ACTA DERMATOVENEROLOGICA

ALPINA, PANNONICA ET ADRIATICA

Volume 24

Issue 2

Ljubljana, June 2015

ISSN 1318-4458

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

ACTA
DERMATOVENEROLOGICA
ALPINA, PANNONICA ET ADRIATICA

Volume 24, Issue 2, June 2015

Editorial Office and Administration
Department of Dermatovenerology, Zaloška 2, SI-1525 Ljubljana, Slovenia. Tel: +386 1 522 41 58, Fax: +386 1 522 43 33; E-mail: office@acta-apa.org

The Journal is published quarterly. The yearly subscription is 55 EUR for individuals and 65 EUR for institutions plus postage.
Indexed and abstracted by: BIOMEDICINA SLOVENICA, EMBASE/Excerpta Medica and Index Medicus/MEDLINE

Submission guidelines
The submission guidelines, updated on 1 January 2012, can be accessed at the following URL address:
http://www.acta-apa.org/submission-guidelines.pdf

Orders and Payments
Orders: Association of Slovenian Dermatovenerologists, Zaloška 2, SI-1525 Ljubljana, Slovenia
Payments: Nova Ljubljanska banka, d.d., Zaloška 7, Ljubljana
IBAN: SI 56020140089341717, SWIFT: LJBA2X, VAT: SI 32325029

Published by
Association of Slovenian Dermatovenerologists, Zaloška 2, SI-1525 Ljubljana, Slovenia

Founded by
A. Kansky in 1992, Ljubljana

Design and print
Design: Modra Jagoda (www.modrajagoda.si)
Copy Editor for articles: Donald F. Reindl
Typesetting: Milan Števanec
Printed on acid free paper ISO 9706 by: Tiskarna Pleško

Journal Acta Dermatovenerologica Alpina, Pannonica et Adriatica is enlisted in Razvid medijev.

Journal Acta Dermatovenerologica Alpina, Pannonica et Adriatica is financially supported by the Slovenian Research Agency (Javna agencija za raziskovalno dejavnost Republike Slovenije).
Printed in 250 copies.

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24(2)

Table of Contents

Belakne (adapalen)

Adapalen je **ZDRAVILO IZBORA ZA ZDRAVLJENJE BLAGIH DO ZMERNIH OBLIK AKEN.**

(European Evidence based Guidelines for the Treatment of Acne, JEADV 2012)

Zdravilo Belakne **DELUJE NA VZROK** *nastajanja aken*

- **PROTIVNETNO**
- **URAVNAVA DIFERENCIACIJO KERATINOCITOV**
- **KOMEDOLITIČNO**
- **PROTIBAKTERIJSKO**

ZA OPTIMALEN REZULTAT ➡ Belakne – v dveh oblikah

gel 0,1%
za mastno kožo

krema 0,1%
za suho, občutljivo kožo

Skrajšan povzetek glavnih značilnosti zdravila

Belakne 1 mg/g gel

Belakne 1 mg/g krema

Sestava: 1 g gela ali kreme vsebuje 1 mg adapalena.

Indikacije: Zdravljenje blagih do zmernih aken s pretežno prisotnimi ogrci, papulami in pustulami na obrazu, prsih ali hrbtu.

Odmerjanje: Zdravilo Belakne se uporablja pri otrocih starejših od 12 let in pri odraslih. Varnost in učinkovitost zdravila Belakne pri otrocih, mlajših od 12 let nista bili dokazani. Zdravilo Belakne je treba nanesti na aknozne spremembe kože enkrat na dan, najbolje po umivanju, zvečer pred spanjem. Tanko plast kreme ali gela je treba z blazinicami prstov nanesti na prizadeta mesta na koži tako, da se izogiba očem in ustnicam. Priporočljivo je, da se oceni izrazitost izboljšanja po 3 mesecih zdravljenja z zdravilom Belakne. Če je potrebno zdravljenje s perkutanimi protibakterijskimi zdravili ali benzoil peroksidom, jih je treba na kožo nanašati zjutraj, zdravilo Belakne pa zvečer.

Kontraindikacije: Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov.

Posebna opozorila in previdnostni ukrepi: Če se pojavi preobčutljivostna reakcija ali hudo draženje, je treba uporabo zdravila prekiniti. Zdravilo Belakne ne sme priti v stik z očmi, usti, robovi nosu ali mukoznimi membranami. Če zdravilo po nesreči pride v stik z očmi, jih je treba izprati s toplo vodo. Ne sme se aplicirati na poškodovano (ureznine in odrgnine), od sonca opečeno ali ekcematozno kožo niti se ga ne sme uporabljati pri bolnikih s hudimi aknami ali aknami na večjih površinah telesa. Pri bolnikih, ki prejemajo retinoidna zdravila se je treba izogibati depilaciji z voskom. Hkratni uporabi zdravila Belakne in perkutanih keratolitikov ali eksfoliacijskih zdravil se je treba izogibati. Ob sočasni uporabi sredstev za luščenje (peeling), medicinskih ali abrazivnih mil, kozmetičnih izdelkov, ki kožo sušijo, adstringentov ali izdelkov, ki dražijo kožo (dišav, lupino limone ali izdelkov, ki vsebujejo alkohol), se lahko stopnjuje učinek draženja. Izpostavljanje sončni svetlobi ali umetnim UV žarkom (vključno s solariji) je treba med uporabo zdravila Belakne zmanjšati na minimum. Kadar se izpostavljenosti soncu ni moč izogniti, je treba uporabljati zaščitna sredstva in zdravljene predele kože zaščititi z obleko.

Interakcije: Ni znanih interakcij pri sočasni uporabi zdravila Belakne z drugimi zdravili, ki jih lahko uporabljamo perkutano. Kljub temu pa zdravila Belakne ne smemo uporabljati skupaj z drugimi retinoidi ali zdravili s podobnim načinom delovanja. Izogibati se je treba uporabi zdravila Belakne skupaj z vitaminom A (vključno s prehranskimi dodatki). Adapalen ni fototoksičen in ne povzroča alergije na svetlobo, vendar pa varnost uporabe adapalena med večkratno izpostavljenostjo soncu ali UV sevanju ni bila dokazana. Večji izpostavljenosti soncu ali UV sevanju se je treba izogibati. Ker je absorpcija adapalena skozi kožo majhna, so interakcije s sistemsko uporabljenimi zdravili zelo malo verjetne.

Nosečnost in dojenje: Ker je na voljo malo podatkov in zaradi možnega prehoda zdravila skozi kožo v krvni obtok, zdravljenje z zdravilom Belakne med nosečnostjo ni priporočljivo. V primeru nepričakovane nosečnosti je treba zdravljenje z zdravilom Belakne prekiniti. Zdravilo Belakne lahko uporabljate med dojenjem, vendar se zdravila ne sme nanašati na predel prsnega koša, da ne pride v stik z dojenčkom. Učinkov adapalena na dojenčka ni pričakovati, ker je sistemska izpostavljenost doječe matere zanemarljiva.

Vpliv na sposobnost vožnje in upravljanja s stroji: Ni vpliva.

Neželeni učinki: Suha koža, draženje kože, občutek toplote na koži, eritem, kontaktni dermatitis, občutek nelagodja na koži, pekoč občutek na koži, srbenje, luščenje kože, očitno poslabšanje aken, bolečina, oteklina, mehurji ali kraste na koži in draženje, rdečina, srbenje ali oteklina očesnih vek.

Vrsta ovojnine in vsebina: Škatla s tubo po 30 g gela ali 30 g kreme.

Režim izdaje: Rp

Imetnik dovoljenja za promet: Belupo d.o.o., Dvoržakova 6, 1000 Ljubljana.

Datum zadnje revizije besedila: 28.5.2012

Podrobnejše informacije o zdravilu in povzetek glavnih značilnosti zdravila so vam na voljo pri strokovnih sodelavcih in na sedežu podjetja Belupo.

BELUPO | Bodimo zdravi!

BELUPO, d.o.o., Dvoržakova ulica 6, 1000 Ljubljana
Tel: 01 300 95 10, faks: 01 432 63 11
E-pošta: info@belupo.si, www.belupo.si

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24:17-20
doi: 10.15570/actaapa.2015.6

Serological diagnosis of syphilis: a comparison of different diagnostic methods

Saša Simčič[1]✉, Marko Potočnik[2]

Abstract

Introduction: Serological tests' limitations in syphilis diagnosis as well as numerous test interpretations mean that patients with discordant serology results can present diagnostic and treatment challenges for clinicians. We analyzed three common diagnostic algorithms for detecting suspected syphilis in high-prevalence populations in Slovenia.
Methods: The prospective study included a total of 437 clinical serum samples from adults throughout Slovenia tested with Rapid Plasma Reagin (RPR), *Treponema pallidum* hemagglutination (TPHA), and an automated chemiluminescence immunoassay (CIA) according to the manufacturer's instructions. In addition to percent agreement, kappa coefficients were calculated as a secondary measure of agreement between the three algorithms.
Results: Overall, of 183 subjects that had seroreactive results, 180 were seroreactive in both the reverse sequence and the European Centre for Disease Prevention and Control (ECDC) algorithm. The traditional algorithm had a missed serodiagnosis rate of 30.0%, the overall percent agreement between the traditional and the reverse algorithm (or the ECDC algorithm) was 87.6%, and the kappa value was 0.733. However, the reverse and ECDC algorithm failed to detect three subjects with positive serodiagnosis determined by additional confirmative treponemal assays.
Conclusions: Our results supported the ECDC algorithm in the serodiagnosis of syphilis in high-prevalence populations and the use of nontreponemal serology to monitor the response to treatment.

Keywords: syphilis, treponema, sexually transmitted infections, serodiagnosis

Received: 17 April 2015 | **Returned for modification:** 3 May 2015 | **Accepted:** 10 May 2015

Introduction

The presence of clinical signs or medical history with direct detection of the bacterium *Treponema pallidum* subsp. *pallidum* in clinical specimens and/or reactive treponemal and non-treponemal tests is required to diagnose syphilis (1, 2). Currently, there are three common approaches to the serological diagnosis of syphilis. First, the US Centers for Disease Control and Prevention (CDC) recommends a traditional screening algorithm starting with a nontreponemal assay (e.g., the Rapid Plasma Reagin [RPR] or Venereal Disease Research Laboratory [VDRL] test) to identify persons with possible untreated infection; this screening is followed by a confirmative treponemal assay (e.g., *Treponema pallidum* hemagglutination [TPHA], *Treponema pallidum* particle agglutination [TPPA], or the fluorescent treponemal antibody-absorption [FTA-ABS] test). Second, an updated reverse sequence algorithm based on the availability of automatable treponemal immunoassay suggests that samples may be screened using a treponemal assay (e.g., enzyme immunoassay [EIA] or chemiluminescence immunoassay [CIA]), and, if reactive, either a quantitative non-treponemal or a second, different treponemal assay is used to assess disease and treatment status and confirm suspected infection. Third, there is the European Centre for Disease Prevention and Control (ECDC) algorithm, which starts with a primary treponemal screening test followed by a second, different confirmative treponemal assay (1, 3–5). However, due to serological tests' limitations and the lack of a reliable gold standard for syphilis diagnosis as well as numerous test interpretations, patients with discordant serology results can present diagnostic and treatment challenges for clinicians (6, 7). Regardless of the algorithm used, the choice of treponemal-specific assays with incomparable performance properties may introduce the possibility of having uncertainty in the serodiagnosis of syphilis.

The goal of this study was to compare two commercially available total antibody treponemal assays: a conventional TPHA test with an automated CIA run on the random access Siemens Immulite® 2000 analyzer. The study was designed to analyze three different algorithms with the implementation of both treponemal tests for detecting suspected syphilis in high-prevalence populations in Slovenia.

Materials and methods

The prospective study included a total of 437 clinical serum samples from adults with suspected syphilis from hospitals and clinics throughout Slovenia submitted for the first time to routine screening for syphilis to our laboratory from September 2013 to December 2014. The syphilis serologic testing for each sample was performed using a RPR test with antigens containing cardiolipin, lecithin, and cholesterol (bioMérieux, Netherlands), a TPHA test with antigens of the Nichols strain of *T. pallidum* (Randox, UK), and an automated CIA with the recombinant antigen Tp17 (Immulite® 2000 Syphilis Screen Test, Siemens, UK) according to the manufacturer's instructions. Samples with discrepant results between RPR, TPHA, and CIA were further tested with other treponemal assays, the IgG-FTA-ABS test (bioMérieux, France), the 19 S IgM-FTA-ABS test (bioMérieux, France) or IgM-EIA test (Captia™ NMT Syphilis IgM, Trinity Biotech, Ireland), and the IgG-Line Immuno Assay (LIA, INNO-LIA Syphilis Score, Fujirebio, Belgium). The remaining 200 samples of a total of 637 samples tested were

[1]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. [2]Department of Dermatovenereology, University Medical Centre Ljubljana, Slovenia. ✉ **Corresponding author: sasa.simcic@mf.uni-lj.si**

randomly selected from our serum collections of non-sexually transmitted disease (STD) clinic patients stored as a part of non-STD routine diagnostics and tested with TPHA and CIA to challenge the specificity of the CIA in comparison with the TPHA assay.

Statistical analyses were performed using IBM® SPSS® software, version 21.0 for Windows. In addition to percent agreement, kappa coefficients were calculated as a secondary measure of agreement. The agreement of the results by kappa values is categorized as very good (0.81 to 1.00), good (0.61 to 0.80), moderate (0.41 to 0.60), fair (0.21 to 0.40), or poor (< 0.20) (8).

Results

Following the testing of the 437 serum samples, the results of the CIA were compared to those of the TPHA test. Overall, 180 subjects had TPHA-positive / CIA-positive results, and 247 subjects had TPHA-negative / CIA-negative results; seven subjects were TPHA-negative / CIA-positive, and three subjects were TPHA-positive / CIA-negative. The overall percent agreement and kappa value were 97.7%, κ = 0.953 (95% confidence interval [CI] = 0.924 to 0.982, $p < 0.001$). These data indicated that there was a very good strength of agreement between the TPHA test and the CIA. Using the TPHA test as the standard test, the CIA had 100% sensitivity and 98.8% specificity. In addition, we analyzed the 200 serum samples of the non-STD clinic-adult patients, and the agreement of the CIA compared to the TPHA test was 100%. All 200 serum samples were TPHA-negative / CIA-negative.

Ten samples from subjects with suspected syphilis and the discordant TPHA and CIA results were further tested to assess the possibility of false test results (Table 1). Three sera found to be positive by the TPHA test were found to be negative by all other tests, suggesting three TPHA false positives (Table 1, patients 1–3). Similarly, three sera found to be positive by the CIA were negative by all other tests, suggesting three CIA false positives (Table 1, patients 8–10). The remaining four samples were positive by the CIA and negative by the TPHA test. All four samples were also positive by the IgG-FTA-ABS test, three of them were positive by the IgG-Inno-LIA test, and one sample was indeterminate. A review of each patient's medical record was performed to determine the reason for testing and the final clinical interpretation of results. Three patients (Table 1, patients 4, 5, and 7) were reactive by the CIA, the IgG-FTA-ABS, and the IgG-Inno-LIA, but nonreactive by the RPR and the TPHA. Because these patients were both highly likely to have major epidemiologic risk factors for syphilis and were not previously treated for syphilis, all three were diagnosed with possible latent syphilis and were treated appropriately. One patient (Table 1, patient 6) was reactive by the CIA and had low titre sera determined by the IgG-FTA-ABS, but had an indeterminate IgG-INNO-LIA and nonreactive RPR and TPHA test. The patient was first syphilis-screened as a blood donor and was managed then by a dermatologist. Because the patient had no contact with syphilis as well as no clinical history of any STD, this finding was interpreted as a probably falsely positive serodiagnosis, and the patient was not treated for syphilis. If the TPHA test had been selected as the screening test for the reverse algorithm or the ECDC algorithm, then four samples positive by other treponemal assays would have been missed, possibly resulting in a false serological result.

In this study, we also found four RPR-positive / TPHA-negative / CIA-negative cases that were confirmed to be biological false-positive reactions. All four had false-positive RPR titers less than 8. A review of each patient's medical record revealed that two patients had hepatitis B virus infection, one patient had herpes zoster, and one had a false-positive reaction of unknown cause.

In addition, we further analyzed the agreement between the three syphilis testing algorithms. Of 437 subjects that were tested for syphilis, 180 had reactive results in both the reverse sequence and the ECDC algorithm. Our results indicated that with the traditional algorithm 126 of the 180 subjects would be diagnosed with syphilis; however, 54 subjects that were RPR-negative / TPHA-positive / CIA-positive would not be diagnosed (Fig. 1). The missed serodiagnosis rate was 30.0%. The overall percent agreement between the traditional and reverse algorithm (or the ECDC algorithm) and kappa value were 87.6%, κ = 0.733 (95% CI = 0.669 to 0.797, $p < 0.001$). The direct comparison of the reverse and ECDC algorithm gave an overall percent agreement and kappa value of 100% and κ = 1.000 (95% CI = 1.000 to 1.000, $p < 0.001$). These data indicated that there was a very good strength of agreement between the reverse and ECDC algorithm. However, both, the reverse and ECDC algorithm failed to detect three subjects with positive serodiagnosis determined by additional confirmative treponemal assays. These three cases were screened reactive by the CIA but were not confirmed by the TPHA test. The selection of a second, analytically less-sensitive treponemal test may introduce the possibility of having a false serological result.

Discussion

The laboratory diagnosis of syphilis still relies on nontreponemal and treponemal serologic tests. Decisions on which treponemal test a laboratory should use depend on many factors, including cost, ease of use, suitability for automation, and performance characteristics. A significant advantage of immunoassays is that they can be automated, significantly reducing labor costs and increasing sample throughput compared to other syphilis tests. There are a number of automated treponemal antibody assays evaluated elsewhere, mostly with relatively high sensitivity and specificity (9–12). One of these, the chemiluminescence immunoassay run on the Siemens Immulite® 2000 analyzer, was evaluated in this study. Although

Table 1 | Serologic results for ten serum samples with discrepant results in the TPHA and the Immulite 2000 CIA. Abbreviations: RPR = rapid plasma reagin, TPHA = *Treponema pallidum* hemagglutination, CIA = chemiluminescence immunoassay, FTA-ABS = fluorescent treponemal antibody-absorption, EIA = enzyme immunoassay, LIA = line immunoassay; ID = indeterminate.

Sample	TPHA	Immulite 2000 CIA	RPR	IgG-FTA-ABS	IgM-FTA-ABS	Captia IgM-EIA	IgG-Inno-LIA
1	1:160	Neg	Neg	Neg	Neg	/	Neg (Tp47/Tp17/Tp15/TmpA 0)
2	1:160	Neg	Neg	Neg	Neg	/	Neg (Tp47/Tp17/Tp15/TmpA 0)
3	1:320	Neg	Neg	Neg	Neg	/	Neg (Tp47/Tp17/Tp15/TmpA 0)
4	Neg	Pos	Neg	1:20	Neg	/	Pos (Tp47/Tp17 1+, Tp15/TmpA 0)
5	Neg	Pos	Neg	1:10	Neg	Neg	Pos (Tp47/Tp17 1+, Tp15/TmpA 0)
6	Neg	Pos	Neg	1:20	Neg	Neg	ID (Tp47/Tp15/TmpA 0, Tp17 2+)
7	Neg	Pos	Neg	1:20	Neg	Neg	Pos (Tp17/TmpA 2+, Tp15 0.5+, Tp47 0)
8	Neg	Pos	Neg	Neg	Neg	Neg	Neg (Tp47/Tp15/TmpA neg/Tp17 0.5+)
9	Neg	Pos	Neg	Neg	Neg	Neg	Neg (Tp47/Tp15/TmpA neg/Tp17 0.5+)
10	Neg	Pos	Neg	Neg	Neg	/	Neg (Tp47/Tp17/Tp15/TmpA neg)

our findings showed a very good strength of agreement between the two treponemal assays (i.e., 97.7%; CIA sensitivity and specificity in high-prevalence populations compared to the reference TPHA test were 100% and 98.8%, respectively), there were samples with discordant results that became a focus for further investigation. Based on the results of other treponemal tests (i.e., IgG-FTA-ABS and IgG-LIA) as well as those of the RPR and the treponemal IgM assays to determine the likelihood of past or recent infection, three samples were interpreted as probable false-positive TPHA results and three samples as probable false-positive CIA results, giving each assay a false-reactive rate similar to that which was previously reported elsewhere (less than 1%) (13–15); that is, 3/437 (0.68 %). Although associations of false-positive results of hemagglutination tests with specific conditions were established, the cause in the three subjects was unknown. In contrast, all three subjects with probable false-positive CIA results were intravenous drug users. Despite our finding, more studies are needed to understand the real cause of false-positive EIAs/CIAs.

Four TPHA-negative samples were positive in the CIA. After analysis with other treponemal and nontreponemal tests, and when evaluated together with patients' history of STD, three samples were interpreted as probable false-negative TPHA results, implying that the CIA may have been more sensitive in detecting latent syphilis than the TPHA. However, one sample was interpreted as probable falsely positive serodiagnosis, even though the CIA as well as the low titre IgG-FTA-ABS test were positive. The patient was advised to be followed up due to a possible seroconversion of the TPHA and RPR. The high specificity of the treponemal screening test is crucial to avoid false positive samples, resulting in lower positive predictive values especially in low-prevalence populations, such as blood donors and pregnant women (16, 17). In this study, among 200 samples of non-STD clinic-patients, all samples were TPHA-negative / CIA-negative, suggesting an excellent agreement and specificity of both treponemal assays.

Traditionally, sera submitted for syphilis testing have been screened using a nontreponemal test, such as RPR. This algorithm has demonstrated reliable performance in correlating results with disease status (5, 7, 18, and 19). Screening for syphilis using a treponemal assay detects a higher number of patients with reactive results compared to traditional screening. Our data indicated that the missed serodiagnosis rate of the traditional screening would be 30.0%. Due to the main limitation of our study of not having clinical information on the patient's symptoms/signs or stage of the disease, we were unable to evaluate the diagnostic accuracy of the algorithms compared with clinical diagnosis. Tong et al. demonstrated the missed diagnosis rate of the traditional screening as 24.2% among 2,749 patients diagnosed with syphilis by clinicians (7). These findings supported past work suggesting that reverse screening may detect a higher rate of screen-reactive patients with past untreated and inappropriate treated syphilis or early syphilis (5, 6). Our data demonstrated that the reverse algorithm, in which serum samples were first tested by the automated CIA, facilitated the detection of patients highly likely to have destructive latent disease stages, while offering the specific and objective screening approach.

The screening strategy for syphilis recommended by the ECDC involves a primary treponemal screening test followed by a second confirmatory treponemal test (1). The results obtained from a large cohort (7) as well as our data support the application of the ECDC algorithm for syphilis screening of a high-prevalence populations. The direct comparison of the reverse and ECDC algorithm in our study gave an overall percent agreement and kappa value of 100% and $\kappa = 1.000$, suggesting that a nontreponemal assay is unnecessary for serodiagnosis of syphilis. Once syphilis has been diagnosed, a nontreponemal test is performed to assess disease activity and treatment status. In the cases in which the first treponemal test is positive and the confirmatory treponemal test is negative, then it is inconclusive whether the first screening test is a false positive or is more sensitive. Consequently, it would be advisable for a laboratory to select two treponemal assays with comparable performance to avoid having discrepant results (20). In order to potentially resolve these discrepancies, the results of other treponemal confirmatory

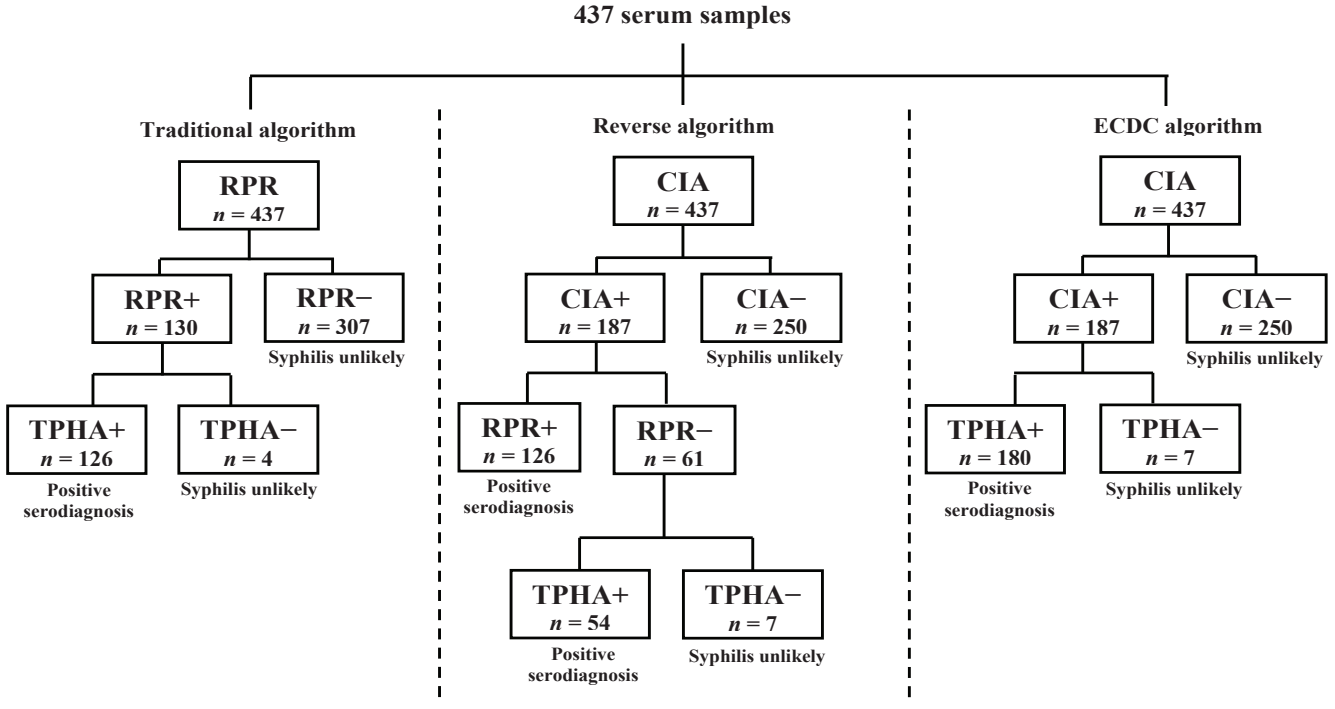

Figure 1 | Various testing algorithms for syphilis serodiagnosis. Abbreviations: RPR = rapid plasma reagin, TPHA = *Treponema pallidum* hemagglutination, CIA = chemiluminescence immunoassay, ECDC = European Centre for Disease Prevention and Control.

tests should be reviewed. In this study, three of a total of 183 syphilis seropositive samples were CIA-positive / TPHA-negative, giving both the reverse and ECDC algorithm a missed serodiagnosis rate of 1.64% that went undetected unless it was further investigated by other treponemal assays.

Our results demonstrate comparable performance among the two treponemal assays evaluated. However, our data suggest that each method has limitations, including the potential for false-positive and false-negative results. In addition, we support the ECDC algorithm in the serodiagnosis of syphilis in high-prevalence populations. Clinicians must still collect other relevant information needed to diagnose and stage patients with suspected syphilis, and they must continue to use nontreponemal serology to monitor response to treatment.

Acknowledgments

We thank Sanja Stopinšek, Institute of Microbiology and Immunology, for her assistance in the statistical data analysis, and Maja Mrgole, Institute of Microbiology and Immunology, for her assistance in the laboratory.

References

1. Janier M, Hegyi V, Dupin N, Unemo M, Tiplica GS, Potočnik M, et al. 2014 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2014;28:1581-93.
2. Ho EL, Lukehart SA. Syphilis: using modern approaches to understand an old disease. J Clin Invest. 2011;121:4584-92.
3. Sena AC, White BL, Sparling PF. Novel Treponema pallidum serologic tests: a paradigm shift in syphilis screening for the 21st century. Clin Infect Dis. 2010;51:700-8.
4. Unemo M. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. Geneva: World Health Organization Document Production Services; c2013. Chapter 10, Syphilis; p. 107-29.
5. Binnicker MJ. Which algorithm should be used to screen for syphilis? Curr Opin Infect Dis. 2012;25:79-85.
6. Park IU, Chow JM, Bolan G, Stanley M, Shieh J, Schapiro JM. Screening for syphilis with the Treponemal immunoassays: analysis of discordant serology results and implications for clinical management. J Infect Dis. 2011;204:1297-304.
7. Tong M, Lin L, Liu L, Zhang H, Huang S, Chen Y, et al. Analysis of 3 algorithms for syphilis serodiagnosis and implications for clinical management. Clin Infect Dis. 2014;58:1116-24.
8. Altman DG. Practical statistics for medical research. London (United Kingdom): Chapman&Hall/CRC; c1999. Chapter 14, Some common problems in medical research; p. 396-439.
9. Cole MJ, Perry KR, Parry JV. Comparative evaluation of 15 serological assays for the detection of syphilis infection. Eur J Clin Microbiol Infect Dis. 2007;26:705-13.
10. Marangoni A, Moroni A, Accardo S, Cevenini R. Laboratory diagnosis of syphilis with automated immunoassays. J Clin Lab Anal. 2009;23:1-6.
11. Binnicker MJ, Jespersen DJ, Rollins LO. Treponema-specific tests for serodiagnosis of syphilis: comparative evaluation of seven assays. J Clin Microbiol. 2011;49:1313-17.
12. Donkers A, Roma Levy H, Letens-van Vliet A. Syphilis detection using the Siemens ADVIA Centaur Syphilis treponemal assay. Clin Chim Acta. 2014;433:84-7.
13. Centers for Disease Control and Prevention. Discordant results from reverse sequence syphilis screening–five laboratories, United States, 2006–2010. MMWR. 2011;60(05):133-7.
14. Loeffelholz MJ, Binnicker MJ. It is time to use Treponema-specific antibody screening tests for diagnosis of syphilis. J Clin Microbiol. 2012;50:1-6.
15. Larsen SA, Pope V, Johnson RE, Kennedy EJ Jr. A manual of tests for syphilis. Washington, DC: American Public Health Association; c1998. Chapter 1, Diagnostic tests; p. 2-52.
16. Binnicker MJ, Jespersen DJ, Rollins LO. Direct Comparison of the traditional and reverse syphilis screening algorithms in a population with a low prevalence of syphilis. J Clin Microbiol. 2012;50:148-50.
17. Lipinsky D, Schreiber L, Kopel V, Shainberg B. Validation of reverse sequence screening for syphilis. J Clin Microbiol. 2012;50:1501.
18. Gu W, Yang Y, Wang Q, Pan B, Guo W, Wu L, et al. Comparing the performance of traditional non-treponemal tests on syphilis and non-syphilis serum samples. Int J STD&AIDS. 2013;24:919-25.
19. Owusu-Edusei K Jr, Peterman TA, Ballard RC. Serologic testing for syphilis in the United States: a cost-effectiveness analysis of two screening algorithms. Sex Transm Dis. 2011;38:1-7.
20. Castro A, Jost H, Cox D, Fakile Y, Kikkert S, Tun Y, et al. A comparison of the analytical level of agreement of nine treponemal assays for syphilis and possible implications for screening algorithms. BMJ Open. 2013;3:e003347.

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24:21-23
doi: 10.15570/actaapa.2015.7

Genome announcement: complete genome sequence of a novel *Mupapillomavirus*, HPV204

Boštjan J. Kocjan[1], Anja Šterbenc[1], Lea Hošnjak[1], Diego Chouhy[2], Elisa Bolatti[2], Adriana A. Giri[2], Mario Poljak[1] ✉

Abstract

Human papillomaviruses (HPVs) are small, non-enveloped viruses with a circular double-stranded DNA genome, etiologically associated with various benign and malignant neoplasms of the skin and mucosa. As of May 30, 2015, 201 different HPV types had been completely sequenced and officially recognized and divided into five PV-genera: *Alpha*-, *Beta*-, *Gamma*-, *Mu*-, and *Nupapillomavirus*. The *Mupapillomavirus* genus currently consists of only two HPV types: HPV1 and HPV63, identified in 1980 and 1993, respectively, both associated with sporadic cases of cutaneous warts. In this preliminary study, we announce the complete genome sequence of a novel HPV type, now officially recognized as HPV204. Based on preliminary data, the genome of HPV204 comprises a total of 7,227 bp and contains five early open reading frames (E1, E2, E4, E6, and E7) and two late ORFs (L1 and L2). No E5 ORF could be identified. Preliminary HPV204 clusters to the *Mu*-PV genus, species Mu-3.

Keywords: human papillomavirus, HPV, HPV204, *Mupapillomavirus*, genomic characterization

Received: 10 April 2015 | **Returned for modification:** 26 April 2015 | **Accepted:** 12 May 2015

Human papillomaviruses (HPVs) are a large family of small, genetically diverse DNA viruses that can cause benign and malignant proliferations of the skin and mucosal epithelia (1, 2). HPVs are taxonomically classified into genera, species, and types based on sequence similarities of the highly conserved L1 genomic region. A novel HPV type is recognized as such when its genome has been fully cloned and deposited to the International HPV Reference Center (www.hpvcenter.se) and its L1 nucleotide (nt) sequence shows less than 90% identity to any other known HPV type (1, 3). As of May 30, 2015, 201 different HPV types belonging to 49 viral species had been completely sequenced and officially recognized and divided into five papillomaviruses (PV)-genera: *Alphapapillomavirus* (*Alpha*-PV), *Betapapillomavirus* (*Beta*-PV), *Gammapapillomavirus* (*Gamma*-PV), *Mupapillomavirus* (*Mu*-PV), and *Nupapillomavirus* (*Nu*-PV) (4). Several additional HPVs have been completely sequenced, mainly using next-generation sequencing, but are not yet officially recognized (5). These are listed in the PapillomaVirus Episteme (PaVE) database, together with the sequences of animal PV genomes (5).

The *Mu*-PV genus currently consists of only two cutaneotrophic HPV types: HPV1 (species Mu-1) and HPV63 (species Mu-2), which are etiologically associated with sporadic cases of skin warts (6). HPV1 was identified in 1980 in tissue specimens of deep plantar warts (7) and fully sequenced 2 years later (8). HPV63 was identified and fully sequenced in 1993 from a tissue specimen of a keratotic lesion (9). In recent years, the number of *Gamma*-PVs has been growing most rapidly, with 81 completely sequenced types to date, followed by *Alpha*- and *Beta*-PV genera, which consist of 65 and 51 recognized types, respectively (4, 10). In contrast, only a single putatively novel *Mu*-PV sequence has been identified in recent years (11), although several modern molecular approaches for virus detection, including metagenomic sequencing, were used (4). We report here the preliminary genome sequence of a novel *Mu*-PV type HPV204.

A partial 200-bp L1 gene nt sequence (ENA accession number: FJ947082) similar to both *Mu*-PVs (HPV1 and HPV63) was originally identified in 2009 using FAP primers and single tube "hanging droplet" PCR (11). A complete viral genome was amplified in 2014 using inverse long-range PCR with primer pair FJ947082-LR-F (5'-GGTATGGGCATTAAGAGGTTTA-3', nt 5,484–5,505) and FJ947082-LR-R (5'-AAGCGTTCTGTTTCAGGATTAA-3', nt 5,483–5,462) and the Platinum *Taq* DNA Polymerase High Fidelity Kit (Invitrogen, Carlsbad, CA). The resulting amplicon of approximately 8 kbp was gel-purified, cloned into a plasmid vector using TOPO XL PCR Cloning Kit (Invitrogen), and sequenced on both strands at Microsynth AG (Balgach, Switzerland) using the primer-walking strategy. The nt sequence of the complete viral genome was assembled using Vector NTI Advance 11 software package (Invitrogen). PV-specific open reading frames (ORFs) were determined using the ORF Finder Tool (http://www.ncbi.nlm.nih.gov/gorf/gorf.html). Preliminary phylogenetic relationships were inferred by Bayesian analysis, based on the entire L1 gene nt sequence of HPV204 and 61 officially recognized HPV types from the *Alpha*-, *Beta*-, *Gamma*-, *Mu*-, and *Nu*-PV genera. Markov Chain Monte Carlo simulations were performed on 107 generations, sampling one state every 1,000 generations, with a burn-in of 10%. The evolutionary substitution model was set as rtREV + Γ + I.

A reference clone, containing the complete genome of HPV204, was deposited in the HPV Reference Center at the Karolinska Institute in Sweden in October 2014, where its nucleotide sequence was confirmed and the type officially designated in January 2015 (http://www.hpvcenter.se/html/refclones.html).

Based on preliminary data, the genome of HPV204 comprises a total of 7,227 bp and contains five early ORFs (E1, E2, E4, E6, and E7), coding proteins involved in viral replication, transcription, and transformation, and two late ORFs (L1 and L2), coding proteins of the capsid. No E5 ORF that is present in some PVs (12) could be identified. The non-coding long control region (LCR) that contains elements responsible for controlling transcription and replication of the viral genome was identified between the L1 and E6 ORFs. Preliminarily, with an L1 nt sequence identity of 66.3% and 66.7% to HPV1 and HPV63, respectively, HPV204 is

[1]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. [2]Virology Area, School of Biochemistry and Pharmaceutical Sciences, Rosario National University, Rosario, Argentina. ✉**Corresponding author: mario.poljak@mf.uni-lj.si**

taxonomically classified as a novel *Mu*-PV type in a new species *Mu*-3. As shown in Figure 1, our preliminary phylogenetic analysis of HPV204 and 61 HPV L1 nt sequences revealed that HPV204 clusters with HPV1 and HPV63, suggesting that the novel virus is most probably an indisputable member of the *Mu*-PV genus.

In conclusion, the identification of HPV204 expands the current knowledge of the genetic diversity of the *Mu*-PV genus and provides further information for the development of molecular tools for identifying and isolating novel *Mu*-PVs. The detailed genomic characterization of HPV204, its tissue tropism, and potential clinical significance are currently under investigation and will be reported soon.

Nucleotide sequence accession number. The complete genome sequence of HPV204 is available in the ENA, GenBank, and DDBJ databases under the following accession number: KP769769.

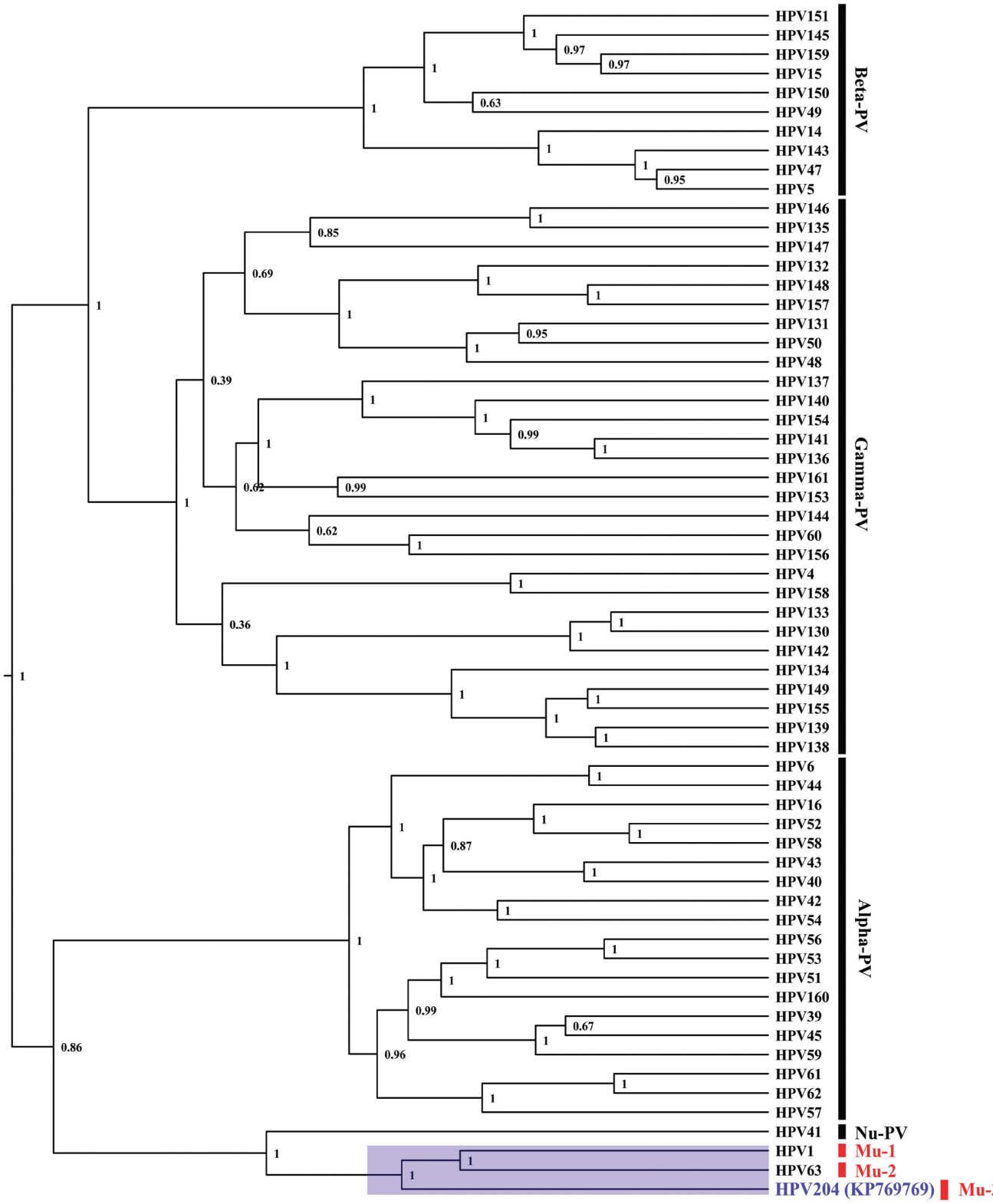

Figure 1 | Phylogenetic position of HPV204 (KP769769) in the *Mu*-PV genus. The numbers at the internal nodes represent Bayesian posterior probability values.

Acknowledgements

This work is result of PhD research and is financially supported by the Slovenian Research Agency (ARRS), which funded AŠ through the Young Researcher Training Program, and in part by Slovenian-Argentinian Bilateral Project BI-AR-15-17-005 and by the European Commission's FP7 Program CoheaHr project (grant number: 603019).

References

1. Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology. 2010;401:70-9.
2. Cubie HA. Diseases associated with human papillomavirus infection. Virology. 2013;445:21-34.
3. de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology. 2004;324:17-27.
4. Kocjan BJ, Bzhalava D, Forslund O, Dillner J, Poljak M. Molecular methods for identification and characterization of novel papillomaviruses. Clin Microbiol Infect. 2015 May 20. [Epub ahead of print].
5. Van Doorslaer K, Tan Q, Xirasagar S, Bandaru S, Gopalan V, Mohamoud Y, et al. The Papillomavirus Episteme: a central resource for papillomavirus sequence data and analysis. Nucleic Acids Res. 2013;41:D571-8.
6. de Villiers EM. Cross-roads in the classification of papillomaviruses. Virology. 2013;445:2-10.
7. Danos O, Katinka M, Yaniv M. Molecular cloning, refined physical map and heterogeneity of methylation sites of papilloma virus type 1a DNA. Eur J Biochem. 1980;109:457-61.
8. Danos O, Katinka M, Yaniv M. Human papillomavirus 1a complete DNA sequence: a novel type of genome organization among papovaviridae. EMBO J. 1982;1:231-6.
9. Egawa K, Delius H, Matsukura T, Kawashima M, de Villiers EM. Two novel types of human papillomavirus, HPV 63 and HPV 65: comparisons of their clinical and histological features and DNA sequences to other HPV types. Virology. 1993;194:789-99.
10. Bzhalava D, Eklund C, Dillner J. International standardization and classification of human papillomavirus types. Virology. 2015;476:341-4.
11. Chouhy D, Gorosito M, Sánchez A, Serra EC, Bergero A, Fernandez Bussy R, et al. New generic primer system targeting mucosal/genital and cutaneous human papillomaviruses leads to the characterization of HPV 115, a novel Beta-papillomavirus species 3. Virology. 2010;397:205-16.
12. Venuti A, Paolini F, Nasir L, Corteggio A, Roperto S, Campo MS, et al. Papillomavirus E5: the smallest oncoprotein with many functions. Mol Cancer. 2011;10:140.

vedno pri roki

Diprosone®

dermalna raztopina 100 ml
krema 30 g in 50 g
mazilo 30 g in 50 g

Ime zdravila: ELOCOM 1 mg/g mazilo; Elocom 1 mg/g krema; Elocom 1 mg/g dermalna raztopina • **SESTAVA:** 1 g mazila/kreme/dermalne raztopine vsebuje 1 mg mometazonfuroata. • **Terapevtske indikacije:** Za lajšanje simptomov vnetnih in srbečih dermatoz, ki se odzivajo na kortikosteroidno terapijo, kot so npr. psoriaza, atopični dermatitis ter draženo in/ali alergijski kontaktni dermatitis. • **Kontraindikacije:** Zdravilo Elocom je kontraindicirano pri obrazni rozacei, aknah vulgaris, atrofiji kože, perioralnem dermatitisu, perianalnem in genitalnem pruritusu, pleničnem izpuščaju, bakterijskih okužbah (npr. impetigu, piodermi), virusnih okužbah (npr. herpes simpleksu, herpes zostru, norican, navadnih bradavicah, kondilomih (condylomata acuminata), mukuskih (molluscum contagiosum), parazitskih in glivičnih okužbah (npr. s kandido ali dermatofiti), tuberkulozi, sifilisu ali reakcijah na cepljenje. Zdravila Elocom ne smete uporabljati na ranah ali na koži z razjedami. Prav tako zdravila Elocom ne smete uporabljati pri bolnikih, ki so preobčutljivi za mometazonfuroat, druge kortikosteroide ali katerokoli pomožno snov. • **Posebna opozorila in previdnostni ukrepi:** Če pride pri uporabi zdravila Elocom do draženja ali preobčutljivosti, je treba bolniku zdravilo ukiniti in mu uvesti ustrezno terapijo. Če pride do pojava okužbe, uporabite ustrezno protiglivično ali protibakterijsko zdravilo oz. antibiotik. Če ni takojšnjega ugodnega odziva na zdravilo, pa morate bolniku ukiniti zdravljenje s kortikosteroidom, dokler ne boste zadostno obvladali okužbe. Zaradi sistemske absorpcije lokalnih kortikosteroidov lahko pride do reverzibilne supresije hipotalamo-hipofizno-adrenalne osi (HPA) z nevarnostjo pojava glukokortikosteroidne insuficience po prenehanju zdravljenja. Pri nekaterih bolnikih lahko sistemska absorpcija lokalnih kortikosteroidov med zdravljenjem povzroči tudi znake Cushingovega sindroma, hiperglikemije in glukozurije. Bolnike, ki uporabljajo lokalni kortikosteroid na veliki površini ali površinah pod okluzivnim povojem, redno naročajte na kontrolne preglede, da boste pri njih ugotovili morebitne znake supresije hipotalamo-hipofizno-adrenalne osi. Pediatrični bolniki so lahko bolj občutljivi za sistemsko toksičnost zdravila celo pri enakovrednih odmerkih, ker imajo večje razmerje med površino kože in telesno maso. Ker pri pediatričnih bolnikih mlajših od 2 let varnosti in učinkovitost zdravila Elocom še nista bila ugotovljena, njegova uporaba v tej starostni skupini ni priporočljiva. Uporaba lokalnih kortikosteroidov pri psoriazi je lahko nevarna iz več razlogov, vključno z recidivi bolezni po nastanku tolerance na zdravilo, tveganjem za nastanek centralizirane pustulozne psoriaze oziroma pojavom lokalne ali sistemske toksičnosti zaradi okvare pregradne funkcije kože. Če se zdravilo uporablja pri psoriazi, je torej pomembno skrbno nadziranje bolnikov. Kakor pri vseh močnih lokalnih kortikosteroidih se je treba tudi pri zdravilu Elocom izogibati nagli ukinitvi zdravljenja. Pri prenehanju dolgoročnega lokalnega zdravljenja z močnimi kortikosteroidi lahko namreč pride do povratnega fenomena, ki se kaže v obliki dermatitisa z močno pordelostjo kože ter zbadajočim in pekočim občutkom. To lahko preprečimo s počasnim zmanjševanjem odmerka zdravila, na primer z intermitentnim zdravljenjem in njegovo poznejšo popolno ukinitvijo. Kortikosteroidi lahko spremenijo videz nekaterih lezij ter tako otežijo postavitev pravilne diagnoze in lahko tudi zapojnijo celjenje. Zdravilo Elocom krema vsebuje propilenglikol, ki lahko povzroči draženje kože. Zdravilo Elocom krema vsebuje stearilalkohol, ki lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis). Različne formulacije zdravila Elocom za lokalno uporabo niso namenjene za očesno uporabo (na primer uporabo na očesnih vekah) zaradi zelo redkega tveganja za nastanek glavkoma simpleks ali subkapsularne katarakte. • **Nosečnost in dojenje** Med nosečnostjo in dojenjem se sme bolnica zdraviti z zdravilom Elocom le po nasvetu zdravnika. Ne glede na to pa se mora v tem obdobju izogibati uporabi zdravila na velikih telesnih površinah ali za daljši čas. Ni zadostnih dokazov o varnosti zdravila v času nosečnosti pri človeku. Lokalna uporaba kortikosteroidov pri brejih živalih lahko povzroči razvojne anomalije pri plodu, vključno z volčjim žrelom in intrauterinim zastojem rasti. Ker pa ni zadostnih in dobro kontroliranih študij z zdravilom Elocom pri nosečnicah, tudi ni znano tveganje za pojav takšnih učinkov pri človeškem plodu. Kljub temu je treba kot pri vseh lokalno uporabljenih kortikosteroidih upoštevati možnost, da bo prehajanje kortikosteroidov skozi placento vplivalo na rast ploda. Kakor drugi lokalno uporabljeni kortikosteroidi se sme tudi zdravilo Elocom uporabljati pri nosečnicah le, če njegova potencialna korist odtehta potencialno tveganje za mater ali plod. Ni znano, ali lahko lokalna uporaba kortikosteroidov vodi do njihove zadostne sistemske absorpcije, da bi lahko v merljivih količinah prehajali v materino mleko. Zdravilo Elocom se sme uporabljati pri doječih materah šele po skrbni oceni razmerja med njegovimi koristmi in tveganji. Če sta indicirana zdravljenje z večjimi odmerki ali dolgotrajna uporaba tega zdravila, pa mora mati prenehati z dojenjem. • **Neželeni učinki:** Zelo redki neželeni učinki so pekoč občutek, folikulitis in srbenje. Med lokalne neželene učinke, o katerih redko poročajo pri uporabi dermalnih kortikosteroidov, sodijo suha koža, draženje kože, dermatitis, maceracija kože, vročinski izpuščaji telangiektazije. Pri uporabi lokalnih kortikosteroidov so lahko pediatrični bolniki bolj občutljivi za supresijo hipotalamo-hipofizno-adrenalne osi in nastanek Cushingovega sindroma od odraslih, ker imajo večje razmerje med površino kože in telesno maso. Kronično zdravljenje s kortikosteroidi lahko zavira rast in razvoj otrok. **Prosimo, preberite celoten seznam porocanih neželenih ucinkov zdravila v poglavju 4.8 Poročila glavnih znacilnosti zdravila.** • **Nacin in režim izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. • **Imetnik dovoljenja za promet:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenija • **Datum zadnje revizije besedila:** 09.08.2013

Diprosone®

krema 30 g in 500 g
mazilo 30 g in 500 g

Ime zdravila: Diprosone 0,5 mg/g mazilo Diprosone 0,5 mg/g mazilo • **SESTAVA:** 1 g mazila ali kreme vsebuje 0,5 mg betametazona v obliki 0,64 mg betametazondipropionata • **Terapevtske indikacije:** Zdravilo Diprosone krema je indicirano za lajšanje vnetnih znakov in srbenja pri dermatozah, ki se odzivajo na kortikosteroide. • **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Zdravilo Diprosone je kontraindicirano povsod, kjer ne predpisujemo kortikosteroidnih zdravil (akne, rosaceae, kožni ulkusi, virusne in glivične infekcije). • **Posebna opozorila in previdnostni ukrepi:** Če se pri uporabi zdravila Diprosone krema pojavi draženje ali senzibilizacija, morate z zdravljenjem prenehati in uvesti ustrezno terapijo. Če ima bolnik okužbo, mu predpišite ustrezen antimikotik ali antibiotik. V primeru, da ni takojšnjega ugodnega odziva, morate kortikosteroid ukiniti, dokler ni dosežen ustrezen nadzor okužbe. Vsak od neželenih učinkov, ki so jih opisovali pri sistemski uporabi kortikosteroidov, vključno s supresijo nadledvične žleze, se lahko pojavi tudi pri lokalni uporabi kortikosteroidov, še posebej pri dojenčkih in otrocih. Sistemska absorpcija lokalnih kortikosteroidov je povečana, če zdravimo obsežne telesne površine ali če uporabljamo okluzivni povoj. V tem primeru ali če pričakujete dolgotrajno uporabo zdravila, upoštevajte ustrezne previdnostne ukrepe, še posebej pri dojenčkih in otrocih. Uporaba v pediatriji: Pediatrični bolniki so lahko bolj občutljivi od odraslih bolnikov na supresijo hipotalamo-hipofizno-renalne (HHS) osi zaradi uporabe lokalnih kortikosteroidov in na učinke eksogenih kortikosteroidov, in sicer zaradi večje absorpcije, ki je posledica velikega razmerja med površino kože in telesno maso. Pri otrocih, ki so prejemali lokalne kortikosteroide, so poročali o supresiji hipotalamo-hipofizno-renalne osi, Cushingovem sindromu, zastoju rasti v višino in pridobivanja telesne mase ter intrakranialni hipertenziji. Znaki supresije nadledvične žleze pri otrocih so npr. nizka plazemska koncentracija kortizola in neodzivnost na stimulacijo z ACTH. Znaki intrakranialne hipertenzije pa so npr. izbočene fontanele, glavobol in obojestranski papiloedem. Zdravilo Diprosone krema vsebuje klorokrezol, ki lahko povzroči alergijske reakcije. Cetil in stearil alkohol lahko povzroči lokalne kožne reakcije(npr. kontaktni dermatitis). Zdravilo Diprosone krema ni namenjeno okularni uporabi. • **Nosečnost in dojenje** Ker varnosti uporabe lokalnih kortikosteroidov pri nosečih ženskah še niso ugotovili, smete zdravila iz te skupine predpisati v času nosečnosti le, če pričakovana korist zdravljenja matere upraviči morebitno tveganje za plod. Pri nosečih ženskah ne smete v veliki meri predpisovati zdravil iz te skupine v večji količini ali za daljši čas. Ker ni znano, ali lahko lokalna uporaba kortikosteroidov vodi do zadostne sistemske absorpcije zdravila za prehajanje zdravila v materino mleko v merljivih količinah, se morate odločiti, ali naj mati preneha dojiti ali pa uporabljati zdravilo, upoštevajoč pomembnost zdravila za mater. • **Neželeni učinki:** Pogosti neželeni učinki so pekoč občutek, srbenje, draženje, suha koža, folikulitis, hipertrihoza, aknam podobni izpuščaji, hipopigmentacija, perioralni dermatitis, alergijski kontaktni dermatitis, maceracija kože, atrofija kože, strije, miliaria in sekundarne okužbe. **Prosimo, preberite celoten seznam porocanih neželenih ucinkov zdravila v poglavju 4.8 Poročila glavnih znacilnosti zdravila.** • **Nacin in režim izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. • **Imetnik dovoljenja za promet:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenija • **Datum zadnje revizije besedila:** 13.01.2014

Diprosalic®

dermalna raztopina 100 ml
mazilo 30 g in 50 g

Ime zdravila: Diprosalic 0,5 mg/30 mg v 1 g mazilo, Diprosalic 0,5 mg/30 mg v 1 g krema, Diprosalic 0,5 mg/20 mg v 1 g dermalna raztopina **Sestava:** 1 g mazila vsebuje 0,5 mg betametazona v obliki 0,64 mg betametazondipropionata in 30 mg salicilne kisline. 1 g dermalne raztopine vsebuje 0,5 mg betametazona v obliki 0,64 mg betametazondipropionata in 20 mg salicilne kisline. • **Terapevtske indikacije:** Zdravilo Diprosalic mazilo učinkuje antiinflamatorno (zdravi vnetja), antipruritično (zdravi srbečico), proti alergijam in keratolitično. Uporabljamo ga lokalno za zdravljenje subakutnih in kroničnih hiperkeratotičnih in suhih dermatoz, ki zahtevajo lokalno zdravljenje s kortikosteroidi kot so: psoriaza, atopični in kronični dermatitis, nevrodermatitis (lichen simplex chronicum), lichen planus, ekzemi (vključno z numularnim ekzemom in ekzematoznim dermatitisom), dishidroza (pompholyx), kožna seboreja na glavi, ichthiosis vulgaris in druge ihtiotične bolezni. • **Kontraindikacije:** preobčutljivost na zdravilni učinkovini etametazondipropionat ali salicilno kislino ali ali katero koli pomožno snov navedenov poglavju 6.1.kjer ne predpisujemo kortikosteroidnih zdravil: akne, rosaceae, kožni ulkusi, virusne in glivične infekcije. • **Posebna opozorila in previdnostni ukrepi:** Znano je, da se kortikosteroidna zdravila absorbirajo skozi kožo. Zato lahko pride po dolgotrajnem zdravljenju ali po nanašanju na obsežnejše površine do sistemskih kortikosteroidnih učinkov. Če uporaba mazila povzroči iritacijo ali senzibilizacijo, je treba zdravljenje prekiniti. Potrebna je pazljivost pri uporabi pod okluzijskim povojem. Zdravilo Diprosalic mazilo ni namenjeno oftalmološki uporabi zato, ga ne smemo nanašati na oči ali v njihovo bližino. Med dolgotrajnim zdravljenjem priporočamo občasno prekinitev uporabe. Bakterijske in glivične okužbe moramo zdraviti z antibiotiki oz. antimikotiki. Previdnost je potrebna tudi pri dolgotrajnem zdravljenju na večjih površinah, zlasti na občutljivih mestih. Takrat moramo zdravljenje začasno prekiniti, in sicer vedno, kadar povzroča salicilna kislina močno izsušitev, povečano preobčutljivost ali neželen prhljaj. Pri dolgotrajnem zdravljenju priporočamo postopno prekinitev. Previdnost je potrebna tudi pri bolnikih z bronhialno astmo oz. drugimi alergičnimi reakcijami zaradi večje verjetnosti preobčutljivosti na salicilate. Uporaba v pediatriji: Pediatrični bolniki so lahko bolj občutljivi od odraslih bolnikov na supresijo hipotalamo-hipofizno-adrenalne (HPA) osi pri uporabi lokalnih kortikosteroidov in na učinke eksogenih kortikosteroidov, ker je absorpcija pri njih večja zaradi večjega razmerja med površino kože in telesno maso. Pri otrocih, ki so prejemali lokalne kortikosteroide, so poročali o supresiji hipotalamo-hipofizno-adrenalne osi, Cushingovem sindromu, zastoju linearne rasti, zapoznelem pridobivanju telesne mase in intrakranialni hipertenziji. Znaki supresije nadledvične žleze pri otrocih so nizka koncentracija kortizola v plazmi in neodzivnost na stimulacijo z ACTH. Znaki intrakranialne hipertenzije so izbočena fontanela, glavobol in obojestranski edem papile. • **Nosečnost in dojenje** Ker varnosti uporabe lokalnih kortikosteroidov pri nosečih ženskah še niso ugotovili, smete zdravila iz te skupine predpisati v času nosečnosti le, če pričakovana korist zdravljenja matere upraviči morebitno tveganje za plod. Pri nosečih ženskah ne smete v veliki meri predpisovati zdravil iz te skupine v večji količini ali za daljši čas.Ker ni znano, ali lahko lokalna uporaba kortikosteroidov vodi do zadostne sistemske absorpcije zdravila za prehajanje zdravila v materino mleko v merljivih količinah, se morate odločiti, ali naj mati preneha dojiti ali pa uporabljati zdravilo, upoštevajoč pomembnost zdravila za mater. • **Neželeni učinki:** Med opisane neželene učinke sodijo pekoč občutek, srbenje, draženje, suha koža, folikulitis, hipertrihoza, aknam podobni izpuščaji, hipopigmentacija, perioralni dermatitis, alergijski kontaktni dermatitis, maceracija kože*, atrofija kože*, strije*, miliaria* *Označeni neželeni učinki so lahko bolj pogosti pri uporabi okluzivnega povoja. **Prosimo, preberite celoten seznam porocanih neželenih ucinkov zdravila v poglavju 4.8 Poročila glavnih znacilnosti zdravila.** • **Nacin in režim izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. • **Imetnik dovoljenja za promet:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenija • **Datum zadnje revizije besedila:** 20.11.2012

Diprogenta®

krema 15 g
mazilo 15 g

Ime zdravila: Diprogenta 0,5 mg/1 mg v 1 g krema, Diprogenta 0,5 mg/1 mg v 1 g mazilo • **SESTAVA:** 1 g kreme Diprogenta vsebuje 0,5 mg betametazona, kar ustreza 0,64 mg betametazondipropionata in 1 mg gentamicina, kar ustreza 1,67 mg gentamicinijevega sulfata. • **Terapevtske indikacije:** Zdravilo Diprogenta je indicirano za lajšanje vnetnih znakov dermatoz, ki se odzivajo na kortikosteroide, če pride do zapletov v obliki sekundarne okužbe z organizmi, ki so občutljivi na gentamicin, ali če sumite na takšno okužbo. Med te bolezni sodijo psoriaza, kontaktni dermatitis (dermatitis venenata), atopični dermatitis (otroški ekcem, alergijski dermatitis), nevrodermitis (lichen simplex chronicus), lichen planus, ekcem (vključno z numularnim ekzemom, ekcemom rok, ekcematoznim dermatitisom), intertrigom, dishidrozo (pompholyx), seboroičnim dermatitisom, eksfoliativnim dermatitisom, fotodermatitisom, dermatitisom zaradi venskega zastoja in anogenitalnim in senilnim pruritusom. • **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. • **Posebna opozorila in previdnostni ukrepi:** Če pri uporabi zdravila Diprogenta nastopi draženje ali senzibilizacija, morate s terapijo prenehati. Vsak od neželenih učinkov, ki so jih opisovali pri sistemski uporabi kortikosteroidov, vključno s supresijo nadledvične žleze, se lahko pojavi tudi pri lokalni uporabi kortikosteroidov, še posebej pri dojenčkih in otrocih. Sistemska absorpcija lokalnih kortikosteroidov je povečana, če zdravimo velike površine telesa ali če uporabimo okluzivni povoj. V tem primeru ali če pričakujete dolgotrajno uporabo zdravila, upoštevajte ustrezne previdnostne ukrepe, še posebej pri dojenčkih in otrocih. Sistemska absorpcija lokalno uporabljenega gentamicina je lahko povečana, če zdravite obsežno površino kože, še posebej če traja zdravljenje dlje časa ali v primeru poškodbe dermisa. V teh primerih bi lahko nastopili neželeni učinki, ki so pojavijo pri sistemski uporabi gentamicina. V teh pogojih je priporočljiva previdna uporaba, še posebej pri dojenčkih in otrocih. Podaljšana uporaba lokalnih antibiotikov občasno omogoči razrast neobčutljivih organizmov, na primer glivic. Če se to zgodi, ali če pride do draženja, senzibilizacije ali superinfekcije, morate zdravljenje z gentamicinom ukiniti in uvesti ustrezno terapijo. Zdravilo Diprogenta ni namenjeno uporabi na očeh. Uporaba v pediatriji: Pediatrični bolniki so lahko bolj občutljivi od odraslih bolnikov na supresijo hipotalamo-hipofizno-adrenalne (HPA) osi pri uporabi lokalnih kortikosteroidov in na učinke eksogenih kortikosteroidov, ker je absorpcija pri njih večja zaradi večjega razmerja med površino kože in telesno maso. Pri otrocih, ki so prejemali lokalne kortikosteroide, so poročali o supresiji hipotalamo-hipofizno-adrenalne osi, Cushingovem sindromu, zastoju linearne rasti, zapoznelem pridobivanju telesne mase in intrakranialni hipertenziji. Znaki supresije nadledvične žleze pri otrocih so nizka koncentracija kortizola v plazmi in neodzivnost na stimulacijo z ACTH. Znaki intrakranialne hipertenzije so izbočena fontanela, glavobol in obojestranski edem papile.Zdravilo Diprogenta krema vsebuje klorokrezol, ki lahko povzroči alergijske reakcije. Cetil in stearil alkohol lahko povzroči lokalne kožne reakcije(npr. kontaktni dermatitis). • **Nosečnost in dojenje** Ker varnosti uporabe lokalnih kortikosteroidov pri nosečih ženskah še niso ugotovili, smete zdravila iz te skupine predpisati v času nosečnosti le, če pričakovana korist zdravljenja matere upraviči morebitno tveganje za plod. Pri nosečih ženskah ne smete predpisovati zdravil iz te skupine v večji količini ali za daljši čas. Ker ni znano, ali lahko lokalna uporaba kortikosteroidov vodi do zadostne sistemske absorpcije zdravila za prehajanje zdravila v materino mleko v merljivih količinah, se morate odločiti, ali naj mati preneha dojiti ali pa uporabljati zdravilo, upoštevajoč pomembnost zdravila za mater. • **Neželeni učinki:** Med opisane neželene učinke sodijo pekoč občutek, srbenje, draženje, suha koža, folikulitis, hipertrihoza, akneiformni izpuščaji, hipopigmentacija, perioralni dermatitis, alergijski kontaktni dermatitis, maceracija kože, atrofija kože, strije, miliarija, preobčutljivost ter razbarvanje kože ter sekundarne okužbe. Zdravljenje z gentamicinom je povzročilo prehodno draženje, vključno z eritemom in pruritusom, vendar zaradi njih običajno ni potrebna prekinitev zdravljenja.**Prosimo, preberite celoten seznam porocanih neželenih ucinkov zdravila v poglavju 4.8 Poročila glavnih znacilnosti zdravila.** • **Nacin in režim izdaje zdravila:** Predpisovanje in izdaja zdravila je le na recept. • **Imetnik dovoljenja za promet:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenija • **Datum zadnje revizije besedila:** 28.11.2012

Lotriderm®

krema 15 g

Ime zdravila: Lotriderm 0,5 mg/g/10 mg/g krema • **SESTAVA:** 1 g kreme vsebuje 10 mg klotrimazola in 0,5 mg betametazona, kar ustreza 0,64 mg betametazondipropionata. • **Terapevtske indikacije:** Zdravilo Lotriderm je indicirano za lokalno zdravljenje naslednjih okužb kože: tinea pedis, tinea cruris in tinea corporis, katerih povzročitelji so Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum in Microsporum canis, in kandidiaza, ki jo povzroča Candida albicans. • **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. • **Posebna opozorila in previdnostni ukrepi:** Zdravila Lotriderm ne smete uporabljati z okluzivnim povojem. Če se pri uporabi zdravila Lotriderm pojavi draženje kože ali senzitizacija, prenehajte z zdravljenjem in takoj uvedite ustrezne terapevtske ukrepe. V primeru bakterijske okužbe mora bolnik sočasno jemati tudi ustrezen antibiotik. Če odziv na zdravljenje ni viden takoj, naj bolnik preneha uporabljati zdravilo Lotriderm, dokler bakterijska okužba ne bo zadovoljivo pozdravljena. Če se bolnik ne odziva na zdravljenje z zdravilom Lotriderm, morate ponoviti mikrobiološke preiskave, da pred uvedbo drugega antimikotika potrdite diagnozo in izključite možnost okužbe z drugimi povzročitelji. Vsi neželeni učinki, ki se pojavijo pri sistemski uporabi kortikosteroidov, vključno s supresijo nadledvične žleze, znaki Cushingovega sindroma, hiperglikemijo in glukozurijo, lahko nastopijo tudi pri zdravljenju z lokalnimi kortikosteroidi. Sistemska absorpcija lokalnih kortikosteroidov je večja pri uporabi močnejših kortikosteroidov, pri daljši uporabi in pri uporabi na večji površini kože. Bolnike, ki prejemajo velike odmerke močnih lokalnih kortikosteroidov na večji površini kože, občasno pregleje in opravite ustrezne preiskave, da ugotovite morebitne znake supresije hipotalamo-hipofizno-supranealne osi. Če ugotovite supresijo, zdravilo bodisi ukinite ali zmanjšajte pogostnost nanašanja, ali pa ga zamenjajte z manj močnim kortikosteroidom. Po prekinitvi uporabe zdravila je pomnilev normalnega delovanja hipotalamo-hipofizno-supranealne osi običajno takojšnja in popolna. V redkih primerih se lahko pojavijo znaki in simptomi odtegnitve kortikosteroidov, zaradi katerih je potrebna dodatna sistemska terapija s kortikosteroidi. Zdravilo Lotriderm ni namenjeno oftalmološki uporabi. Uporaba v pediatriji: Pediatrični bolniki so v primerjavi z odraslimi bolj občutljivi na supresijo hipotalamo-hipofizno-supranealne osi, ki jo sprožijo lokalni kortikosteroidi, in na učinke eksogenih kortikosteroidov, ker je pri njih absorpcija zdravila skozi kožo večja zaradi večjega razmerja med površino kože in telesno maso. Pri otrocih, ki so prejemali lokalne kortikosteroide, so poročali o supresiji hipotalamo-hipofizno-supranealne osi, Cushingovem sindromu, zastoju rasti v višino in pridobivanja teže ter intrakranialni hipertenziji. Znaki supresije nadledvične žleze pri otrocih so npr. nizka plazemska koncentracija kortizola in neodzivnost na stimulacijo z ACTH. Znaki intrakranialne hipertenzije pa so npr. izbočene fontanele, glavobol in obojestranski papiloedem. Pri pleničnem izpuščaju ne priporočamo uporabe zdravila Lotriderm. • **Nosečnost in dojenje** Ker varnosti uporabe lokalnih kortikosteroidov pri nosečih ženskah še niso ugotovili, smete zdravila iz te skupine predpisati v času nosečnosti le, če pričakovana korist zdravljenja matere upraviči morebitno tveganje za plod. Pri nosečih ženskah ne smete v veliki meri predpisovati zdravil iz te skupine v večji količini ali za daljši čas. Ker ni znano, ali lahko lokalna uporaba kortikosteroidov vodi do zadostne sistemske absorpcije zdravila za prehajanje zdravila v materino mleko v merljivih količinah, se morate odločiti, ali naj mati preneha dojiti ali pa uporabljati zdravilo, upoštevajoč pomembnost zdravila za mater. • **Neželeni učinki:** V redkih primerih so pri kombiniranem zdravljenju s klotrimazolom in betametazondipropionatom poročali o naslednjih neželenih učinkih: parestezije, makulopapulozni izpuščaj, edem in sekundarne okužbe. Neželeni učinki klotrimazola so bili: eritem, občutek zbadanja, mehurji, luščenje kože, edem, srbenje, urtikarija in splošno draženje kože. Pri uporabi lokalnih kortikosteroidov so poročali o naslednjih lokalnih neželenih učinkih: pekoč občutek, srbenje, draženje in suhost kože, folikulitis, hipertrihoza, aknam podobni izpuščaji, hipopigmentacija, perioralni dermatitis, alergijski kontaktni dermatitis, maceracija kože, sekundarne okužbe, atrofija kože, strije in miliarija, krhkost kapilar (ekhimoze), senzibilizacija. Pri otrocih, ki so prejemali lokalne kortikosteroide, so poročali o supresiji hipotalamo-hipofizno-supranealne (HHS) osi, Cushingovem sindromu in intrakranialni hipertenziji. Znaki supresije nadledvične žleze pri otrocih so: zastoj rasti v višino in pridobivanja teže, nizka plazemska koncentracija kortizola in neodzivnost na stimulacijo z ACTH. Znaki intrakranialne hipertenzije so npr. izbočene fontanele, glavobol in obojestranski papiloedem. Pri uporabi kombinacije klotrimazola in betametazon dipropionata so poročali o naslednjih neželenih učinkih: okužba, parestezije, makulopapulozni izpuščaj in edem. Pri uporabi samega klotrimazola so poročali o naslednjih neželenih učinkih: eritem, mehur, luščenje kože, pruritus, urtikarija, draženje kože, edem, bolečina. Pri uporabi lokalnih kortikosteroidov so poročali o naslednjih lokalnih neželenih učinkih: okužba, folikulitis, motnje hipotalamo-hipofizne osi in supresija nadledvične žleze, Cushingov sindrom, slabo pridobivanje telesne mase, zvišan intrakranialni tlak, izbočenje fontanel, glavoboli, papiloedem, krhke kapilare, občutek pečenja kože, pruritus, draženje kože, suha koža, hipertrihoza, dermatitis z aknami, hipopigmentacija kože, dermatitis, kontaktni dermatitis, maceracija kože, atrofija kože, strije na koži, apokrina miliarija in vročinski izpuščaj, ekhimoze, alergijski dermatitis, zastoj rasti, zmanjšana koncentracija kortizola v krvi, nenormalen izvid ACTH stimulacije. **Prosimo, preberite celoten seznam porocanih neželenih ucinkov zdravila v poglavju 4.8 Poročila glavnih znacilnosti zdravila.** • **Nacin in režim izdaje zdravila:** Predpisovanje in izdaja zdravila je na recept. • **Imetnik dovoljenja za promet:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, Slovenija • **Datum zadnje revizije besedila:** 14.11.2012

MSD **Merck Sharp & Dohme, inovativna zdravila d.o.o.**
Šmartinska cesta 140, 1000 Ljubljana,
telefon: 01/ 520 42 01, faks: 01/ 520 43 49/50
Pripravljeno v Sloveniji, april 2015

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe. Samo za strokovno javnost. Izdaja zdravil na recept.

EXP 04-2017
DERM-1148664-0000

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24:25-29
doi: 10.15570/actaapa.2015.8

Diagnosis and treatment of bacterial prostatitis

Jerneja Videčnik Zorman[1] ✉, Mojca Matičič[1], Samo Jeverica[2], Tomaž Smrkolj[3]

Abstract

Prostate inflammation is a common syndrome, especially in men under 50. It usually presents with voiding symptoms and pain in the genitourinary area, and sometimes as sexual dysfunction. Based on clinical and laboratory characteristics, prostatitis is classified as acute bacterial prostatitis, chronic bacterial prostatitis, chronic inflammatory and non-inflammatory prostatitis or chronic pelvic pain syndrome, and asymptomatic inflammatory prostatitis. Bacterial prostatitis is most often caused by infection with uropathogens, mainly Gram-negative bacilli, but Gram-positive and atypical microorganisms have also been identified as causative organisms of chronic prostatitis. According to reports by several authors, *Chlamydia trachomatis* and *Trichomonas vaginalis* are some of the most common pathogens, making chronic prostatitis a sexually transmitted disease. Diagnosis and treatment of acute and chronic bacterial prostatitis in particular can be challenging.

Keywords: bacterial prostatitis, diagnosis, treatment, sexually transmitted disease

Received: 15 April 2015 | **Returned for modification:** 3 May 2015 | **Accepted:** 29 May 2015

Introduction

Prostate inflammation is an important health issue in sexually active men. It is characterized by high prevalence and frequent recurrences and can have an impact on quality of life because of voiding symptoms, pain, and sexual dysfunction (1). The prevalence of symptoms suggesting prostatitis is approximately 8.2% (2). They account for 8% of visits to urologists and up to 1% of visits to primary care physicians (2–5).

The prostate gland has several natural defense mechanisms against infection: the production of antibacterial substances and mechanical flushing of the prostatic part of the urethra by voiding and ejaculation. Poor drainage of secretions from distal ducts or urine reflux into prostate tissue can lead to inflammation, scaring, or formation of stones. The majority of bacterial prostatitis follows a urinary tract infection (6, 7). Risk factors for bacterial prostatitis are stricture of the urethra, urinary tract instrumentation (i.e., transrectal biopsy of the prostate gland), or urethritis due to sexually transmitted pathogens (8, 9).

Classification

Prostatitis is a broad diagnosis that encompasses four clinical entities, from acute febrile illness requiring immediate antimicrobial treatment to an incidental finding in an asymptomatic male noted during an evaluation for other urologic conditions. Based on clinical and laboratory presentation, prostatitis is classified into the following categories as recommended by the United States National Institutes of Health (Table 1) (10).

Acute bacterial prostatitis

A small minority of men, less than 1% of all prostatitis cases, have acute bacterial prostatitis. This is an acute febrile illness, and prompt antibiotic treatment is necessary. The patient presents with symptoms of urinary tract infection (urgency and dysuria), prostate inflammation (perineal, penile, or rectal pain), and systemic infection (fever and malaise). The prostate gland is tender and enlarged on rectal examination. A swollen enlarged prostate may rarely cause obstruction of urine flow. Acute prostatitis can lead to prostatic abscess or epididymitis. A prostatic abscess is suspected when a patient fails to improve despite proper antibiotic treatment. It is estimated that in 5 to 10% of cases acute inflammation can result in chronic prostatitis (11).

Chronic bacterial prostatitis

Chronic bacterial prostatitis accounts for 5 to 10% of all prostatitis cases. Symptoms of prostate inflammation last for more than 3 months. Patients complain of urgency, dysuria, and perineal, penile, or even lower back pain. When urine cultures obtained over the course of an illness repeatedly grow the same bacterial strain,

Table 1 | **National Institutes of Health Consensus Classification of Prostatitis (10).**

Type	Description
I. Acute bacterial prostatitis	Acute inflammation of the prostate with PMNL and bacteria in urine
II. Chronic bacterial prostatitis	Chronic inflammation of the prostate with PMNL and bacteria in EPS/urine after prostate massage or in semen
III. Chronic prostatitis/chronic pelvic pain syndrome • Inflammatory • Noninflammatory	Symptoms of prostatitis and: • PMNL in EPS/urine after prostate massage or in semen • No PMNL in EPS/urine after prostate massage or in semen
IV. Asymptomatic prostatitis	PMNL and/or bacteria in EPS/urine after prostate massage or in semen or in the prostate tissue in an asymptomatic male

Note. PMNL = polymorphonuclear leucocytes, EPS = expressed prostatic secretions

[1]Clinic for Infectious Diseases and Febrile Illnesses, University Clinical Centre Ljubljana, Ljubljana, Slovenia. [2]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. [3]Department of Urology, University Clinical Centre Ljubljana, Ljubljana, Slovenia. ✉ **Corresponding author: jerneja.videcnik@gmail.com**

chronical bacterial prostatitis can be suspected with high certainty. However this finding is present in less than half of patients (12). Between symptomatic episodes, the patient may be completely symptom-free. In patients with recurrent urinary tract infection, detailed examination must be performed to exclude any anatomical abnormalities predisposing to infection (i.e., stones or foreign bodies within the urinary tract, bladder cancer, enterovesical fistula, etc.).

Chronic prostatitis or chronic pelvic pain syndrome

Chronic prostatitis or chronic pelvic pain syndrome (inflammatory and noninflammatory) represents the vast majority (80 to 90%) of all prostatitis cases. Patients experience pelvic or perineal pain and possible voiding symptoms. Based on the presence of white blood cells present in expressed prostate secretions, semen, or urine after prostate massage, chronic prostatitis is subdivided into two categories: inflammatory and noninflammatory.

Asymptomatic prostatitis

Asymptomatic prostatitis accounts for approximately 10% of all prostatitis cases. It is diagnosed when inflammatory cells are identified on prostate biopsy or noted in semen during urological evaluation for other reasons in a male with no symptoms of prostate inflammation.

Causative organisms in prostatitis

The most common pathogens of acute and chronic bacterial prostatitis are Enterobacteriae (*Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp.). Other microorganisms, such as *Enterococcus* spp. and *Staphylococcus* spp., are found less frequently.

Apart from aerobic bacteria, chronic bacterial prostatitis can be due to anaerobes, with *Peptostreptococcus* spp. and Bacteroides spp. being most often isolated. Because anaerobes are not cultured as part of the routine procedure, their role in bacterial prostatitis may be underestimated (13, 14). Samples of urine, expressed prostatic secretions, or semen need to be transported and cultivated under special conditions when anaerobes are suspected.

A significant number of chronic bacterial prostatitis cases are caused by sexually transmitted microorganisms. A study performed by Škerk et al. that included 1,442 males with chronic prostatitis revealed that *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Ureaplasma urealyticum* were the causative pathogens in half of the patients (15).

The prevalence of urogenital infections with *C. trachomatis* is very similar in both men and women (16). *C. trachomatis* is transmitted almost exclusively by sexual intercourse, and thus sexually active men under age 35 are usually affected. In men, chlamydial infection can cause urethritis, epididymitis, and chronic prostatitis, and it may also play a role in male infertility (17–20). It has

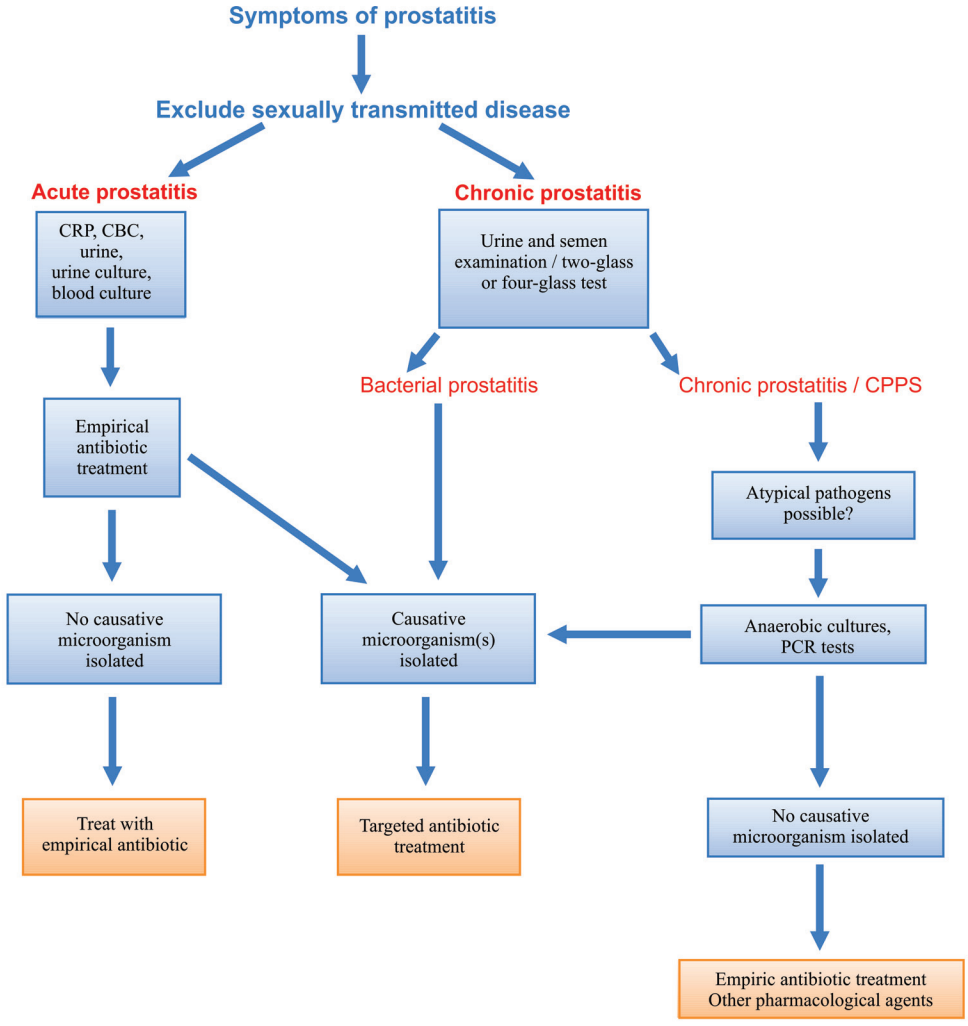

Figure 1 | Diagnosis algorithm for suspected prostatitis. CRP: C-reactive protein, CBC: complete blood count, CPPS: chronic pelvic pain syndome

been shown in mouse models that *C. trachomatis* may persist in the prostate, establishing an immune-privileged niche, avoiding the host immune system. A chronically infected gland can serve as a reservoir of continuous transmission of infection (21).

Prostatitis caused by *Trichomonas vaginalis* is more often found in young sexually active men with frequent episodes of urethritis (15, 21). Identifying the causative organism is very difficult, with molecular assays being most useful. *Neisseria gonorrhoeae* is also considered a causative microorganism of prostatitis (15).

Diagnostic tests in suspected prostatitis

Clinical presentation and laboratory tests are used to differentiate and categorize the four types of prostatitis.

When acute bacterial prostatitis is suspected, midstream urine is examined for bacterial culture, and blood cultures and blood are examined for complete blood count, C-reactive protein, procaltitonin, and prostate-specific antigen (PSA). Prostate massage should not be performed and could be harmful.

In the diagnosis of chronic prostatitis or chronic pelvic pain syndrome, several special diagnostic tests should be performed.

Meares–Stamey four-glass test

Preparation:
No antibiotics should have been taken for 1 month before the test, the patient should not have ejaculated for 2 days, and a full bladder is required.
Prostate massage:

- The penis should be cleaned well to prevent contamination.
- A 5 to 10 ml sample of first-void urethral urine is collected (from the distal urethra).
- The patient passes a further 100 to 200 ml of urine and then collects 5 to 10 ml of mid-stream bladder urine.
- By digital rectal examination, massage of the prostate gland is performed for 1 minute and any expressed prostatic secretions (EPS) are collected in a sterile container (a dry prostate massage is reasonably common).
- Immediately after the massage, 5 to 10 ml of post-massage urine is collected.

All three urine samples are examined with microscopy and quantitative culture.

When atypical pathogens are suspected, special microbiological testing should be considered. Prostatitis caused by *C. trachomatis*, *U. urealyticum*, or *T. vaginalis* can be diagnosed using molecular assays or with isolation of the causative organism in the samples of EPS, semen, or urine after prostate massage with the absence of the organisms in the urethral swab before ejaculation or prostate massage.

For prostate inflammation, ≥ 10 polymorphonuclear leucocytes (PMNL) per high-power field (400×) is considered diagnostic. In cases of a dry expressate, a PMNL count of 10 per high-power field greater in the last urine sample than in the first and second urine samples is diagnostic. To assign an organism to the prostate, the colony count in the expressed prostatic secretions and in the last urine sample should be at least 10 times greater than in the first and second urine sample (23).

Two-glass test

The four-glass test is seldom used in regular clinical practice because it is difficult to perform, time-consuming, and unpleasant for the patient. The sensitivity of the two-glass test is similar to the Meares–Stamey four-glass test. Urine samples are obtained before and after prostate massage.

Urine and semen examination

A first-void urine sample and semen are examined with microscopy and quantitative culture. Budía et al. showed that the sensitivity of semen samples was higher than EPS samples for the diagnosing chronic bacterial prostatitis. For Gram-negative organisms, the sensitivity of semen cultures was 97% versus to 82.4% for EPS cultures, and for Gram-positive organisms the sensitivity of semen samples was 100% versus 16.1% for EPS (25).

Additional tests

When a sexually transmitted disease is suspected (especially in men with prostatitis under age 35, older men with multiple sexual partners, etc.), screening for other sexually transmitted infections should be performed: *C. trachomatis*, *Treponema pallidum*, *N. gonorrhoeae*, hepatitis B virus, and HIV virus.

Only 60% of patients with acute prostatitis and 20% of patients with chronic prostatitis have elevated PSA level. A decrease after successful antibiotic treatment correlates with clinical and microbiological improvement (26–28).

Prostate biopsy culture is neither sensitive nor specific (because inflammation in the gland is not uniformly distributed) (29). When a prostatic abscess is suspected, transrectal ultrasound or a computer tomography scan of the gland should be performed.

Treatment

Only selected antibiotic compounds are suitable for treating bacterial infection of the prostate. Most antibiotic agents penetrate the acutely inflamed prostate, but this is not the case with a chronically inflamed gland. Prostate capillaries are nonporous and lack an antibiotic transport mechanism. Only non-protein-bound antibiotic molecules with a small molecular size, high lipid solubility, low degree of ionization, and high concentration in the serum can reach an adequate concentration in prostate tissue.

Fluoroquinolones have the best pharmacological properties for treating bacterial prostatitis, allowing concentrations in the prostate to be 10 to 50% of that in the serum (30–32). Antibiotics with good penetration into the prostate tissue also include trimethoprim-sulfamethoxazole, clindamycin, doxycycline, and azithromycin. Cephalosporins, carbapenems, piperacillin and some of the aminoglycosides also attain therapeutic levels in prostate tissue. Nitrofurantoin levels in the prostate are nontherapeutic (33–39). The major threat is the growing resistance of microorganisms, especially to fluoroquinolones.

There are several differences in treatment recommendations for acute and chronic bacterial prostatitis (40–48). In the case of acute bacterial prostatitis, empirical antibiotic treatment should be started immediately after urine and possible blood cultures are obtained and tailored to the isolated organisms later on. Treatment of chronic bacterial prostatitis should be delayed until culture and susceptibility results are available. When infection with *N. gonorrhoeae* is diagnosed, a patient also has to be treated for possible infection with *C. trachomatis* or urogenital mycoplasma. When a sexually transmitted organism is diagnosed, sexual part-

ners have to be examined and treated simultaneously. Our recommendations for the treatment of bacterial prostatitis are summarized in Table 2.

When acute urinary retention develops as a complication of acute bacterial prostatitis, suprapubic tap should be performed to alleviate retention because urethral catheterization may worsen infection and is contraindicated.

Prostatic abscesses larger than 1 cm in diameter should be surgically drained.

Treatment of noninflammatory chronic prostatitis / chronic pelvic pain syndrome is difficult in most cases. In a well-designed systematic study performed by Nickel et al., only one-third of patients had modest improvement during 1 year of follow-up (49). Antimicrobial treatment proved unsuccessful in most cases. Adding an alpha blocker improved symptomatic outcomes, but mainly in patients that were alpha blocker–naive (50). None of the controlled trials support various non-pharmacological methods or surgical procedures (51).

Table 2 | Recommendations for treatment of acute and chronic prostatitis (40–45).

ACUTE PROSTATITIS: treatment duration 2 to 4 weeks
• Ciprofloxacin 400 mg every12 h iv or 500 mg po BID • Levofloxacin 500 mg every 24 h iv or 500 mg po QD • TMP/SMX 160/800 mg po BID • Gentamicin 5 mg/kg every 24 h iv ± ampicillin 2 g every 6 h iv
CHRONIC PROSTATITIS: treatment duration 6 weeks to 3 months
• Ciprofloxacin 500 mg po BID • Levofloxacin 500 mg po QD • TMP/SMX 160/800 mg po BID
Pathogen targeted: • Enterococcus spp.: ampicillin/vankomycin/levofloxacin • Pseudomonas aeruginosa: ciprofloxacin/piperacillin-tazobactam/imipenem • ESBL pos. enterobacteria: ertapenem • Neisseria gonorrhoeae: ceftriaxone (+ azithromycin/doxycycline) • Chlamydia trachomatis, urogenital mycoplasma: azithromycin/doxycycline • Anaerobes: clindamycin/azithromycin • Trichomonas vaginalis: metronidazole

References

1. McNaughton Collins M, Pontari MA, O'Leary MA, Calhoun EA, Santanna J, Landis JR, et al. Quality of life is impaired in men with chronic prostatitis: the chronic prostatitis collaborative research network. J Gen Intern Med. 2001;16:656-62.
2. Krieger JN, Lee SW, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. Int J Antimicrob Agents. 2008;31:S85-90.
3. Mehik A, Hellstrom P, Lukkarinen O, Sarpola A, Jarvelin M. Epidemiology of prostatitis in Finish men: a population-based cross-sectional study. BJU Int. 2000;86:443-8.
4. Rizzo M, Marchettti F, Travaglini F, Trinchieri A, Nickel JC. Prevalence, diagnosis and treatment of prostatitis in Italy: a prospective urology outpatient practice study. BJU Int. 2003;92:955-9.
5. Collins MM, Stafford RS, O'Leary MA, Barry MJ. How common is prostatitis? A national survey of physician visits. J Urol. 1998;159:1224-8.
6. Fair WR, Parrish RF. Antibacterial substances in prostatic fluid. Prog Clin Biol Res. 1981;75:247-64.
7. Nickel JC, Olson ME, Barbas A, Benediktsson H, Dasgupta MK, Costerton JW. Pathogenesis of bacterial prostatitis in an animal model. Br J Urol. 1990;66:47-54.
8. Millan-Rodriguez F, Palou J, Bujons-Tur A, Musquera-Felip M, Sevilla-Cecilia C, Serrallach-Orejas M, et al. Acute bacterial prostatitis: two different sub-categories according to a previous manipulation of the lower urinary tract. World J Urol. 2006;24:45-50.
9. Pontari MA1, Joyce GF, Wise M, McNaughton-Collins M. Urologic Diseases in America project. Prostatitis. J Urol. 2007;177:2050-7.
10. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA. 1999;281:236-7.
11. Yoon BI, Han DS, Ha US, Lee SJ, Sohn DW, Kim HW, et al. Clinical courses following acute bacterial prostatitis. Prostate Int. 2013;1:89-93.
12. Nickel JC, Moon T. Chronic bacterial prostatitis: an evolving clinical enigma. Urology. 2005;66:2-8.
13. Magri V, Restelli A, Marras E, Perletti G. A severely symptomatic case of anaerobic chronic bacterial prostatitis successfully resolved with moxifloxacin therapy. Anaerobe. 2010;16:206-9.
14. Szöke L, Török L, Dósa E, Nagy E, Scultéty S. The possible role of anaerobic bacteria in chronic prostatitis. Int J Androl. 1998;21:163-8.
15. Skerk V, Krhen I, Schonwald S, Cajic V, Markovinovic L, Roglic S, et al. The role of unusual pathogens in prostatitis syndrome. Int J Antimicrob Agents. 2004;24:S53-6.
16. Mackern-Oberti JP, Motrich RD, Breser ML, Sánchez LR, Cuffini C, Rivero VE. Chlamydia trachomatis infection of the male genital tract: an update. J Reprod Immunol. 2013;100:37-53.
17. Skerk V, Krhen I, Cajić V, Markovinović L, Puntarić A, Roglić S, et al. The role of Chlamydia trachomatis in prostatitis syndrome—our experience in diagnosis and treatment. Acta Dermatovenerol Croat. 2007;15:135-40.
18. Weidner W, Diemer T, Huwe P, Rainer H, Ludwig M. The role of Chlamydia trachomatis in prostatitis. Int J Antimicrob Agents. 2002;19:466-70.
19. Ouzounova-Raykova V, Ouzounova I, Mitov IG. May Chlamydia trachomatis be an aetiological agent of chronic prostatic infection? Andrologia. 2010;42:176-81.
20. Mazzoli S, Cai T, Addonisio P, Bechi A, Mondaini N, Bartoletti R. Chlamydia trachomatis infection is related to poor semen quality in young prostatitis patients. Eur Urol. 2010;57:708-14.
21. Mackern Oberti JP, Motrich RD, Breser ML, Cejas H, Cuffini C, Maccioni M, et al. Male rodent genital tract infection with Chlamydia muridarum: persistence in the prostate gland that triggers self-immune reactions in genetically susceptible hosts. J Urol. 2011;186:1100-6.
22. Abdolrasouli A, Amin A, Baharsefat M, Roushan A, Mofidi S. Persistent urethritis and prostatitis due to Trichomonas vaginalis: a case report. Can J Infect Dis Med Microbiol. 2007;18:308-10.
23. Meares EM Jr, Stamey TA. Bacterial localisation patterns in bacterial prostatitis and urethritis. Invest Urol. 1968;5:492-518.
24. Nickel JC, Shoskes D, Wang Y, Alexander RB, Fowler JE Jr, Zeitlin S, et al. How does the pre-massage and post-massage 2-glass test compare to the Meares–Stamey 4-glass test in men with chromic prostatitis/chronic pelvic pain syndrome? J Urol. 2006;176:119-24.
25. Budía A, Luis Palmero J, Broseta E, Tejadillos S, Benedicto A, Queipo JA, et al. Value of semen culture in the diagnosis of chronic bacterial prostatitis: a simplified method. Scand J Urol Nephrol. 2006;40:326-31.
26. Schaeffer AJ, Wu SC, Tennenberg AM, Kahn JB. Treatment of chronic bacterial prostatitis with levofloxacin and ciprofloxacin lowers serum prostate specific antigen. J Urol. 2005;174:161-4.
27. Sutcliffe S, Nevin RL, Pakpahan R, Elliott DJ, Cole SR, De Marzo AM, et al. Prostate involvement during sexually transmitted infections as measured by prostate-specific antigen concentration. Br J Cancer. 2001;105:602-5.
28. Bozeman CB, Carver BS, Eastham JA, Venable DD. Treatment of chronic prostatitis lowers serum prostate specific antigen. J Urol. 2002;167:1723-6.
29. Lee JC, Muller CH, Rothman I, Agnew KJ, Eschenbach D, Ciol MA, et al. Prostate biopsy culture findings of men with chronic pelvic pain syndrome do not differ from those of healthy controls. J Urol. 2003;169:584-7.
30. Charalabopoulos K, Karachalios G, Baltogiannis D, Charalabopoulos A, Giannakopoulos X, Sofikitis N. Penetration of antimicrobial agents into the prostate. Chemotherapy. 2003;49:269-79.
31. Drusano GL, Preston SL, Van Guilder M, North D, Gombert M, et al. A population pharmacokinetic analysis of the penetration of the prostate by levofloxacin. Antimicrob Agents Chemother. 2000;44:2046-51.
32. Wagenlehner FM, Kees F, Weidner W, Wagenlehner C, Naber KG. Concentrations of moxifloxacin in plasma and urine, and penetration into prostatic fluid and ejaculate, following single oral administration of 400 mg to healthy volunteers. Int J Antimicrob Agents. 2008;31:21-6.
33. Bergmann M, Lederer B, Takacs F. Tissue concentrations of sulfametrol-trimethoprim in the human prostate. Urologe A. 1979;18:335-7.
34. Perletti G, Skerk V, Magri V, Markotic A, Mazzoli S, Parnham MJ, et al. Macrolides for the treatment of chronic bacterial prostatitis: an effective application of their unique pharmacokinetic and pharmacodynamic profile (Review). Mol Med Rep. 2011;4:1035-44.
35. Klotz T, Braun M, Bin Saleh A, Orlovski M, Engeletmann U. Penetration of a single infusion of ampicillin and sulbactam into prostatic tissue during transurethral prostatectomy. Int Urol Nephrol. 1999;31:203-9.
36. Goto T, Makinose S, Ohi Y, Yamauchi D, Kayajima T, Kayajima T, et al. Diffusion of piperacillin, cefotiam, minocycline, amikacin and ofloxacin into the prostate. Int J Urol. 1998;5:243-6.

37. Nowick WJ Jr. Levels of cefotaxime in body fluids and tissues: a review. Rev Infect Dis. 1982;4:S346-53.
38. Morita M, Nakagawa T, Suzuki K. Ceftazidime concentration in human prostatic tissue and serum following intravenous injection. Hinyokika Kiyo. 1991;37659-62.
39. Nishikawa G, Ikawa K, Nakamura K, Yamada Y, Zennami K. Prostatic penetration of meropenem in humans, and dosage considerations for prostatitis based on a site-specific pharmacokinetic/pharmacodynamic evaluation. Int J Antimicrob Agents. 2013;41:267-71.
40. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. Clin Infect Dis. 2010;50:1641-52.
41. Grabe M, Bartoletti R, Bjerklund-Johansen HM, Cek RS, Pickard P, et al. Guidelines on urological infections. [Internet]. European association of urology. c2015 - [cited 2015 April 13]. Available from: http://www.uroweb.org/guidelines/online-guidelines/?no_cache=1.
42. Sharp VJ, Takacs EB. Prostatitis: diagnosis and treatment. A Fam Physician. 2010;82:397-406.
43. British association for the management of sexual health and HIV. United Kingdom national guideline for the management of prostatitis 2008. [Internet]. c2015 - [cited 2015 April 13]. Available from: www.bashh.org/guidelines.
44. Čižman M, Beović B. Kako predpisujemo protimikrobna zdravila v bolnišnici. Druga dopolnjena izdaja. [Prescribing antimicrobials in a hospital. 2nd ed]. Ljubljana (Slovenia): Sekcija za protimikrobno zdravljenje Slovenskega zdravniškega društva; c2013. p. 87-8. Slovene.
45. Perletti G, Marras E, Wagenlehner FME, Magri V. Antimicrobial therapy for chronic bacterial prostatitis. Cochrane Database Syst Rev. 2013;12:8.
46. Rees J, Abrahams M, Doble A, Cooper A. The Prostatitis Expert Reference Group (PERG). Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis / chronic pelvic pain syndrome: a consensus guideline. BJU Int 2015; doi: 10.1111/bju.13101. [Epub ahead of print].
47. Vahlensieck W, Ludwig M, Wagenlehner FM, Naber K, Fabry W. Prostatitis: Diagnostik und Therapie. Aktuelle Urol. 2013;44:117-23. German.
48. Dickson G. Prostatitis—diagnosis and treatment. Aust Fam Physician. 2013; 42:216-9.
49. Nickel JC, Downey J, Ardern D, Clark J, Nickel K. Failure of a monotherapy strategy for difficult chronic prostatitis / chronic pelvic pain syndrome. J Urol. 2004; 172:551-4.
50. Murphy AB, Macejko A, Taylor A, Nadler RB. Chronic prostatitis: management strategies. Drugs. 2009;69:71-84.
51. El-Hakim A, Shah DK, Smith AD. Advanced therapy for prostatitis: minimally invasive and invasive therapies. Curr Urol Rep. 2003;1:44-50.

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

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24:31-35
doi: 10.15570/actaapa.2015.9

Laboratory diagnosis and epidemiology of herpes simplex 1 and 2 genital infections

Urška Glinšek Biškup[1], Tina Uršič[1], Miroslav Petrovec[1] ✉

Abstract

Herpes simplex virus types 1 and 2 are the main cause of genital ulcers worldwide. Although herpes simplex virus type 2 is the major cause of genital lesions, herpes simplex virus type 1 accounts for half of new cases in developed countries. Herpes simplex virus type 2 seroprevalence rises with sexual activity from adolescence through adulthood. Slovenian data in a high-risk population shows 16% seroprevalence of HSV-2. HSV-1 and HSV-2 DNA in genital swabs was detected in 19% and 20.7%, respectively. In most cases, genital herpes is asymptomatic. Primary genital infection with herpes simplex virus types 1 and 2 can be manifested by a severe clinical picture, involving the vesicular skin and mucosal changes and ulcerative lesions of the vulva, vagina, and cervix in women and in the genital region in men. Direct methods of viral genome detection are recommended in the acute stage of primary and recurrent infections when manifest ulcers or lesions are evident. Serological testing is recommended as an aid in diagnosing genital herpes in patients with reinfection in atypical or already healed lesions. When herpes lesions are present, all sexual activities should be avoided to prevent transmission of infection. Antiviral drugs can reduce viral shedding and thus reduce the risk of sexual transmission of the virus.

Keywords: genital herpes, herpes simplex virus type 1 and 2, sexually transmitted infection, seroprevalence

Received: 26 March 2015 | **Returned for modification:** 12 April 2015 | **Accepted:** 29 April 2015

Introduction

Herpes simplex virus (HSV) types one and two (HSV-1 and HSV-2) are the main cause of genital herpes, which is the main cause of genital ulcers worldwide. Most genital herpes is caused by HSV-2, but more recently there has been an increase in infections caused by HSV-1 (1, 2). A serious complication of genital herpes is neonatal herpes, usually caused by HSV-2. It can lead to the death of a newborn, but fortunately this complication is rare. Infection is acquired most commonly via sexual activity (oral, vaginal, or anal). Most infections manifest with mild symptoms or are even asymptomatic, which increases the risk of transmission. The highest possibility of virus transmission is during outbreak periods when lesions are present. Use of antiviral agents and condoms reduces the possibility of virus transmission (3).

Herpes simplex virus

HSV-1 and HSV-2 are members of *Herpesviridae* family. The genomes of both types of HSV are highly identical and they share many immunogenic epitopes in the outer membrane proteins. Both types of viruses differ in envelope glycoproteins G (gG1 and gG2). Purified glycoproteins specific for HSV-1 (gG-1) or HSV-2 (gG-2) are used as antigens to detect type-specific antibodies (4, 5).

Epidemiology

HSV occurs worldwide, with no specific seasonal variation, and naturally can only infect humans. For infection initiation, HSV must come into direct contact with mucosal surfaces (6).

The type of HSV infection depends on the immunologic status of the infected person. Initial primary infection is manifested in persons without previously present serum antibodies against HSV. Initial non-primary infection is manifested in persons with pre-existing antibodies to HSV-1 or HSV-2 type and a new infection with the other HSV type. Recurrent infection occurs when there are pre-existing antibodies to the same type of HSV causing current infection (2).

The virus remains in a latent stage for the life of the host. Periodic reactivations of the virus and viral shedding occur in the presence of lesions or with mild or no symptoms. Persons with the latent virus are a reservoir for virus shedding and transmission. Symptomatic recurrent infections are associated with a shorter duration of viral shedding and fewer lesions (1).

Although HSV-1 and HSV-2 infections affect different parts of the body, and have different manners of transmission, their clinical manifestations and symptoms can overlap. HSV-1 infections are usually limited to the oropharyngeal area and most commonly occur in children from 6 months to 3 years of age, rising until adolescence. HSV-2 is usually sexually transmitted, and antibodies against HSV-2 are rarely detected before adolescence (1). In recent years. the principal cause of genital herpes is HSV-1 in most women and young men, although severe genital herpes with frequent recurrences are still more commonly caused by HSV-2 (4, 7).

Genital herpes transmission usually occurs through genital-genital or oral-genital contact. Transmission mostly occurs from asymptomatic carriers of the virus. On the other hand, transmission is most likely during the presence of visible lesions in the partner (7, 8). Only 30% of seropositive people are aware of their HSV-2 infection, and 20% of them have no symptoms. Moreover virus shedding has also been found during asymptomatic periods (7, 9, 10). Use of condoms only partly protects from infection; condoms do not cover the entire genital area, and virus shedding is also found in parts of the genital tract without visible lesions (7, 9, 10).

Neonatal herpes infection is rare, occurring in fewer than 1 in

[1]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia. ✉ **Corresponding author: mirc.petrovec@mf.uni-lj.si**

3,000 live births, but has high mortality and severe manifestations for disseminated disease (11). Infection can be acquired in utero or intrapartum. Most commonly, neonatal herpes results from exposure of a newborn to infected maternal genital secretions during delivery. During the primary infection of women, the risk for virus transmission is higher (12). Most newborn infections are due to HSV-2 (13).

Important synergy has been found between HSV-2 and human immunodeficiency virus (HIV). HSV-2 infection increases the risk of HIV infection due to mucosal disruption caused by genital ulcers, which are an entryway for HIV (4).

Genital herpes prevalence

Several factors influence the prevalence of HSV-1 and HSV-2 infections. In developed countries, including the US, HSV-1 prevalence decreased (in 1999–2004 in comparison to 1988–1994) in the general population, which correlates with a higher probability of HSV-1 genital infection. The higher probability of HSV-1 infection is due to a lower seroprevalence of HSV-1 in adolescents and changed sexual behavior that includes choosing oral sex over vaginal sex (4).

Globally, HSV-2 is still the main cause of genital herpes. With the onset of sexual activity, the prevalence of HSV-2 begins to rise, usually from adolescence through adulthood.

Women are more susceptible to HSV-2 infection than men (14). The HSV-2 prevalence rate is also higher in MSM compared to heterosexual men and in HIV-positives compared to the general population, and higher HSV-2 seroprevalence is found in urban environments compared to rural ones (4, 14). The risk factors for HSV-2 infection are the same as for other sexually transmitted infections (STIs): a high number of sexual partners throughout one's lifetime, young age at the onset of sexual activity, and previous history of STIs (15).

The worldwide HSV-2 seroprevalence is between 10 and 40%. In Australia HSV-2 seropositivity is 13% (16), whereas in Canada and the US it is 17% (4, 17) and in Central and South America between 23 and 43% (14, 18, 19). In Europe the HSV-2 seroprevalence is between 5% and 20%, and in the Middle East below 10% (14, 20–23). In Asia the HSV-2 seroprevalence is between 10 and 20%, and in Africa > 50% (24–26).

Regarding groups at higher risk for HSV-2 infection, a higher proportion of those infected is found among female sex workers and among those infected with HIV (60 to 95%). Among pregnant women, seroprevalence of HSV-2 ranges between 7 and 42% (3, 14).

Genital herpes prevalence in Slovenia

A small Slovenian survey was performed between 2006 and 2008, at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia in which 99 men and 128 women were included whose sera were tested due to suspicion of genital herpes sent from three different clinics for sexually transmitted diseases for determining serological status. The mean age of women was 36.7 years and for men 36.2 years. Specific HSV-1 and HSV-2 IgG antibodies were detected by enzyme-linked immunosorbent assay HerpeSelect® HSV 1 and HSV-2 IgG (Focus Diagnostics). IgG antibodies against HSV-1 were detected in 69.6% and against HSV-2 in 29.5% of patient samples examined. Infections with HSV-2 virus was more frequently detected in females, but the difference was not statistically significant (women 33.6% versus men 24.2%; Fig. 1). The HSV-2 seroprevalence increases simultaneously from puberty onwards, and in the age group > 56 years in the women's group it reaches 50% and in the male group more than 70%.

According to data obtained at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia, from 2009 to 2014, 1,767 serum samples (239 men and 1,528 women) were sent from various Slovenian health institutions, including clinics for sexually transmitted diseases, for the serological confirmation of genital herpes. The mean age of women was 31.4 years and for men 38 years. IgG antibodies against HSV (type-nonspecific) were detected in 85.6% (women 85.8% versus men 81.6%) using the Enzygnost ®Anti-HSV/IgG Assay (Siemens Healthcare Diagnostics). Antibodies against HSV-2 were detected in 16% (women 15.6% versus men 18.6%) of patient samples examined, using Liaison® HSV-2 IgG (DiaSorin S.p.A.). The HSV and HSV-2 seroprevalence increases with age, and in the age group > 56 years it reaches 97% for HSV (both sexes, Fig. 2A) and 48.4% for HSV-2 (women 55% versus men 36%; Fig 2B).

In the last 5 years, between 2009 and 2014, 174 genital swabs were sent to the Institute of Microbiology and Immunology, Faculty of Medicine Ljubljana, Slovenia, for molecular diagnostics of genital herpes. Of these, 59 swabs belonged to men and 115 swabs belonged to women. The median age of women was 37 years and for men 40 years. HSV-1 DNA was detected in 19% of all patients tested, but more frequently in women (20%) than in men (16.9%). HSV-2 DNA was detected in 20.7% of all patients tested, but the frequencies in both sexes were nearly the same (men 20.3% versus women 20.9%). Men infected with HSV-1 were younger in comparison to men in which HSV-2 DNA was detected, but the difference was not statistically significant (median 29 years vs. 41 years; $P = 0.10$). Women infected with HSV-1 were significantly younger compared to women in whom HSV-2 DNA was detected (median 22.5 years vs. 51 years; $P < 0.0001$).

A Slovenian survey carried out in 2003, which included 4,000 pregnant women, showed an HSV-1 seroprevalence of 86.9% and HSV-2 seroprevalence of 9.9%. In 7.1% of pregnant women, IgG against HSV-1 and HSV-2 were present, whereas 11% of pregnant women did not have HSV antibodies (27).

Clinical manifestations of genital herpes

The incubation period ranges from 2 to 10 days. Most HSV infections are subclinical. In symptomatic infections, clinical manifestations of primary infection of the genital area with HSV-1 or HSV-2 are typically characterized by painful vesicular and ulcerative lesions. After acquisition of HSV infection at a mucocutaneous site, papules and macules appear, which develop into pustular

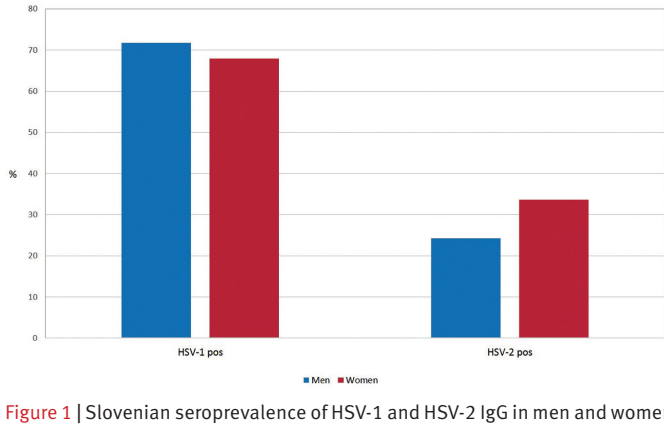

Figure 1 | Slovenian seroprevalence of HSV-1 and HSV-2 IgG in men and women.

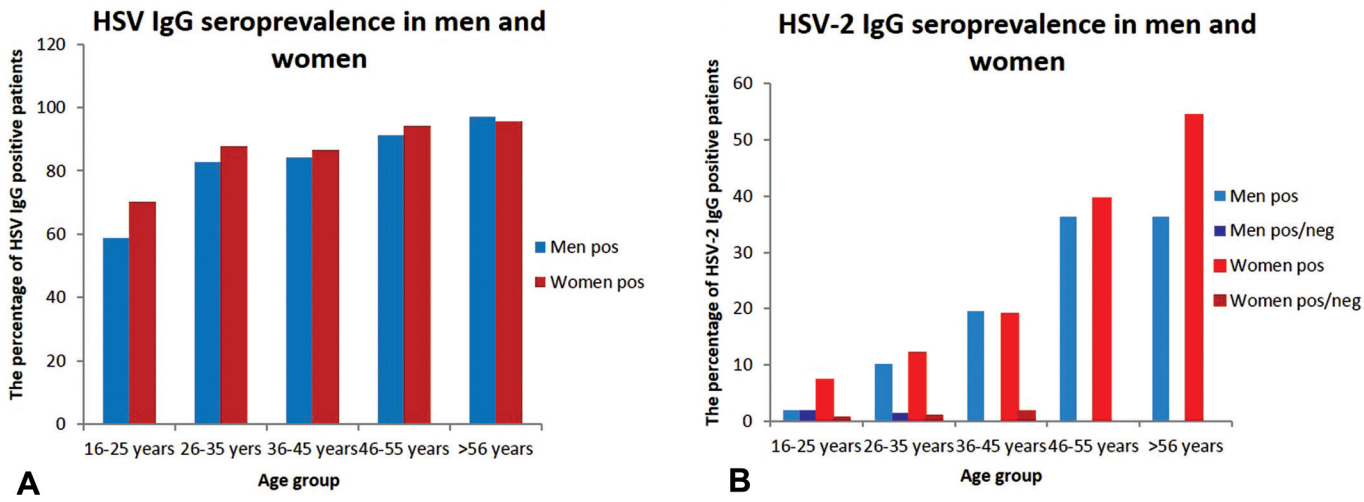

Figure 2 | Slovenian seroprevalence of HSV (Fig. 2A) and HSV-2 (Fig. 2B) in both sexes by age group.

and ulcerative lesions. After 4 to 15 days, the lesions crust and re-epithelize (1, 3). Primary infection can be associated with fever, dysuria, localized inguinal adenopathy, and malaise in both men and women. Paresthesias and dysesthesias that involve the lower extremities and perineum are common. In women with primary infection, lesions appear on the vulva and are usually bilateral (28), with involvement of the cervix. Lesions may involve also the perineum, buttocks, and/or vagina. In men, primary infection results in vesicular lesions on the glans of penis or the penile shaft (28). There is also a possibility of extra-genital lesions occurring in both sexes. Systemic complication in the form of aseptic meningitis can occur in both men and women. Viral excretion may persist for up to 3 weeks (1). Clinically, an acute episode of genital herpes is similar in infection regardless of the type of HSV causing infection, but recurrences are less frequent and less severe in HSV-1 infection (29).

Primary infection is associated with larger quantities of virus shedding in the genital tract and a longer period of viral shedding, on average 3 weeks (8). Systemic symptoms include headache and myalgia. Locally, fungal and bacterial superinfections can occur. The most severe clinical complication is meningitis. The presence of pre-existing antibodies to a different HSV type results in milder disease. Recurrent infections are common in the 1st year after primary infection; they are manifested with milder symptoms and shorter duration (3, 7).

Vertical transmission from an infected mother to fetus is usually manifested with vesicular lesions on the skin of infected babies. Infection can result in a disseminated disease in the newborn with central nervous system involvement; neonatal death of untreated newborns is up to 50% (11, 30). Neonatal herpes can be localized to the skin, eye, and mouth, or is manifested in the form of encephalitis with or without skin involvement or as a disseminated infection that involves multiple organs (31, 32).

Diagnosis

Genital herpes can be diagnosed by clinicians if typical papular lesions progress to vesicle and ulcers are present. Although the features in patients can be highly variable, a definitive diagnosis should be confirmed with laboratory findings (33). Laboratory-confirmed HSV diagnosis is important for appropriate treatment selection, and type identification gives important information about disease prognosis. Differentiating between HSV-1 and HSV-2 is possible only with laboratory diagnostics, and laboratory confirmation is also necessary to exclude other possible causes of ulcers in the genital area (3).

With regard to different guidelines for laboratory diagnosis of genital herpes, for patients with symptoms, detection of viral DNA by nucleic acid amplification tests (NAAT) is most appropriate. Virus isolation on cell cultures can also be performed (34).

In the absence of symptoms, swab testing for preventing HSV transmission is not appropriate, because viral shedding is intermittent (8). For populations at high risk of HSV infection, serological testing is recommended. The best practice is using a combination of type-specific serologic testing and direct virus-detection methods in order to differentiate the type of infecting virus as well as primary and recurrent infections (33, 34). Because of their low sensitivity and specificity, cytological examination using conventional staining procedures (Tzanck smears, the Papanicolaou test, or Romanowsky stains) are not recommended for reliable diagnosis of HSV infections (33–35).

Specimen collection and transportation

The sample of choice is a swab sample of active herpetic lesions. Before sampling, necrotic tissue should be removed. Typically swabs are taken from the base of lesion (3). The sample should be taken in the first 24 h after the lesions occur; when crusting of lesions begins, the sensitivity of tests declines rapidly (29). In the presence of vesicles, the vesicle should be unroofed and a swab of the vesicle base should be taken. Collection of vesicular fluid or exudate from small vesicles in combination with a swab of the lesion base is also an appropriate sample (34, 36). When only older lesions are present, the recovery rate of HSV drops sharply; for patients with such lesions, another sampling is advised when fresh new lesions appear (36). After sampling, the swab should immediately be placed in viral transport medium (VTM) and transported to the laboratory at 4 °C. When immediate transport is not possible, samples should be placed on ice in a cooling box, without freezing, but the overall transport time should not exceed 48 hours (29, 36). Vesicle fluid aspiration is taken and transported in a sterile syringe; if disseminated infection is suspected, blood for PCR should be taken with anticoagulant (EDTA). Other samples that may occasionally be tested are swabs of the cervix, urethra,

or vagina (36). The blood sample for serological methods should be taken in a tube without anticoagulant.

Methods for direct detection of the virus

For direct HSV detection, available tests include antigen detection by direct immunofluorescence, nucleic acid amplification tests (NAATs) for viral DNA detection, and viral culture (29). NAATs are currently the most sensitive and specific methods. Among them, real-time PCR is recommended as a preferred diagnostic method (37). With high sensitivity and specificity, real-time PCR offers accurate diagnosis to a clinician. It allows both typing of HSV and quantification of viral load (in fluid samples). The risk of false positive results occurring due to sample contamination before amplification should be prevented with carefully planned procedures in the molecular laboratory (29). Regarding transport and storage of samples, real-time PCR can tolerate less stringent conditions than samples for viral isolation (36). The important advantage of molecular methods is the possibility of detection of asymptomatic HSV shedding, but one should be aware that a negative PCR result does not exclude HSV infection because virus shedding is intermittent (36).

HSV antigen detection may be a suitable alternative for smaller laboratories as an alternative to viral culture or PCR when fresh lesions are present and the swab is of high quality (rich in cells). The appropriate transport conditions are less stringent than for viral culture. Demonstration of antigen with direct immunofluorescence assay (DIF) is rapid, but with lower sensitivity in comparison to PCR, and is appropriate only for patients with fresh lesions (29, 36).

Viral culture as a gold standard of laboratory HSV detection is possible only in highly specialized laboratories. Low-cost and well-established methodology supports the use of viral culture. This is a highly specific method, but it has low sensitivity, and appropriate sample handling with a continuous cold chain of sample transport to preserve virus viability is very important. Sensitivity is even lower for recurrences, which is why successful viral culture is mostly successful from fresh lesions in primary HSV infection (29, 35, 36). The main advantage of viral culture is typing of viral isolates, and this is a prerequisite for phenotypic antiviral susceptibility testing (36).

Antibody detection methods

The detection of antibodies to HSV is recommended as an aid to diagnosing genital herpes and is particularly useful in identifying an asymptomatic carrier of HSV infection (29).

A defining characteristic of HSV infections is a slow antibody response. There are many tests available to detect HSV antibodies, and the majority of newer tests can now differentiate between types of HSV. Serological assays that are not type-specific are of no value in managing genital herpes (33). Differentiation of HSV types is possible on the basis of glycoprotein G (gG-1 and gG-2). The disadvantage of a glycoprotein-based test is an inability to detect IgM antibodies. IgM detection is possible with assays based on other groups of glycoproteins (gA- gI), but not the differentiation of HSV types (35, 36). Detection of HSV-2 antibodies confirm sexually transmitted infection, and detection of HSV-1 antibodies as a confirmation of genital herpes is not useful because of the high seroprevalence of HSV-1 in the general population (38).

Type-specific HSV IgG antibodies usually become detectable within 2 weeks to 3 months after the initial infection (39). For IgG-negative patients, detection of IgM antibodies increases the ability to detect early infection. Seroconversion as a confirmation of primary infection has limited application, and the occurrence of IgM antibodies is sometimes delayed, even up to 3 months after initial infection, probably due to localized infection of mucosa. IgM antibodies can also be detected during recurrent infection, and tests for IgM detection have poor sensitivity. Because of all of these limitations, serology is not optimal for confirmation of acute HSV infection (33, 36).

Serological testing in the general population is not recommended. Regarding different guidelines, it can be useful in the following circumstances:

- As an aid in diagnosing genital herpes infection, especially to differentiate between primary and recurrent infection;
- In patients with a history of recurrent or atypical lesions, or in patients with healing lesions with negative direct methods;
- For managing sexual partners of people with genital herpes when a risk of transmission exists;
- For identifying HSV infection in high-risk groups, although testing people in high-risk groups is not routinely recommended (33, 36).

Testing pregnant women for the presence of HSV antibodies is not routinely recommended in Europe. Although it is not cost-effective, rather careful examination of the vulva for the presence of lesions indicating HSV infection at the onset of delivery is advised (33). It is recommended that one define the serological status of both the pregnant woman and her partner and, in the case of HSV type mismatch or a negative status of the pregnant women, use of condoms or abstinence from direct sexual contact is advised. In newborns, detection of antibodies is not appropriate because one cannot distinguish between passive, maternal, and newborn antibodies (36).

For detecting HSV-2 antibodies, rapid point-of-care (POC) serological assays also are available. The test can be performed from capillary blood or a serum. The main advantage of assays is that they provide results rapidly, with relatively high sensitivities and specificities (38).

Prevention of HSV transmission

Screening of the general population is not recommended. If serology is performed in patients without any history of genital herpes, appropriate counseling should be provided (2).

During the presence of lesions, patients are advised to abstain from all sexual contact. Condom use is advisable and could prevent the majority of infection if properly used (40). However, transmission of virus is also possible from parts of the genital area without visible lesions, and areas that cannot be covered by a condom, and so protection is still only partial (7, 9, 10, 40).

Antiviral drugs can reduce viral shedding and thus reduces the risk of virus transmission (3, 33). There are no specific recommendations regarding management of partners of HSV-positive patients, but testing and counseling should be offered to partners (2, 33).

Pregnant women with recurrent genital herpes have a low risk of transmission of infection to the fetus or newborn. There is currently no reliable method to identify women that are asymptomatically shedding HSV at the time of delivery (12, 33).

If there are no genital lesions visible at the time of delivery, even for seropositive pregnant women, there is no indication for

a cesarean section (41). The exception is pregnant women that acquire HSV infection in the third trimester, especially if symptoms of genital herpes develop in the period 6 weeks before delivery. For these cases, most guidelines recommend delivery with a cesarean section because of the very high risk of viral shedding (12, 33, 41).

There is no effective vaccine available, but intensive studies are in progress (42, 43).

Acknowledgement

This work was supported by the Slovenian Research Agency (Research Program P3-0083).

References

1. Knipe DM, Howley PM. Fields virology. 6th ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; c2013. Chapter 60, Herpes simplex viruses; p. 1823-97.
2. Garland SM, Steben M. Genital herpes. Best Pract Res Clin Obstet Gynaecol. 2014;28:1098-110.
3. Gupta R, Warren T, Wald A. Genital herpes. Lancet. 2007;370:2127-37.
4. Xu F, Sternberg MR, Kottiri BJ, McQuillan GM, Lee FK, Nahmias AJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296:964-73.
5. Strick L, Wald A. Type-specific testing for herpes simplex virus. Expert Rev Mol Diagn. 2004;4:443-53.
6. Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet. 2001;357:1513-8.
7. Patel R. Genital herpes. Medicine. 2014;42:354-8.
8. Tronstein E, Johnston C, Huang ML, Selke S, Magaret A, Warren T, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. JAMA. 2011;305:1441-9.
9. Johnston C, Zhu J, Jing L, Laing KJ, McClurkan CM, Klock A, et al. Virologic and immunologic evidence of multifocal genital herpes simplex virus 2 infection. J Virol. 2014;88:4921-31.
10. Schiffer JT, Corey L. Rapid host immune response and viral dynamics in herpes simplex virus-2 infection. Nat Med. 2013;19:280-90.
11. Stephenson-Famy A, Gardella C. Herpes simplex virus infection during pregnancy. Obstet Gynecol Clin North Am. 2014;41:601-14.
12. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. JAMA. 2003;289:203-9.
13. Pirš M, Paro Panjan D. Okužbe z virusom herpes simpleks pri nosečnicah in novorojenčkih. [Herpes simplex infection during pregnancy and the neonatal period]. Medicinski razgledi. 2006;45(Suppl 3):97-108. Slovene.
14. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. J Infect Dis. 2002;186(Suppl 1):S3-28.
15. Mertz GJ, Benedetti J, Ashley R, Selke SA, Corey L. Risk factors for the sexual transmission of genital herpes. Ann Intern Med. 1992;116:197-202.
16. Sasadeusz JJ, Silvers JE, Kent HE, Devenish W, Hocking J, Garland SM. Prevalence of HSV-2 antibody in a Melbourne antenatal population attending a tertiary obstetric hospital. Aust N Z J Obstet Gynaecol. 2008;48:266-72.
17. Patrick DM, Dawar M, Cook DA, Krajden M, Ng HC, Rekart ML. Antenatal seroprevalence of herpes simplex virus type 2 (HSV-2) in Canadian women: HSV-2 prevalence increases throughout the reproductive years. Sex Transm Dis. 2001; 28:424-8.
18. Carvalho M, de Carvalho S, Pannuti CS, Sumita LM, de Souza VA. Prevalence of herpes simplex type 2 antibodies and a clinical history of herpes in three different populations in Campinas City, Brazil. Int J Infect Dis. 1998;3:94-8.
19. Hildesheim A, Mann V, Brinton LA, Szklo M, Reeves WC, Rawls WE. Herpes simplex virus type 2: a possible interaction with human papillomavirus types 16/18 in the development of invasive cervical cancer. Int J Cancer. 1991;49:335-40.
20. Rabenau HF, Buxbaum S, Preiser W, Weber B, Doerr HW. Seroprevalence of herpes simplex virus types 1 and type 2 in the Frankfurt am Main area, Germany. Med Microbiol Immunol. 2002;190:153-60.
21. de Ory F, Pachon I, Echevarria JM, Ramirez R. Seroepidemiological study of herpes simplex virus in the female population in the autonomous region of Madrid, Spain. Eur J Clin Microbiol Infect Dis. 1999;18:678-80.
22. Vyse AJ, Gay NJ, Slomka MJ, Gopal R, Gibbs T, Morgan-Capner P, et al. The burden of infection with HSV-1 and HSV-2 in England and Wales: implications for the changing epidemiology of genital herpes. Sex Transm Infect. 2000;76:183-7.
23. Isacsohn M, Smetana Z, Rones ZZ, Raveh D, Diamant Y, Samueloff A, et al. A sero-epidemiological study of herpes virus type 1 and 2 infection in Israel. J Clin Virol. 2002;24:85-92.
24. Eberhart-Phillips JE, Dickson NP, Paul C, Herbison GP, Taylor J, Cunningham AL. Rising incidence and prevalence of herpes simplex type 2 infection in a cohort of 26 year old New Zealanders. Sex Transm Infect. 2001;77:353-7.
25. Auvert B, Ballard R, Campbell C, Carael M, Carton M, Fehler G, et al. HIV infection among youth in a South African mining town is associated with herpes simplex virus-2 seropositivity and sexual behaviour. AIDS. 2001;15:885-98.
26. Weiss HA, Buve A, Robinson NJ, Van Dyck E, Kahindo M, Anagonou S, et al. The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. AIDS. 2001;15(Suppl 4):S97-108.
27. Lorber N. Primerjava prekuženosti nosečnic z virusoma herpes simplex tipa 1 in 2 v Sloveniji v desetletnem razmiku [The comparison of herpes simplex type 1 and 2 prevalence in pregnant women in Slovenia during a ten-year period; bachelor's thesis]. Ljubljana: University of Ljubljana; 2006. 64 p. Slovene.
28. Knipe DM, Howley PM. Fields virology. 5th ed. Philadelphia (PA): Wolters Kluwer Health/Lippincott Williams & Wilkins; c2007. Herpes simplex viruses; p. 2501-602.
29. Singh A, Preiksaitis J, Ferenczy A, Romanowski B. The laboratory diagnosis of herpes simplex virus infections. Can J Infect Dis Med Microbiol. 2005;16:92-8.
30. Kimberlin DW. Neonatal herpes simplex infection. Clin Microbiol Rev. 2004;17:1-13.
31. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics. 2001;108:230-8.
32. Whitley RJ, Soong SJ, Hirsch MS, Karchmer AW, Dolin R, Galasso G, et al. Herpes simplex encephalitis: vidarabine therapy and diagnostic problems. N Engl J Med. 1981;304:313-8.
33. Patel R, Alderson S, Geretti A, Nilsen A, Foley E, Lautenschlager S, et al. 2010 European guideline for the management of genital herpes [Internet]. c2010 - [cited 2015 Apr 8]. Available from: http://www.iusti.org/regions/europe/pdf/2010/Euro_Guideline_2010_herpes.pdf.
34. Domeika M, Bashmakova M, Savicheva A, Kolomiec N, Sokolovskiy E, Hallen A, et al. Guidelines for the laboratory diagnosis of genital herpes in eastern European countries. Euro Surveill. 2010;15.
35. Anderson NW, Buchan BW, Ledeboer NA. Light microscopy, culture, molecular, and serologic methods for detection of herpes simplex virus. J Clin Microbiol. 2014;52:2-8.
36. Belec A. Herpes simplex virus (HSV) infections. Laboratory diagnosis of sexually transmitted infections, including human immunodeficiency virus. [Internet]. World Health Organization; c2013 - [cited 2015 Apr 8]. Available from: http://apps.who.int/iris/bitstream/10665/85343/1/9789241505840_eng.pdf?ua=1.
37. van Doornum GJ, Guldemeester J, Osterhaus AD, Niesters HG. Diagnosing herpesvirus infections by real-time amplification and rapid culture. J Clin Microbiol. 2003;41:576-80.
38. Wald A, Ashley-Morrow R. Serological testing for herpes simplex virus (HSV)-1 and HSV-2 infection. Clin Infect Dis. 2002;35(Suppl 2):S173-82.
39. Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. Clin Microbiol Rev. 1999;12:1-8.
40. Stanaway JD, Wald A, Martin ET, Gottlieb SL, Magaret AS. Case-crossover analysis of condom use and herpes simplex virus type 2 acquisition. Sex Transm Dis. 2012;39:388-93.
41. Straface G, Selmin A, Zanardo V, De Santis M, Ercoli A, Scambia G. Herpes simplex virus infection in pregnancy. Infect Dis Obstet Gynecol. 2012;2012:1-6.
42. Belshe RB, Leone PA, Bernstein DI, Wald A, Levin MJ, Stapleton JT, et al. Efficacy results of a trial of a herpes simplex vaccine. N Engl J Med. 2012;366:34-43.
43. Zhu XP, Muhammad ZS, Wang JG, Lin W, Guo SK, Zhang W. HSV-2 Vaccine: current status and insight into factors for developing an efficient vaccine. Viruses-Basel. 2014;6:371-90.

FIDIMED

Lepa in zdrava koža

Perfect SKIN Hyaluron

PREHRANSKO DOPOLNILO S **100 mg HIALURONSKE KISLINE**

Poskrbite za naravno lepoto in sijaj vaše kože

- Za zdravo in privlačno kožo,
- zdrave lase in nohte,
- normalno obarvanost kože.

Fidimedova posvetovalnica

MODRA ŠTEVILKA 080 3235

Strokovno svetovanje vsak delovnik med 9. in 13. uro.

Vitamini biotin, niacin in vitamin B_2 ter mikroelement cink prispevajo k ohranjanju lepe in zdrave kože. Baker prispeva k normalni obarvanosti kože, vitamin C pa ima vlogo pri nastajanju kolagena za normalno delovanje kože. Hialuronska kislina, naravna sestavina kože in vezivnega tkiva, zaokrožuje sestavo prehranskega dopolnila Perfect Skin Hyaluron.

Perfect Skin Hyaluron je na voljo v lekarnah, specializiranih prodajalnah ter prek spletne strani www.fidimed.si. Prehransko dopolnilo ni nadomestilo za uravnoteženo in raznovrstno prehrano ter zdrav način življenja. Priporočenega dnevnega odmerka se ne sme prekoračiti.

PharmaSwiss
Choose More Life

PHS0914-03, September 2014

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2015;24:37-41
doi: 10.15570/actaapa.2015.10

Poikilodermatous mycosis fungoides: clinical and histopathological analysis of a case and literature review

Oleg Pankratov[1], Svetlana Gradova[1] ✉, Svetlana Tarasevich[2], Valentin Pankratov[3]

Abstract

Poikilodermatous mycosis fungoides is a rare distinct clinical variant of cutaneous T-cell lymphoma (CTCL), formerly referred to as poikiloderma vasculare atrophicans or parapsoriasis variegata. Mycosis fungoides (MF) is a malignant neoplasm of T-lymphocyte origin, most commonly memory CD4+ T-cells. We report here a patient with generalized poikilodermatous skin lesions whose diagnosis of mycosis fungoides was made only a few years after the onset of his disease due to its bizarre clinical behavior and a natural reluctance to diagnose this disease in children and adolescents. The variability of atypical clinical presentations of MF and its similarity to benign inflammatory and noninflammatory skin disorders may become a source of considerable confusion and controversy, challenging a dermatologist to make a precise diagnosis. Therefore, scrupulous clinicopathological correlation is an absolute necessity.

Keywords: mycosis fungoides, poikilodermatous variant, case report

Received: 27 March 2015 | **Returned for modification:** 5 April 2015 | **Accepted:** 12 May 2015

Background

Poikilodermatous mycosis fungoides is a rare distinct clinical variant of cutaneous T-cell lymphoma (CTCL), formerly referred to as poikiloderma vasculare atrophicans or parapsoriasis variegata. Mycosis fungoides (MF) is a malignant neoplasm of T-lymphocyte origin, most commonly memory CD4+ T-cells (1–3). Its classic (Alibert) variant presents a chronic, slowly progressing disease with erythematous scaly patches at the onset that gradually evolve over time into infiltrated plaques and tumors. Apart from this classic form, there are poikilodermatous and erythrodermic variants (the latter should not be confused with Sézary's syndrome). There are also a wide range of rare atypical presentations including hypo- and hyperpigmented, verrucous, hyperkeratotic, follicular, lichenoid papular, palmoplantar psoriasiform, granulomatous, vesicular, bullous, and pustular variants, which have been described in the literature (1). These are clinically unusual cases that run a similar course to that of classic MF.

In 1906 the pioneering American pediatrician Abraham Jacobi described a complex dermatologic disease characterized by telangiectasia, pigmentation, and atrophy, which he subsequently termed poikiloderma vasculare atrophicans (PVA).

Formerly, poikiloderma vasculare atrophicans of Jacobi was considered a separate clinical entity or a premalignant condition. Later, it was believed that PVA represented a stage or an outcome of various dermatoses, such as mycosis fungoides, parapsoriasis, dermatomyositis, scleroderma, lupus erythematosus, lichen ruber planus, genodermatoses, and so on. However, in recent years these opinions have been challenged by many competent dermatologists. Nowadays poikiloderma vasculare atrophicans is recognized as a clinical variant of patch stage MF (4–6); and poikilodermatous findings on non–sun-exposed areas should be considered MF until proven otherwise.

Poikilodermatous MF is usually characterized by the development of large plaques or generalized skin involvement (7–9). However, at the onset of the disease the lesions may present either small plaques or papules arranged in a net-like pattern, which makes it very similar to lichen ruber planus. The typical patches often show a predilection to the major flexural areas and trunk, and present with erythema, mild scaling, mottled dyspigmentation (hyper- and hypopigmentation) with atrophy, and telangiectases. As a result of atrophy and thinning, the patient's skin surface may be reminiscent of "cigarette paper." As opposed to classic MF, poikilodermatous lesions are generally asymptomatic or mildly pruritic and are usually stable or slowly increasing in size (10, 11). Lymph node enlargement is a frequent finding in patients with MF, but it does not necessarily correlate with histological lymphomatous involvement. Dermatopathic lymphadenitis is often observed in such patients (12).

The first manifestation of poikilodermatous MF usually occurs at an earlier age than that of classic MF, and a male predominance was reported for both forms.

Histopathology of poikilodermatous lesions discloses an atypical T-cell infiltrate in the papillary dermis, often with evident epidermotropism (1, 13). However, Pautrier microabscesses are not as common in comparison to classic MF. Melanophages and melanin incontinence are also observed, along with ectasia of the superficial dermal vessels and epidermal atrophy.

Immunohistological staining commonly shows either a prevalence of the CD4+, CD8– pattern or CD8+, CD4– immunophenotype, which is more often seen in hypopigmented variants of MF.

Case report

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma. We present here a patient with its uncommon poikilodermatous variant.

A 29-year-old Caucasian man presented to the City Clinical Skin and Venereal Diseases Clinic in November 2014 with an 18-year history of a diffuse skin affection involving his trunk, neck,

[1]Department of Dermatology, Belarusian Medical Academy of Post-Graduate Education, Minsk, Belarus. [2]Department of Dermatology, City Clinical Skin and Venereal Diseases Clinic, Minsk, Belarus. [3]Department of Dermatology, Belarusian State Medical University, Minsk, Belarus. ✉**Corresponding author: svetlana.gradova@gmail.com**

and extremities. The first eruption appeared on his skin at age eleven. At that time there were a few separate well-defined asymptomatic hypopigmented patches on his chest and left shoulder, which resolved spontaneously without treatment. The patient could not recall any cause that could have triggered the onset of his disease with the exception of sun exposure, which had occurred immediately before the appearance of the first manifestation. However, he denied any possibility of sunburn because his skin had always easily tanned prior to the disease.

After a while, a similar eruption reappeared. However, this time the lesions were persistent and the circumstances forced him to seek medical help. Based on the clinical findings (asymptomatic well-defined hypopigmented patches without obvious atrophy), a diagnosis of vitiligo was made.

At age fourteen, these patches transformed into hyperpigmented plaques with slight atrophy. Thus, the diagnosis was changed to morphea. After that, the patient underwent several courses of treatment for morphea, but they appeared to have only a temporary benefit. The lesions disappeared at one site and simultaneously arose at another. Finally, there was a gradual spread of the skin problems in recent years, although they remained almost asymptomatic throughout the progression. The patient mentioned only a slight burning sensation appearing in wintertime within the last 2 years, which was alleviated by emollients and short courses of medium-strength topical corticosteroids.

Later, in 2012, the skin lesions suddenly changed their appearance and began to spread relatively quickly. The patient's clinical examination at that time showed widespread hyperpigmented patches and small papules with a tendency towards a net-like arrangement within the same distribution area. These papules were not typical planar ones, but had a distribution and arrangement highly suggestive of a diagnosis of lichen ruber planus. Considering those changes, a punch biopsy was performed, and according to the histopathological findings a diagnosis of lichen ruber planus was confirmed (although immunohistological studies were not performed at that time). Although the patient has received a few courses of treatment for lichen ruber planus in the last 3 years, they have shown no efficacy.

Currently, the patient's general health is unimpaired. Although he is rather thin, he denies any episodes of weight loss. The patient complains of no symptoms apart from dry skin, which worsens in winter, and soreness and irritation of the skin after sun exposure in summer.

Data collected from patient's mother revealed some interesting facts that may contribute to the diagnosis and may help in defining the causes of his disease. She told us that she delivered her only son at term, but during the pregnancy she experienced oligohydramnios and the boy was born with neonatal hypotrophy, weighing barely 2.3 kg. Apart from this, at birth her son was covered with what she called a "coat," which began to exfoliate within the first days, and in a week his skin became "normal" and remained healthy until age eleven. Unfortunately, the exact diagnosis is unknown because the documents were lost. However, taking everything into account, the patient might have suffered from one of the ichthyosiform dermatoses. In addition, he had congenital angiomata cavernosum (presumably, according to mother's description) localized on the left earlobe, which was treated with radiotherapy at the age of 3 months. With the exception of these details, the patient's past medical and family histories were non-contributory. The patient's history also did not reveal any occupational hazards.

Physical examination revealed bilateral axillary lymphadenopathy. A few separate slightly enlarged lymph nodes showing no tenderness to palpation were found in both axillae. The entire surface of the skin was very thin, crinkled, and scaly, and had a characteristic wrinkled, "cigarette-paper" appearance. The skin affections had a diffuse distribution with only several small islands of uninvolved skin on the trunk and lower extremities (Fig. 1).

The palms, soles, scalp, and face (excluding a single plaque over the left eyebrow) seemed to be spared. The hair on the head, in the axilla, and in the groin was also preserved, although it appeared thin. At the same time, lanugo hair (equally on healthy skin and on the affected areas) was absent over the entire body surface. The fingernails and toenails were intact. The skin lesions presented confluent poikilodermatous patches and plaques with mottled hyper- and hypopigmentation, atrophy, and telangiectasias. Almost all of these patches, especially those located on the thighs and the lateral aspects of the trunk, were also remarkable for the net-like distributed plane lichenoid papules. A few ill-defined erythematous patches could be observed on the ante-

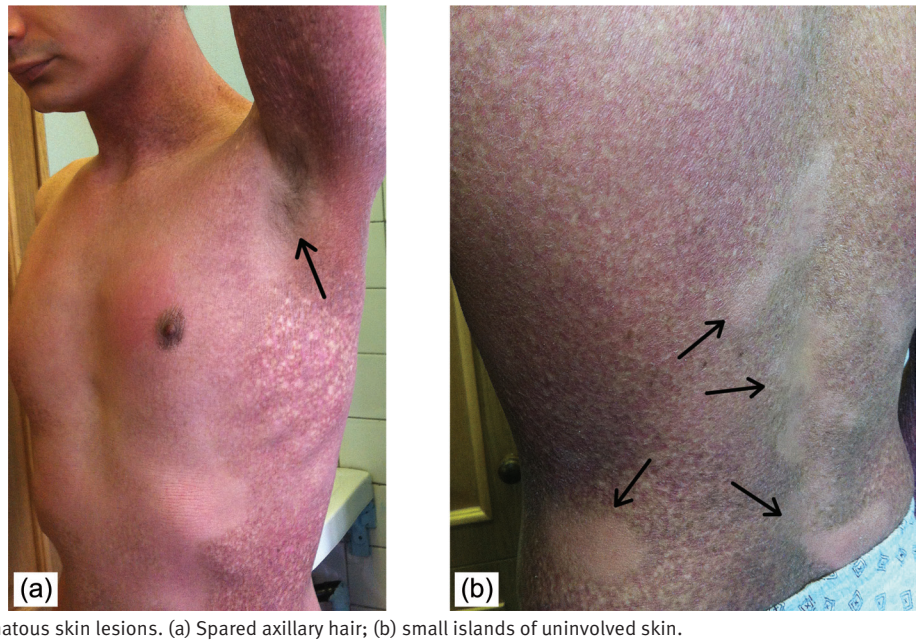

Figure 1 | Diffuse poikilodermatous skin lesions. (a) Spared axillary hair; (b) small islands of uninvolved skin.

rior chest and in the paraumbilical area. They were both visibly and palpably slightly infiltrated. The anterior aspects of the shins showed several confluent plaques with a grayish-brown tint and evident infiltration.

It should be noted that the earlobe that had been exposed to X-rays in infancy had shrunk and almost disappeared, whereas the other one stayed absolutely intact (Fig. 2).

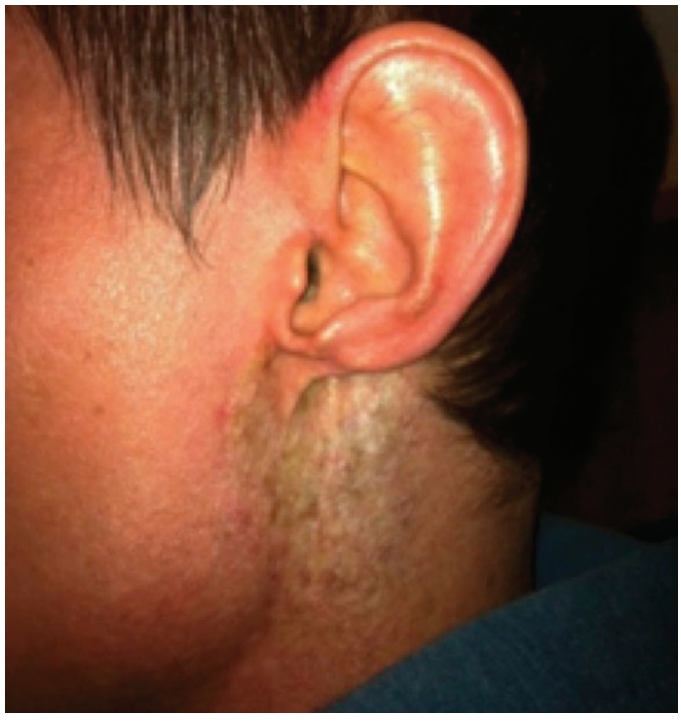

Figure 2 | Shrunk earlobe and the scar that remained after exposure to X-rays.

Taking into consideration the aforementioned features and the past medical history, we were inclined to regard the condition as a rare poikilodermatous form of MF. Because the patient had such diversified skin lesions, it was decided to obtain four punch biopsy specimens from representative areas: an erythematous patch on the anterior aspect of the chest, a typical poikilodermatous patch on the right flank, a lichenoid papule on the right thigh, and the plaque on the anterior aspect of the left shin (Fig. 3).

Histologically, the first erythematous patch showed thickened epidermis with marked acanthosis, adopting a psoriasiform appearance, and focal parakeratosis. There was a superficial lymphohistiocytic infiltrate surrounding small blood vessels with an obvious tendency to palisade along the basal membrane of the epidermis. Pigmentary incontinence and basal cell hydropic degeneration were noted in some fields. Within the epidermis, there were a relatively small number of atypical lymphoid cells with a clear halo, distributed singly and in clusters. However, clear Pautrier microabscesses were absent (Fig. 4).

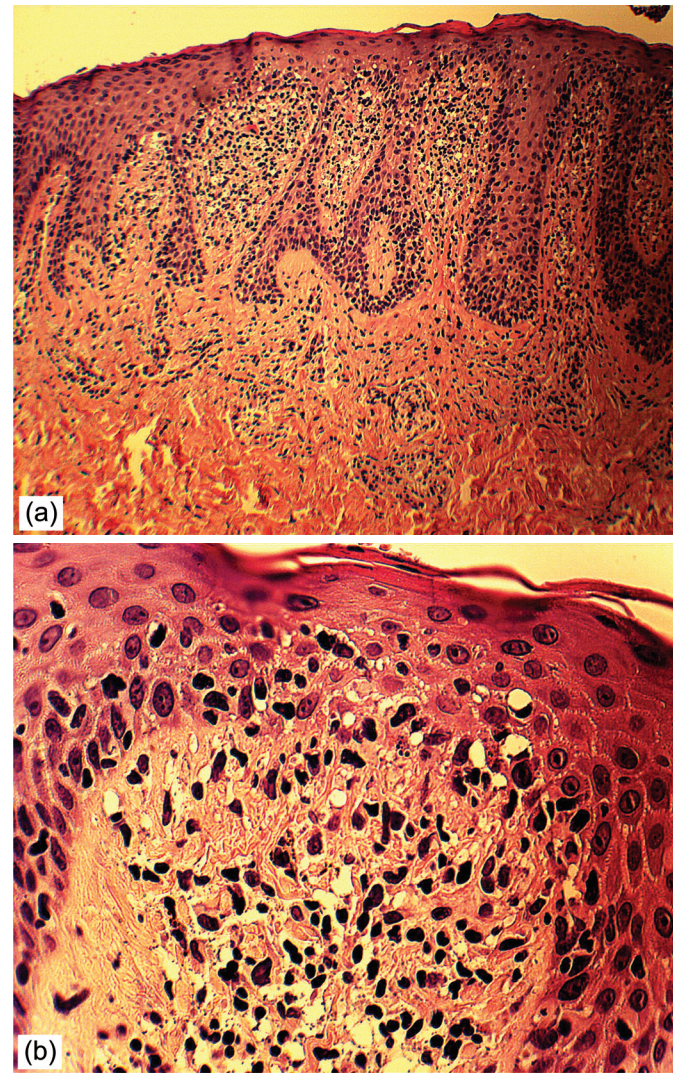

Figure 4 | First specimen taken from the erythematous patch on the anterior aspect of the chest (A: H&E, ×160, B: H&E, ×640).

The second specimen with poikilodermatous changes revealed thinned, atrophic epidermis with mild hyperkeratosis and focal parakeratosis, focal spongiosis, and epidermotropism of atypical lymphocytes. There were an increased number of dilated blood vessels with lymphohistiocytic infiltrate surrounding them. An increased pigmentation of the basal layer of the epidermis and prominent melanin incontinence with melanophages were found (Fig. 5).

The third specimen was of particular interest. The findings

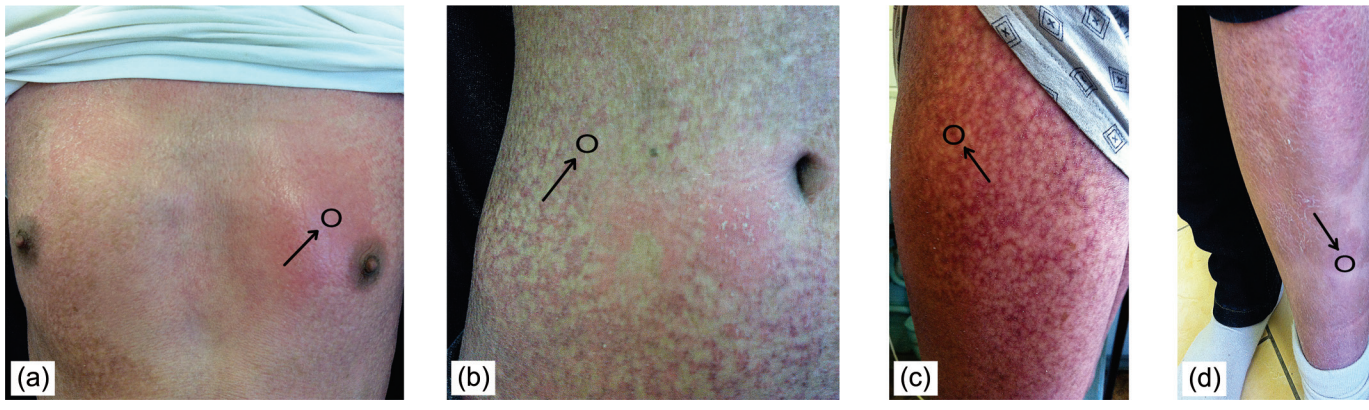

Figure 3 | Areas from which punch biopsy specimens were taken. (a) Erythematous patch on the anterior aspect of the chest; (b) Poikilodermatous patch on the right flank; (c) Lichenoid papule on the right thigh; (d) Plaque on the anterior aspect of the left shin.

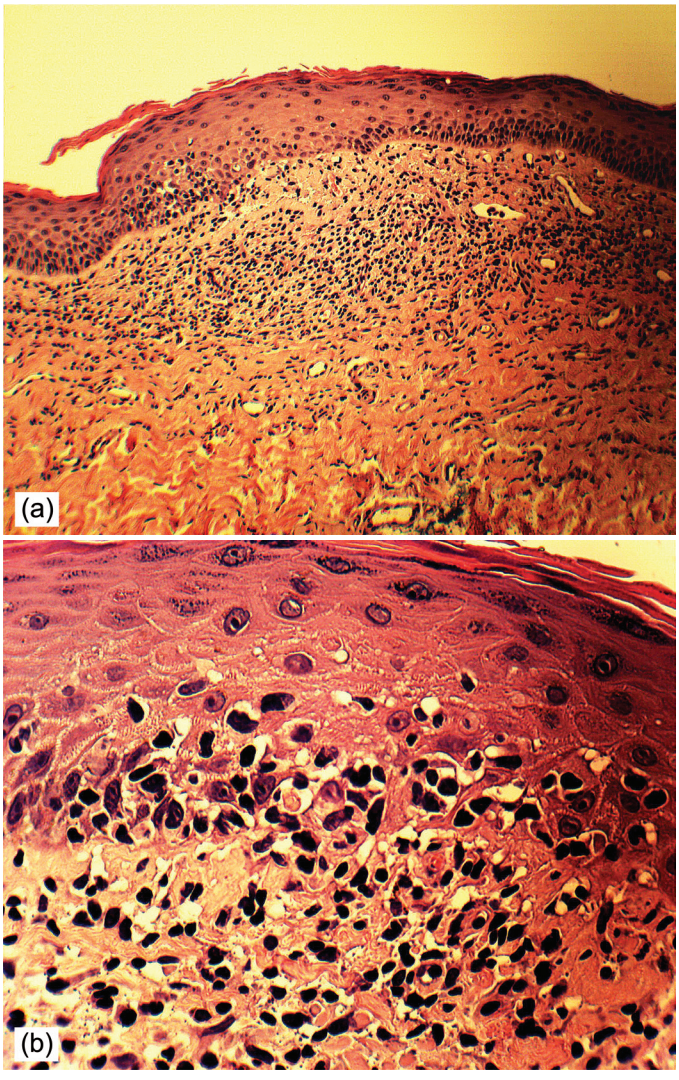

Figure 5 | Second specimen taken from the typical poikilodermatous patch on the right flank (A: H&E, ×160, B: H&E, ×640).

were very similar to those found in lichen ruber planus. They comprised such characteristic features as lymphohistiocytic bandlike infiltrate occupying the upper dermis and obscuring the dermoepidermal junction, irregular acanthosis resembling the typical saw-toothed appearance, extensive liquefactive degeneration of the basal layer of the epidermis with subepidermal clefts (Max Joseph spaces), pigmentary incontinence, and numerous cytoid bodies forming huge clusters. Nevertheless, in lichen planus the enumerated signs are usually seen along the entire specimen, whereas in ours they were distributed in a very well-organized, repetitive pattern showing the focuses with apparent histopathological changes alternating with relatively spared areas. In addition, a close-up view revealed atypia of the lymphocytes (Fig. 6).

Finally, the histological findings received from the biopsy on the plaques from the patient's shin corresponded to the classic patch or early plaque stage of MF. They included slightly acanthotic epidermis with occasional necrotic keratinocytes, basal cell hydropic degeneration, perivascular lymphohistiocytic infiltrate with the presence of atypical lymphoid cells, and overt epidermotropism (Fig. 7).

The immunohistological studies of all the specimens also revealed an unusual pattern with simultaneous presence of both CD4+ and CD8+.

Suspecting misdiagnosis, it was decided to reassess the biopsy findings that had been received in 2012 with additional sectioning of the preserved paraffin blocks. An appraisal of both slides was

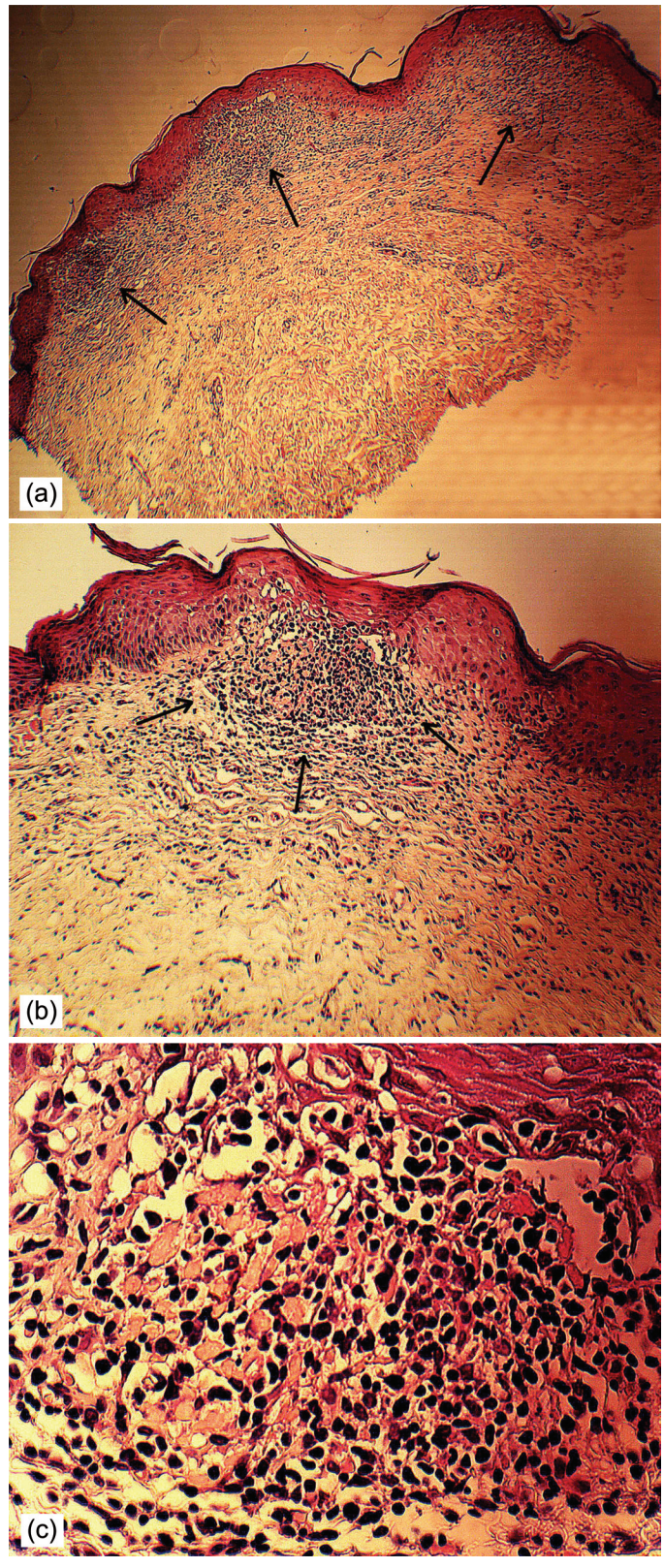

Figure 6 | Third specimen taken from the lichenoid papule on the right thigh. Note the unusual pattern of repetitive focuses of lymphohistiocytic infiltrate alternating with the relatively spared areas (A: H&E, ×64, B: H&E, ×160, C: H&E, ×640).

made. Although the first one made 3 years ago showed the histopathological features of lichen planus, the second one received by additional sectioning revealed the signs of MF, although they were not apparent.

Discussion

Although the exact duration of MF in our patient could not be es-

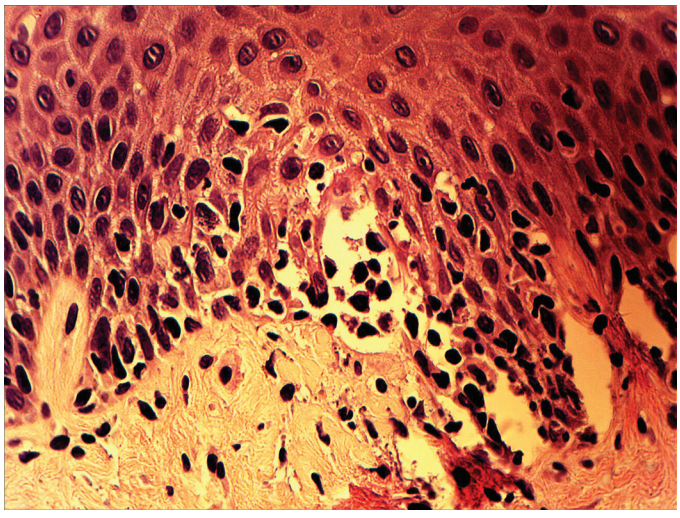

Figure 7 | Fourth specimen taken from the plaque on the anterior aspect of the left shin (H&E, ×640).

tablished (because tests such as biopsy and immunohistochemistry were not performed at the time of the onset of his disease), we can state that 3 years ago he definitely received that diagnosis. The patient's medical history also highly suggests the presence of the disease from the very beginning of the case. His first complaints (asymptomatic hypopigmented patches or macules), which were regarded as vitiligo, in fact correspond to the diagnosis of hypopigmented variant of MF. Despite its extremely rare occurrence, in children and adolescents it can be seen more often. However, a natural reluctance to diagnose MF in children in addition to its clinical resemblance to vitiligo, tinea versicolor, pityriasis alba, or postinflammatory hypopigmentation often result in misdiagnosis.

The further development of the patient's symptoms and the replacement of hypopigmentation by hyperpigmentation can also be easily explained by the underlying histological changes. One of the main diagnostic pointers at any stage of MF is palisading of lymphocytes along the basal layer of the epidermis, usually accompanied by extensive basal cell hydropic degeneration. Research has shown that any damage to the basal layer of the epidermis and the entire area of the basal membrane (e.g., basal cell liquefactive degeneration) may cause pigment incontinence, which clinically manifests as hyperpigmentation. Consequently, the progression of pathological processes in the patient's skin resulted in a naturally determined appearance of pigmentation within the lesions.

When our patient developed papules within the pigmented patches, they were interpreted as lichen ruber planus based on the histological data. Unfortunately, it is not uncommon when lichen planus is histologically confused with MF. The bandlike infiltrate obscuring the dermoepidermal junction with cytoid body formation, confluent hyperkeratosis, irregular acanthosis, basal cell liquefactive degeneration, and apoptosis may closely mimic lichen planus. However, in our case at that stage misdiagnosis could have been avoided if additional block sectioning with subsequent immunohistochemical staining had been performed.

The case described here might be of particular interest for many dermatologists because it demonstrates very unusual clinical behavior of MF, in which one its rare variants is transformed into another that imitates benign dermatoses, thus posing definite obstacles in making a precise diagnosis.

To summarize, the diagnosis of MF and its rare atypical variants in particular is usually not obvious. Diagnostic mistakes might occur because of the clinical and in some cases histopathological similarity between MF and common benign dermatoses; for example, lichen ruber planus, morphea, which are dermatoses that can be associated with hypo- or hyperpigmentation, and other disorders.

Consequently, scrupulous assessment and juxtaposition of all the data collected, paying attention to the very minute details, may help to make the diagnosis more evident.

The histopathological features of the early stages of MF are often subtle or mimic other dermatoses; as a result, they can easily be overlooked. Thus, multiple biopsies with additional block sectioning and immunohistochemistry may be essential for obtaining an accurate diagnosis. Moreover, prior treatment before the biopsy masks characteristic features. Therefore, careful clinicopathological correlation is the only clue for the right diagnosis.

References

1. Calonje E, Brenn T, Lazar A, McKee PH. McKee's pathology of the skin with clinical correlations. 4th ed. Edinburgh: Elsevier Saunders; 2012: p. 1819.
2. Elder DE, Elenitsas R, Johnson BL Jr., Murphy GF, Xu X. Lever's histopathology of the skin. 10th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2009: p. 1280.
3. James WD, Berger TG, Elston DM. Andrews' diseases of the skin. Clinical dermatology. 10th ed. Edinburgh: Saunders Elsevier; 2006: p. 972.
4. Kreuter A, Hoffmamm K, Altmeyer A. A case of poikiloderma vasculare atrophicans, a rare variant of cutaneous T-cell lymphoma, responding to extracorporeal photopheresis. J Am Acad Dermatol. 2005;52:706-8.
5. Kikuchi A, Naka W, Harada T, Sakuraoka K, Harada R, Nishikawa T. Parapsoriasis en plaques: its potential for progression to malignant lymphoma. J Am Acad Dermatol. 1993;29:419.
6. Burg G, Dummer R, Nestle F.O, Doebbeling U, Haeffner A. Cutaneous lymphomas consist of a spectrum of nosologically different entities including mycosis fungoides and small plaque parapsoriasis. Arch Dermatol. 1996;132:567-572.
7. Lindae ML, Abel EA, Hoppe RT, Wood GS. Poikilodermatous mycosis fungoides and atrophic large plaque parapsoriasis exhibit similar abnormalities of T cell antigen expression. Arch Dermatol. 1988;124:366.
8. Abbott RA, Sahni D, Robson A, Agar N, Whittaker S, Scarisbrick JJ. Poikilodermatous mycosis fungoides: a study of its clinicopathological, immunophenotypic and prognostic features. J Am Acad Dermatol. 2011;65:313.
9. Farley-Loftus R, Mandal R, Latkowski JA. Poikilodermatous mycosis fungoides. Dermatol Online J. 2010;16:8.
10. Brecher A. Mycosis fungoides. Dermatol Online J. 2003;9:23.
11. Howard MS, Smoller BR. Mycosis fungoides: classic disease and variant presentations. Semin Cutan Med Surg. 2000;19:91.
12. Pimpinelli N, Olsen EA, Santucci M, Vonderheid E, Haeffner AC, Stevens S, et al. Defining early mycosis fungoides. J Am Acad Dermatol. 2005;53:1053-1063.
13. Dougherty J. Poikiloderma atrophicans vasculare. Arch Dermatol. 1971;103:550.

1. odobreno anti-TNF zdravilo[#2,3,4] s strani EMA[*] - bistveni preobrat v zdravljenju psoriaze.

Več kot **15** let izkušenj iz kliničnih študij in vsakdanjega življenja.[5]

Več kot **1** milijon zdravljenih bolnikov.[6]

Več kot **4** milijone bolnikov-let skupaj.[†6]

Spreminjamo življenja[1]

Enbrel® etanercept

* Evropska agencija za zdravila (European Medicines Agency, EMA)
\# tumorje nekrotizirajoči faktor (Tumor necrosis factor, TNF)
† vse indikacije

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 ultravijolično 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 takšni 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: Pri predpisovanju bolnikom s kongestivnim srčnim popuščanjem je potrebna previdnost. 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. Starejše osebe (< 65 let): 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:** 20.4.2015 Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Literatura: **1.** Scott LJ. Etanercept: A Review of Its Use in Autoimmune Inflammatory Diseases. Drugs. 2014; 74:1379-1410. **2.** Povzetek glavnih značilnosti Zdravila Enbrel, 20.4.2015. **3.** Povzetek glavnih zdravila Humira, oktober 2014. **4.** Povzetek glavnih zdravila Remicade, september 2014. **5.** Maese PJ, Goffe B, Metz J et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a ramdomised trial. Lancet 2000; 356: 385-390. **6.** Data on file , PSUR 21, March 2014

ENB-13-15 **Samo za strokovno javnost**

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

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.

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

Natančno preberite skrajšan povzetek lastnosti o zdravilu!

LEO®

LEO

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

Datum zadnje revizije 15. 11. 2012

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.

9 ODOBRENIH INDIKACIJ
največ med biološkimi zdravili za samoinjiciranje[1]

Več kot
750.000 BOLNIKOV
po svetu se zdravi z zdravilom HUMIRA*[2]

Več kot
17 LET KLINIČNIH IZKUŠENJ
z začetki pri revmatoidnem artritisu[3]

71 KLINIČNIH RAZISKAV
v največji publikaciji o varnosti zaviralcev TNF-α[3]

HUMIRA zaupanje
Edinstveni temelji za prihodnost

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. *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. *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. *Pediatrični bolniki s Crohnovo boleznijo:* < 40 kg: 40 mg 0.teden, ki mu sledi 20 mg 2.teden; ≥ 40 kg: 80 mg 0.teden, ki mu sledi 40 mg 2.teden. 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 4XE Velika Britanija. Datum revizije besedila: 2.9.2014

Literatura: 1. Povzetek glavnih značilnosti zdravila HUMIRA, september 2014; **2.** Interni podatki, AbbVie Inc.
3. Burmester GR et all, Ann Rheum Dis. 2013 Apr;72(4):517-24; *podatki do decembra 2013

AbbVie Biofarmacevtska družba d.o.o., Dolenjska cesta 242c, Ljubljana, Tel.: 01 320 80 60, Fax.: 01 320 80 61, www.abbvie.si
SiHUM140064a Samo za strokovno javnost. Datum priprave oglasa: september 2014

abbvie

HUMIRA adalimumab
destination you

Zdravilo Zelboraf® je zaviralec BRAF kinaze z dokazanim podaljšanjem preživetja v primerjavi z dakarbazinom in izkušnjami pri zdravljenju več tisoč bolnikov z neoperabilnim ali metastaskim melanomom s pozitivno mutacijo BRAF V600E/K.[1]

Fotografija je simbolična.

Skrajšan povzetek glavnih značilnosti zdravila ZELBORAF

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Ime zdravila: Zelboraf 240 mg filmsko obložene tablete
Kakovostna in količinska sestava: Ena tableta vsebuje 240 mg vemurafeniba (v obliki precipitata vemurafeniba in hipromeloze acetat sukcinata). **Terapevtske indikacije:** vemurafenib je indiciran za samostojno zdravljenje odraslih bolnikov z neresektabilnim ali metastatskim melanomom, s pozitivno mutacijo BRAF V600. **Odmerjanje in način uporabe:** zdravljenje z vemurafenibom mora uvesti in nadzorovati usposobljen zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje raka. Odmerjanje: priporočeni odmerek vemurafeniba je 960 mg (4 tablete po 240 mg) dvakrat na dan (to ustreza celotnemu dnevnemu odmerku 1920 mg). Vemurafenib lahko vzamemo s hrano ali brez nje, izogibati pa se moramo stalnemu jemanju obeh dnevnih odmerkov na prazen želodec. Zdravljenje z vemurafenibom moramo nadaljevati do napredovanja bolezni ali pojava nesprejemljive toksičnosti. Če bolnik izpusti odmerek, ga lahko vzame do 4 ure pred naslednjim odmerkom za ohranitev sheme dvakrat na dan. Obeh odmerkov pa ne sme vzeti hkrati. Če bolnik po zaužitju vemurafeniba bruha, ne sme vzeti dodatnega odmerka zdravila, ampak mora z zdravljenjem normalno nadaljevati. Prilagoditve odmerjanja: za obvladovanje neželenih učinkov ali ob podaljšanju intervala QTc je potrebno zmanjšanje odmerka, začasna prekinitev in/ali dokončno prenehanje zdravljenja (za podrobnosti o prilagoditvi odmerka, prosimo glejte SmPC zdravila). Zmanjšanje odmerka pod 480 mg dvakrat na dan ni priporočljivo. Če se pri bolniku pojavi ploščatocelični karcinom kože, priporočamo nadaljevanje zdravljenja brez zmanjšanja odmerka vemurafeniba. *Posebne populacije*: za bolnike, starejše od 65 let, prilagajanje odmerka ni potrebno. O bolnikih z okvaro ledvic ali jeter je na voljo malo podatkov. Bolnike s hudo okvaro ledvic ali z zmerno do hudo okvaro jeter je treba pozorno spremljati. Varnost in učinkovitost vemurafeniba pri otrocih in mladostnikih, mlajših od 18 let, še nista bili dokazani. Podatkov ni na voljo. Način uporabe: tablete vemurafeniba je treba zaužiti cele, z vodo. Ne sme se jih žvečiti ali zdrobiti. **Kontraindikacije:** preobčutljivost na zdravilno učinkovino ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** pred uporabo vemurafeniba je treba z validirano preiskavo potrditi, da ima bolnik tumor s pozitivno mutacijo BRAF V600. Dokazi o učinkovitosti in varnosti vemurafeniba pri bolnikih s tumorji z izraženo redko BRAF V600 mutacijo, ki ni V600E ali V600K, niso prepričljivi. Vemurafeniba se ne sme uporabljati pri bolnikih z malignim melanomom, ki ima divji tip BRAF. *Preobčutljivostne reakcije:* v povezavi z vemurafenibom so bile opisane resne preobčutljivostne reakcije, vključno z anafilaksijo. Hude preobčutljivostne reakcije lahko vključujejo Stevens-Johnsonov sindrom, generaliziran izpuščaj, eritem ali hipotenzijo. Pri bolnikih, pri katerih se pojavijo resne preobčutljivostne reakcije, je treba zdravljenje z vemurafenibom dokončno opustiti. *Kožne reakcije:* pri bolnikih, ki so prejemali vemurafenib, so v ključnem kliničnem preskušanju poročali o hudih kožnih reakcijah, vključno z redkim Stevens-Johnsonovim sindromom in toksično epidermalno nekrolizo. Po prihodu vemurafeniba na trg so v povezavi z njim poročali o reakciji na zdravilo z eozinofilijo in sistemskimi simptomi (DRESS, *Drug Reaction with Eosinophilia and Systemic Symptoms*). Pri bolnikih, pri katerih se pojavi huda kožna reakcija, je treba zdravljenje z vemurafenibom dokončno opustiti. *Podaljšanje intervala QT:* v nekontrolirani, odprti študiji faze II pri predhodno zdravljenih bolnikih z metastatskim melanomom, so opazili podaljšanje intervala QT, odvisnega od izpostavljenosti vemurafenibu. Podaljšanje intervala QT lahko poveča tveganje za ventrikularne aritmije, vključno s t. i. *Torsade de Pointes*. Z vemurafenibom ni priporočljivo zdraviti bolnikov z elektrolitskimi motnjami (vključno z magnezijem), ki jih ni mogoče odpraviti, bolnikov s sindromom dolgega intervala QT in bolnikov, zdravljenih z zdravili, ki podaljšajo interval QT. Pred zdravljenjem z vemurafenibom, en mesec po zdravljenju in po spremembi odmerka je treba pri vseh bolnikih posneti elektrokardiogram (EKG) in kontrolirati elektrolite (vključno z magnezijem). Nadaljnje kontrole so priporočljive predvsem pri bolnikih z zmerno do hudo jetrno okvaro, in sicer mesečno prve 3 mesece zdravljenja, potem pa na 3 mesece oziroma pogosteje, če je to klinično indicirano. Zdravljenja z vemurafenibom ni priporočljivo uvesti pri bolnikih, ki imajo interval QTc > 500 milisekund (ms). *Bolezni oči:* poročali so o resnih neželenih učinkih na očeh, vključno z uveitisom, iritisom in zaporo mrežnične vene. Bolnikom je treba oči redno kontrolirati glede morebitnih neželenih učinkov na očeh. *Ploščatocelični karcinom kože:* pri bolnikih, zdravljenih z vemurafenibom, so bili opisani primeri ploščatoceličnega karcinoma kože, vključno s ploščatoceličnim karcinomom, opredeljenim kot keratoakantom ali mešani keratoakantom. Priporočljivo je, da vsi bolniki pred uvedbo zdravljenja opravijo dermatološki pregled in da so med zdravljenjem deležni rednih kontrol. Vsako sumljivo spremembo je treba izrezati, poslati na histopatološko oceno in jo zdraviti v skladu z lokalnimi smernicami. Med zdravljenjem in do šest mesecev po zdravljenju ploščatoceličnega karcinoma mora zdravnik enkrat mesečno pregledati bolnika. Pri bolnikih, ki se jim pojavi ploščatocelični karcinom kože, je priporočljivo nadaljevati zdravljenje brez zmanjšanja odmerka. Nadzor se mora nadaljevati še 6 mesecev po prenehanju zdravljenja z vemurafenibom ali do uvedbe drugega antineoplastičnega zdravljenja. Bolnikom je treba naročiti, naj svojega zdravnika obvestijo o pojavu kakršnih koli sprememb na koži. *Ploščatocelični karcinom, ki se ne nahaja na koži:* pri bolnikih, ki so prejemali vemurafenib v kliničnih preskušanjih, so poročali o primerih ploščatoceličnega karcinoma, ki se ne nahaja na koži. Bolnikom je treba pred uvedbo zdravljenja in na 3 mesece med zdravljenjem pregledati glavo in vrat (pregled mora obsegati vsaj ogled ustne sluznice in palpacijo bezgavk). Poleg tega morajo bolniki pred zdravljenjem in na 6 mesecev med zdravljenjem opraviti računalniško tomografijo (CT) prsnega koša. Pred in po končanem zdravljenju ali kadar je klinično indicirano, je priporočljivo opraviti pregled zadnjika in ginekološki pregled (pri ženskah). Po prenehanju zdravljenja z vemurafenibom se mora nadzor glede ploščatoceličnega karcinoma, ki se ne nahaja na koži, nadaljevati še 6 mesecev ali do uvedbe drugega antineoplastičnega zdravljenja. Nenormalne spremembe je treba obravnavati v skladu s klinično prakso. *Novi primarni melanom:* v kliničnih preskušanjih so poročali o novih primarnih melanomih. Bolnike s takšnimi primeri so zdravili z ekscizijo, bolniki pa so nadaljevali z zdravljenjem brez prilagoditve odmerka. Nadzor nad pojavom kožnih lezij je treba izvajati, kot je navedeno zgoraj pri ploščatoceličnem karcinomu kože. *Druge malignosti:* glede na mehanizem delovanja lahko vemurafenib povzroči napredovanje rakov, povezanih z mutacijo RAS. Pred dajanjem vemurafeniba bolnikom, ki so imeli ali imajo raka, povezanega z mutacijo RAS, skrbno razmislite o koristih in tveganjih. *Poškodbe jeter:* med uporabo vemurafeniba so poročali o poškodbah jeter, vključno s primeri hudih poškodb. Pred uvedbo zdravljenja in mesečno med zdravljenjem oz. kot je klinično indicirano, je treba kontrolirati jetrne encime (transaminaze in alkalno fosfatazo) ter bilirubin. Laboratorijske nepravilnosti je treba obvladati z zmanjšanjem odmerka, prekinitvijo zdravljenja ali prenehanjem zdravljenja (za podrobnosti o prilagoditvi odmerka, prosimo glejte SmPC zdravila). *Jetrna okvara:* Bolnikom z jetrno okvaro začetnih odmerkov ni treba prilagajati. Bolnike, ki imajo zaradi metastaz v jetrih blago jetrno okvaro in nimajo hiperbilirubinemije, se lahko nadzoruje v skladu s splošnimi priporočili. Podatkov o bolnikih z zmerno do hudo jetrno okvaro je le malo; pri takih bolnikih je izpostavljenost lahko večja. Tako je posebej po prvih tednih zdravljenja potreben skrben nadzor, saj lahko po daljšem obdobju (več tednih) pride do kopičenja. *Ledvična okvara:* bolnikom z blago ali zmerno ledvično okvaro začetnih odmerkov ni treba prilagajati. Pri bolnikih z hudo ledvično okvaro je treba vemurafenib uporabljati previdno ter jih pozorno spremljati. *Fotosenzibilnost:* pri bolnikih, ki so v kliničnih študijah prejemali vemurafenib, je bila opisana blaga do huda fotosenzibilnost. Vsem bolnikom je treba naročiti, naj se med jemanjem vemurafeniba ne izpostavljajo soncu. V primeru fotosenzibilnosti stopnje 2 (nepreneslijivo) ali več so priporočljive prilagoditve odmerka. Ženske v rodni dobi morajo med zdravljenjem in vsaj še 6 mesecev po zdravljenju uporabljati učinkovito kontracepcijsko zaščito. Vemurafenib lahko zmanjša učinkovitost hormonskih kontraceptivov. *Sočasno dajanje ipilimumaba:* pri sočasni uporabi ipilimumaba in vemurafeniba so v preskušanju faze I poročali o asimptomatskih zvišanjih transaminaz in bilirubina stopnje 3. Glede na te preliminarne podatke sočasna uporaba ipilimumaba in vemurafeniba ni priporočljiva. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** *vplivi vemurafeniba na substrate CYP* vemurafenib lahko poveča izpostavljenost v plazmi tistih snovi, ki se presnavljajo pretežno s CYP1A2; v takem primeru je treba razmisliti o prilagoditvi odmerka. Vemurafenib lahko zmanjša plazemsko izpostavljenost zdravilom, ki se presnavljajo pretežno s CYP3A4. Tako je lahko učinkovitost kontracepcijskih tablet, ki se presnavljajo s CYP3A4 in se uporabljajo sočasno z vemurafenibom, zmanjšana. Pri substratih CYP3A4, ki imajo ozko terapevtsko okno, je treba razmisliti o prilagoditvi odmerka. Zaenkrat še ni znano ali lahko vemurafenib pri 100 µM koncentraciji v plazmi, ki je bila opažena pri bolnikih v stanju dinamičnega ravnovesja (približno 50 µg/ml), zmanjša plazemske koncentracije sočasno dajanih substratov CYP2B6, kot je bupropion. Kadar se vemurafenib pri bolnikih z melanonom uporabi hkrati z varfarinom (CYP2C9), je potrebna previdnost. Tveganja za klinično pomemben učinek na sočasno uporabljene učinkovine, ki so substrati CYP2C8, pa ni mogoče izključiti. Zaradi dolge razpolovne dobe vemurafeniba je mogoče, da popolnega inhibitornega učinka vemurafeniba na sočasno dajano zdravilo ne opazimo, dokler ne mine 8 dni zdravljenja z vemurafenibom. Po končanem zdravljenju z vemurafenibom bo morda potreben 8-dnevni premor, da se izognemo interakcijam z nadaljnjim zdravljenjem. *Vpliv vemurafeniba na transportne sisteme zdravil* možnosti, da vemurafenib morda poveča izpostavljenost drugih zdravil, ki se prenašajo s P-gp, ni mogoče izključiti. Možen vpliv vemurafeniba na druge prenašalce trenutno ni znan. *Vplivi sočasno uporabljenih zdravil na vemurafenib* študije *in vitro* kažejo, da sta presnova s CYP3A4 in glukuronidacija odgovorni za presnovo vemurafeniba. Zdi se, da je tudi izločanje z žolčem pomembna pot izločanja. Vemurafenib je treba uporabljati previdno v kombinaciji z močnimi inhibitorji CYP3A4, glukuronidacije in/ali prenašalnih beljakovin (npr. ritonavirjem, sakvinavirjem, telitromicinom, ketokonazolom, itrakonazolom, vorikonazolom, posakonazolom, nefazodonom, atazanavirjem). Sočasna uporaba močnih induktorjev P-gp, glukuronidacije, in/ali CYP3A4 (npr. rifampicina, rifabutina, karbamazepina, fenitoina ali šentjanževke [Hypericum perforatum]) lahko vodi v suboptimalno izpostavljenost vemurafenibu in se ji je treba izogibati. Študije *in vitro* so pokazale, da je vemurafenib substrat sekretornih prenašalcev, P-gp in BCRP. Vplivi induktorjev in inhibitorjev P-gp in BCRP na izpostavljenost vemurafenibu niso znani. Ne moremo pa izključiti možnosti, da imajo lahko zdravila, ki vplivajo na P-gp (npr. verapamil, ciklosporin, ritonavir, kinidin, itrakonazol) ali BCRP (npr. ciklosporin, gefitinib), vpliv na farmakokinetiko vemurafeniba. Za zdaj ni znano, ali je vemurafenib substrat tudi za druge beljakovinske prenašalce. **Neželeni učinki:** med najpogostejšimi neželenimi učinki (> 30 %), o katerih so poročali v zvezi z vemurafenibom, so artralgija, utrujenost, kožni izpuščaj, fotosenzibilnostna reakcija, navzea, alopecija in srbenje. Zelo pogosto je bil opisan ploščatocelični karcinom kože. Sledijo najpogostejši neželeni učinki, ki so se pojavili pri bolnikih, zdravljenih z vemurafenibom v študiji faze II in III in dogodki iz varnostnih poročil vseh preskušanj in obdobja po prihodu zdravila na trg. *Zelo pogosti:* ploščatocelični karcinom kože, seboroična keratoza, kožni papilom, zmanjšanje teka, glavobol, disgevzija, kašelj, driska, bruhanje, slabost, zaprtost, fotosenzibilna reakcija, aktinična keratoza, kožni izpuščaj, makulo-papulozen izpuščaj, papulozen izpuščaj, srbenje, hiperkeratoza, eritem, alopecija, suha koža, sončne opekline, artralgija, mialgija, bolečina v okončini, mišično-skeletne bolečine, bolečine v hrbtu, utrujenost, pireksija, periferni edem, astenija, zvišanje GGT. *Pogosti:* folikulitis, bazalnocelični karcinom, novi primarni melanom, ohromelost sedmega živca, omotica, uveitis, sindrom palmarno-plantarne eritrodisestezije, panikulitis (vključno z nodoznim eritemom), pilarna keratoza, artritis, zvišanje ALT, alkalne fosfataze, bilirubina in izguba telesne mase, podaljšanje QT. *Posebne populacije*: pri starejših bolnikih (≥ 65 let) je možna večja verjetnost neželenih učinkov, vključno s ploščatoceličnim karcinomom kože, zmanjšanjem teka in motnjami srčnega ritma. Med neželene učinke stopnje 3, ki so bili med kliničnimi preskušanji vemurafeniba pri ženskah opisani pogosteje kot pri moških, spadajo kožni izpuščaj, artralgija in fotosenzibilnost. Poročanje o domnevnih neželenih učinkih: prosimo, da o neželenih učinkih, ki jih opazite pri zdravljenju z zdravilom Zelboraf, poročate v skladu s Pravilnikom o farmakovigilanci (Uradni list RS, št. 57/14), na obrazcu za poročanje, ki je objavljen na spletni strani www.jazmp.si. Prosimo, da izpolnjen obrazec pošljete Univerzitetnemu kliničnemu centru Ljubljana, Interna klinika, Center za zastrupitve, Zaloška cesta 2, SI-1000 Ljubljana, faks: + 386 (0)1 434 76 46, ali na elektronski naslov: farmakovigilanca@kclj.si, lahko pa tudi Javni agenciji RS za zdravila in medicinske pripomočke (JAZMP), Sektor za farmakovigilanco, Ptujska ulica 21, SI- 1000 Ljubljana, faks: + 386 (0)8 2000 510, ali na elektronski naslov: h-farmakovigilanca@jazmp.si. **Režim izdaje zdravila:** Rp/Spec **Imetnik dovoljenja za promet:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, Velika Britanija **Verzija: 4.0/14 Informacija pripravljena:** Januar 2015 Samo za strokovno javnost.

1. Povzetek glavnih značilnosti zdravila Zelboraf, dostopano 6. 1. 2014 na http://www.ema.europa.eu/docs/sl_SI/document_library/EPAR_-_Product_Information/human/002409/WC500124317.pdf

PG-2-15-ZEL-TG

DODATNE INFORMACIJE SO NA VOLJO PRI:
Roche farmacevtska družba d.o.o., Vodovodna cesta 109, 1000 Ljubljana

Zelboraf®
vemurafenib
Učinkovitost. Dokazi. Izkušnje.

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe Merck Sharp & Dohme! SESTAVA: Ena viala vsebuje 100 mg infliksimaba. Infliksimab je himerno človeško–mišje monoklonsko protitelo IG1 pridobljeno v mišjih hibridoma celicah s tehnologijo rekombinantne DNK. Po rekonstituciji vsebuje en mililiter 10 mg infliksimaba. **INDIKACIJE:** (i) V kombinaciji z metotreksatom za zmanjšanje znakov in simptomov revmatoidnega artritisa ter izboljšanje funkcije sklepov pri odraslih bolnikih z aktivno boleznijo, kadar odziv na protirevmatična zdravila, ki vplivajo na imunsko odzivnost, vključno z metotreksatom, ni zadosten; in pri odraslih bolnikih s hudo, aktivno in progresivno boleznijo, ki še niso bili zdravljeni z metotreksatom ali drugimi protirevmatičnimi zdravili. (ii) Zdravljenje zmerno do močno aktivne Crohnove bolezni pri odraslih bolnikih, ki se niso odzvali na celoten in ustrezen ciklus zdravljenja s kortikosteroidom in/ali zdravilom za zaviranje imunske odzivnosti, ali pri tistih, ki ne prenašajo tovrstne terapije ali ki imajo medicinske kontraindikacije zanjo; zdravljenje aktivne Crohnove bolezni s fistulami pri odraslih bolnikih, ki se niso odzvali na celoten in ustrezen ciklus konvencionalnega zdravljenja. (iii) Zdravljenje hude, aktivne Crohnove bolezni pri otrocih in mladostnikih, starih od 6 do 17 let, ki se niso odzvali na običajno terapijo, ter pri tistih, ki ne prenašajo teh običajnih načinov zdravljenja oziroma imajo kontraindikacije zanje. (iv) Zdravljenje zmerno do močno aktivnega ulceroznega kolitisa pri odraslih bolnikih, ki so se nezadostno odzvali na običajno zdravljenje, ter pri tistih, ki ne prenašajo takšnega zdravljenja ali imajo medicinske kontraindikacije zanj. (v) Zdravljenje močno aktivnega ulceroznega kolitisa pri pediatričnih bolnikih, starih od 6 do 17 let, ki so se nezadostno odzvali na običajno zdravljenje, na primer na kortikosteroide in 6-MP ali AZA, ter pri tistih, ki ne prenašajo takšnega zdravljenja ali imajo medicinske kontraindikacije zanj. (vi) Zdravljenje hudega aktivnega ankilozirajočega spondilitisa pri odraslih bolnikih, ki so se nezadostno odzvali na konvencionalno terapijo. (vii) Zdravljenje aktivnega in napredujočega psoriatičnega artritisa pri odraslih bolnikih v primeru nezadostnega odziva na predhodno zdravljenje s protirevmatičnimi zdravili DMARD v kombinaciji z metotreksatom ali samostojno pri bolnikih, ki ne prenašajo metotreksata ali pri katerih je metotreksat kontraindiciran. (viii) Zdravljenje zmerne do hude psoriaze s plaki pri odraslih bolnikih, ki se niso odzvali na druge sistemske terapije ali pa imajo kontraindikacijo zanje ali jih ne prenašajo. **ODMERJANJE IN NAČIN UPORABE:** Revmatoidni artritis: Odmerek je 3 mg/kg v intravenski infuziji v času 2 ur. Temu naj sledita dodatni infuziji z odmerkoma 3 mg/kg, 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Če se bolnik nezadostno odzove na zdravilo ali če pri njem odziv pozneje izgine, mu lahko tudi postopoma povečujete odmerek za približno 1,5 mg/kg na vsakih 8 tednov, do največ 7,5 mg/kg. Druga možnost pa je, da bolniku daste 3 mg/kg že na vsake 4 tedne. Zmerno do močno aktivna Crohnova bolezen: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, temu pa naj sledita še dodatni infuziji zdravila v odmerku 5 mg/kg v 2. tednu po prvi infuziji. Če se bolnik ne odzove na zdravljenje po 2 odmerkih zdravila, mu ne smete več dajati infliksimaba. Pri bolnikih, ki so se odzvali na zdravilo, so druge možnosti nadaljnjega zdravljenja naslednje: Vzdrževalno zdravljenje: Dodatni infuziji v odmerku 5 mg/kg 6 tednov po prvem odmerku, čemur naj sledijo infuzije na vsakih 8 tednov, ali ponovno dajanje zdravila: Infuzija odmerka 5 mg/kg, če se ponovijo znaki in simptomi bolezni. Aktivna Crohnova bolezen s fistulami: Intravenski infuziji 5 mg/kg v času 2 ur naj sledita dodatni infuziji 5 mg/kg 2 in 6 tednov po prvi infuziji. Pri bolnikih, ki se odzovejo na zdravilo, so možnosti nadaljnjega zdravljenja naslednje: Vzdrževanje: Dodatne infuzije z odmerkom 5 mg/kg na vsakih 8 tednov, ali ponovno dajanje: Infuzija 5 mg/kg zdravila, če se ponovijo znaki in simptomi bolezni, čemur naj sledijo infuzije z odmerkom 5 mg/kg na vsakih 8 tednov. Ulcerozni kolitis: Odmerek je 5 mg/kg v obliki intravenske infuzije, ki naj traja 2 uri. Temu naj sledita dva dodatna infuzijska odmerka po 5 mg/kg v 2. in 6. tednu po prvi infuziji, potem pa zdravilo infundirajte bolniku na vsakih 8 tednov. Ankilozirajoči spondilitis: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, čemur naj sledita dodatni infuziji z odmerkoma 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 6 do 8 tednov. Psoriatični artritis: Odmerek je 5 mg/kg v intravenski infuziji v času 2 ur, čemur naj sledita dodatni infuziji z odmerkoma 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Psoriaza: 5 mg/kg, dano v obliki 2 urne intravenske infuzije, potem pa dodatne infuzije odmerkov 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Ponovna uporaba zdravila za vse indikacije: V primeru prekinitve vzdrževalnega zdravljenja, in potrebe po ponovni uvedbi zdravljenja, ni priporočljiva ponovna uporaba uvodne sheme. V tem primeru bolniku najprej ponovno uvedite zdravilo Remicade v enkratnem odmerku, pozneje pa mu spet predpišite vzdrževalni odmerek zdravila v skladu s priporočili, ki so podana zgoraj. Crohnova bolezen (pri bolnikih, starih od 6 do 17 let): Običajen odmerek je 5 mg/kg. Bolniku ga dajte v obliki 2 urne intravenske infuzije, ki naj ji sledita še dve infuziji v istem odmerku, in sicer 2 in 6 tednov po prvi infuziji, potem pa nadaljujte z infuzijami za vzdrževalno zdravljenje na vsakih 8 tednov. Ulcerozni kolitis (od 6 do 17 let): Odmerek je 5 mg/kg v intravenski infuziji, ki traja 2 uri. Temu naj sledita dodatni infuziji z odmerkom 5 mg/kg 2 in 6 tednov po prvi infuziji, potem pa na vsakih 8 tednov. Skrajšane infuzije pri indikacijah za odrasle bolnike: Pri skrbno izbranih bolnikih, ki so dobro prenesli vsaj 3 začetne 2-urne infuzije zdravila Remicade in so trenutno na vzdrževalnem zdravljenju, lahko razmislite o skrajšanju naslednjih infuzij, vendar ne na manj kot 1 uro. Če pri skrajšani infuziji nastopi z njo povezana reakcija in je treba zdravljenje nadaljevati, lahko pri naslednjih infuzijah razmislite o uporabi manjše hitrosti infundiranja. Uporabe skrajšanih infuzij v odmerkih > 6 mg/kg niso proučevali. **KONTRAINDIKACIJE:** Bolniki z anamnezo preobčutljivosti na infliksimab, druge miši beljakovine ali katero od pomožnih snovi. Bolniki s tuberkulozo ali z drugimi hudimi okužbami, kakor so npr. sepsa, abscesi in oportunistične okužbe. Bolniki z zmernim do hudim srčnim popuščanjem (razred III/IV po NYHA). **POVZETEK POSEBNIH OPOZORIL, PREVIDNOSTNIH UKREPOV IN INTERAKCIJ:** Za izboljšanje sledljivosti bioloških zdravil, mora biti v kartoteki bolnika, ki zdravilo prejema, jasno dokumentirano (ali navedeno), zaščiteno ime in številka serije zdravila. Zdravljenje z infliksimabom je bilo povezano z akutnimi infuzijskimi reakcijami, vključno z anafilaktičnim šokom in poznimi preobčutljivostnimi reakcijami. Če se pojavi akutna infuzijska reakcija, morate infuzijo takoj prekiniti. Na voljo morajo biti sredstva za nujno pomoč. Za preprečevanje blagih in prehodnih učinkov lahko bolnikom pred zdravljenjem z zdravilom Remicade daste premedikacijo. Če se pojavijo resne reakcije, morate uvesti simptomatično zdravljenje in bolniku ne smete več dajati infuzij tega zdravila. Če bolnik po daljšem obdobju ponovno prejme zdravilo Remicade, ga morate skrbno spremljati zaradi morebitnega pojava znakov in simptomov pozne preobčutljivosti. Pred, med in po zdravljenju z zdravilom Remicade morate bolnike skrbno spremljati, da ugotovite morebitne okužbe, npr. tuberkulozo. Bolnika ne smete več zdraviti s tem zdravilom, če dobi resno okužbo ali sepso. Zaviranje TNFα lahko prikrije simptome okužbe. Bolniki, ki jemljejo zaviralce TNF, so bolj občutljivi za resne okužbe. Uporabo zdravila Remicade prekinite, če se pri bolniku pojavi nova resna okužba ali sepsa, in mu uvedite ustrezno protimikrobno ali protiglivično terapijo, dokler ne bo okužba obvladana. Pred začetkom zdravljenja z zdravilom Remicade, morate vse bolnike pregledati in preiskati, da ugotovite morebitno aktivno ali neaktivno tuberkulozo. Če se pri bolnikih, zdravljenih z zdravilom Remicade, razvije resna sistemska bolezen, je treba posumiti na invazivno glivično okužbo, kot so aspergiloza, kandidiaza, pnevmocistoza, histoplazmoza, kokcidioidomikoza ali blastomikoza, poleg tega pa je pri teh bolnikih že zgodaj v poteku preiskav potreben posvet z zdravnikom, ki ima strokovno znanje iz diagnostike in zdravljenja invazivnih glivičnih okužb. Bolnike, pri katerih obstaja tveganje za okužbo z virusom hepatitisa B, je treba oceniti, ali imajo znake okužbe s HBV, preden smete pri njih uvesti zdravljenje z zdravilom Remicade. Bolnike s simptomi ali znaki motenj delovanja jeter morate pregledati oz. opraviti preiskave, da ugotovite morebitne znake poškodbe jeter. Kombiniranje zdravila Remicade in abatacepta oz. anakinre ni priporočljivo. Priporočamo, da živih cepiv in povzročiteljev okužb v terapevtske namene ne dajete sočasno z zdravilom Remicade. Pri pediatričnih bolnikih s Crohnovo boleznijo če je le mogoče opravite vsa cepljenja, v skladu s tekočimi veljavnimi smernicami za cepljenje otrok, preden pri njih uvedete zdravljenje z zdravilom Remicade. Relativno pomanjkanje TNFα kot posledica anti TNF terapije lahko sproži avtoimunski proces. Infliksimab in druga zdravila, ki zavirajo TNFα, so bila v redkih primerih povezana z nevritisom vidnega živca, epileptičnimi napadi in novim pojavom ali poslabšanjem kliničnih simptomov in/ali z rentgenskimi znaki demielinizirajoče bolezni osrednjega živčevja, vključno z multiplo sklerozo in demielinizirajoče bolezni perifernega živčevja, vključno z Guillain Barréjevim sindromom. Pri odločanju o uvedbi zdravljenja pri bolnikih, ki so težki kadilci in imajo zato povečano tveganje za nastanek rakave bolezni, je potrebna previdnost. Glede na sedanje znanje ni mogoče izključiti tveganja za pojav limfomov ali drugih malignih bolezni pri bolnikih, zdravljenih z zaviralci TNF. Previdnost je potrebna tudi pri odločanju o uvedbi zdravljenja z zaviralci TNF pri bolnikih z rakavimi boleznimi v preteklii anamnezi ter pri odločanju o tem, ali naj nadaljujete z zdravljenjem pri bolnikih, pri katerih se pojavi nov nova rakava bolezen. Zdravilo Remicade morate uporabljati previdno pri bolnikih z blagim srčnim popuščanjem (razred I/II po NYHA). Pri bolnikih, ki so jemali zaviralce TNF, vključno z zdravilom Remicade, so poročali o pojavu pancitopenije, levkopenije, nevtropenije in trombocitopenije. Pri bolnikih, zdravljenih z zdravilom Remicade, ki so bili stari 65 let ali več, je bila incidenca resnih okužb večja kot pri bolnikih, ki so bili mlajših od 65 let. Pri zdravljenju starostnikov je torej treba posvetiti posebno pozornost tveganju za nastanek okužbe. Obstajajo znaki, da sočasna uporaba metotreksata in drugih imunomodulatorjev pri bolnikih z revmatoidnim artritisom, psoriatičnim artritisom in Crohnovo boleznijo zmanjša tvorbo protiteles proti infliksimabu in poveča koncentracijo infliksimaba v plazmi. Ni videti, da bi imeli kortikosteroidi klinično pomemben vpliv na farmakokinetiko infliksimaba. **NEŽELENI UČINKI:** Najpogostejši neželeni učinek zdravila, o katerem so poročali v kliničnih preskušanjih, je bila okužba zgornjih dihal, ki se je pojavila pri 25,3 % bolnikov, zdravljenih z infliksimabom, in pri 16,5 % bolnikov iz kontrolne skupine. Med najresnejše, z uporabo zaviralcev TNF povezane neželene učinke zdravila, o katerih so poročali pri uporabi zdravila Remicade, sodijo reaktivacija HBV, kronično srčno popuščanje, resne okužbe (vključno s sepso, oportunističnimi okužbami in TB), serumska bolezen (pozne preobčutljivostne reakcije), hematološke reakcije, sistemski eritematozni lupus/lupusu podoben sindrom, demielinizirajoče bolezni, dogodki v zvezi z jetri ali žolčnikom, limfom, hepatosplenični limfom celic T (HSTCL), črevesni ali perianalni absces (pri Crohnovi bolezni) ter resne z infuzijo povezane reakcije. **NAČIN IN REŽIM IZDAJE ZDRAVILA:** Zdravilo je zaradi svojih lastnosti, svoje relativne novosti ali zaradi varovanja javnega zdravja namenjeno izključno za zdravljenje, ki ga je mogoče spremljati samo v bolnišnici. **IMETNIK DOVOLJENJA ZA PROMET Z ZDRAVILOM:** Janssen Biologics B.V., Einsteinweg 101, 2333-CB-Leiden, Nizozemska **DATUM ZADNJE REVIZIJE BESEDILA:** 25. julij 2013 **PRIPRAVLJENO V SLOVENIJI:** junij 2014. Za dodatne informacije poklicite na predstavništvo Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana, tel: 01/5204 349, faks 01/5204 350. **LITERATURA:** Povzetek glavnih značilnosti zdravila Remicade. **IZDAL IN ZALOŽIL:** Merck Sharp & Dohme, inovativna zdravila d.o.o., Šmartinska cesta 140, 1000 Ljubljana. **SAMO ZA STROKOVNO JAVNOST.** GAST-1122414-0001 EXP: 10/2016

HITER, MOČAN IN PODALJŠAN UČINEK!

BELODERM
0,05 % betametazondipropionat

beloderm

Beloderm sedaj na voljo **v 3 oblikah**:

1. krema - za zdravljenje akutnih, eksudativnih kožnih sprememb
2. mazilo - za zdravljenje kroničnih dermatoz ter ko je potreben okluzivni učinek
3. **NOVO!** **dermalna raztopina - za zdravljenje dermatoz na lasišču in na poraščenih delih telesa**

Uporaba zdravila Beloderm 0,5 mg/g dermalna raztopina:

- Nekaj kapljic zdravila bolnik nanese (s pomočjo kapalke) na prizadeto kožo 2 x/dan in nežno vtre
- Po nanosu se zdravila ne izpira
- Po nanosu zdravila si umije roke

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

SESTAVA: 1 gram kreme, mazila ali dermalne raztopine vsebuje 0,5 mg betametazona. **INDIKACIJE:** Bolezni kože, ki jih zdravimo z lokalnimi kortikosteroidi: **alergijske bolezni kože** - akutne, subakutne in kronične oblike kontaktnega alergijskega dermatitisa, profesionalnega dermatitisa, atopični dermatitis (nevrodermitis), dermatitis pod plenico, intertriginozni dermatitis, ekcematozni numularni dermatitis, dishidrotični dermatitis; **akutni in kronični nealergijski dermatitisi** - fotodermatitisi, dermatitisi kot posledica rentgenskega sevanja, toksične reakcije zaradi pikov insektov; **druge bolezni kože** - psoriasis vulgaris, pemphigus vulgaris, lichen ruber planus, lichen simplex chronicus, lupus erythematodes chronicus discoides, erythrodermia, erythema exsudativum multiforme, erythema anulare centrifugum in druge vrste eritemov. **ODMERJANJE:** Zdravljenje naj ne bo daljše od 3 tednov. Količino zdravila Beloderm krema, mazilo ali dermalna raztopina, ki je potrebna za prekritje obolele površine kože, z rahlim vtiranjem nanašamo v tankem sloju dvakrat na dan. Na področjih kože z debelim roževinastim slojem je potrebna pogostejša aplikacija. Zdravljenje je potrebno nadaljevati do kliničnega izboljšanja. Pri uporabi zdravila Beloderm krema ali mazilo pri otrocih je potrebna previdnost, uporaba zdravila naj bo čim krajša. Varnost in učinkovitost zdravila Beloderm dermalna raztopina pri otrocih, mlajših od 18 let, še nista bili dokazani. Če zdravilo Beloderm uporabljate na obrazu ali pri otrocih, zdravljenje ne sme trajati več kot 5 dni. **KONTRAINDIKACIJE:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov, virusna okužba s kožnimi spremembami (herpes, norice, koze), kožna tuberkuloza in kožne spremembe pri lupusu, akne, rozacea, perioralni dermatitis. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Če pri prvi uporabi zdravila Beloderm nastopi preobčutljivostna reakcija na koži je treba terapijo takoj prekiniti. Uporaba zdravila Beloderm ni priporočljiva v kombinaciji z okluzivnimi povoji, razen, če tako predpiše zdravnik. Dolgotrajna uporaba na koži obraza ni priporočljiva, ker lahko povzroči dermatitis, ki se kaže kot rozacea, perioralni dermatitis in akne. Zdravilo se ne sme uporabljati na očeh ali v periokularnem območju zaradi možnosti nastanka katarakte, glavkoma, glivične okužbe oči in poslabšanja okužbe z virusom herpesa. Zdravilo Beloderm se ne sme uporabljati za zdravljenje varikoznih ulkusov goleni. Pri otrocih, zaradi večje površine kože glede na telesno maso in nezadostno razvito rogeno plast kože, obstaja možnost sistemske absorpcije sorazmerno večje količine betametazona, kar lahko vodi do manifestacij sistemske toksičnosti. Izogibati se je treba uporabi pod plenicami (še zlasti plastičnimi), ker le te delujejo kot okluzija in prav tako lahko povzročijo večjo absorpcijo učinkovin. Pri otrocih, bolnikih z jetrno insuficienco in bolnikih, ki potrebujejo dolgotrajno zdravljenje, je potrebna previdnost, še zlasti pri hkratni uporabi okluzivnega povoja zaradi možnosti povečane absorpcije betametazona in pojava sistemskih neželenih učinkov. Na nekaterih delih telesa, kjer obstaja neke vrste naravna okluzija (dimlje, pazduha in perianalno področje), je pri lokalni uporabi zdravila Beloderm možen nastanek strij, zato naj bo uporaba zdravila na teh delih telesa čimbolj omejena. Lahko se pojavijo simptomi, povezani z odtegovanjem zdravila, v teh primerih je potrebno nadomestno jemanje kortikosteroidov. V primeru glivičnih ali sekundarnih bakterijskih infekcij kožnih lezij je potrebna dodatna uporaba antimikotikov oz. antibiotikov. Na lasišču je treba zdravilo Beloderm uporabljati previdno zaradi izredno močne prekrvavitve in povečane absorpcije. Zdravilo Beloderm 0,5 mg/g krema vsebuje cetil in stearilalkohol, ki lahko povzroči lokalne kožne reakcije. **INTERAKCIJE:** Medsebojno delovanje zdravila Beloderm z drugimi zdravili ni znano. **NOSEČNOST IN DOJENJE:** Uporaba zdravila Beloderm je pri nosečnicah dovoljena samo v primeru, ko zdravnik oceni, da je pričakovana korist za mater večja od možnega tveganja za plod. V takih primerih je treba uporabljati najmanjše učinkovite odmerke čim krajši čas na čim manjši telesni površini. Po presoji zdravnika lahko zdravilo Beloderm uporabljajo tudi doječe matere, vendar se zdravilo pred dojenjem ne sme nanašati na kožo dojk. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA S STROJI:** Zdravilo Beloderm nima vpliva na sposobnost vožnje in upravljanja s stroji. **NEŽELENI UČINKI: Pogosti:** sekundarne okužbe, občutek pečenja, srbenje, draženje, suhost, folikulitis, hipertrihoza, aknam podobni izpuščaji, hipopigmentacija, teleangiektazije, perioralni dermatitis, alergijski kontaktni dermatitis, maceracija kože, atrofija kože, strije, miliarija. **Redki:** insuficienca nadlevične žleze. **VRSTA OVOJNINE IN VSEBINA:** Škatla s tubo po 40 g kreme ali mazila; vsebnik s 100 ml dermalne raztopine (bela plastenka z rumeno varnostno navojno zaporko iz HDPE in bela kapalka iz LDPE). **REŽIM IZDAJE:** Zdravilo se izdaja samo na recept. **IMETNIK DOVOLJENJA ZA PROMET:** Belupo d.o.o., Dvoržakova 6, 1000 Ljubljana, Slovenija. **DATUM ZADNJE REVIZIJE BESEDILA:** 11.04.2014.

Gradivo je namenjeno samo strokovni javnosti. Podrobnejše informacije o zdravilu in povzetek glavnih značilnosti zdravila so vam na voljo pri strokovnih sodelavcih in na sedežu podjetja Belupo.
Datum priprave informacije: februar 2015

BELUPO | Bodimo zdravi!

BELUPO, d.o.o., Dvoržakova ulica 6, 1000 Ljubljana
Tel: 01 300 95 10, faks: 01 432 63 11 • E-pošta: info@belupo.si, www.belupo.si

Z BELUPOM DO ZDRAVE KOŽE!

INTERNATIONAL FEDERATION
OF PSORIASIS ASSOCIATIONS

4th World Psoriasis & Psoriatic Arthritis Conference
July 8 - 11, 2015
Stockholm Waterfront Congress Center

The International Federation of Psoriasis Associations welcomes You to the 4th WORLD PSORIASIS & PSORIATIC ARTHRITIS CONFERENCE 2015

â€œPsoriasis - new insights and innovationsâ€

REGISTRATION IS NOW OPEN!

@PsoriasisIFPA
#WPPAC15

ORGANISED BY

PSORIASIS INTERNATIONAL NETWORK

PSORIASIS 2016

PARIS, 7-9 JULY 2016

5th CONGRESS OF THE PSORIASIS INTERNATIONAL NETWORK

SCIENTIFIC PROGRAMME COORDINATED BY

Solapso

PSORIASIS 2016 on facebook

NEWSLETTER

If you wish to be informed on updates about the conference, please submit your email address here:

Enter your email address OK

An action by FRT FONDATION RENÉ TOURAINE

WELCOME ADDRESS

Dear Colleagues and Friends,

On behalf of the **Psoriasis International Network (PIN)** of FRT-Fondation René Touraine, represented by professors Luigi Naldi and Thomas Luger, it is our great pleasure to cordially invite you to participate to PSORIASIS 2016 - 5th Congress of the Psoriasis international Network. **SOLAPSO – Latin American Society of Psoriasis** is one of the most dynamic regional psoriasis networks within PIN and was handed the responsibility of the scientific coordination of the congress by the assembly of PIN National Representatives.

This congress series is directly aimed to serve the needs of practicing dermatologists involved in psoriasis care across countries in outpatient services, hospital settings, and private practice, focusing on the patient management and therapeutic strategies with a special emphasis on the daily medical practice. Therefore, we have invited keynote speakers throughout the world and from all fields of psoriasis research and care to report on their experiences and deliver insight into the latest results and clinical studies.

For 2016, in close collaboration with SOLAPSO, the 5th Congress of the Psoriasis International Network proposes a dynamic, interdisciplinary and interactive programme, including rheumatology points. A special attention will be given to psoriasis management in different scenarios, psoriatic arthritis and psychodermatology.

Furthermore, topics such as therapeutic targets in psoriasis, psoriasis in paediatrics, phototherapy, topical and systemic treatments and combined therapies, life quality and adherence to treatment, patient education, registries, pharmacoeconomics and psoriasis and internal medicine will also be addressed in workshops which allow you to directly interact with internationally experienced speakers.

Make sure that you don't miss this unique opportunity to update your knowledge on psoriasis, and take also the advantage to enjoy Paris at this wonderful time of the year!

Sincerely,

Luigi NALDI, Italy
President of PIN
Scientific Committee

Thomas LUGER, Germany
President
of FRT Scientific Board

Nelida RAIMONDO, Argentina
President
of SOLAPSO

ORGANISED BY

PSORIASIS INTERNATIONAL NETWORK

PSORIASIS 2016

PARIS, 7-9 JULY 2016

5th CONGRESS OF THE PSORIASIS INTERNATIONAL NETWORK

SCIENTIFIC PROGRAMME COORDINATED BY

Solapso

NEWSLETTER

If you wish to be informed on updates about the conference, please submit your email address here:

Enter your email address OK

SCIENTIFIC PROGRAMME

Main Scientific Topics

- Therapeutic targets in psoriasis
- Psoriasis in paediatrics
- Psoriasis management in different moments
- Psoriatic arthritis
- Phototherapy
- Topical, systemic and biologics treatments (including biosimilars)
- Combined therapies and transition treatments
- Life quality and adherence to treatment
- Patient-oriented therapies and patient education
- Psychodermatology
- Registries: regional differences and uncovered needs
- Pharmacoeconomics and accessibility in a globalised world
- Internal Medicine and Psoriasis

Scientific Programme

The scientific programme will be available on line in September 2015