Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23(2)

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Canes-Nail™

NOVO

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

1. korak **Odstranjevanje okuženega nohta**

2-3 tedne

2. korak **Nadaljevanje zdravljenja okuženega dela kože s protiglivično kremo**

4 tedni

Zdravljenje v dveh korakih omogoča:

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

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

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

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

Samo za strokovno javnost.

SI.BCC.11.2012.0042

Bayer HealthCare

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23:25-26
doi: xxxxxxxxxxxxxxxxxxxxx

Prevalence, genotype distribution, and risk factors for hepatitis C infection among HIV-infected individuals in Slovenia: a 1986–2013 update

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Abstract

Introduction: Since the introduction of highly active antiretroviral therapy, chronic hepatitis C has become one of the leading causes of non–AIDS-related morbidity and mortality in patients with HIV infection. Two previous Slovenian nationwide studies published in 2002 and 2009 showed a very low prevalence of hepatitis C virus (HCV) infection among Slovenian HIV-infected individuals (14.5% and 10.7%, respectively).

Methods and results: The presence of HCV infection was tested in 579/639 (90.6%) patients that were confirmed as HIV-positive in Slovenia by the end of 2013. Among them, 7.6% (44/579) of HIV-infected individuals were anti-HCV–positive, and 33/44 (75%) anti-HCV–positive patients were also HCV RNA–positive. HCV genotype 1 was most prevalent among HIV-infected patients (68%), followed by genotype 3 (20%), genotype 4 (8%), and genotype 2 (4%). Anti-HCV positivity was significantly higher in those that acquired HIV by the parenteral route (91.8%) than in those that acquired HIV by the sexual route (2.8%).

Discussion: Slovenia remains among the countries with the lowest prevalence of HCV infection in HIV-infected individuals. Because the burden of HIV among men who have sex with men in Slovenia is disproportionately high and increasing rapidly, the current favorable situation could change quickly and should be therefore monitored regularly.

Received: 24 April 2014 | **Returned for modification:** 8 May 2014 | **Accepted:** 30 May 2014

Introduction

Due to the use of highly active antiretroviral therapy (HAART), which has prolonged the survival of HIV-infected individuals (1), and significant overlap in the transmission pathways of hepatitis C virus (HCV) and HIV, chronic hepatitis C has become one of the leading causes of non–AIDS-related morbidity and mortality in patients with HIV infection (2). Coinfection with HCV occurs in 25% of HIV-infected individuals, although rates vary widely in different patient populations and are the highest among intravenous drug users (IVDU) and men who have sex with men (MSM) (3–5).

Slovenia is a small central European country with a relatively low prevalence but increasing incidence of HIV infection (6). The burden of HIV among MSM in Slovenia is disproportionately high and increasing quickly, whereas it is very low among IVDU (7). In our previous nationwide studies published in 2002 and 2009, we found a very low prevalence of HCV infection among Slovenian HIV-infected individuals (14.5% and 10.7%, respectively) (8, 9). Because several developed countries have recently faced a dramatic increase in the incidence of acute hepatitis C among HIV-infected MSM (10–12), here we have updated the HCV infection prevalence data in Slovenian HIV-infected individuals.

Methods

For the purpose of this study, data collected for the most recent published study on the topic (9) were updated with those obtained from 230 Slovenian individuals that were newly diagnosed as HIV-positive between 1 January 2009 and 31 December 2013. Overall, 579 of 639 (90.6%) patients that were confirmed as HIV-positive by the end of 2013 were tested for the presence of HCV infection.

The presence of anti-HCV was determined using the Ortho HCV Assay (Ortho Diagnostic Systems). Anti-HCV reactive specimens were confirmed by the Inno-Lia HCV Ab III Update Assay (Innogenetics, Zwijndrecht, Belgium). HCV RNA was detected using several generations of commercial HCV RNA viral load assays.

Results

Among 579 individuals included in the study, 505 (87.2%) were men and 74 (12.8%) women, and mean age at the time of HIV diagnosis was 37.4 years (range 0–76 years). The sexual transmission route was predominant (483.5/579, 83.5%), followed by the parenteral HIV transmission route (24.5/579, 4.2%), mother-to-child transmission (6/579, 1.0%), and transmission by human bite (1/579, 0.2%) (13). The route of transmission was unknown for 64/579 (11.1%) HIV-infected individuals. MSM accounted for 62.9% of all HIV-infected individuals included in the study.

The presence of anti-HCV antibodies was detected in 7.6% (44/579) HIV-infected individuals. Thirty-three out of 44 (75%) seropositive patients were also HCV RNA–positive. HCV RNA was not detected in any of the 535 anti-HCV–negative HIV-infected individuals. HCV genotype 1 was most prevalent among HIV-infected patients (68%), followed by genotype 3 (20%), genotype 4 (8%), and genotype 2 (4%).

Anti-HCV positivity was significantly higher in those that acquired HIV by the parenteral route (91.8%) than in those that acquired HIV by the sexual route (2.8%).

Discussion

In Slovenia, screening for HCV infection has been the standard of

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medical care in management of HIV-infected individuals since 2001. The study performed in 2002 demonstrated a low prevalence (14.5%) of HCV infection among Slovenian HIV-infected individuals (8). In a follow-up study performed on 87% of the entire population of Slovenian HIV-infected individuals identified by the end of 2008, the prevalence of HCV infection decreased to 10.7% (9). In the present study, which included 90.6% of the entire population of Slovenian HIV-infected individuals identified by the end of 2013, a further decrease in the prevalence of HCV infection was observed and reached only 7.6%. The predominance of HCV genotype 1 among HIV-infected individuals followed by HCV genotype 3 remained unchanged and is in agreement with the HCV genotype distribution in the general population of HCV-positive individuals in Slovenia (14). As noticed in our previous studies, the HCV infection in those that acquired HIV by the parenteral route predominated over individuals that acquired HIV by the sexual route. There are probably two main reasons for the unusual relatively low prevalence of HCV infection among Slovenian HIV-infected individuals. Namely, the IVDU population in Slovenia has so far largely been spared from HIV infection and it also seems that the MSM population in Slovenia has so far largely been spared from HCV infection. However, the situation may change in the near future because we recently detected a few acute hepatitis C cases among HIV-infected MSMs.

Conclusion

Slovenia remains among the countries with the lowest prevalence of HCV infection among HIV-infected individuals. Because the burden of HIV among MSMs in Slovenia is disproportionately high and increasing rapidly, the current favorable situation could quickly change and should therefore be monitored regularly.

Results from this study were partially presented at the 7th Romanian National HIV/AIDS Congress and 2nd Central European HIV Forum in Sibiu Romania May 29-30, 2014, Sibiu, Romania. Published abstract: Seme K, et al. Low prevalence of hepatitis C infection among HIV-infected individuals in Slovenia: a nationwide study, 1985-2013. BMC Infectious Diseases 2014; 14 (Suppl 4): O15.

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Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23:27-31
doi: xxxxxxxxxxxxxxxxxxxxx

Management of moderate to severe plaque psoriasis in pregnancy and lactation in the era of biologics

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Abstract

Psoriasis is not uncommon in the reproductive years and therefore in pregnant patients. There are limited data about the impact of psoriasis on the course and prognosis of pregnancy and about the impact of pregnancy on the course of psoriasis. Usually the disease improves during pregnancy and patients experience worsening between 4 and 6 weeks after delivery. A safe option for patients with limited disease is topical therapy, including moisturizers and topical steroids as well as UVB phototherapy. In the case of active psoriasis or even psoriasis worsening during pregnancy, there might be a need for continuation or even introduction of systemic therapy. Methotrexate and acitretin are known teratogens and mutagens, and they must be avoided. Ciclosporin may be regarded as a possible rescue therapy for pregnant psoriasis patients in the case of severe disease. Post-marketing experience regarding the safety of biologics is accumulating, with largely reassuring results. All four biologics approved for the treatment of moderate to severe psoriasis–etanercept, infliximab, adalimumab, and ustekinumab–are not currently recommended in pregnant psoriasis patients. The existing evidence implies that the risk of biologics in pregnancy is relatively low and that the risk of fetal drug exposure may be outweighed by the benefits for the mother.

Received: 2 April 2014 | **Returned for modification:** 21 April 2014 | **Accepted:** 6 May 2014

Introduction

Psoriasis vulgaris is a chronic immune-mediated inflammatory skin disease. It accounts for more than 80% of all cases of psoriasis (1). Moderate to severe psoriasis is considered a systemic disease with several psoriasis comorbidities such as metabolic syndrome, psoriatic arthritis, depression, and anxiety (2).

The severity of psoriasis must be assessed for proper management of the disease. Mild psoriasis is defined as body surface area (BSA) ≤ 10 and psoriasis area and severity index (PASI) ≤ 10 and dermatology life quality index (DLQI) ≤ 10. Moderate to severe psoriasis is defined as BSA > 10 or PASI > 10 and DLQI > 10. Some special clinical situations such as involvement of visible areas, face, scalp, genitals, palms, and soles may change mild psoriasis to moderate or severe despite the lesser extent of affected skin. Mild disease is most commonly successfully managed topically, and in refractory psoriasis with the addition of phototherapy. Moderate to severe psoriasis cannot be successfully controlled with topical therapy, and therefore phototherapy and systemic therapy are the recommended methods of treatment (3, 4).

The prevalence of psoriasis ranges from 2 to 3% in the Caucasian population. Women and men are affected equally, and the disease usually starts between the second and fourth decades of life. The average age of diagnosis in women is 28. These are the reproductive years and therefore psoriasis is not uncommon in pregnant patients (1). It is estimated that in the United States there is a range of approximately 65,000 to 107,000 births to women with psoriasis annually, of whom 9,000 to 15,000 have moderate to severe disease (5).

Moderate to severe psoriasis may lead to complications in the course of gestation, preterm delivery, and low birth weight (6). A large study that included 1,463 mothers with psoriasis and 11,704 randomly selected mothers without the disease showed that pregnant women with severe psoriasis had a higher risk of giving birth to a newborn with low birth weight. They observed an increased risk of complications such as premature labor, cesarean delivery, and preeclampsia among pregnant psoriasis patients treated with systemic therapy. Conversely, mothers with mild psoriasis had no significantly higher odds for complications during the course of pregnancy (7). The influence of pregnancy on the clinical course of psoriasis is unpredictable; however, usually the disease improves during pregnancy and patients experience worsening between 4 and 6 weeks after delivery. In a study of pregnant psoriasis patients, 55% reported improvement, 21% experienced no change, and 23% reported worsening of disease. Postpartum, only 9% of patients experienced improvement, 65% worsened, and 26% showed no appreciable changes in disease activity (8). In another retrospective study of 91 pregnant women with psoriasis, 56% of patients experienced improvement, 18% remained unchanged, and 26% worsened (9). Improvement could probably be attributed to the immunoendocrine interactions observed in pregnancy with a higher ratio of estrogen to progesterone (10).

Management of psoriasis in pregnancy and lactation

Dermatologists are faced with questions about the safety of different therapeutic modalities during gestation and lactation. Teratogenic and other possible adverse risks for the child must be balanced with the risk from uncontrolled skin inflammation affecting the course of pregnancy and postpartum period. Adjustment of therapy in a patient planning to become pregnant or during early pregnancy is needed.

Currently there are limited data on the safe administration of drugs during pregnancy. Pregnant women are excluded from prospective clinical trials due to ethical reasons. Knowledge only slowly accumulates from inadvertent as well as intentional drug exposure during pregnancies in the form of case reports and various registry collectives. Valuable data on the safety of systemic drugs for treating psoriasis can be drawn from the larger population of inflammatory arthritis and inflammatory bowel disease patients treated with the same agents while pregnant and breastfeeding. Another source of information on the safe use of

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drugs in pregnancy is the US Food and Drug Administration (FDA) pregnancy categories system (Table 1) (11, 12).

Patient counseling before conception is invaluable. A woman with psoriasis of reproductive age should be asked about her childbearing plans in order to choose appropriate medications and provide education (13). About half of patients with psoriasis experience improvement or remission during pregnancy (8, 9). An option for these women may be discontinuation of medications or topical therapy including moisturizers and low- to moderate-potency topical steroids or UVB phototherapy. These represent the first-line therapy for pregnant or breastfeeding psoriasis patients, provided the disease is limited (11, 13). If moderate to severe psoriasis remains active or even worsens during pregnancy, there might be a need for continuation of systemic treatment. Some of these medications are known teratogens and mutagens, and they must be avoided. Others may be used relatively confidently.

Methotrexate

Methotrexate has been widely used in the systemic treatment of moderate to severe psoriasis since 1958 due to its efficacy, extensive clinical experience, and low cost (14). It inhibits the synthesis of DNA by competitive binding to dihydrofolate reductase and has been known as an abortifacient, as well as a mutagen and teratogen agent in animals and humans. It is classified as FDA category X and is absolutely contraindicated during pregnancy. The sensitive period for the occurrence of malformations is between 6 and 8 weeks after conception and the dose required to produce defects is greater than 10 mg per week (16). The abnormalities can occur even in doses lower than 10 mg weekly (16). Methotrexate increases the risk of abortion and birth defects, such as central nervous system, craniofacial, limb, gastrointestinal, and cardiopulmonary malformations, as well as growth delay (15, 17, 18). Because 6 to 8 weeks after conception is the critical period for abnormalities, a "washout" period of at least 3 months is advisable before conceiving, and supplementation with folic acid during this period and throughout pregnancy is recommended (15). Methotrexate has been linked to disturbances in spermatogenesis, such as chromosomal abnormalities and alterations in the sperm mobility. However, a prospective study of 42 fetuses whose fathers were exposed to weekly doses between 7.5 and 30 mg 3 months before or until conception reported no birth abnormalities (19). Methotrexate is transferred into breast milk in significantly lower concentrations compared to maternal serum. It could be present in child tissues for months and therefore it should not be used during lactation (11, 20, 21).

Ciclosporin

Ciclosporin has been classified as a traditional systemic agent for psoriasis treatment and has been approved for this indication since 1993. It is usually given as a short-term therapy for 2 to 4 months (4). It is a selective immunomodulator by acting as a calcineurin inhibitor (22). The drug passively crosses the placental blood barrier to achieve 10 to 50% of the maternal plasma concentration (23). It is not teratogenic in animals or humans. It is classified as FDA category C. There are limited data on the effect of ciclosporin in pregnant psoriasis patients. The majority of information on its use during pregnancy derives from registries of transplant recipients, who usually receive higher doses than psoriasis patients. The drug has no mutagenic properties; namely, no increase of congenital malformations nor any special malformation pattern has been noted. However, there was an increased risk of premature delivery and low birth weight (24–26). Ciclosporin is not absolutely contraindicated in pregnancy and has been used successfully in pregnant women. It may be regarded as a possible rescue therapy for pregnant psoriasis patients in the case of severe disease after thorough risk and benefit analysis together with the patient (11). Cyclosporine is excreted in breast milk at variable levels. Although there are reports of safe infant exposure during lactation with normal development and growth, the current recommendation is that breastfeeding should be avoided while taking ciclosporin due to concerns of immunosuppression in the infant (4, 27).

Acitretin

Acitretin belongs to the group of retinoids. The exact mechanism of action has not been completely clarified, although it affects cellular differentiation and proliferation. Due to lack of efficacy given as a monotherapy, it is no longer suggested among the first-choice therapies for moderate to severe psoriasis patients (4). Acitretin is a well-known teratogen probably acting by affecting cellular differentiation and proliferation. It is classified as FDA category X and is absolutely contraindicated during pregnancy. Acitretin administered in the first trimester of pregnancy increases the risk of spontaneous abortion and congenital defects, such as central nervous system, craniofacial, limb, thymic, and cardiovascular malformations (28). Therefore pregnancy should be avoided during and up to 2 years after the end of therapy, which makes acitretin an impractical and unsuitable therapy for women in their reproductive years. Despite the short elimination half-life of acitretin of only 2 days, it can be converted in small amounts to etretinate with a much longer

Table 1 | **U.S. FDA categories for drug safety during pregnancy.**

FDA pregnancy category	Definition
A	Controlled studies in animals and women have shown no risk in the first trimester, possible fetal harm is remote
B	Animal reproduction studies have failed to demonstrate risk to the fetus but there are no well-controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect that was not confirmed in well-controlled studies in pregnant women in the first trimester of pregnancy
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, or there are no animal reproduction studies and no adequate and well-controlled studies in humans
D	Evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks if life-threatening or serious disease
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, drug is contraindicated

half-life of 100 days, especially by concomitant intake of ethanol. Therefore, women of childbearing age should be discouraged from taking acitretin, and in the case of using this treatment the decision to avoid pregnancy is mandatory. The drug should be introduced on the second or third day of the menstrual cycle, after at least 1 month of satisfactory double contraception. Monthly pregnancy tests are recommended (4).

Literature reports only minimal excretion of acitretin into breast milk; however, breastfeeding should be avoided due to the potential for cumulative neonatal toxicity (21, 29).

Biologics

Currently four biologic agents are approved for moderate to severe psoriasis treatment, which is inadequately controlled with conventional systemic agents or if these agents are contraindicated. Etanercept, infliximab, and adalimumab belong to the TNF inhibitors, which prevent the activation of TNF-α receptor by binding to circulating TNF-α. Ustekinumab is an IL-12/23 inhibitor that blocks the activity of IL12 and IL23 by binding to their p40 subunit. According to current manufacturers' recommendations, all biologic agents should be discontinued for variable periods of time prior to conception depending on elimination half-life and the duration of the biologic effect of these drugs. Reliable contraception should be introduced. Etanercept should be discontinued at least 3 weeks prior to conception. The intervals for infliximab, adalimumab and ustekinumab are at least 6 months, at least 5 months, and up to 15 weeks, respectively (30). The reason for these guidelines is a lack of controlled studies of biologics in pregnant women. However, postmarketing experience regarding the safety of these drugs is accumulating and being published, with largely reassuring results. All four approved biologics for psoriasis treatment are classified as Pregnancy FDA category B, which means there is no risk from animal studies; however, there are no adequate and controlled studies in women receiving biologic agents during pregnancy (11, 13). Experience with exposure to biologics in pregnancy is slowly accumulating, especially in the setting of inflammatory bowel disease and inflammatory arthritis patients. In the case of unplanned conception, most women stop the biological therapy at the time of pregnancy confirmation (31).

Despite some isolated reports of congenital malformations in children exposed to biologics during pregnancy, data from various inflammatory bowel disease and rheumatologic registries show that major congenital malformations after exposure to biologics prior to conception or during the first 3 months of pregnancy occur at rates that are lower than the estimated population rate, which is approximately 3% (32, 33). No specific or consistent pattern of malformations connected to exposure to biologics has been reported so far (34–36). A large collection of 131 pregnancies exposed to infliximab from the Centocor safety database reported no increased risk of adverse outcomes such as miscarriages, therapeutic terminations of pregnancy, and congenital malformations when compared with the general population (37). The OTIS (Organization for Teratology Information Specialists) registry reported 100 pregnancies exposed to etanercept, which had similar live birth rates and similar rates of major congenital malformations compared to a control group of pregnant patients with inflammatory arthritis not exposed to etanercept (38). The same registry reported 66 pregnancies exposed to adalimumab for rheumatoid arthritis during the first trimester, comparing them to non-adalimumab treated patients and healthy controls. There was no increased risk or evidence of a specific pattern of major or minor birth defects connected with adalimumab exposure (39). Ustekinumab is a relatively new biologic drug and experience during pregnancy is extremely limited. One reported case of its use during pregnancy in a psoriasis patient reported an uncomplicated pregnancy and a healthy infant delivered at term (40). Accumulated data may be reassuring that termination of pregnancy is not necessary for women that inadvertently become pregnant while taking biologics. An exposure to biologics during the first trimester does not seem to hold an increased risk of congenital defects or other unfavorable outcomes of pregnancy.

The structure of infliximab, adalimumab, and ustekinumab is an IgG1 monoclonal antibody, whereas etanercept is a fusion protein. It is well known that maternal IgG antibodies are large hydrophilic proteins of more than 100 kDa and cannot cross the placenta by simple diffusion, but are actively transported via Fc receptors on the syncytiotrophoblast. These receptors have not been observed before week 14 of gestation; however, the active transport of IgG immunoglobulins begins during the second trimester and rapidly increases over the third trimester, leading to higher fetal levels of IgG in comparison to those in maternal circulation. The half-life of immunoglobulins in an infant is considerably longer than in adults (41–43). Infliximab, adalimumab, and ustekinumab are actively transported through the placenta in the same way as natural maternal antibodies reaching high blood levels in the newborn after being exposed in the late second and third trimester. Both infliximab and adalimumab have been found in newborns in much higher concentrations than in their mothers' peripheral blood, and they remain detectable from 2 to 7 months after birth. The median concentration of infliximab measured in cord blood at delivery was 160% of maternal, whereas the median concentration of adalimumab in cord blood was 153% of that detected in maternal serum (44–46). There is no published human study on ustekinumab so far; however, in an animal study on cynomolgus macaques ustekinumab was detected in fetal serum as well as in the serum of infants as long as 120 days postpartum (47). Etanercept, on the other hand, shows considerably less transplacental transport than the IgG immunoglobulins. The concentration of etanercept in cord blood after treatment in the second and third trimester was 4 to 7% of that in maternal blood (48, 49).

There is a concern that the use of biologics that actively cross the placenta during pregnancy could result in immunosuppression in a newborn and increase the risk of infection. One case of a fatal disseminated bacillus Calmette-Guérin (BCG) infection after regular vaccination in an infant delivered to a mother with Crohn's disease that was treated throughout pregnancy with infliximab was reported (50). Therefore, infliximab, adalimumab and ustekinumab, which are IgG antibodies, should be discontinued as soon as pregnancy is recognized or in the case of difficult-to-control disease at least before gestational week 30 or preferably between weeks 20 and 22. This would probably limit significant intrauterine and postnatal drug exposure of an infant and, likewise, the risk of infection (36, 51).

The administration of live vaccines in a newborn that was exposed to biologic medication during the late second and third trimester should be postponed until 6 to 7 months of age or until the biological agent is no longer detectable in the infant circulation (13, 31, 36). Routine vaccinations with non-live vaccines appear to be safe and responses appear to be appropriate (44, 46).

Breastfeeding during therapy with biologics is not generally recommended, although the levels of the drugs detectable in

breast milk are significantly lower than those in maternal circulation. Two to 3 days after the infusion of infliximab, the milk concentration was 1/200 of that in maternal serum (52). Six days after injection of adalimumab, the level of drug detected in milk was 1/100 of that in maternal serum (53). Etanercept was detected in milk in extremely small concentrations; namely, 1/800 of that in maternal serum (49). Absorption of a biologic drug from milk is probably minimal because of protein structure degradation in the infant's digestive system. Therefore biologic medications could be compatible during breastfeeding (13, 31, 54).

There are limited data on men exposed to biologic drugs at the time of conception. So far there are no specific reports on adverse pregnancy outcomes (37, 55).

Conclusion

Pregnant and lactating women with psoriasis should be managed with caution. Topical therapy including emollients and topical steroids as well as UVB phototherapy is regarded as a safe option for these patients. In the case of uncontrollable psoriasis and a need for more potent systemic treatment, methotrexate and acitretin must be strictly avoided. However, ciclosporin may be considered as an option for controlling the disease. Newer biologic agents are currently not recommended due to a lack of controlled studies in pregnant women. Information regarding their use during pregnancy and lactation is slowly accumulating, mostly from pregnant patients with inflammatory arthritis and inflammatory bowel disease. Biologics may be considered as a possible therapy for pregnant psoriasis patients. Data collected so far show that biologics currently marketed for psoriasis treatment are not connected with higher incidence of unfavorable pregnancy outcomes and congenital malformations. There are concerns about immunosuppression in infants exposed to biologics in the late second and third trimesters of pregnancy, especially to monoclonal IgG antibodies such as infliximab, adalimumab, and ustekinumab. These drugs actively cross the placenta similarly to natural antibodies, leading to higher infant drug levels at delivery compared to the levels in maternal circulation, and they should be discontinued at least in the second trimester to limit significant intrauterine and postnatal drug exposure of an infant and the risk of infection. The administration of live vaccines in a newborn exposed to biologic medication during the late second and third trimesters should be postponed at least until 6 to 7 months of age. Breastfeeding during therapy with biologics is currently not recommended; however, it could be considered reasonable in the future because only negligible amounts of drug pass into the milk. The decision to use biological therapy during pregnancy should take into account benefits and risks and should be made on a case-by-case basis after careful discussion with the patient.

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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 mišje 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:** 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 ne dajete sočasno. 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 preteklí 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:** 02/2012. **TISKANO V SLOVENIJI:** junij 2012. Za dodatne informacije pokličite 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. DERM-1044434-0000 EXP: 06/2014**

Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23:33-34
doi: xxxxxxxxxxxxxxxxxxxxx

Epidermolysis bullosa simplex with mottled pigmentation: the first Slovenian case

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Abstract

Epidermolysis bullosa simplex with mottled pigmentation is a rare subtype of epidermolysis bullosa simplex that is characterized by nonscarring blistering and reticulated hyperpigmentation. We report the first Slovenian case of a newborn with blisters, who later presented with hyperpigmented macules in the first year of life. A missense p.Pro25Leu mutation in the KRT5 gene was confirmed.

Received: 14 January 2014 | **Returned for modification:** 11 February 2014 | **Accepted:** 10 March 2014

Introduction

Epidermolysis bullosa simplex (EBS) is a group of genetic diseases in which blisters occur spontaneously or after minor trauma. The blister is localized in the basal layer of epidermal cells, although the recent classification of EBS also includes three disorders that result in a plane of separation within the suprabasal epidermis (suprabasal EBS). Because of the characteristic level of cleavage, EBS is sometimes termed epidermolytic EBS. Most of the cases are inherited in an autosomal dominant mode, but cases of recessive EBS also exist. Table 1 presents classification of major types of EBS. The prevalence of different forms of EBS has not been systematically studied and can therefore only be estimated. The prevalence of localized EBS is estimated at five to 20 per million, whereas the prevalence of the generalized form is about two per million (1). In 2003, an epidemiological study of EBS in Slovenia was performed, and a prevalence of 14 per million was recorded. According to clinical manifestation, the patients had localized EBS (previously called Weber–Cockayne) and generalized EBS or other (previously called Köbner) variants. Molecular defects were detected in Keratin 14 in five patients and in Keratin 5 in two patients (2). So far, no EBS with mottled pigmentation in Slovenia has been described.

EBS with mottled pigmentation is a rare subtype of EBS and is usually autosomal dominant inherited, but a few "de novo" mutations have been described. It is characterized by nonscarring blistering and reticulated hyperpigmentation. We present a case of a "de novo" mutation in the KRT5 gene.

Case report

A 16-day-old boy presented to our clinic with blisters and crusts on his fingers and toes and erosions on the gluteus and around the navel. Blistering and crusts on the fingers were already observed in the first days following birth (Fig. 1). He had previously been treated for staphylococcal infection with a systemic antibiotic, without success. New blisters were forming and were healing without sequelae. Thorough physical examination did not reveal any other abnormalities. The family history was negative for skin diseases, including blistering. A biopsy of the lesion was performed at the age of 6 weeks. Histopathologic and electromicroscopic examination revealed vacuolae in the basal layer of keratinocytes and suggested a diagnosis of EBS. At the age of 6 months the patient presented with asymptomatic hyperpigmented macules on the extremities and later on the entire body, excluding the face (Fig. 2). This suggested a rare type of EBS with mottled pigmentation. Gene sequencing was performed when the patient was 11 months old. No DNA variants were noted in the Keratin 14 gene, but a pathogenic heterozygote Keratin 5 mutation KRT5:c.74C>T variant (missense KRT5:p.Pro25Leu mutation) was identified, which means that the child is heterozygous for a C>T nucleotide substitution in exon 1, resulting in the replacement of a proline codon with a leucine codon at amino acid position in the KRT5 gene. The lesions were treated with topical antibiotic. The parents were instructed to prevent potential trauma and infections.

Table 1 | **Classification of major types of EBS (1).**

	Inheritance	Protein defect	Gene defect
EBS localized (Weber–Cockayne)	AD	Keratin 5, 14	KRT5, KRT14
EBS generalized, other (Köbner)	AD	Keratin 5, 14	KRT5, KRT14
EBS Dowling–Meara	AD	Keratin 5, 14	KRT5, KRT14
EBS with mottled pigmentation	AD	Keratin 5, 14	KRT5, KRT14
Autosomal recessive EBS (not associated with muscular dystrophy)	AR	Keratin 14	KRT14
EBS with muscular dystrophy	AR	Plectin	PLEC1
EBS Ogna	AD	Plectin	PLEC1
EBS superficialis	AD	Unknown	Unknown
Skin fragility-ectodermal dysplasia syndrome	AR	Plakophilin-1	PKP1
Lethal acantolytic EB	AR	Desmoplakin	DSP

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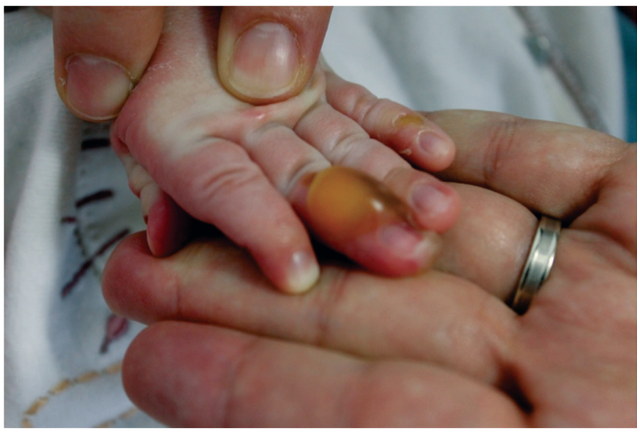

Figure 1 | Blisters on the hand (age: 3 weeks).

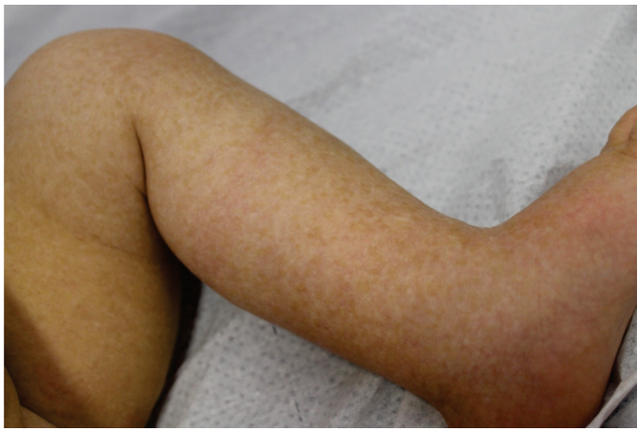

Figure 2 | Hyperpigmented macules on the lower extremities (age: 1 year).

Discussion

EBS is an inherited mechanobullous disorder characterized by skin fragility and blister formation following minor trauma of the skin (3). EBS with mottled pigmentation is a rare variant of EBS, first reported by Fischer and Gedd-Dahl in 1979, which presents with nonscarring blistering and slowly progressive reticulated hyperpigmentation (4). Multiple families and some sporadic cases have been reported all over the world. The blisters usually appear at birth and tend to decrease with age, only rarely appearing in adults. Hyperpigmentation usually begins later in infancy and childhood, making EBS with mottled pigmentation difficult to distinguish from other subtypes of EBS in the neonatal period. Adults can also develop punctate palmoplatar hyperkeratosis and nail dystrophy (5). The diagnosis is based on typical clinical findings, family history, gene mapping, and molecular analysis. Similar to other subtypes of EBS, mutations in EBS with mottled pigmentation are in the Keratin 5 and Keratin 14 genes and the intermediate filament (IF) proteins, expressed in basal keratinocytes in the epidermis and related complex epithelia (6). The mutation most commonly found in EBS with mottled pigmentation is the missense p.Pro25Leu mutation, which is also thought to be responsible for the aberrant pigmentation. There is growing evidence showing that keratin proteins functionally interact with melanin pigments, their malfunction resulting in aberrant melanosome uptake and consequently in hyperpigmented areas (7, 8).

Conclusion

The missense p.Pro25Leu mutation was confirmed in our patient. The case illustrates that a diagnosis of a phenotype of EBS cannot always be made as the first signs of the disease appear during the neonatal period, but prolonged follow-up and monitoring are required. Because there was no family history of blistering disease or hyperpigmentation now or in the past, we assume that the mutation appeared “de novo.” Gene mapping of the parents could be performed to confirm this hypothesis. Sporadic “de novo” mutations on genes for Keratin 5 and 14 have been described previously (9, 10). However, this is the first confirmed Slovenian case of EBS with mottled pigmentation.

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Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2014;23:35-37
doi: xxxxxxxxxxxxxxxxxxxxx

Valproate-related erythrodermia with reversible encephalopathy: a rare but serious adverse reaction, case report

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Abstract

Cutaneous adverse reactions to antiepileptic drugs (AEDs) are usually easily recognized in daily clinical practice when they manifest as a morbilliform or maculopapular rash within the first few weeks after introducing an AED. Valproate (VPA)-induced encephalopathy is a rare but serious complication, presenting with impaired consciousness, with or without hyperammonemia, normal liver enzymes, and normal serum level of VPA. A 2-year-old Caucasian boy with severe developmental disability and pharmacoresistant epilepsy presented with fever, generalized erythrodermia, and encephalopathy, which resolved after discontinuation of valproate. Sodium valproate (30 mg/kg/day) was introduced 5 months previously, as the third drug in combination with vigabatrin and levetiracetam, due to frequent daily seizures. The clinical condition of generalized erythrodermia and encephalopathy was recognized by the treating physician as a possible adverse reaction to VPA: with the Naranjo scale it was probably associated with VPA (six points) and possibly associated with vigabatrin and levetiracetam (three and two points, respectively). After valproate withdrawal, the patient recovered completely. This case is of interest because erythrodermia was a clue to the recognition of valproate-related adverse reaction with severe central nervous system involvement without hyperammonemia and with normal liver enzymes—a very rare occurrence.

Received: 31 January 2014 | **Returned for modification:** 6 February 2014 | **Accepted:** 10 March 2014

Introduction

Adverse reactions to antiepileptic drugs (AEDs) occur to a certain degree in almost 80% of patients and are a major concern for physicians (1, 2). Cutaneous adverse reactions to an AED are usually promptly recognized by the patient and clinicians because they typically manifest as a maculopapular rash within the first weeks after the introduction of a specific AED. Although skin rashes may occur with any AED, the risk is highest for phenytoin (10%), carbamazepine (8.7%), and lamotrigine (6.2%) (1, 3). Valproic acid, vigabatrine, levetiracetam, and benzodiazepines have lower risks (1). A recent retrospective study of 3,793 Chinese epilepsy patients showed skin side effects manifesting as any type of rash in 137 cases (3.6%) (4). The underlying mechanism of the drug-related maculopapular rash, which represents the most common allergic reaction to drugs and is observed in 2 to 3% of hospitalized patients (5), may be either immune-mediated hypersensitivity (6) or non-immune-mediated individual susceptibility as an idiosyncratic reaction (1, 3, 7).

Idiosyncratic reactions (IDR) are rare, accounting for only 6 to 10% of all adverse drug reactions in general, but they can be life-threatening (8). The most frequently occurring IDRs–Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)–are associated with the use of lamotrigine, carbamazepine, phenytoine, and phenobarbital (7, 9).

The term antiepileptic drug hypersensitivity syndrome (ADHS) or drug-related rash with eosinophilia and systemic reaction (DRESS) represents a rash that typically occurs during the first weeks of therapy with one of the following AEDs: phenytoin, lamotrigine, or carbamazepine. In addition to exanthema, there is also involvement of one or more internal organs, most frequently the liver, GI tract, kidneys, lungs, CNS, and hematopoietic system. In its most severe form, systemic ADHS or DRESS is associated with high fever, maculopapular exanthema, and multiple organ failure, mainly acute hepatopathy, and may be life-threatening (7).

Valproic acid (VPA), a broad-spectrum antiepileptic drug, has been used in therapy for epilepsy since 1967. VPA is a branched-chain fatty acid with anticonvulsive action due to the combined pharmacological effect of increased γ-amino-butyric acid (GABA) levels inhibiting N-methyl-d-aspartate (NMDA) receptors and a blockade of neuronal sodium channels. VPA also affects a variety of metabolic pathways. The side effects of VPA are many and well known; however, serious adverse reactions such as hepatotoxicity, encephalopathy, coagulation disorders, pancreatitis, and bone marrow suppression are rare (10).

The aim of this paper is to alert physicians and clinical pharmacists to a rare but serious encephalopathic manifestation of ADR, in which the cutaneous symptom was an important diagnostic clue.

Case report

A 2-year-old Caucasian boy had suffered severe B streptococcal meningoencephalitis at the age of 2 months, with resultant severe global developmental delay (DQ < 25), microcephaly, generalized hypotonia with tetraparesis, and pharmacoresistant epilepsy. Because of his frequent daily seizures, he was treated with many AEDs. Clinical improvement, with an important reduction in seizures, was achieved 5 months prior to admission, when sodium valproate (30 mg/kg/day) was added to the combination of vigabatrin (40 mg/kg/day) and levetiracetam (40 mg/kg/day). At a regular follow-up visit 2 months prior to admission, the normal therapeutic drug level of VPA was determined (597 μmol/L). His development started to improve; slowly, he became more alert and attentive in non-verbal communication, he achieved better head control and was able to sit with support, and he began to smile in response to his parents.

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Suddenly, on the 3rd day of an acute upper respiratory tract infection, he became somnolent, and then his condition deteriorated to lethargy and coma, with reaction only to painful stimuli. Laboratory tests ruled out sepsis (hemoculture was negative), CRP was 93 mg/L, and mild leukocytosis (15L), thrombocytopenia (49), and eosinophilia (7%), mildly elevated ALT (1.17 µkat/L) and normal AST (0.03 µkat/L), gamma-GT (0.50 µkat/L), and normal ammonia (42; 9 µmol/L) were found. Renal function and blood pressure were normal, and plasma therapeutic drug monitoring for sodium valproate was not performed. MRI showed gadolinium enhancement of meningeal coverings as in meningitis, and therefore he was treated with a third-generation cephalosporin and acyclovir, but his condition did not improve over the next few days. Lumbar puncture did not confirm any pathogenic organisms or inflammatory response within the CNS.

On the 2nd day after admission, his skin became diffusely red and edematous, including facial edema (Figure 1). All common infectious causes were excluded. Recalling a similar patient with high fever, diffuse erythrodermia, and irritability, but no lethargy, probably related to VPA (unpublished), the treating physician considered the possibility of an adverse reaction to an AED and decided to stop sodium valproate immediately. The child continued to receive vigabatrin and levetiracetam and he also received intravenous antihistamines. The second day after cessation of VPA the erythrodermia became less intense and the patient's level of consciousness started to improve, and after 5 days his mental state slowly returned to the previous baseline. According to the Naranjo ADR probability scale, the total score for sodium valproate in this case was six points and ADR was assigned as probable, in comparison to vigabatrin (three points) and levetiracetam (two points).

Figure 1 | Facial edema with erythrodermia.

Discussion

The clinical recognition of an adverse drug reaction (ADR) is very important because drug withdrawal may be the necessary therapeutic procedure or another drug should be administered (2, 3, 11). Maculopapular exanthema, as the most frequent ADR to antiepileptic drugs such as carbamazepine or lamotrigine, is well recognized among physicians, especially severe cutaneous reactions such as SJS or TEN (3, 4, 7). However, rashes are not common adverse reactions to VPA. Valproate-induced vasculitis as an ADR has been reported, with an incidence of less than 1/1000 (12). Although rare, a clinician should be aware of cutaneous eruptions as a possible adverse event related to VPA (13).

Erythrodermia, on the other hand, is a very rare symptom and not as well known as a possible drug-associated adverse reaction. A maculopapular or generalized erythematous rash associated with facial edema is usually a predictor of DRESS syndrome (14). In our patient, along with erythrodermia, diffuse edema was present, but due to CNS involvement and fever at admission, along with MRI findings, a diagnosis of meningoencephalitis was initially suspected and antibiotic treatment started. Only after 2 days, when no clinical improvement was observed, with negative results of CSF and other tests for infection, and because of progressive deterioration of the child's condition, was the possibility of systemic drug-induced hypersensitivity syndrome considered. Eosinophilia and thrombocytopenia, in addition to CNS involvement in our patient, were sufficient evidence for the diagnosis of DRESS syndrome, which includes fever, rash, hematological abnormalities, lymphadenopathy, and single or multiple internal organ involvement (7).

In addition, according to the Naranjo ADR probability scale (2) used as an assessment tool, the adverse event was probably related to sodium valproate (six points). After discontinuation of this drug, the patient's clinical condition returned to the previous level and all symptoms of the adverse event resolved.

The causal relationship between the clinical picture in our patient and the other two AEDs–vigabatrin and levetiracetam–was graded with three and two points on the Naranjo scale, indicating the only possible relationship (2). Both drugs have more favorable pharmacokinetics and do not bind significantly to plasma proteins or influence hepatic metabolism, and no clinically significant adverse effects of vigabatrin and levetiracetam in combination with sodium valproate have been reported (2, 3, 7, 10).

Encephalopathy with normal ammonia during VPA treatment was reported in 13 of 19 patients in a German study, but no patient had erythrodermia. The mechanism of a direct toxic effect of VPA on neurotransmitters was postulated for encephalopathy (15). All patients recovered after VPA withdrawal, as was the case in our patient. The same toxic mechanism might be responsible for erythrodermia.

Patients with brain damage and intellectual disability may be at a higher risk of VPA-induced encephalopathy without hyperammonemia or elevated valproate levels (16). Our patient had a pronounced developmental delay after severe meningoencephalitis early in life; therefore he was at higher risk of VPA-induced encephalopathy. The VPA levels were not monitored.

Three forms of encephalopathy have been described in children and adults treated with VPA: encephalopathy due to the direct toxic effect of VPA with high serum levels of VPA and normal ammonia, hyperammonemic encephalopathy, and encephalopathy with impaired liver function (15–17). However, none of these forms include erythrodermia. We presume that our patient clinically belongs to the early phases of DRESS syndrome. This report highlights the increased potential for adverse reactions when prescribing antiepileptics as polytherapy, and therefore cooperation

between clinical pharmacists and clinicians is important. This occurs in many hospitals in Slovenia (18, 19), but was absent in this case.

In the field of serious cutaneous ADRs such as Stevens–Johnson syndrome or DRESS syndrome, there was some hope of finding biochemical markers or genetic predictors, but at present it is impossible to assess the risk of these severe reactions in each patient.

The role of genetic factors involved in idiosyncratic drug reactions is so far limited to the presence of human leukocyte antigen HLA-B*1502 allele as a risk factor for skin hypersensitivity. For carbamazepine-induced SJS/TEN, a strong association has been found with the HLA-B*1502 allele in southeast Asian patients, but not in Caucasian and Japanese patients. Future research may help reveal additional genetic predictors of susceptibility to severe adverse reactions to antiepileptic drugs.

Conclusion

Drug-induced hypersensitivity reactions are of major medical concern because they are associated with high morbidity and high mortality. Antiepileptics are known to be quite well tolerated and safe, but physicians and clinical pharmacists should constantly be aware of the risk of adverse effects. From a clinical point of view, cutaneous manifestations may represent an important diagnostic clue to severe ADR and should always be kept in mind.

Acknowledgment

The authors are grateful to Dianne Jones for correcting their English.

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Terapevtske indikacije – Topikalno zdravljenje psoriaze na lasišču pri odraslih. Topikalno zdravljenje blage do zmerne psoriaze v plakih na koži po telesu (psoriaza vulgaris) pri odraslih.

Odmerjanje in način uporabe – Daivobet gel nanašamo na prizadete dele enkrat dnevno. Priporočljivo trajanje zdravljenja je 4 tedne za lasišče in 8 tednov za kožo po telesu. Če je po tem obdobju potrebno nadaljevati ali ponovno uvesti zdravljenje, se lahko zdravljenje nadaljuje po zdravniškem pregledu in pod rednim zdravniškim nadzorom. Pri uporabi zdravil, ki vsebujejo kalcipotriol, maksimalni dnevni odmerek ne sme presegati 15 g. Zdravil, ki vsebujejo kalcipotriol, ne smemo uporabljati na površini, večji od 30 % telesne površine. Pred uporabo pretresite stekleničko in nanesite Daivobet gel na prizadeto mesto. Daivobet gela se ne sme nanesti neposredno na obraz ali oči. Po uporabi si umijte roke. Za doseganje optimalnega učinka, prhanje ali kopanje oziroma umivanje lasišča takoj po nanosu Daivobet gela ni priporočljivo. Daivobet gel naj učinkuje na koži čez noč ali čez dan. Pediatrična populacija: varnost in učinkovitost Daivobet gela pri otrocih, mlajših od 18 let, nista bili dokazani, zato uporabe Daivobet gela pri omenjeni populaciji ne priporočamo.

Kontraindikacije – Preobčutljivost za zdravilni učinkovini ali katerokoli pomožno snov. Daivobet gel je kontraindiciran pri eritrodermični, eksfoliativni in pustulozni psoriazi. Ker Daivobet gel vsebuje kalcipotriol, je kontraindiciran pri bolnikih z znanimi motnjami presnove kalcija. Ker Daivobet gel vsebuje kortikosteroid, je prav tako kontraindiciran pri naslednjih obolenjih: virusne (npr. herpes ali varicella) lezije kože ter glivične in bakterijske okužbe, okužbe s paraziti, spremembe na koži zaradi tuberkuloze ali sifilisa, perioralni dermatitis, atrofija kože, strije, krhke vene v koži, ihtioza, akne vulgaris, akne rozacea, rozacea, razjede, rane, perianalni ali genitalni pruritus.

Posebna opozorila in previdnostni ukrepi – Bolnika je treba podučiti o pravilni uporabi zdravila, da se izogne nanosu ali naključnemu prenosu zdravila na obraz, usta in oči. Po vsaki uporabi si je potrebno umiti roke, da preprečimo nehoteni prenos zdravila na omenjene predele. Daivobet mazilo vsebuje močan steroid skupine III, zato se je potrebno izogibati sočasni uporabi drugih kortikosteroidov. Neželeni učinki, ki so jih ugotovili pri sistemskem zdravljenju s kortikosteroidi, kot npr. supresija delovanja skorje nadledvične žleze ali pa vpliv na nadzor sladkorne bolezni, se lahko zaradi sistemske absorpcije zdravila pojavijo tudi med topikalnim zdravljenjem s kortikosteroidi. Izogibati se moramo tudi uporabi kortikosteroidov pod okluzivnimi povoji, saj se s tem poveča njihova sistemska absorpcija. Izogibati se moramo uporabi zdravila na velikih predelih prizadete kože, na sluznicah ali v kožnih gubah, saj se s tem sistemska absorpcija kortikosteroidov poveča. Ker zdravilo vsebuje kalcipotriol, se ob prekoračitvi največjega dnevnega odmerka (15 g) lahko pojavi hiperkalciemija. Ko zdravljenje prekinemo, se koncentracija kalcija v serumu hitro normalizira. Pri zdravljenju psoriaze s topikalnimi kortikosteroidi obstaja nevarnost nastanka generalizirane pustulozne psoriaze, ob prekinitvi zdravljenja z njimi pa lahko pride do povratnega učinka (rebound effect). Zato priporočamo zdravniško kontrolo tudi v času po končanem zdravljenju. Pri dolgotrajni uporabi se poveča tveganje za pojav lokalnih in sistemskih neželenih učinkov zaradi kortikosteroida. V primeru pojava neželenih učinkov zaradi dolgotrajne uporabe kortikosteroidov je potrebno zdravljenje prekiniti. Izkušenj s kombinacijo Daivobet mazila in drugih topikalnih izdelkov za zdravljenje psoriaze na istem predelu, sočasno sistemsko uporabo drugih zdravil za zdravljenje psoriaze oziroma sočasno uporabo fototerapije ni na voljo.

Medsebojno delovanje z drugimi zdravili ter druge oblike interakcij – Študij medsebojnega delovanja niso izvedli

Nosečnost in dojenje – Nosečnost: Daivobet gel se med nosečnostjo lahko uporablja le, če potencialne koristi opravičujejo morebitno tveganje. Dojenje: Pri predpisovanju Daivobet gela doječim materam, je potrebna previdnost. Bolnico je potrebno poučiti, da v času dojenja ne uporablja Daivobet gela na prsih.

Neželeni učinki – Pri približno 8 % bolnikov, ki so uporabljali Daivobet gel, so se pojavili neželeni učinki, ki pa niso bili resni. Učinki, med katerimi so večinoma različne reakcije na koži, najpogosteje pruritus, so običajno blagi. Občasno se pojavijo: poslabšanje psoriaze, pekoč občutek v koži, bolečine in draženje kože, folikulitis, dermatitis, eritem, akne, suha koža,izpuščaj, pustulozni izpuščaj. Naslednji neželeni učinki so najverjetneje povezani s farmakološkimi skupinami kalcipotriola oziroma betametazona: Kalcipotriol – Neželeni učinki vključujejo: reakcije na mestu aplikacije zdravila, pruritus, draženje kože, pekoč in bodeč občutek v koži, suho kožo, eritem, izpuščaj, dermatitis, ekcem, poslabšanje psoriaze, fotosenzitivnost in preobčutljivostne reakcije, vključno z zelo redkimi primeri angiodema in obraznega edema. V zelo redkih primerih se po topikalni uporabi lahko pojavijo sistemski učinki, kot npr. hiperkalciemija ali hiperkalciurija. Betametazon (v obliki dipropionata) – Lokalne reakcije, ki se lahko pojavijo po topikalni uporabi, še posebej, če ta traja dalj časa, vključujejo atrofijo kože, teleangiektazije, strije, folikulitis, hipertrihozo, perioralni dermatitis, alergijski kontaktni dermatitis, depigmentacijo in koloidno milio. Pri zdravljenju psoriaze obstaja možnost nastanka generalizirane pustulozne psoriaze. Sistemski učinki so pri topikalni uporabi kortikosteroidov pri odraslih redki, so pa lahko hudi. Lahko se pojavijo zaviranje delovanja skorje nadledvične žleze, katarakta, infekcije, vpliv na nadzor sladkorne bolezni in povišanje intraokularnega tlaka, zlasti po dolgotrajni uporabi. Sistemski učinki se pogosteje pojavijo, če zdravilo uporabimo pod okluzijo (plastika, kožne gube), pri uporabi zdravila na velikih površinah kože ali po dolgotrajni uporabi.

Preveliko odmerjanje – Uporaba odmerkov, večjih od priporočenih, lahko povzroči zvišanje koncentracije kalcija v serumu, ki pa se hitro zniža, ko zdravljenje prekinemo. Dolgotrajna topikalna uporaba prevelikih odmerkov kortikosteroidov lahko zavre delovanje hipofize in nadledvične žleze, kar povzroči sekundarno adrenalno insuficienco, ki je običajno reverzibilna. V takšnih primerih je indicirano simptomatsko zdravljenje. V primeru kronične toksičnosti je zdravljenje s kortikosteroidi potrebno postopno prekiniti.

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2014;23:39-41
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Elastosis perforans serpiginosa: a case successfully treated with intralesional steroids and topical allium cepa-allantoin-pentaglycan gel

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Abstract

Elastosis perforans serpiginosa is a rare skin disease in which abnormal elastic fibers, other connective tissue elements, and cellular debris are expelled from the papillary dermis through the epidermis. Three clinical variants of EPS can be detected: idiopathic, reactive, and drug-induced. Clinically it consists of small horny or umbilicated papules arranged in a linear, arciform, circular, or serpiginous pattern. It usually occurs in young adults and shows a predilection for the head and neck. The lesions are generally asymptomatic or slightly itching. Several treatments have been reported with poor long-term success; these include intralesional and topical corticosteroids, tazarotene, imiquimod, and cryotherapy. We report a case of 40-year-old black woman affected by elastosis perforans serpiginosa that was referred to our department and treated with intralesional injections of triamcinolone acetonide and topical application of allium cepa-allantoin-pentaglycan gel.

Received: 4 March 2014 | **Returned for modification:** 29 April 2014 | **Accepted:** 19 May 2014

Introduction

Elastosis perforans serpiginosa (EPS) is a rare skin disease generally involving the nape of the neck, face, upper and lower extremities, and trunk, occurring without sex predilection.

Clinically it consists of small horny or umbilicated papules arranged in a linear, arciform, circular, or serpiginous pattern (1). Histologically, it is characterized by abnormal elastic fibers, other connective tissue elements, and cellular debris that are ejected from the papillary dermis through the epidermis.

No treatment of choice can be extrapolated from data in the literature, although several therapies have been proposed to manage patients with EPS.

We describe the case of a 40-year-old black woman affected by EPS that was referred to our department and treated with intralesional injections of triamcinolone acetonide 40 mg/ml and topical application of allium cepa-allantoin-pentaglycan gel.

Case report

A 40-year-old black woman came to our department with a 1-year history of inflammatory lesions on the nape of the neck. Physical examination revealed multiple follicular lesions, confluent into papules and erythematous-crusted plaques, slightly itching, with hypopigmented and atrophic areas, resembling acne keloidalis nuchae (Fig. 1).

A family history was impossible to draw up and the patient's personal history was negative for any significant disease or drug use.

Then we performed a skin biopsy, whose histological examination revealed a thick fibrous dermic band associated with an increase in fragmented elastic fibers and deposits of calcified material, which was ejected over the skin through the infundibular ostium (Figs. 2, 3). The abnormal presence of elastic fibers in the superficial dermis and the appearance of transepidermal elimination suggested a diagnosis of EPS. The presence of calcified material was probably due to a follicular inflammatory process or a traumatic event such as scratching.

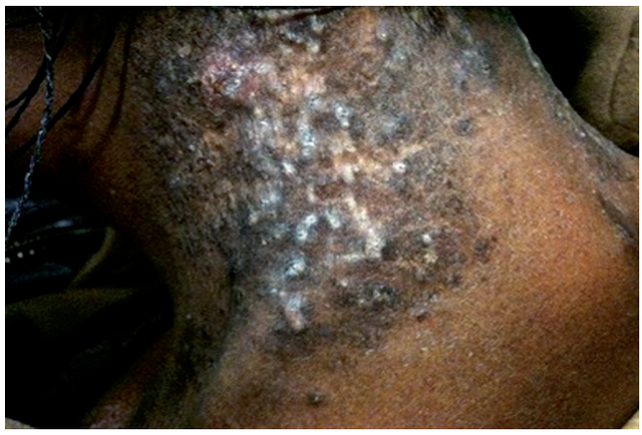

Figure 1 | Patient on presentation to our department with papular eruption on the neck.

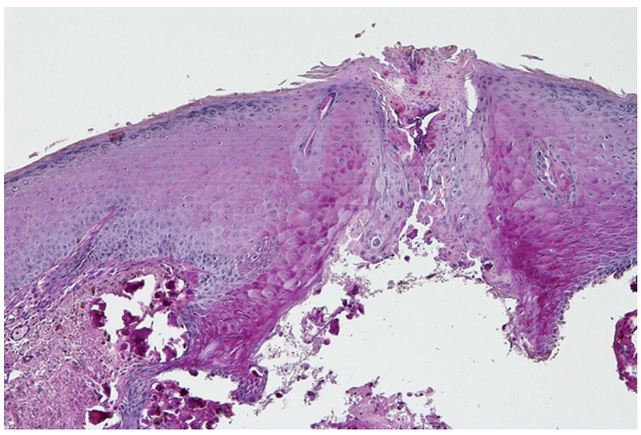

Figure 2 | Biopsy specimen demonstrating transepidermal elimination of altered elastic fibers.

The patient was treated unsuccessfully before the biopsy with oral isotretinoin (0.8 mg/kg/die) for 3 months and, after the histological finding, with high-potency topical corticosteroids (clobet-

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asol twice/day for 4 weeks), topical tazarotene (twice/day for 8 weeks), and cryotherapy (three applications for 10 seconds each, every week).

Because multiple therapies had failed, the patient was treated with intralesional injections of triamcinolone acetonide (40 mg/ml) every 15 days for 3 months and with topical application of allium cepa-allantoin-pentaglycan gel twice/day.

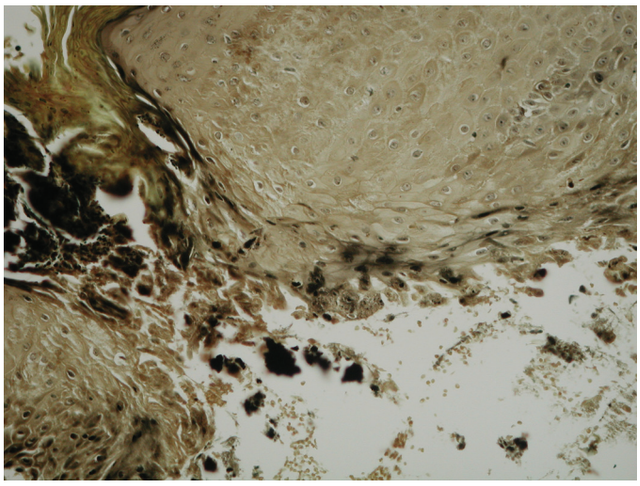

Figure 3 | Biopsy specimen with elastic fiber stain.

After 4 weeks of treatment, the disease was somewhat improved. After 8 weeks of therapy, physical examination revealed a moderate improvement of skin lesions and the patient reported a reduction in itching (Fig. 4).

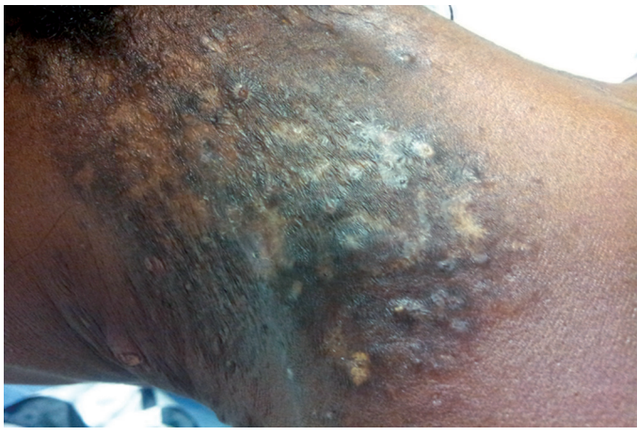

Figure 4 | After 2 months of therapy with intralesional injections of triamcinolone acetonide (40 mg/ml) every 15 days.

Discussion

Elastosis perforans serpiginosa is rare and affects both males and females without racial or geographical preferences; it usually occurs in young adults, even if it can also be observed in childhood or during old age.

In EPS, altered elastic fibers are recognized as non-self material and then extruded through the epidermis (2).

Three clinical variants of EPS can be detected: idiopathic, with a genetic base without any well-known cause; reactive, related to systemic diseases such as Marfan syndrome, Ehlers–Danlos syndrome, Down syndrome, pseudoxanthoma elasticum, and other fibrous tissue diseases (1, 3); and drug-induced, caused by D-penicillamine (4).

Although the pathophysiology of EPS is almost unknown, it has been suggested that a local trigger (biochemical or mechanical) in the dermis could result in the formation of epidermal and follicular channels through which the irritating agent is extruded (5). In most cases, the trigger remains unknown, except for the D-penicillamine–induced forms, because it is a copper chelator able to delay the enzymatic function and the correct deposition of elastic fibers (4).

The molecular mechanism as the basis of the transepidermal elimination of elastic fibers is poorly understood. Optical and electron microscopic analyses showed that the altered elastic fibers generally fill a tortuous channel through the epidermis, and flattened keratinocytes immediately surrounding the perforating channel desquamate directly into the central plug (6).

Fujimoto et al. postulated that the interaction between elastic materials and keratinocytes plays an important part in this extrusion mechanism. They hypothesized that abnormal elastic fibers accumulated in the dermis can be potent inducers of movement and terminal differentiation of keratinocytes via the 67 kDa protein, an elastin receptor. The expression of the 67kDa elastic binding protein has not been reported in normal epidermal keratinocytes, but it can be overexpressed in elastin-rich connective tissues (6).

Several treatments have been described with poor long-term success; they consist of calcipotriene ointment, topical tretinoin, oral isotretinoin (7), glycolic or salicylic acid, topical tazarotene (2), intralesional and topical corticosteroids (8), curettage (1), cryotherapy (9), narrow band ultraviolet B radiation, Er:YAG, CO_2, and dye lasers (10–12).

Differential diagnosis of EPS includes acne keloidalis nuchae, porokeratosis of Mibelli, actinic granuloma, dermatophyte infections, and cutaneous larva migrans.

In our case, we observed papules and nodules of the neck imitating acne keloidalis nuchae and so the patient was initially treated with oral isotretinoin (13-15). After treatment failure, a histological examination was performed to achieve the diagnosis.

Elastosis perforans serpiginosa still represents a clinical and therapeutic challenge, and our experience confirms that intralesional corticosteroids and topical application of allium cepa-allantoin-pentaglycan gel could be an effective therapeutic option (16).

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HUMIRA
ZAUPANJE

Edinstveni temelji za prihodnost

ŽE 10 LET V SLOVENIJI[1]

9 ODOBRENIH INDIKACIJ IN NAJBOLJ PREDPISANO BIOLOŠKO ZDRAVILO ZA SAMOINJICIRANJE[2]

VEČ KOT 750.000 BOLNIKOV PO VSEM SVETU SE ZDRAVI Z ZDRAVILOM HUMIRA*[3]

NA VOLJO V VEČ KOT 85 -TIH DRŽAVAH*[3]

VEČ KOT 23.000 BOLNIKOV V PODATKOVNI BAZI KLINIČNIH RAZISKAV[4]

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71 KLINIČNIH RAZISKAV V NAJVEČJI PUBLIKACIJI O VARNOSTI ZAVIRALCEV TUMOR NEKROTIZIRAJOČEGA FAKTORJA[4]

SIHUM140046 Priprava mateteriala april 2014.

HUMIRA adalimumab 10 LET

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA Humira 40 mg raztopina za injiciranje v napolnjeni injekcijski brizgi. Sestava: Ena 0,8 ml napolnjena injekcijska brizga z enim odmerkom vsebuje 40 mg adalimumaba. Adalimumab je rekombinantno humano monoklonsko protitelo. **Terapevtske indikacije:** Revmatoidni artritis: v kombinaciji z metotreksatom: zdravljenje zmernega do hudega aktivnega revmatoidnega artritisa pri odraslih bolnikih, kadar odziv na imunomodulirajoča zdravila, vključno z metotreksatom, ni zadosten; zdravljenje hudega, aktivnega in progresivnega revmatoidnega artritisa pri odraslih, ki prej še niso dobivali metotreksata. 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. 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:** 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. 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. Otroci in mladostniki s poliartikularnim JIA: stari od 2.leta starosti: 24 mg/m2 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; od 13.leta starosti: 40 mg adalimumaba vsak 2.teden ne glede na telesno površino. Uporaba zdravila Humira pri otrocih, 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. 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:** 19. 9. 2013

ENBREL- EDINI TOPNI DIMERNI TNF RECEPTOR[4-9]

Enbrel® etanercept

Izbira v revmatologiji in dermatologiji[1]

Več kot 20 let in skupaj 3 miljone bolnikovih let kliničnih izkušenj za vse indikacije[2,3]

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)]

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. Etanercept je pridobljen z rekombinantno DNA tehnologijo v ovarijskih celicah kitajskega hrčka. **Indikacije:** (1,2) Revmatoidni artritis (RA) - zmeren do hud aktiven RA pri odraslih (v kombinaciji z metotreksatom), kadar odziv na zdravljenje s protirevmatičnimi zdravili, ki vplivajo na imunsko odzivnost, 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) 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. Aktivni in progresivni PA pri odraslih, če je bil odziv na zdravljenje s protirevmatičnimi zdravili, ki vplivajo na imunsko odzivnost, nezadosten. (1,2) Ankilozirajoči spondilitis (AS) - hud aktiven AS pri odraslih, če je bil odziv na konvencionalno zdravljenje nezadosten. (1,2) 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 drugo zdravljenje kontraindicirano ali ga ne prenašajo. (1,2,3) Otroška psoriaza v plakih - težka kronična psoriaza v plakih pri otrocih in mladostnikih od 6. leta starosti naprej, pri katerih se z drugo sistemsko terapijo ali fototerapijo bolezni ne da zadostno obvladati ali je 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. *Psoriaza v plakih:* do 12 tednov je mogoče uporabljati tudi 50 mg dvakrat na teden, čemur sledi 25 mg dvakrat na teden ali 50 mg enkrat na teden, če je treba. Zdravljenje mora trajati 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:* Priporočen 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 psoriaza v plakih:* 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. *Ukinitev zdravljenja:* o ukinitvi je treba razmisliti, če ni odziva po 4 mesecih (JIA) ali 12 tednih (otroška psoriaza v plakih) 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 odstranjevanja 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 strogo nadzorovati. Zdravljenje je treba prekiniti, če pride do hude 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, posebno pri bolnikih, ki so težko bolni ali imunokompromitirani. Pri aktivni tuberkulozi zdravljenja ni dovoljeno uvesti, pri neaktivni ("latentni") tuberkulozi pa se mora 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, okuženim s HBV, je potrebna previdnost. Take bolnike je treba ves čas zdravljenja in še več tednov po njem 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) 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: Možnega tveganja za razvoj limfomov, levkemije ali drugih hematopoetičnih ali čvrstih rakavih obolenj ni možno izključiti. Previdnost je potrebna pri preudarku o uporabi antagonistov TNF pri bolnikih z anamnezo malignosti ali pri preudarku 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 panctopenije in zelo redkih primerih aplastične anemije, tudi s smrtnim izidom. Posebna 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 težak alkoholni hepatitis. Wegenerjeva granulomatoza: Enbrela ni priporočljivo uporabljati za zdravljenje te bolezni. Hipoglikemija pri bolnikih, ki se zdravijo zaradi sladkorne bolezni: Med zdravljenjem so poročali o hipoglikemiji, zato bo morda treba zmanjšati odmerek zdravila proti sladkorni 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 kroničnі vnetni črevesni bolezni in uveitisu. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno zdravljenje z anakinro ali z abatacieptom: 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 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, običajno pri dojenčkih 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. Resni neželeni učinki so bili: norice z znaki in simptomi aseptičnega meningitisa, ki se je pozdravil brez posledic, vnetje slepiča, gastroenteritis, depresija/osebnostne motnje, kožne razjede in ezofagitis/gastritis, streptokoki septični šok (streptokoki skupine A), diabetes mellitus tipa I in okužbe mehkih tkiv ter postoperativnih ran. V kliničnih preskušanjih pri bolnikih z JIA so poročali o 4 primerih sindroma aktivacije makrofagov. V obdobju trženja so pri bolnikih z JIA poročali o kroničnі 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:** 9. 1. 2014 **Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.**

Literatura: 1. Povzetek glavnih značilnosti zdravila Enbrel, 9.1.2014 **2.** Yamauchi P. et al. The treatment of psoariss and psoriatic arthritis with etanercept: pratical considerations on monotherapy, combination therapy, and safety. Dermatol Clin 22 (2004) 449-459. **3.** Data on file, Amgen, Inc. 2013. **4.** Povzetek glavnih značilnosti zdravila Remicade. 2013. Janssen Biologics B.V. **5.** Povzetek glavnih značilnosti zdravila Humira. 2013. Abbott Biotechnology Ltd. **6.** Povzetek glavnih značilnosti zdravila Orencia. 2013. Bristol-Myers Squibb Pharmaceuticals Ltd. **7.** Povzetek glavnih značilnosti zdravila Mabthera. 2013. Roche Products Ltd. **8.** Povzetek glavnih značilnosti zdravila Cimzia. July 2012. UCB Pharma SA. **9.** Povzetek glavnih značilnosti zdravila Simponi. September 2012. Janssen Biologics B.V.

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Advantan®
Metilprednizolon aceponat

BAYER

Brez kompromisov: MOČAN IN DOBRO PRENOSLJIV[1]

- Hitro učinkovanje[2]
- Kratkotrajno zdravljenje[2]
- Odlični terapevtski rezultati[2]
- Dobra prenosljivost[2]
- Od 4. meseca starosti dalje[3]

dermalna emulzija | krema | mazilo

POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila, ki ga dobite pri naših strokovnih sodelavcih ali na sedežu družbe.

Ime zdravila Advantan 1 mg/g krema, Advantan 1 mg/g mazilo. **Kakovostna in količinska sestava** 1 g kreme vsebuje 1 mg metilprednizolonaceponata (MPA). Pomožne snovi: cetil in stearilalkohol (2,5 g/100 g), butilhidroksitoluen E321 (0,006 g/100 g). 1 g mazila vsebuje 1 mg metilprednizolonaceponata (MPA). **Farmacevtska oblika** krema, bela krema, mazilo, belo do rahlo rumeno mazilo. **Terapevtske indikacije** Atopični dermatitis (endogeni ekcem, nevrodermitis), kontaktni ekcem, degenerativni, dishidrotični, vulgarni ekcem, ekcem pri otrocih. **Odmerjanje in način uporabe** Na splošno je potrebno zdravilo Advantan glede na prizadete predele nanesti v tanki plasti enkrat na dan in rahlo vtreti. Na splošno naj odrasli zdravila ne uporabljajo dlje kot 12 tednov, otroci pa ne dlje kot 4 tedne. **Kontraindikacije** Tuberkuloza ali sifilitični procesi na področju, ki ga je treba zdraviti; virusne bolezni (npr. norice, herpes zoster), rozacea, perioralni dermatitis, postvakcinacijske kožne reakcije v predelu potrebnem zdravljenja. Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. **Posebna opozorila in previdnostni ukrepi** Dodatno specifično zdravljenje je potrebno pri bakterijskih in/ali glivičnih okužbah. Če zdravilo Advantan krema po daljši uporabi kožo preveč izsuši, je treba preiti na eno od oblik, ki vsebujejo več maščob (Advantan mazilo). Pri nanašanju na kožo obraza je treba paziti, da zdravilo Advantan ne pride v oči. Doslej niso opazili, da bi zdravilo Advantan prizadelo adrenokortikalno funkcijo - ne pri odraslih ne pri otrocih, niti pri uporabi na velikih površinah (40 – 60 % telesne površine) niti pod okluzijo. Kljub temu pa je treba zdravilo Advantan pri zdravljenju velikih površin uporabljati čim krajši čas. Uporaba kortikoidov za lokalno uporabo na velikih površinah telesa ali pri dolgotrajni uporabi še posebej pod okluzijo, pomembno poveča tveganje za neželene učinke. Kot je znano pri sistemskih kortikoidih se lahko tudi pri lokalno uporabljenih kortikoidih (npr. pri velikih odmerkih ali pri dolgotrajni uporabi, pri uporabi pod okluzijo ali na koži okoli oči) razvije glaukom. Zdravilo Advantan 1 mg/g krema vsebuje cetil in stearilalkohol ter butilhidroksitoluen (E321), zato lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis) ali draženje oči in mukoznih membran. **Nosečnost in dojenje** Na splošno se je treba v prvem trimesečju nosečnosti izogibati lokalnim pripravkom, ki vsebujejo kortikoide. Pri terapevtskih indikacijah za zdravljenje z zdravilom Advantan je treba skrbno pretehtati koristi in tveganja med nosečnostjo in dojenjem. Še posebej se je treba izogibati zdravljenju velikih predelov ali dolgotrajni uporabi. Doječe matere naj zdravila ne aplicirajo na dojke. **Neželeni učinki** V posameznih primerih se pri zdravljenju z zdravilom Advantan lahko pojavijo neželeni učinki, kot so srbenje, pekoč občutek, eritem ali vezikulacija. Naslednji neželeni učinki se lahko pojavijo, če se pripravki za lokalno uporabo, ki vsebujejo kortikoide uporabljajo na velikih površinah telesa (okoli 10 % in več) ali pri dolgotrajni uporabi (več kot 4 tedne): lokalni simptomi kot atrofija kože, teleangiektazije, strije, aknam podobne spremembe kože in sistemski učinki kortikoidov zaradi absorpcije. Med kliničnimi preskušanji se navedeni neželeni učinki niso pojavljali pri uporabi zdravila Advantan do 12 tednov (odrasli) in 4 tednov (otroci). Kot pri drugih kortikoidih za lokalno uporabo se v redkih primerih pojavijo še naslednji neželeni učinki: folikulitis, hipertrihoza, perioralni dermatitis, razbarvanje kože, alergijske reakcije na koži na katerokoli sestavino zdravila. **Imetnik dovoljenja za promet** Intendis GmbH Berlin, Max-Dohrn-Strasse 10, 10589 Berlin, Nemčija **Datum zadnje revizije besedila** 14.4.2011.

Ime zdravila Advantan 1 mg/g dermalna emulzija. **Kakovostna in količinska sestava** 1 g dermalne emulzije vsebuje 1 mg metilprednizolonaceponata. Pomožne snovi: srednjeverižni nasičeni trigliceridi, kaprilo-kaprino-stearinski triglicerid, polioksietilen-(2)-stearilalkohol, polioksietilen-(21)-stearilalkohol, benzilalkohol, natrijev edetat, 85 odstotni glicerol, prečiščena voda. **Farmacevtska oblika** Dermalna emulzija, oljna in vodna emulzija, bela motna. **Terapevtske indikacije** Blag do zmeren akutni eksogeni ekcem (alergijski kontaktni dermatitis, iritantni kontaktni dermatitis, numularni (mikrobni) ekcem, dishidroza, navadni ekcem) in endogeni ekcem (atopijski dermatitis, nevrodermitis), hujše oblike seboroičnega dermatitisa. **Odmerjanje in način uporabe** Zdravilo Advantan 1 mg/g dermalna emulzija je potrebno na prizadete predele nanesti v tanki plasti enkrat na dan in rahlo vtreti. Pri odraslih zdravila naj ne bi uporabljali dlje kot 2 tedna. V primeru hujših oblik seboroičnega dermatitisa se prizadetih delov obraza ne sme zdraviti dlje kot en teden. Pri otrocih mora zdravljenje trajati čim krajši čas.Če se koža med uporabo zdravila Advantan 1 mg/g dermalna emulzija pretirano izsuši, je glede na bolnikov tip kože priporočljivo uporabiti dodatno nevtralno zdravljenje (emulzijo V/O ali enofazno maščobno mazilo). **Kontraindikacije** preobčutljivost za zdravilno učinkovino ali katerokoli od pomožnih snovi, tuberkulozne ali sifilitične spremembe, virusne okužbe (npr. herpes ali norice), rozacea, perioralni dermatitis, razjede, navadne akne, atrofične bolezni kože, povakcinacijske kožne reakcije na predelu, ki ga je potrebno zdraviti. Zdravila Advantan 1 mg/g dermalna emulzija se ne sme nanašati na oči in odprte rane. V prvem trimesečju nosečnosti se zdravilo Advantan 1 mg/g dermalna emulzija ne sme aplicirati na več kot 20 % kožne površine. Zaradi pomanjkanja izkušenj je uporaba kontraindicirana pri otrocih do 4. meseca starosti. Pri starejših otrocih, npr. dojenčkih po 4. mesecu in malih otrocih do 3 let, je treba skrbno oceniti razmerje med koristjo in tveganjem. Bakterijske in glivične kožne bolezni. **Posebna opozorila in previdnostni ukrepi** Glukokortikoidi naj se uporabljajo v čim manjšem odmerku, še posebej pri otrocih, in le toliko časa kot je nujno potrebno za dosego in vzdrževanje želenega terapevtskega učinka. V primeru bakterijskih kožnih bolezni in/ali glivičnih okužb je potrebno dodatno specifično zdravljenje. Lokalna uporaba glukokortikoidov lahko poslabša lokalne okužbe na koži. Med uporabo zdravila Advantan 1 mg/g dermalna emulzija je treba paziti, da ne pride v stik z očmi, odprtimi ranami in sluznicami. Zdravila Advantan 1 mg/g dermalna emulzija se ne sme uporabljati za zdravljenje velikih površin kože (več kot 40 % kožne površine). Zdravilo Advantan 1 mg/g dermalna emulzija se ne sme uporabljati na intertriginoznih predelih. Pri zdravljenju obsežnih predelov (40 – 60 % kožne površine) z zdravilom Advantan 1 mg/g dermalna emulzija doslej niso opazili motenj adrenokortikalnega delovanja niti pri odraslih niti pri otrocih in tudi ne pod nepropustnim povojem. Kljub temu se zdravilo Advantan 1 mg/g dermalna emulzija ne sme uporabljati pod nepropustnimi (okluzivnimi) povoji. Previdnost je potrebna pri uporabi plenic, ker lahko delujejo okluzivno. Uporaba kortikosteroidov za lokalno uporabo na velikih površinah telesa ali dolgotrajna uporaba , posebno pod nepropustnim povojem, pomembno poveča tveganje za pojav neželenih učinkov. Pri zdravljenju velikih površin kože, še zlasti med nosečnostjo in dojenjem, mora zdravljenje trajati čim krajši čas, ker ni mogoče povsem izključiti absorpcije in sistemskega učinka. Kot velja za vse glukokortikoide, lahko nestrokovna uporaba prikrije klinične simptome. Zdravilo lahko vsebuje stearilalkohol, ki lahko povzroči lokalne kožne reakcije (npr. kontaktni dermatitis). Nosečnost in dojenje: O uporabi zdravila Advantan 1 mg/g dermalna emulzija pri nosečnicah ni dovolj podatkov. Pred uporabo zdravila Advantan 1 mg/g dermalna emulzija med nosečnostjo ali dojenjem skrbno pretehtati koristi in tveganje. Na splošno se je treba v prvem trimesečju nosečnosti izogibati lokalnim pripravkom, ki vsebujejo kortikoide. Med nosečnostjo in dojenjem se je zlasti treba izogibati zdravljenju velikih površin kože, dolgotrajni uporabi in nepropustnim povojem. Doječe matere naj zdravila ne aplicirajo na dojke. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij** Zaradi absorpcije lahko zdravljenje na velikih površinah kože ali dolgotrajno zdravljenje povzroči podobne interakcije, kot se pojavijo pri sistemskem zdravljenju. Doslej ni znanih medsebojnih delovanj z drugimi zdravili. **Neželeni učinki** Občasno lahko zdravilo Advantan 1 mg/g dermalna emulzija povzroči blago draženje kože, npr. blag in prehoden pekoč občutek. Redkeje se pojavijo srbenje, eritem, suha koža, luščenje in folikulitis. Preobčutljivostne reakcije na sestavine. Čeprav tega v kliničnih preskušanjih doslej niso ugotavljali, lahko lokalna uporaba steroidov zlasti med dolgotrajno uporabo povzroči atrofijo kože, teleangiektazije, strije in/ali akne. Kot velja za vse glukokortikoide se lahko, čeprav redko, pojavijo folikulitis, hipertrihoza, perioralni dermatitis, alergijski kontaktni dermatitis, depigmentacije (razbarvanje kože) in sistemsko delovanje. **Imetnik dovoljenja za promet** Intendis GmbH Berlin, Max-Dohrn-Strasse 10, 10589 Berlin, Nemčija **Datum zadnje revizije besedila** 13.3.2009

Reference: 1 Zaumseil R-P, Fuhrmann H, Kecskés A, et al. Methylprednisolone aceponate (Advantan®) – an effective topical corticoid therapy with few side effects; Jahrbuch der Dermatologie 1992; 93: 247–263. **2** Bieber T, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03 % in children and adolescents with an acute flare of severe atopic dermatitis. Allergy 2007; 62: 184–9. **3** Povzetek glavnih značilnosti zdravila Advantan dermalna emulzija.

Samo za strokovno javnost.

L.SI.11.2012.0201