteroid and cyclosporine therapy was stopped gradually over the next 7 months. (Fig. 2c).

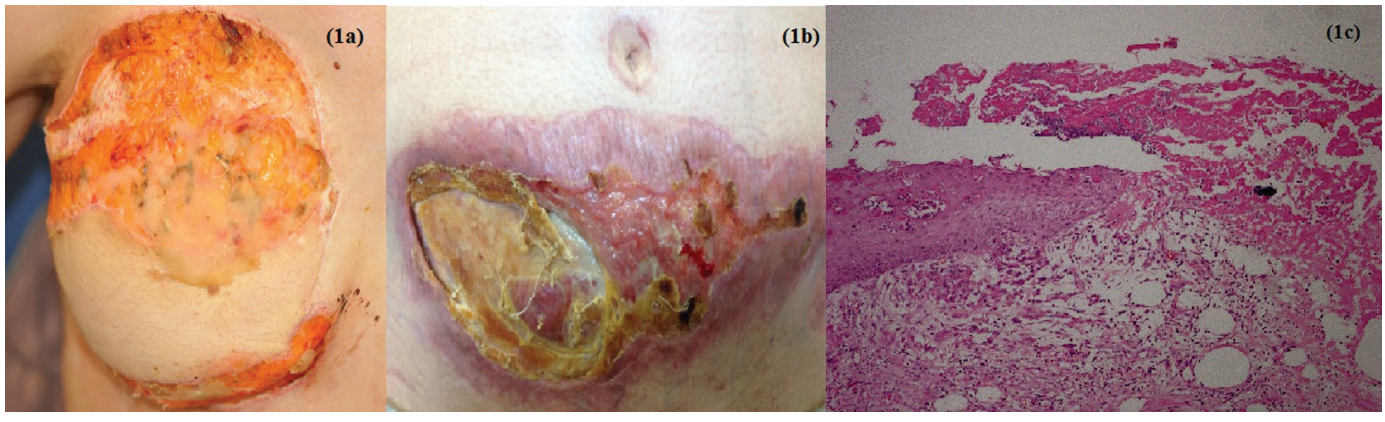

Figure 1 | **a–b)** Ulcers on the patient's right breast and infraumbilical region, **c)** Ulceration with granulation tissue (hematoxylin and eosin stain, ×100)

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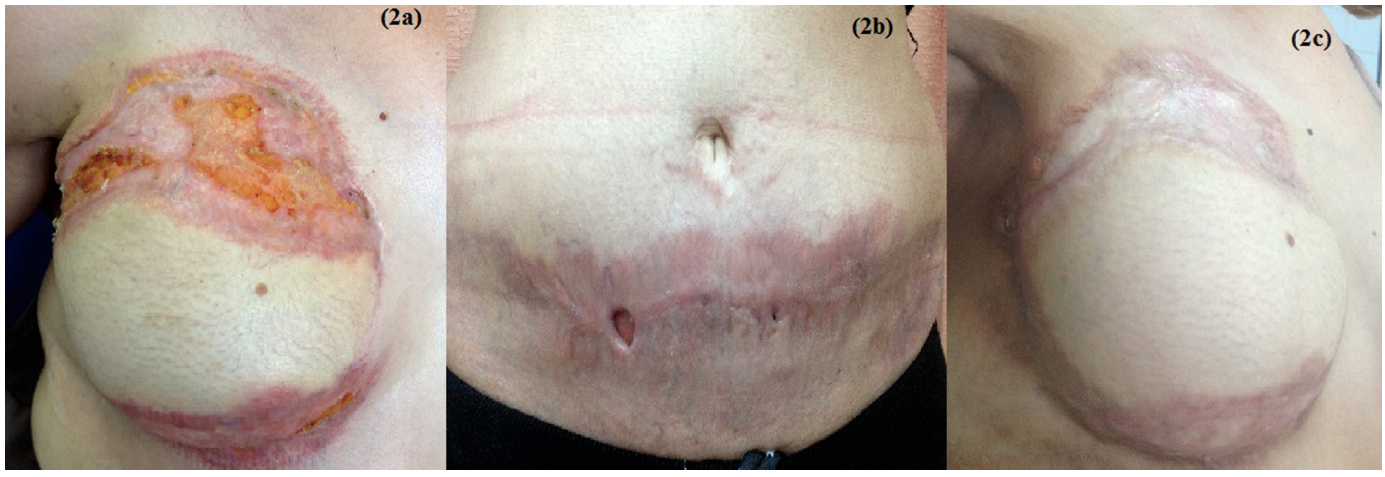

Figure 2 | a–b) Appearance of the lesions after primary closure, c) Scar tissue left by the ulcers.

Discussion

Pyoderma gangrenosum typically presents with sterile pustules that turn into painful ulcers. The ulcers usually have irregular, undermined, and violaceous colored borders that extend rapidly (2). It has been suggested that PG can be triggered by many surgical procedures as the result of tissue damage. Pyoderma gangrenosum lesions may also mimic surgical wound infections. Misdiagnosis as wound infection can expose patients to unnecessary antibiotic therapies that are not appropriate for initial management (5).

The aim of therapy is to modulate the immune system and reduce the inflammatory process. Systemic treatments include corticosteroids, cyclosporine, azathioprine, intravenous immunoglobulin, infliximab, and etanercept (6). Surgery should be avoided if possible. The pathergy phenomenon that may occur with surgical procedures can result in wound enlargement. Most reported cases of PG treated with surgical procedures have had poor patient outcomes. Nonetheless, there have been reports of patients treated successfully with gentle sharp debridement, skin grafting, and reconstruction. Chen et al. reported a patient with vulvar PG that was successfully managed through surgical debridement and primary closure without flap reconstruction (7).

Our case presented above details the successful treatment course of a patient that developed extensive PG after breast reconstruction. In our case, surgery accelerated the wound healing course and reduced potential complications of immunosuppressive therapy. We suggest that primary closure may be performed for patients with PG without recurrence in combination with immunosuppressant medication such as systemic corticosteroids and cyclosporine.

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Very recent HIV infection accompanied by *Pneumocystis jirovecii* pneumonia and *Mycobacterium avium* complex immune reconstitution inflammatory syndrome: a case report

Katarina Čurić[1], Mario Poljak[2], Alojz Ihan[2], Janez Tomažič[1]✉

Abstract

A small proportion of HIV-infected patients rapidly progress to AIDS; indeed, some individuals have been known to progress to AIDS within a year after primary infection. Pneumonia caused by *Pneumocystis jirovecii* (PCP) is the most frequent AIDS-defining illness. However, PCP can also rarely occur during primary HIV infection as a result of the severe immunosuppression that may accompany the early stage of HIV infection. Immune reconstitution inflammatory syndrome (IRIS) comprises two distinct syndromes: paradoxical IRIS and unmasking IRIS. Infections with *Mycobacterium avium* complex during antiretroviral therapy are almost always localized and related to IRIS. We describe an unusual case of PCP and *Mycobacterium avium* complex–IRIS that occurred less than 3 months after primary HIV infection.

Keywords: HIV, immune reconstitution inflammatory syndrome, IRIS, *Pneumocystits jirovecii*, *Mycobacterium avium* complex

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Case report

A 34-year-old otherwise healthy woman presented to our institution in May 2013 with a 3-week history of dry cough and malaise, later accompanied by progressive shortness of breath, high-grade fever, and nausea. Her general practitioner performed chest radiographs, which showed diffuse bilateral infiltrates in the middle and lower lung fields, but empirical therapy for suspected atypical pneumonia with azithromycin was without benefit.

There was no history of intravenous drug use, prior sexually transmitted diseases, or blood transfusions. She tested negative for HIV in 2008, as did her ex-boyfriend. The patient reported several unprotected incidents of sexual intercourse with different male partners in the Philippines at the beginning January 2013 followed by a transient 2-week febrile flu-like illness. At presentation, the patient was febrile (39.3 °C) with oxygen saturation of 94% on room air, respiration rate 60 breaths/minute, tachycardia 116 bpm, and blood pressure 128/83 mmHg, but otherwise unremarkable physical examination.

Blood tests revealed elevated C-reactive protein (186 mg/l), sedimentation rate (100 mm/h), and lactic dehydrogenase (7.85 µkat/l) with a normal white blood cell count. (1,3)-beta-D glucan was positive.

High-resolution computer tomography showed ground glass opacities in the lingula and lower lung fields. HIV-1/2/O screening assays were highly reactive, and HIV-1 Western blot and HIV1/2 immunoblot tests confirmed HIV-1 infection. Direct immunofluorescent assay of induced sputum confirmed *Pneumocystis jirovecii* infection. Parenteral trimethoprim/sulfamethoxazole (TMP/SMX) with corticosteroids was initiated. HIV-1 viral load was extremely high (1,232,000 copies of HIV-1 RNA/mL) and CD4 T-cell count was 110 cells/mm³ (6%). Plasma cytokine concentrations were high, interleukin-6 reached 427 pg/ml, and interleukin-8 61 pg/ml. HIV genotyping revealed HIV-1 subtype A1 without evidence of transmitted HIV drug resistance. HLA B5701 was negative, the HIV tropism assay showed CCR5 tropic viruses only, and the Aware BED EIA HIV-1 Incidence Test (Calypte Biomedical Corporation, Portland, Oregon) indicated recent HIV infection. HLA typing using sequence-specific oligonucleotide-primed PCR and Luminex technology identified HLA-A*01, HLA-A*03, HLA-B*27, and HLA-B*35: all not associated with rapid development of HIV-related immunodeficiency; in contrast, HLA-B*27 is associated with slow disease progression. Antiretroviral therapy (ART) with tenofovir/emtricitabine and raltegravir was initiated. After 21 days of treatment, the patient was discharged on prophylactic doses of TMP/SMX. Chest radiographs were nearly normal, the HIV-1 viral load drastically declined (427 copies/ml), the CD4 count rose to 250 cells/mm³, and cytokine concentrations normalized. After 25 days, the patient was readmitted with progressive dyspnea, dry cough, chest pain, headache, subfebrile temperatures, and persistent rash. Clinically, she was tachypneic (40/min), tachycardic (128/min), and subfebrile (37.3 °C); a rash was hardly noticeable, and on auscultation expiratory wheezes on the right side and prolonged expirium were heard. Except for elevated C-reactive protein (84 mg/l), blood tests were unremarkable. The HIV-1 viral load further declined to 188 copies/ml and the CD4 T cell count was 356 cells/mm³ (13%). Chest radiographs showed a consolidation above the right hilum. Oxygen therapy and TMP/SMX with corticosteroids was restarted. Bronchoalveolar lavage was negative for *P. jirovecii*, *Legionella pneumophila*, *Mycobacterium tuberculosis*, and other pathogenic bacteria and fungi. At that time, diagnosis of lower respiratory system infection in the setting of PCP-related immune reconstitution inflammatory syndrome (PCP-IRIS) was most probable due to negative microbiological tests and rapid restoration of immunity. After 2 weeks of therapy, the intensity of consolidation regressed and the patient was discharged on prophylactic doses of TMP/SMX and ART. Twenty days after bronchoscopy, bronchoalveolar lavage was positive (40 colonies) for *Mycobacterium avium* complex (MAC). The patient successfully recovered after 14 months of MAC-IRIS treatment with clarithromycin and ethambutol with CD4 counts of 324 cells/mm³ and a viral load of < 40 copies/ml.

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Discussion

The suspicion that our patient's condition was a rapidly progressing HIV infection and not a primary HIV infection was supported by several facts: (i) the flu-like illness after traveling to the Philippines was probably primary HIV infection; (ii) the patient is infected with HIV-1 subtype A1, which is rarely found in Slovenia (1); and (iii) a high HIV-1 viral load and low CD4 T cells with rapid virological/immunological improvement after ART initiation. After primary HIV infection of mild intensity, profound immunosuppression occurred, leading to greater susceptibility to *P. jirovecii* infection—which is a characteristic pathogen in the late stages of AIDS and is only rarely seen in the early phase of HIV infection.

There is no consensus on optimal timing for initiation of ART in patients with acute opportunistic infection (2). In patients with PCP, growing evidence supports starting ART early rather than waiting for completion of PCP treatment. A randomized controlled trial compared early versus delayed ART in 282 HIV-infected patients diagnosed with opportunistic infection, of whom 63% had PCP (3). Early ART was associated with a significant decrease in AIDS progression and death without an increase in IRIS (3).

Initially we believed that a second episode of acute lower respiratory infection was related to the rare clinical entity PCP-IRIS due to rapid immunological restoration and a drop in HIV RNA after 6 weeks of ART. Subsequently, we unexpectedly isolated MAC from bronchoalveolar lavage but, because of the patient's improvement, MAC treatment was not initiated until repeated bronchoscopy showed a positive histology and culture. During the ART era, MAC infection has developed into a completely new disease. Previously, it had occurred as a disseminated disease in patients with massive immunodeficiency (4), but under ART it is mostly localized and related to IRIS that most often occurs within 3 months of initiating treatment (5), as in our patient; it is an unmasking of subclinical disease. MAC-IRIS can present with very diverse signs and symptoms: most often lymph nodes, the liver, or the gastrointestinal tract are involved, but essentially any organ could be involved, including the lungs (6).

HIV infection in our patient progressed very rapidly with two different opportunistic infections: PCP and, surprisingly, MAC-IRIS. Rapid progression of HIV infection into AIDS is linked to certain human as well as viral characteristics/markers. Interestingly, not a single HLA gene previously linked with rapid HIV progression (7) was identified in our patient. In contrast, a high HIV-1 viral load that does not fall dramatically after primary HIV infection, which is a strong marker of rapid HIV progression (8), was observed in our patient. The literature suggests that some rapid progressors are infected with rapidly replicating HIV strains and have viral population with higher heterogeneity than HIV viral controllers (8–10). Unfortunately, we were not in a position to measure these parameters in our patient. Although our patient experienced an unusual and challenging 1st year of her HIV-1 infection, she is currently doing well: after a favorable response to standard anti-MAC treatment, she is asymptomatic with normal chest radiographs, an unmeasurable HIV-1 viral load, and 318 CD4 T cells/mm^3.

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Lamellar ichthyosis–like eruption associated with ponatinib

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To the Editor:

A 51-year-old woman presented with a 5-month history of slowly spreading erythematous rash and complaint of pruritus. Dermatological examination revealed erythematous coalescing patches with dry scales on the trunk and kserosis predominantly on the extremities (Figs. 1a, b).

The patient was diagnosed with Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL) in 2012. Initially, she was treated with tyrosine kinase inhibitors, including imatinib and nilotinib. However, complete remission was not achieved. Therefore, she was started on ponatinib, 45 mg daily. An erythematous rash developed 1 month after ponatinib treatment was started. Skin biopsy from the abdominal lesion showed laminated orthokeratosis, a normal granular layer, and a thickened granular layer in some areas. Moreover, there were effacement of the rete ridges and sparse perivascular lymphocytic infiltration around superficial dilated vessels (Fig. 2). Based on clinical and histopathological features, the patient was diagnosed with lamellar ichthyosis–like eruption. Complete clearance of the eruption was achieved after 10 days of treatment with topical clobetasol propionate and urea 2% twice daily. However, kserosis recurred on the extremities within 1 month. Despite the cutaneous side effect, the patient was able to continue chemotherapy. ALL did not respond to 9 months of therapy with ponatinib.

Acquired ichthyosis can be associated with medications, malignancies, and autoimmune, infectious, neurological, nutritional, endocrine, and metabolic diseases (1, 2). Histologically, acquired ichthyosis is usually characterized by compact or laminated orthohyperkeratosis, a reduced or absent granular layer, and the absence of inflammatory infiltrate in the dermis (1, 2). However, mild perivascular lymphohistiocytic infiltrate in the dermis has also been reported (1).

In our case, ichthyosis may be due to malignancy or medication use. However, the patient had ALL for 3 years and she did not have any cutaneous lesions during imatinib or nilotinib therapy. Furthermore, the skin lesions occurred within 1 month of ponatinib therapy. Therefore, we associated the ichthyosis-like eruption with ponatinib rather than malignancy.

Ponatinib is a third-generation tyrosine kinase inhibitor that has been used in chronic myelogenous leukemia and ALL treatment in recent years. Nonspecific rash and kserosis have been reported with ponatinib and other tyrosine kinase inhibitors (3). Recently, new cases of cutaneous eruptions induced by ponatinib have been reported, which include two cases of pythriasis rubra pilaris–like eruption, a folliculocentric form, a seborrhoeic form, an ichthyosiform eruption, and neutrophilic panniculitis (3–5). The mechanism of the cutaneous eruptions has not been clearly defined. However, it has been considered that signal inhibition of kinases and dysregulation of the inflammatory pathways may lead to altered immune regulation and abnormal epidermal growth (3, 6).

In this case report, we present a new cutaneous side effect of ponatinib "lamellar ichthyosis." The patients should be informed about possible cutaneous side effects and appropriate skin care to avoid unnecessary drug cessation. The recognition of the cutaneous toxicities of new anti-cancer therapies will improve the quality of life in cancer patients and perhaps the discovery of new drugs with a better side-effect profile.

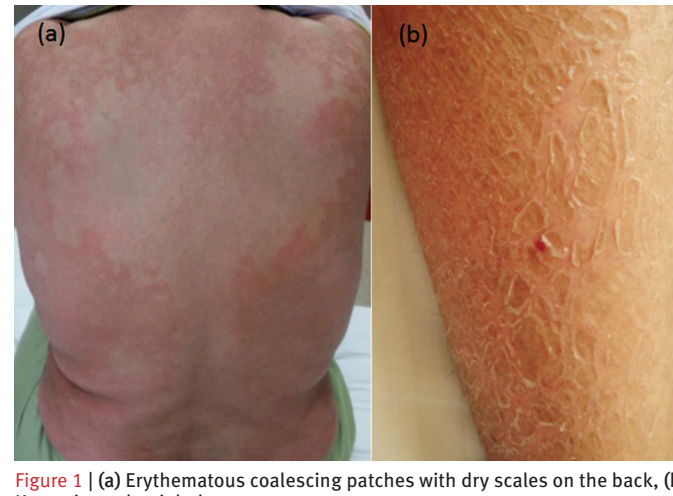

Figure 1 | **(a)** Erythematous coalescing patches with dry scales on the back, **(b)** Kserosis on the right leg.

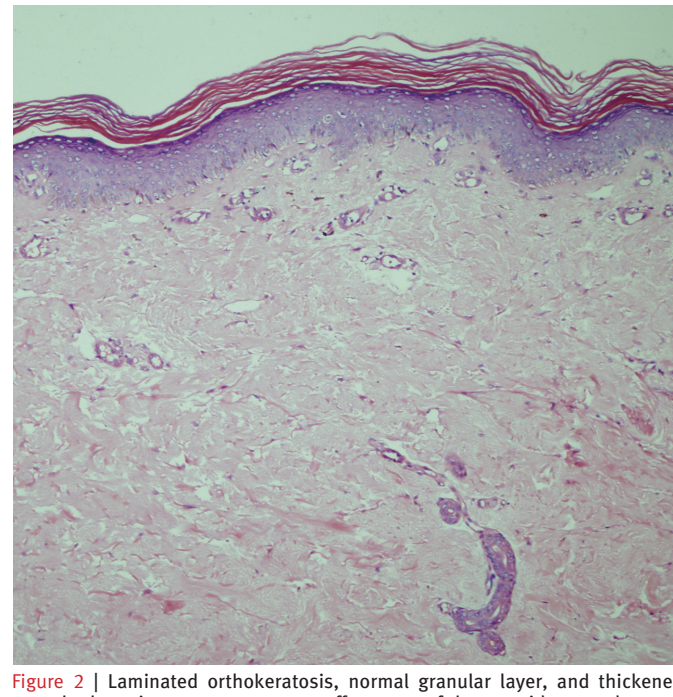

Figure 2 | Laminated orthokeratosis, normal granular layer, and thickened granular layer in some areas, some effacement of the rete ridges, and sparse perivascular lymphocytic infiltration around superficial dilated vessels (H&E, ×100)

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In Memoriam: Marija Berčič, 1928–2016

Our beloved teacher, mentor, and colleague of many years, Marija "Mojca" Berčič, passed away on September 3rd, 2016.

Mojca was born on April 14th, 1928 in Črna na Koroškem, where she also attended primary school. She started attending secondary school in Ptuj and then transferred to a school in Klagenfurt during the Second World War, before finally graduating from the classical secondary school in Maribor.

She graduated from the Ljubljana Medical School and passed her board exam in dermatology and venereal diseases at the Ljubljana Department of Dermatology.

Mojca spent her entire career working at the Maribor General Hospital's Department of Skin and Venereal Diseases. After passing her board exam, she became head of the pediatric department as well as the newly established histopathology laboratory.

She received further training in dermatopathology under Vladimir Milavec at the Ljubljana Department of Dermatology and Venereal Diseases, under Zvonimir Zambal at the Zagreb Department of Skin and Venereal Diseases, and under Albert Bernard Ackerman in New York. In 1986, she defended her doctoral dissertation at the Zagreb Department of Skin and Venereal Diseases.

Mojca attended research conferences in Slovenia and abroad, advised a number of residents, and also taught at the Medical College for many years. She contributed to Milan Betetto and Janez Fettich's textbook for medical and stomatology students, *Mala Dermatovenerologija* (Pocket Dermatology), which was published in 1993.

In addition to conducting research and practicing medicine, Mojca also performed many other functions: she joined the Slovenian Medical Association (SZD) in 1953 and its Section for Dermatology and Venereal Diseases in 1958, became the first secretary of the SZD's Medical and Historical Section (headquartered in Maribor) in 1968 and a close associate of its chairman, chief physician Eman Pertl, was the chair of the executive committee of the SZD's Section for Dermatology and Venereal Diseases from 1980 to 1984, was a member of the executive committee of the Yugoslav Association for Dermatology and Venereal Diseases from 1980 to 1991, started serving as the co-editor of the journal *Acta dermatovenerologica Alpina, Pannonica et Adriatica* in 1992, was a member of the Austrian Association of Dermatologists, and was a member of the International Society of Dermatopathology.

With her expertise, organizational skills, teaching efforts, journalism activity, and extensive research, Mojca contributed significantly to the development of our department and to Slovenian dermatology in general. She was awarded the rank of honorary chief physician for the latter.

Even after she retired, she continued to maintain contact with the profession, participated in our research conferences, and worked assiduously for the Medical and Historical Section, contributing significantly to its development. The committee of the SZD's Medical and Historical Section made her an honorary member.

We are grateful to our respected colleague and mentor for all the efforts she invested in the development of dermatology in Maribor and in Slovenia in general.

Mojca will be remembered forever by the members of the editorial board of *ACTA dermatovenerologica*, the ZSD, and its Medical Historical Section.

Jovan Miljković

NATIONAL SUCCINT STATEMENT

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

Cosentyx 150 mg solution for injection in pre-filled pen
Composition: Each-pre filled pen contains 150 mg secukinumab in 1 ml. Secukinumab is a recombinant fully human monoclonal antibody selective for interleukin-17A. Secukinumab is of the IgG1/κ class produced in Chinese Hamster Ovary (CHO) cells. **Therapeutic indications:** Plaque psoriasis: moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Psoriatic arthritis: alone or in combination with methotrexate (MTX) in adult patients when the response to previous disease modifying anti rheumatic drug (DMARD) therapy has been inadequate. Ankylosing spondylitis: in adults who have responded inadequately to conventional therapy. **Posology:** Cosentyx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Cosentyx is indicated. *Dosage:* For all indications initial dosing is at Weeks 0, 1, 2 and 3, followed by monthly maintenance dosing starting at Week 4. Consideration should be given to discontinuing treatment in patients who have shown no response by 16 weeks of treatment. Some patients with an initial partial response may subsequently improve with continued treatment beyond 16 weeks. *Recommended dose:* Plaque psoriasis: 300 mg of secukinumab. Each 300 mg dose is given as two subcutaneous injections of 150 mg. Psoriatic arthritis: 150 mg or 300 mg of secukinumab. For patients with concomitant moderate to severe plaque psoriasis or who are anti-TNFα inadequate responders (IR), the recommended dose is 300 mg by subcutaneous injection. Each 300 mg dose is given as two subcutaneous injections of 150 mg. For other patients, the recommended dose is 150 mg by subcutaneous injection. Ankylosing spondylitis: 150 mg of secukinumab. *Elderly patients (aged 65 years and over):* No dose adjustment is required. *Renal impairment/hepatic impairment:* Cosentyx has not been studied in these patient populations. No dose recommendations can be made. *Paediatric population:* The safety and efficacy of Cosentyx in children below the age of 18 years have not yet been established. No data are available. **Method of administration:** Cosentyx is to be administered by subcutaneous injection. If possible, areas of the skin that show psoriasis should be avoided as injection sites. After proper training in subcutaneous injection technique, patients may self-inject Cosentyx if a physician determines that this is appropriate. However, the physician should ensure appropriate follow-up of patients. Patients should be instructed to inject the full amount of Cosentyx according to the instructions provided in the package leaflet. **Contraindications:** Severe hypersensitivity reactions to the active substance or to any of the excipients listed. Clinically important, active infection (e.g. active tuberculosis). **Special warnings and precautions for use:** Infections: Cosentyx has the potential to increase the risk of infections. In clinical studies infections have been observed most of these were mild or moderate upper respiratory tract infections such as nasopharyngitis and did not require treatment discontinuation. Related to the mechanism of action of Cosentyx, non serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies (3.55 per 100 patient years for secukinumab 300 mg versus 1.00 per 100 patient years for placebo). Caution should be exercised when considering the use of Cosentyx in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, the patient should be closely monitored and Cosentyx should not be administered until the infection resolves. No increased susceptibility to tuberculosis was reported from clinical studies. However, Cosentyx should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Cosentyx in patients with latent tuberculosis. Crohn's disease: Caution should be exercised when prescribing Cosentyx to patients with Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both Cosentyx and placebo groups. Patients who are treated with Cosentyx and have Crohn's disease should be followed closely. Hypersensitivity reactions: In clinical studies, rare cases of anaphylactic reactions have been observed in patients receiving Cosentyx. If an anaphylactic or other serious allergic reactions occur, administration of Cosentyx should be discontinued immediately and appropriate therapy initiated. Latex sensitive individuals: The removable cap of the Cosentyx pre filled pen contains a derivative of natural rubber latex. No natural rubber latex has to date been detected in the removable cap. Nevertheless, the use of Cosentyx pre filled pens in latex sensitive individuals has not been studied and there is therefore a potential risk for hypersensitivity reactions which cannot be completely ruled out. Vaccinations: Live vaccines should not be given concurrently with Cosentyx. Patients receiving Cosentyx may receive concurrent inactivated or non live vaccinations. In a study, after meningococcal and inactivated influenza vaccinations, a similar proportion of healthy volunteers treated with 150 mg of secukinumab and those treated with placebo were able to mount an adequate immune response of at least a 4 fold increase in antibody titres to meningococcal and influenza vaccines. The data suggest that Cosentyx does not suppress the humoral immune response to the meningococcal or influenza vaccines. Concomitant immunosuppressive therapy: In psoriasis studies, the safety and efficacy of Cosentyx in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. Women of childbearing potential: Women of childbearing potential should use an effective method of contraception during treatment and for at least 20 weeks after treatment. Pregnancy: There are no adequate data from the use of secukinumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Cosentyx in pregnancy. Breast-feeding: It is not known whether secukinumab is excreted in human milk. Because of the potential for adverse reactions in nursing infants from secukinumab, a decision on whether to discontinue breast feeding during treatment and up to 20 weeks after treatment or to discontinue therapy with Cosentyx must be made taking into account the benefit of breast feeding to the child and the benefit of Cosentyx therapy to the woman. Fertility: The effect of secukinumab on human fertility has not been evaluated. Effects on ability to drive and use machines: Cosentyx has no or negligible influence on the ability to drive and use machines. **Interaction with other medicinal products and other forms of interaction:** Live vaccines should not be given concurrently with Cosentyx. No interaction studies have been performed in humans. There is no direct evidence for the role of IL 17A in the expression of CYP450 enzymes. The formation of some CYP450 enzymes is suppressed by increased levels of cytokines during chronic inflammation. Thus, anti inflammatory treatments, such as with the IL 17A inhibitor secukinumab, may result in normalisation of CYP450 levels with accompanying lower exposure of CYP450 metabolised co medications. Therefore, a clinically relevant effect on CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin) cannot be excluded. On initiation of secukinumab therapy in patients being treated with these types of medicinal products, therapeutic monitoring should be considered. No interaction was seen when Cosentyx was administered concomitantly with methotrexate (MTX) and/or corticosteroids in arthritis studies (including in patients with psoriatic arthritis and ankylosing spondylitis). **Undesirable effects:** ***Very common:*** Upper respiratory tract infections. ***Common:*** Oral herpes, Rhinorrhoea, Diarrhea. ***Uncommon:*** Oral candidiasis, Tinea pedis, Otitis externa, Neutropenia, Conjunctivitis, Urticaria. ***Rare:*** Anaphylactic reactions.

Marketing authorisation holder: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR,United Kingdom. **Additional information and literature:** Novartis Pharma Services Inc., Podružnica v Sloveniji, Verovškova ulica 57, 1000 Ljubljana. **General classification for supply:** Rp/Spec. **Please read the summary of product characteristics before prescribing. This text was last revised in** December 2015.

Only for expert public.

COS-AD04-03/16-SI

NOVARTIS

Novartis Pharma Services Inc., Podružnica v Sloveniji
Verovškova 57, 1000 Ljubljana, telefon: 01/300-75-50

Cosentyx®
secukinumab

Enbrel 50 mg raztopina za injiciranje v napolnjenem injekcijskem peresniku

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

ENBREL 25 mg prašek in vehikel za raztopino za injiciranje[1]
ENBREL 50 mg raztopina za injiciranje v napolnjeni injekcijski brizgi[2]
ENBREL 10 mg prašek in vehikel za raztopino za injiciranje za uporabo pri otrocih[3]

ENBREL 50 mg raztopina za injiciranje v napolnjenem injekcijskem peresniku[4]**Sestava in oblika zdravila:** (1) Ena viala vsebuje 25 mg etanercepta. (2) Ena napolnjena injekcijska brizga vsebuje 50 mg etanercepta. (3) Ena viala vsebuje 10 mg etanercepta. (4) En napolnjen injekcijski peresnik vsebuje 50 mg etanercepta. Etanercept je pridobljen z rekombinantno DNA tehnologijo v ovarijskih celicah kitajskega hrčka. **Indikacije:** (1,2,4) Revmatoidni artritis (RA) - zmeren do hud aktiven RA pri odraslih (v kombinaciji z metotreksatom), kadar odziv na zdravljenje z imunomodulirajočimi zdravili, vključno z metotreksatom (če ta ni kontraindiciran), ni zadosten. Monoterapija, kadar bolnik ne prenese metotreksata ali kadar trajno zdravljenje z njim ni primerno. Hud, aktiven in napredujoč RA pri odraslih, ki še niso dobivali metotreksata. (1,2,3,4) Juvenilni idiopatski artritis (JIA) - poliartritis (pozitiven ali negativen za revmatoidni faktor) in razširjen oligoartritis pri otrocih in mladostnikih, starih 2 leti ali več, ki so se nezadostno odzvali na zdravljenje z metotreksatom ali ga niso prenašali. Psoriatični artritis pri mladostnikih, starih 12 let ali več, ki so se nezadostno odzvali na zdravljenje z metotreksatom ali ga niso prenašali. Artritis, povezan z entezitisom, pri mladostnikih, starih 12 let ali več, ki so se nezadostno odzvali na konvencionalno zdravljenje ali ga niso prenašali. (1,2,4) Psoriatični artritis (PA) - aktiven in progresiven PA pri odraslih, če je bil odziv na zdravljenje z imunomodulirajočimi zdravili nezadosten. (1,2,4) Ankilozirajoči spondilitis (AS) - hud aktiven AS pri odraslih, če je bil odziv na konvencionalno zdravljenje nezadosten. (1,2,4) Radiografsko nezaznavni aksialni spondilartritis - Zdravljenje odraslih s hudim radiografsko nezaznavnim aksialnim spondilartritisom in objektivnimi znaki vnetja, ki imajo nezadostni odziv na NSAID. (1,2,4) Psoriaza v plakih (PP) - zmerna do huda PP pri odraslih, ki se ne odzovejo na drugo sistemsko zdravljenje, vključno s ciklosporinom, metotreksatom ali psoralenom in ultravijoličnо svetlobo UV-A (PUVA), oziroma je pri njih le-to kontraindicirano ali ga ne prenašajo. (1,2,3,4) Otroška PP - huda kronična PP pri otrocih in mladostnikih od 6. leta starosti naprej, pri katerih se z drugo sistemsko terapijo ali fototerapijo bolezni ne da zadostno obvladati ali jih bolniki ne prenašajo. **Odmerjanje in način uporabe:** Zdravljenje z Enbrelom lahko uvede in nadzoruje le zdravnik specialist, ki ima izkušnje z zdravljenjem navedenih stanj. Bolniki, ki se zdravijo z Enbrelom, naj prejmejo opozorilno kartico za bolnika. Odrasli (vse indikacije): 25 mg dvakrat na teden ali 50 mg enkrat na teden. Klinični odziv pri RA, PA, AS in radiografsko nezaznavnem aksialnem spondilartritisu je običajno dosežen v 12 tednih zdravljenja. Če v tem obdobju ni odziva, je treba o nadaljevanju zdravljenja skrbno razmisliti. *PP:* Če je treba je mogoče uporabljati tudi 50 mg dvakrat na teden do 12 tednov, čemur sledi 25 mg dvakrat na teden ali 50 mg enkrat na teden. Zdravljenje je treba nadaljevati do remisije, vendar največ 24 tednov. Za nekatere bolnike bo morda primerno stalno zdravljenje, daljše od 24 tednov. Če po 12 tednih ni odziva, je treba zdravljenje prekiniti. Če je indicirano ponovno zdravljenje, je odmerek 25 mg dvakrat na teden ali 50 mg enkrat na teden. Pediatrična populacija: *JIA:* Priporočeni odmerek je 0,4 mg/kg telesne mase (do največ 25 mg na odmerek) 2-krat na teden subkutano z razmikom med odmerki 3-4 dni ali 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden. *Otroška PP:* 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden do največ 24 tednov. Če je indicirano ponovno zdravljenje, je odmerek 0,8 mg/kg (do največ 50 mg na odmerek) enkrat na teden. *Prekinitev zdravljenja:* o prekinitvi je treba razmisliti, če ni odziva po 4 mesecih (JIA) ali 12 tednih (otroška PP) zdravljenja. Način uporabe: subkutana injekcija. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov, sepsa ali možnost nastanka sepse ter aktivne okužbe, vključno s kroničnimi ali lokaliziranimi okužbami. **Posebna opozorila in previdnostni ukrepi:** Okužbe: Pred zdravljenjem, med njim in po njem je treba bolnike pregledati glede okužb in pri tem upoštevati, da je povprečni razpolovni čas izločanja etanercepta iz telesa približno 70 ur (razpon 7-300 ur). Poročali so o primerih resnih okužb. Bolnike, pri katerih se med zdravljenjem pojavi nova okužba, je treba skrbno spremljati. Zdravljenje je treba prekiniti, če pride do resne okužbe. Previdnost je potrebna pri zdravljenju bolnikov s ponavljajočimi se ali kroničnimi okužbami v anamnezi ali z drugimi osnovnimi stanji, ki bi lahko povečala dovzetnost za okužbe. Tuberkuloza: Pred začetkom zdravljenja je treba vse bolnike pregledati glede aktivne kot tudi neaktivne ('latentne') tuberkuloze. Priporočljivo je, da se ti testi vpišejo v bolnikovo opozorilno kartico. Obstaja nevarnost lažno negativnih rezultatov tuberkulinskega kožnega testa, še posebej pri bolnikih, ki so hudo bolni ali imunokompromitirani. Pri aktivni tuberkulozi se zdravljenja ne sme uvesti, pri neaktivni ('latentni') tuberkulozi pa je treba pred uvedbo zdravljenja in v skladu z nacionalnimi priporočili začeti zdravljenje latentne tuberkuloze s tuberkulostatiki. Vsem bolnikom je treba naročiti, naj poiščejo zdravniško pomoč, če se med zdravljenjem ali po njem pojavijo znaki/simptomi tuberkuloze. Reaktivacija hepatitisa B: Pri bolnikih, ki so kdaj že bili okuženi s HBV in so se zdravili z antagonisti TNF, vključno z Enbrelom, so poročali o reaktivaciji hepatitisa B. Pred uvedbo zdravljenja je treba bolnike preiskati na okužbo s HBV. Če je bolnik pozitiven na HBV, je pred uvedbo zdravljenja priporočljivo posvetovanje s specialistom za zdravljenje hepatitisa B. Pri dajanju Enbrela bolnikom, ki so že bili okuženi s HBV, je potrebna previdnost. Take bolnike je treba ves čas zdravljenja in še več tednov po prekinitvi spremljati glede znakov in simptomov aktivne okužbe s HBV. Če se razvije okužba s HBV, je treba zdravljenje prekiniti in uvesti učinkovito protivirusno ter ustrezno podporno zdravljenje. Hepatitis C: Poročali so o poslabšanju hepatitisa C, potrebna je previdnost. Alergijske reakcije: poročali so o alergijskih reakcijah, vključno z angioedemom in urtikarijo, opisani pa so tudi primeri resnih reakcij. Če se pojavi kakršnakoli resna alergijska ali anafilaktična reakcija, je treba zdravljenje prekiniti in uvesti ustrezno zdravljenje. (2,4) Pokrovček igle vsebuje lateks, ki lahko povzroči preobčutljivostne reakcije, če z Enbrelom ravna oseba z znano ali možno preobčutljivostjo na lateks ali če ga damo taki osebi. Imunosupresija: Za antagoniste TNF, vključno z Enbrelom, velja, da lahko vplivajo na naravno odpornost bolnika proti okužbam in malignim obolenjem. Bolniki, zelo izpostavljeni virusu noric, naj začasno prekinejo zdravljenje. Maligne in limfoproliferativne bolezni: Tveganja za razvoj limfomov, levkemije ali drugih hematopoetičnih ali čvrstih rakavih obolenj ni mogoče izključiti. Previdnost je potrebna pri razmisleku o uporabi antagonistov TNF pri bolnikih z anamnezo malignosti ali pri razmisleku o nadaljevanju zdravljenja pri bolnikih, pri katerih se pojavi malignost. *Kožni rak:* Pri bolnikih, zdravljenih z antagonisti TNF, vključno z Enbrelom, so poročali o melanomu in nemelanomskem kožnem raku. Priporočamo občasen pregled kože. Cepljenja: Med zdravljenjem bolnik ne sme prejeti živih cepiv. Tvorba avtoprotiteles: Zdravljenje lahko sproži nastajanje avtoimunskih protiteles. Hematološke reakcije: Poročali so o redkih primerih pancitopenije in zelo redkih primerih aplastične anemije, tudi s smrtnim izidom. Previdnost je potrebna pri bolnikih, ki imajo krvno diskrazijo v anamnezi. Vse bolnike in starše/skrbnike je treba opozoriti, da morajo v primeru pojava znakov ali simptomov, ki kažejo na krvno diskrazijo ali okužbo, med zdravljenjem takoj poiskati zdravniško pomoč. V primeru krvne diskrazije je treba zdravljenje prekiniti. Nevrološke bolezni: Pri bolnikih z demielinizirajočimi obolenji, ali pri tistih, ki imajo povečano tveganje zanje, je treba pred zdravljenjem skrbno pretehtati tveganja in koristi, vključno z nevrološko oceno. Kongestivno srčno popuščanje (KSP): Pri predpisovanju bolnikom s KSP je potrebna previdnost. O nastanku KSP so redko poročali tudi pri bolnikih brez predhodne srčno-žilne bolezni. Izsledki sicer še niso dokončni, vendar podatki kažejo na morebitno tendenco k poslabšanju popuščanja pri bolnikih, zdravljenih z Enbrelom. Alkoholni hepatitis: Ne sme se uporabljati za zdravljenje alkoholnega hepatitisa. Previdnost je potrebna pri uporabi pri bolnikih, ki imajo tudi zmeren do hud alkoholni hepatitis. Wegenerjeva granulomatoza: Enbrela ni priporočljivo uporabljati za zdravljenje te bolezni. Hipoglikemija pri bolnikih, ki se zdravijo zaradi sladkorne bolezni: Po uvedbi zdravljenja so poročali o hipoglikemiji, zato bo morda treba zmanjšati odmerek zdravila za zdravljenje sladkorne bolezni. Starostniki: Potrebna je previdnost, posebno pozornost je treba posvetiti pojavljanju okužb. Pediatrična populacija: Priporočamo, da pred začetkom zdravljenja, če je le mogoče, opravite vsa cepljenja v skladu z veljavnimi smernicami. Pri bolnikih z JIA, ki so se zdravili z Enbrelom, so poročali o kronični vnetni črevesni bolezni in uveitisu. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno zdravljenje z anakinro ali z abataceptom: klinična korist teh dveh kombinacij ni dokazana, zato nista priporočljivi. Sočasno zdravljenje s sulfasalazinom: potrebna je previdnost. **Plodnost, nosečnost in dojenje:** Ženske v rodni dobi morajo med zdravljenjem in še tri tedne po prenehanju le-tega uporabljati ustrezno metodo kontracepcije. Uporaba med nosečnostjo ni priporočljiva. Etanercept prehaja placento. Uporaba živih cepiv v prvih 16 tednih po tem, ko so matere dojenčkov prejele zadnji odmerek Enbrela, pri dojenčkih običajno ni priporočljiva. Bolnica mora med zdravljenjem prenehati dojiti ali pa prekiniti zdravljenje, pri čemer je treba upoštevati tako korist dojenja za otroka kot korist zdravljenja za mater. **Neželeni učinki:** Odrasli: *Zelo pogosti (≥ 1/10):* Okužbe (vključno z okužbami zgornjih dihal, bronhitisom, cistitisom in kožnimi okužbami), reakcije na mestu injiciranja (vključno s krvavitvijo, podplutbami, eritemom, srbenjem, bolečino in oteklino). *Pogosti (≥ 1/100 do < 1/10):* alergijske reakcije, nastanek avtoprotiteles, pruritus, zvišana telesna temperatura. Pediatrična populacija: Na splošno so bili neželeni učinki po vrsti in pogostnosti podobni tistim pri odraslih. Vrste okužb, opaženih v kliničnih preskušanjih pri bolnikih z JIA, starih 2-18 let, so bile na splošno blage do zmerne in skladne s tistimi, ki jih pogosto vidimo pri skupinah ambulantnih pediatričnih bolnikov. Hudi neželeni učinki so bili: norice z znaki in simptomi aseptičnega meningitisa, ki je izzvenel brez posledic, vnetje slepiča, gastroenteritis, depresija/osebnostne motnje, kožne razjede, ezofagitis/gastritis, streptokokni septični šok (streptokoki skupine A), sladkorna bolezen tipa I in okužbe mehkih tkiv ter postoperativnih ran. V kliničnih preskušanjih pri bolnikih z JIA so poročali o 4 primerih sindroma aktivacije makrofagov. Viri iz obdobju trženja so pri bolnikih z JIA poročali o kronični vnetni črevesni bolezni in uveitisu. **Način in režim izdaje:** Rp/Spec. **Imetnik dovoljenja za promet:** Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 01.04.2016
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Pfizer Luxembourg SARL, GRAND DUCHY OF LUXEMBOURG, 51, Avenue J.F. Kennedy, L – 1855,
Pfizer, podružnica Ljubljana, Letališka cesta 3c, 1000 Ljubljana

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Canes-Nail™

NOVO

Do zdravih nohtov v dveh korakih in le 6-tih tednih

1. korak

Odstranjevanje okuženega nohta

2-3 tedne

2. korak

Nadaljevanje zdravljenja okuženega dela kože s protiglivično kremo

4 tedni

Zdravljenje v dveh korakih omogoča:

- Hitro in temeljito odstranjevanje okuženega dela nohta
- Dnevno viden napredek[1]
- Enostavno zdravljenje brez bolečin[1]
- Globinsko odstranjevanje glivic[2]

Podrobni prikaz zdravljenja okuženega dela nohta si lahko ogledate na www.canesnail.si

Skrajšan povzetek glavnih značilnosti zdravila
Ime zdravila: Canespor 10 mg/g krema. **Sestava:** 1 g kreme vsebuje 10 mg bifonazola. **Terapevtske indikacije:** za zdravljenje kožnih mikoz, ki jih povzročajo dermatofiti, kvasovke, plesni in druge glivice (npr. Malassezia furfur) ter okužbe s Corynebacteriumom minutissimum: tinea pedum, tinea manuum, tinea corporis, tinea inguinalis, pityriasis versicolor, površinske kandidoze in eritrazma. **Odmerjanje in način uporabe:** Kremo Canespor uporabljamo enkrat na dan, najbolje zvečer pred spanjem. Na prizadeto kožo nanesemo tanko plast zdravila in ga vtremo. Učinek je trajnejši, če kremo Canespor uporabljamo pravilno in dovolj dolgo. Običajno traja zdravljenje: mikoz na stopalu in med prsti (tinea pedum, tinea pedum interdigitalis) - 3 tedne; mikoz po telesu, rokah in v kožnih gubah (tinea corporis, tinea manuum, tinea inguinalis) – 2 do 3 tedne; okužb rožene plasti kože, blagih, kroničnih, površinskih okužb (pityriasis versicolor, eritrazma) – 2 tedna; površinskih kandidoz kože – 2 do 4 tedne. Za površino v velikosti dlani zadostuje večinoma že majhna količina kreme. Otroci: Pregled kliničnih podatkov kaže, da uporaba bifonazola pri otrocih ne povzroča škodljivih učinkov. Kljub temu naj se bifonazol pri dojenčkih uporablja le pod zdravniškim nadzorom. **Kontraindikacije:** Preobčutljivost za bifonazol, cetil in stearilalkohol ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Bolniki z anamnezo preobčutljivostnih reakcij na druge imidazolske antimikotike (npr. ekonazol, klotrimazol, mikonazol) morajo previdno uporabljati zdravila, ki vsebujejo bifonazol. Paziti je treba, da zdravilo ne pride v stik z očmi. Krema Canespor vsebuje cetil in stearilalkohol, ki lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis). Pri bolnikih, ki so preobčutljivi za cetil in stearilalkohol, je priporočljivo, da namesto kreme Canespor uporabljajo raztopino Mycospor. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Ni podatkov o medsebojnem delovanju z drugimi zdravili. **Nosečnost in dojenje:** Prve 3 mesece nosečnosti smejo ženske bifonazol uporabiti šele potem, ko zdravnik oceni razmerje koristi in tveganja. Dojenje: Ni znano, ali se bifonazol pri človeku izloča v materinem mleku. Doječe matere smejo bifonazol uporabiti šele potem, ko zdravnik oceni razmerje koristi in tveganja. Med obdobjem dojenja ženska bifonazola ne sme uporabljati v predelu prsi. Plodnost: Predklinične študije niso pokazale, da bi bifonazol vplival na plodnost samcev ali samic. **Neželeni učinki:** Splošne težave in spremembe na mestu aplikacije: bolečine na mestu uporabe, periferni edemi (na mestu uporabe); bolezni kože in podkožja: kontaktni dermatitis, alergijski dermatitis, eritem, srbenje, izpuščaj, urtikarija, mehur, eksfoliacija kože, ekcem, suha koža, draženje kože, maceracija kože, pekoč občutek na koži. Ti neželeni učinki po prekinitvi zdravljenja izginejo. **Način in režim izdaje:** Izdaja zdravila je brez recepta v lekarnah. **Imetnik dovoljenja za promet:** Bayer d. o. o., Bravničarjeva 13, 1000 Ljubljana. **Datum zadnje revizije:** 20.10.2011. **Datum priprave informacije**: april 2012. **Vse informacije o zdravilu dobite pri Bayer d.o.o.**

Literatura:
1. Canes-Nail; Navodila za uporabo.
2. Canespor krema; Povzetek glavnih značilnosti zdravila.

Samo za strokovno javnost.

SI.BCC.11.2012.0042

Bayer HealthCare

Hitrost v zdravljenju aktinične keratoze

Rp V*

* le za zdravljenje kože pri nehiperkeratotični, nehipertrofični aktinični keratozi pri odraslih bolnikih: le po priporočilu dermatologa ali onkologa

Enkrat dnevno, 3 zaporedne dni

Aktinična keratoza na obrazu in lasišču pri odraslih bolnikih
Eno tubo zdravila Picato® 150 µg/g gel (ki vsebuje 70 µg ingenol mebutata) je treba enkrat dnevno nanesti na prizadeti predel in postopek ponavljati 3 zaporedne dni.

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Ime zdravila Picato 150 mikrogramov/gram gel

Kakovostna in količinska sestava 1 g gela vsebuje 150 mg ingenol mebutata. Vsaka tuba vsebuje 70 µg ingenol mebutata v 0,47 g gela.

Terapevtske indikacije Zdravilo Picato je indicirano za zdravljenje kože pri nehiperkeratotični, nehipertrofični aktinični keratozi pri odraslih bolnikih.

Odmerjanje in način uporabe

Odmerjanje: *Aktinična keratoza na obrazu in lasišču pri odraslih bolnikih* Eno tubo zdravila Picato 150 µg/g gel (ki vsebuje 70 µg ingenol mebutata) je treba enkrat dnevno nanesti na prizadeti predel in postopek ponavljati 3 zaporedne dni. *Pediatrična populacija* Zdravilo Picato ni primerno za uporabo pri pediatrični populaciji. *Starejši bolniki* Prilagoditev odmerka ni potrebna

Način uporabe: Vsebina tube zadošča za zdravljenje površine 25 cm^2 (npr. 5 cm x 5 cm). Vsebino tube je treba nanesti na eno zdravljeno površino velikosti 25 cm^2. Tuba je namenjena samo enkratni uporabi, zato jo po uporabi zavrzite. Gel iz tube iztisnite na konico prsta, ga enakomerno porazdelite po celotni površini prizadetega mesta in počakajte 15 minut, da se posuši. Vsebino ene tube lahko uporabite za zdravljenje enega mesta v velikosti 25 cm^2. Samo za enkratno uporabo.

Za zdravljenje vratu: če je več kot polovica zdravljenega mesta na zgornjem delu vratu, je treba uporabiti odmerjanje za obraz in lasišče. Če je več kot polovica zdravljenega mesta na spodnjem delu vratu, je treba uporabiti odmerjanje za trup in okončine. Bolnikom naročite, naj si po nanosu zdravila Picato nemudoma umijejo roke z milom in vodo. Če se zdravi roke, je treba umiti samo prst, s katerim se je nanesel gel. 6 ur po nanosu zdravila Picato ne umivajte mesta zdravljenja in se ga ne dotikajte. Po preteku tega časa lahko zdravljeno mesto umijete z blagim milom in vodo.

Zdravila Picato ne nanašajte takoj po prhanju ali manj kot 2 uri pred spanjem.

Po nanosu zdravila Picato zdravljenega mesta ne pokrivajte z neprepustnimi povoji. Optimalne učinke zdravljenja je mogoče oceniti približno 8 tednov po zdravljenju. Če se pri kontrolnem pregledu ugotovi nepopoln učinek, je treba znova skrbno oceniti zdravljenje in razmisliti o ponovni obravnavi. Klinični podatki o zdravljenju za več kot en cikel zdravljenja, ki traja 2 ali 3 zaporedne dni, niso na voljo. Klinični podatki o zdravljenju več kot enega mesta niso na voljo. Klinični podatki o zdravljenju pri imunokomprimiranih bolnikih niso na voljo, vendar ni pričakovati sistemskih tveganj, saj se ingenol mebutat ne absorbira sistemsko.

Kontraindikacije Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov.

Posebna opozorila in previdnostni ukrepi

Izpostavljenost oči Stik z očmi je treba preprečiti. Če pride do nenamerne izpostavitve, je treba oči nemudoma izprati z velikimi količinami vode in bolnik naj čim prej poišče zdravniško pomoč. Pričakovati je da se bodo v primeru nenamerne izpostavitve oči zdravilu Picato pojavile težave z očmi, kot so bolečina očesa, edem vek in periorbitalni edem.

Zaužitje Zdravila Picato se ne sme zaužiti. Če pride do nenamernega zaužitja, naj bolnik spije veliko vode in poišče zdravniško pomoč.

Splošno Nanašanje gela Picato se ne priporoča, dokler koža, zdravljena s predhodnimi zdravili ali kirurško, ni zaceljena. Zdravila se ne sme nanašati na odprte rane ali dele kože s poškodovano kožno pregrado. Zdravilo Picato se ne sme uporabljati v bližini oči, na notranjem predelu nosnic, na notranjem predelu ušes ali na ustnicah.

Lokalni odzivi kože Pričakuje se, da se bodo po nanosu zdravila Picato na koži pojavili lokalni odzivi, kot so eritem, prhljaj/luščenje in nastajanje krast . Lokalizirani odzivi kože so prehodni in se običajno pojavijo v 1 dnevu od začetka zdravljenja, največjo intenzivnost pa dosežejo en teden po zaključku zdravljenja. Pri zdravljenju obraza in lasišča lokalizirani kožni odzivi običajno izzvenijo v 2 tednih od začetka zdravljenja, pri zdravljenju predelov na trupu in okončinah pa v 4 tednih. Učinka zdravljenja morda ne bo mogoče ustrezno oceniti, dokler se ne pozdravijo lokalni odzivi kože.

Izpostavljenost soncu Izvedene so bile študije, ki so ocenile vpliv UV-sevanja na kožo po enkratni ali večkratni uporabi gela z ingenol mebutatom, 100 µg/g. Gel z ingenol mebutatom ni pokazal nobenega potenciala za draženje zaradi svetlobe ali za fotoalergijske učinke. Vendar pa se je treba zaradi narave bolezni izogibati čezmerni izpostavitvi sončni svetlobi (tudi porjavitvenim svetilkam in solarijem) ali izpostavitev čim bolj zmanjšati.

Obravnava aktinične keratoze Pri lezijah, ki so klinično atipične za aktinično keratozo ali so sumljive za malignost, je treba opraviti biopsijo, za določitev primernega zdravljenja.

Medsebojno delovanje z drugimi zdravili in druge oblike interakcij Študij medsebojnega delovanja niso izvedli. Menijo, da interakcije s sistemsko absorbiranimi zdravili niso verjetne, saj se zdravilo Picato ne absorbira sistemsko.

Plodnost, nosečnost in dojenje

Nosečnost Podatkov o uporabi ingenol mebutata pri nosečnicah ni. Študije na živalih so pokazale blago toksičnost za zarodek/plod (glejte poglavje 5.3). Tveganja za ljudi, ki prejemajo kožno zdravljenje z ingenol mebutatom, so malo verjetna, saj se zdravilo Picato ne absorbira sistemsko. Iz previdnostnih razlogov se je uporabi zdravila Picato med nosečnostjo bolje izogibati.

Dojenje Učinkov na dojene novorojence/otroke se ne pričakuje, ker se zdravilo Picato ne absorbira sistemsko. Doječim materam je treba dati navodilo, da novorojenček/dojenček še 6 ur po nanosu zdravila Picato ne sme priti v telesni stik z zdravljenim mestom.

Plodnost Študij plodnosti z ingenol mebutatom niso izvedli.

Neželeni učinki

Povzetek varnostnega profila Neželeni učinki, o katerih so najpogosteje poročali, so lokalni kožni odzivi, vključno z eritemom, prhljajem/luščenjem, krastami, otekanjem, vezikulacijo/pustulacijo in erozijo/ulceracijo na mestu uporabe gela z ingenol mebutatom; glejte preglednico 1 za izraze po MedDRA. Po nanosu gela z ingenol mebutatom se je pri večini bolnikov (> 95 %) pojavil en ali več lokalnih kožnih odzivov. Pri zdravljenju obraza in lasišča so poročali o okužbi na mestu nanosa.

Seznam neželenih učinkov v obliki preglednice V preglednici 1 je prikazana izpostavitev 499 bolnikov z aktinično keratozo zdravilu Picato 150 µg/g ali 500 µg/g v štirih z vehiklom nadzorovanih študijah 3. faze, v katere sta bila skupaj vključena 1002 bolnika. Bolniki so enkrat dnevno prejemali lokalno zdravljenje (površine 25 cm^2) z zdravilom Picato v koncentraciji 150 µg/g 3 zaporedne dni ali 500 µg/g 2 zaporedna dneva ali lokalno zdravljenje z vehiklom. V preglednici so predstavljeni neželeni učinki v skladu z MedDRA, razvrščeni po organskih sistemih in anatomski umestitvi.

Pogostnost neželenih učinkov je opredeljena kot:
zelo pogosti (≥ 1/10); pogosti (≥ 1/100 do < 1/10); občasni (≥ 1/1.000 do < 1/100); redki (≥ 1/10.000 do < 1/1.000); zelo redki (< 1/10.000) in neznana (ni mogoče oceniti iz razpoložljivih podatkov).
V razvrstitvah pogostnosti so neželeni učinki navedeni po padajoči resnosti.

Opis izbranih neželenih učinkov Lokalni kožni odzivi pri zdravljenju »obraza/lasišča« oziroma »trupa/okončin«, pri katerih je bila incidenca > 1-odstotna, so: eritem na mestu uporabe (94 % oz. 92 %), luščenje kože na mestu uporabe (85 % oz. 90 %), krasta na mestu uporabe (80 % oz. 74 %), oteklina na mestu uporabe (79 % oz. 64 %), vezikule na mestu uporabe (13 % oz. 20 %), pustule na mestu uporabe (43 % oz. 23 %) in erozija mesta uporabe (31 % oz. 25 %).

Incidenca hudih lokalnih odzivov na koži obraza in lasišča je bila 29-odstotna, na koži trupa in okončin pa 17-odstotna. Hudi lokalni odzivi na koži pri zdravljenju »obraza/lasišča« oziroma »trupa/okončin«, pri katerih je bila incidenca > 1-odstotna, so: eritem na mestu uporabe (24 % oz. 15 %), luščenje kože na mestu uporabe (9 % oz. 8 %), krasta na mestu uporabe (6 % oz. 4 %), oteklina mesta uporabe (5 % oz. 3 %) in pustule na mestu uporabe (5 % oz. 1 %).

Dolgotrajno sledenje Spremljali so celokupno 198 bolnikov s popolno ozdravitvijo lezij na 57. dan (184 se jih je zdravilo z zdravilom Picato in 14 z vehiklom) še 12 mesecev. Rezultati niso spremenili varnostnega profila zdravila Picato

Preveliko odmerjanje Preveliko odmerjanje zdravila Picato lahko povzroči povečano incidenco lokalnih odzivov kože. Obravnava prevelikega odmerjanja naj obsega zdravljenje kliničnih simptomov.

Posebna navodila za shranjevanje Shranjujte v hladilniku (2 °C - 8 °C). Odprte tube po prvem odprtju zavrzite.

Vrsta ovojnine in vsebina Večplastne eno odmerne tube z notranjo plastjo iz polietilena velike gostote (HDPE) in aluminijasto pregradno membrano. Pokrovčki iz HDPE.
Zdravilo Picato 150 µg/g gel je pakirano v škatli s 3 tubami, od katerih vsaka vsebuje 0,47 g gela.

Imetnik dovoljenja za promet LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Danska

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Zastopnik v Sloveniji Pharmagan, d.o.o., Vodopivčeva 9, 4000 Kranj

Preglednica 1 Neželeni učinki po organskih sistemih v skladu z MedDRA

Pogostnost		
Organski sistem	**Obraz in lasišče**	**Trup in okončine**
Infekcijske in parazitske bolezni		
pustule na mestu nanosa	zelo pogosti	zelo pogosti
okužba na mestu nanosa	pogosti	
Bolezni živčevja		
glavobol	pogosti	
Očesne bolezni*		
edem veke	pogosti	
bolečina v očesu	občasni	
periorbitalni edem	pogosti	
Splošne težave in spremembe na mestu aplikacije		
erozija na mestu nanosa	zelo pogosti	zelo pogosti
vezikule na mestu nanosa	zelo pogosti	zelo pogosti
oteklina na mestu nanosa	zelo pogosti	zelo pogosti
luščenje kože na mestu nanosa	zelo pogosti	zelo pogosti
krasta na mestu nanosa	zelo pogosti	zelo pogosti
eritem na mestu nanosa	zelo pogosti	zelo pogosti
bolečina na mestu nanosa**	zelo pogosti	pogosti
pruritus na mestu nanosa	pogosti	pogosti
draženje na mestu nanosa	pogosti	pogosti
izcedek na mestu nanosa	občasni	
parestezija na mestu nanosa	občasni	občasni
razjeda na mestu nanosa	občasni	občasni
občutek toplote na mestu nanosa		občasni

*: Oteklina na mestu nanosa na obrazu ali lasišču se lahko razširi na predel oči.
**: Vključno s pekočim občutkom na mestu nanosa.


Končno.
Prvo zdravilo z odobreno indikacijo za zdravljenje zmerne do hude oblike **Hidradenitis suppurativa**
Bližina me osrečuje
Zaradi HS sem se počutila nevredna dotika
Manj abscesov in manj bolečin
Počutim se dobro sama s seboj
Zdravilo Humira je indicirano za zdravljenje aktivne zmerne do hude oblike **hidradenitis suppurativa** (acne inversa) pri odraslih bolnikih, ki se ne odzovejo zadovoljivo na konvencionalno HS zdravljenje.[1]
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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA Humira 40 mg raztopina za injiciranje v napolnjeni injekcijski brizgi.**Sestava** Ena 0,8 ml napolnjena injekcijska brizga z enim odmerkom vsebuje 40 mg adalimumaba. Adalimumab je rekombinantno humano monoklonsko protitelo. **Terapevtske indikacije** *Revmatoidni artritis:* v kombinaciji z metotreksatom: zdravljenje zmernega do hudega aktivnega revmatoidnega artritisa pri odraslih bolnikih, kadar odziv na imunomodulirajoča zdravila, vključno z metotreksatom, ni zadosten; zdravljenje hudega, aktivnega in progresivnega revmatoidnega artritisa pri odraslih, ki prej še niso dobivali metotreksata. *Juvenilni idiopatski artritis:* Poliartikularni juvenilni idiopatski artritis (JIA): v kombinaciji z metotreksatom za zdravljenje aktivnega poliartikularnega JIA pri otrocih in mladostnikih od 2.leta starosti, ki se ne odzovejo ustrezno na eno ali več imunomodulirajočih antirevmatičnih zdravil. Artritis, povezan z entezitisom: za zdravljenje aktivnega artritisa, povezanega z entezitisom pri bolnikih, starih 6 let in več, ki so se neustrezno odzvali ali so intolerantni za običajno zdravljenje. *Ankilozirajoči spondilitis:* zdravljenje hudega aktivnega ankilozirajočega spondilitisa pri odraslih, ki se na konvencionalno terapijo ne odzovejo ustrezno. *Aksialni spondiloartritis brez radiografskega dokaza za AS:* zdravljenje odraslih s hudim aksialnim spondiloartritisom brez radiografskega dokaza za AS, toda z objektivnimi znaki vnetja s povišanimi CRP in/ali MRI, ki so nezadostno reagirali na ali ne prenašajo nesteroidnih protivnetnih zdravil. *Psoriatični artritis:* zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih, če odziv na predhodno zdravljenje z imunomodulirajočimi antirevmatiki ni bil ustrezen. *Psoriaza:* zdravljenje zmerne do hude kronične psoriaze v plakih pri odraslih bolnikih, ki se ne odzovejo na druge sistemske terapije ali imajo kontraindikacije zanje. *Psoriaza v plakih pri pediatričnih bolnikih:* zdravljenje hude psoriaze v plakih pri otrocih in mladostnikih od 4. leta starosti, ki so se neustrezno odzvali na ali niso ustrezni kandidati za topikalno zdravljenje in fototerapije. *Hidradenitis supuprativa:* zdravljenje aktivne zmerne do hude oblike hidradenitis suppurativa (acne inversa) pri odraslih bolnikih, ki se ne odzovejo zadovoljivo na konvencionalno zdravljenje. *Crohnova bolezen:* zdravljenje zmerne do hude, aktivne Crohnove bolezni pri odraslih bolnikih, ki se ne odzovejo na popoln in ustrezen ciklus zdravljenja s kortikosteroidom in/ali imunosupresivom, ali pa takšno zdravljenje ni mogoče. *Crohnova bolezen pri pediatričnih bolnikih:* zdravljenje hude aktivne Crohnove bolezni pri pediatričnih bolnikih (od 6.leta starosti), ki se ne odzovejo zadovoljivo na konvencionalno zdravljenje, vključno s primarno prehransko terapijo, kortikosteroidom in imunomodulatorjem, ali pri tistih, ki imajo intoleranco ali kontraindikacije za tako zdravljenje. *Ulcerozni kolitis:* zdravljenje zmerno do močno aktivnega ulceroznega kolitisa pri odraslih bolnikih, ki se ne odzovejo zadostno na običajno zdravljenje ali le-to ni mogoče. **Odmerjanje in način uporabe** Odmerjanje: Zdravljenje mora uvesti in nadzorovati zdravnik specialist. *Revmatoidni artritis:* odrasli bolnik: 40 mg adalimumaba vsak 2.teden v enkratnem odmerku v subkutani injekciji. *Ankilozirajoči spondilitis, aksialni spondiloartritis brez radiografskega dokaza za AS in psoriatični artritis:* 40 mg adalimumaba v enkratni subkutani injekciji vsak 2.teden. *Psoriaza:* odrasli bolniki: začetni odmerek 80 mg subkutano, ki mu sledi 40 mg subkutano čez en teden in nato 40 mg subkutano vsak 2.teden. Pri bolnikih z nezadostnim odzivom na zdravljenje, se lahko po 16 tednih pokažejo koristi zaradi povečanja pogostnosti odmerjanja na 40 mg vsak teden. *Hidradenitis suppurativa:* 160 mg 1. dan, sledi 80 mg 15. dan in nato 29. dan odmerek 40 mg vsak teden. *Crohnova bolezen:* med indukcijo pri odraslih bolnikih z zmerno do hudo, aktivno Crohnovo boleznijo 80 mg 0. teden in nato 40 mg 2. teden. Po indukcijskem zdravljenju je priporočeni odmerek 40 mg v subkutani injekciji vsak drugi teden. *Ulcerozni kolitis:* med indukcijo pri odraslih bolnikih z zmerno do močno aktivnim ulceroznim kolitisom 160 mg 0. teden in 80 mg 2. teden. Po indukcijskem zdravljenju 40 mg v subkutani injekciji vsak 2.teden. *Pediatrična populacija: Juvenilni idiopatski artritis: Poliartikularni JIA od 2. do 12.leta starosti:* 24 mg/m^2 telesne površine do največjega enkratnega odmerka 20 mg (za bolnike, stare 2 do < 4 leta) in do največjega enkratnega odmerka 40 mg (za bolnike, stare 4 - 12 let) adalimumaba, vsak 2.teden v subkutani injekciji; *Poliartikularni JIA od 13.leta starosti:* 40 mg adalimumaba vsak 2.teden ne glede na telesno površino. Uporaba zdravila Humira pri bolnikih, starih manj kot 2 leti, za to indikacijo ni primerna. *Pediatrični bolniki s psoriazo ali ulceroznim kolitisom:* Varnost in učinkovitost zdravila Humira pri otrocih, starih 4-17 let, ni bila potrjena. Uporaba pri otrocih, starih manj kot 4 leta, za to indikacijo ni primerna. *Artritis, povezan z entezitisom:* Priporočeni odmerek pri bolnikih, starih 6 let in več, je 24 mg/m^2 telesne površine do največjega posamičnega odmerka 40 mg adalimumaba vsak drugi teden v subkutani injekciji. *Psoriaza v plakih pri pediatričnih bolnikih:* Priporočeni odmerek je 0,8 mg na kilogram telesne mase (do največ 40 mg na odmerek), ki se ga da subkutano enkrat na teden, v primeru prvih dveh odmerkov, nato pa vsak drugi teden. *Hidradenitis suppurativa pri pediatričnih bolnikih:* Varnost in učinkovitost zdravila. Hidradenitis suppurativa pri pediatričnih bolnikih: Varnost in učinkovitost zdravila Humira pri otrocih, starih 12-17 let, ni bila potrjena. Uporaba pri otrocih, starih manj kot 12 let, za to indikacijo ni primerna. *Pediatrični bolniki s Crohnovo boleznijo:* < 40 kg: 40 mg 0.teden, ki mu sledi 20 mg 2.teden. Po uvodnem zdravljenju je priporočeni odmerek 20 mg vsak drugi teden v obliki subkutane injekcije; ≥ 40 kg: 80 mg 0.teden, ki mu sledi 40 mg 2.teden. Po uvodnem zdravljenju je priporočeni odmerek 40 mg vsak drugi teden v obliki subkutane injekcije. Uporaba pri otrocih, starih manj kot 6 let, za to indikacijo ni primerna. *Pediatrični bolniki s psoriatičnim artritisom in aksialnim spondiloartritisom, vključno z anksiloznim spondilitisom:* Uporaba pri teh bolnikih ni primerna. Način uporabe: uporablja se kot subkutana injekcija. **Kontraindikacije** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Aktivna tuberkuloza ali druge hude okužbe in oportunistične okužbe. Zmerno do hudo srčno popuščanje. **Posebna opozorila in previdnostni ukrepi** *Okužbe:* Bolniki so bolj dovzetni za resne okužbe. Okvarjena pljučna funkcija lahko zveča tveganje za razvoj okužbe. Bolnike je zato treba pred, med in po zdravljenju natančno kontrolirati glede okužb, vključno s tuberkulozo. *Reaktivacija hepatitisa B:* Reaktivacijo hepatitisa B so opažali pri bolnikih, ki so dobivali antagonist TNF in ki so bili kronični nosilci virusa. *Nevrološki zapleti:* Antagonisti TNF so bili v redkih primerih povezani s pojavom ali poslabšanjem kliničnih simptomov in/ali rentgenoloških znakov demielinizirajoče bolezni osrednjega živčnega sistema, vključno z multiplo sklerozo in optičnim nevritisom, in periferne demielinizirajoče bolezni, vključno z Guillain-Barré- jevim sindromom. *Malignomi in limfoproliferativne bolezni:* V kontroliranih delih kliničnih preizkušanj z antagonisti TNF je bilo opaženih več primerov malignomov, vključno z limfomi. *Hematološke reakcije:* Redko opisana pancitopenija, vključno z aplastično anemijo. *Cepljenja:* Uporaba živih cepiv pri dojenčkih, ki so bili izpostavljeni adalimumabu in utero, ni priporočljiva še 5 mesecev po materini zadnji injekciji adalimumaba med nosečnostjo. *Kongestivno srčno popuščanje:* Pri bolnikih z blagim srčnim popuščanjem potrebna previdnost. *Avtoimunska dogajanja:* Zdravljenje lahko povzroči nastanek avtoimunskih protiteles. *Sočasna uporaba bioloških DMARDS ali antagonistov TNF:* Sočasna uporaba z drugimi biološkimi DMARDS (t.j.anakinra in abacept) ali z drugimi antagonisti TNF ni priporočljiva. *Operacije:* Bolnika, ki med zdravljenjem potrebuje operacijo, je treba natančno nadzirati glede okužb. Starejši ljudje: Posebna pozornost glede tveganja okužb. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** V kombinaciji z metotreksatom, je bilo nastajanje protiteles v primerjavi z monoterapijo manjše. Kombinacija zdravila Humira in anakinre ter zdravila Humira in abatacepta ni priporočljiva. **Nosečnost in dojenje** Ženske ne smejo dojiti vsaj pet mesecev po zadnjem zdravljenju z zdravilom Humira. **Neželeni učinki** *Najpogostejši neželeni učinki* so okužbe (kot je nazofaringitis, okužba zgornjih dihal in sinusitis), reakcije na mestu injiciranja (eritem, srbenje, hemoragija, bolečina ali otekanje), glavobol in mišično-skeletne bolečine. Drugi pogostejši neželeni učinki: različne vrste okužb; benigni tumor, karcinom kože; levkopenija, trombocitopenija, levkocitoza; preobčutljivost, alergije; zvišanje lipidov, hipokalemija, hiperurikemija, nenormalni nivo natrija v krvi, hipokalcemija, hiperglikemija, hipofosfotemija, dehidracija; spremembe razpoloženja, anksioznost, nespečnost; glavobol, parestezije, migrena, stisnenje živčnih korenin; motnje vidnega zaznavanja, konjunktivitis, vnetje veke, otekanje oči; vertigo; tahikardija; hipertenzija, zardevanje, hematom; kašelj, astma, dispneja; bolečine v trebuhu, navzeja in bruhanje, gastroinestinalna krvavitev, dispepsija, bolezen gastroezofagealnega refluksa, Sjögrenov sindrom; zvišani jetrni encimi; izpuščaj, poslabšanje ali pojav psoriaze, urtikarija, modrice, dermatitis, oniholiza, čezmerno znojenje, alopecija, srbenje; mišičnoskeletne bolečine, mišični spazmi; hematurija, ledvična okvara; reakcija na mestu injiciranja, bolečina v prsih, edemi, povišana telesna temperatura; koagulacija in motnje krvavenja, prisotnost avtoprotiteles, zvišanje laktat dehidrogenaze v krvi; slabše celjenje. **Način in režim izdajanja** Predpisovanje in izdaja zdravila je le na recept. **Imetnik dovoljenja za promet** AbbVie Ltd, Maidenhead, SL6 4UB Velika Britanija. **Datum revizije besedila:** 19.11.2015.

Vir: 1. Humira Povzetek glavnih značilnosti zdravila

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