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LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

EFFACLAR DUO [+]

Učinkuje **na oba tipa lezij in povnetne madeže**
Brez vpliva na toleranco

BREZ PARABENA - BREZ OLJA - NEKOMEDOGENO

Indikacije: blage do zmerne akne

- kot monoterapija
- kot dodatek zdravilnim terapijam
- po terapiji, za ohranitev rezultatov

1 nanos zjutraj in/ali zvečer

Tekstura gel-kreme:

Mat učinek
Vlaži
Odlična podlaga za ličila

ČIŠČENJE KOŽE

EFFACLAR
PENEČI GEL

Brez mila
pH 5,5
Brez barvil
Brez parabena

Na voljo v 200 in 400 ml

La Roche-Posay. Predan dermatologiji.

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Multiple widespread epidermal cysts of the skin: an unusual presentation

Mehmet Eren Yuksel[1], Funda Tamer[2] ✉

Received: 18 February 2016 | **Returned for modification:** 17 April 2016 | **Accepted:** 27 April 2016

To the Editor:

A 31-year-old male patient presented with multiple subcutaneous masses for further clinical evaluation. He stated that the lesions first appeared on both legs and that they had gradually increased in size and number over the previous six years. A physical examination revealed multiple skin-colored subcutaneous nodules on the left zygomatic area, back, chest, dorsum of the right arm, forearm, right little finger, right thigh, and both legs (Figs. 1–2). His past medical history was unremarkable. There was no history of trauma, surgery, or drug injection. None of his family members had similar lesions. However, the patient admitted that his father had died of hepatocellular carcinoma at age 42. His complete blood count was within normal limits. The chemistry panel was within normal limits except for high levels of alanine transaminase and gamma-glutamyl transferase (65 µ/l and 72 µ/l; the reference ranges were 5 to 55 µ/l and 9 to 64 µ/l, respectively). Six of the more prominent lesions were surgically removed because of cosmetic concerns. The patient did well postoperatively. The histopathological examination revealed multiple epidermal cysts with a minimum size of 1.5 × 1 × 0.7 cm and a maximum size of 6 × 3.5 × 2.5 cm.

Epidermal cysts are common, benign, spherical cutaneous lesions that usually present in hair-bearing areas such as the scalp, face, neck, and trunk. It has been suggested that epidermal cysts occur due to invagination of epidermis into the dermis as a result of trauma. They are usually small and asymptomatic. However, cysts greater than 5 cm are classified as giant epidermal cysts. Giant epidermal cysts are rare and they may lead to cosmetic concerns or pain due to pressure on surrounding structures. These cysts are more likely to rupture and become infected. Furthermore, malignant transformation of giant epidermal cysts has been reported (1). Subcutaneous tumors such as lipomas, neurofibromas, and hemangiomas should be included in the differential diagnosis. Ultrasonography, computed tomography, and magnetic resonance imaging may be helpful; however, histopathological examination is mandatory to reach a definitive diagnosis (2).

Multiple epidermal cysts may be associated with Gardner syndrome, which is an autosomal dominant disease characterized by cutaneous lesions, osteomas, and intestinal polyposis. Moreover, Won et al. reported a 6-year-old male patient with Lowe syndrome and multiple epidermal cysts on the scalp. Nevertheless, these lesions were thought to be coincidental (3).

Epidermal cysts can also occur due to administration of cyclosporine and tacrolimus. Ahn et al. reported multiple epidermal cysts varying from 0.5 cm to 3 cm in diameter on the neck and back of a 44-year-old renal transplant recipient receiving tacrolimus (4).

Small epidermal cysts may be removed by a minimal incision method. However, traditional elliptical excision is the appropriate technique for treatment of large cysts greater than 2 cm in diameter. In addition, Park et al. reported a small incision method using negative pressure suction to excise large epidermal cysts. Incomplete excisions or fragmentation of the lining may lead to infection and recurrence (5). Draining epidermal cysts using an erbium:yttrium aluminum garnet laser has also been reported as an effective treatment option with good cosmetic results (6). We recently explained the surgical removal of epidermal inclusion cysts with the squeeze technique in detail, which minimizes the risk of wound infection, recurrence, and scar formation (7).

Epidermal cysts may be multiple, but they are usually localized. The patient we presented above had multiple, widespread epidermal cysts on his face, trunk, right little finger, arms, and legs.

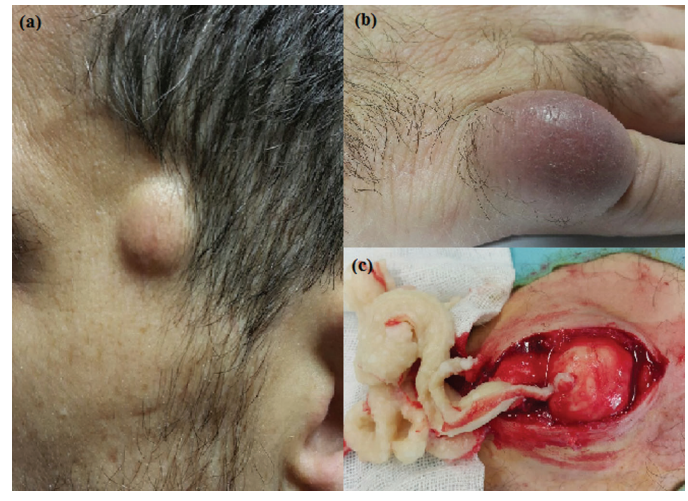

Figure 1 | **(a, b)** Epidermal cysts on the left zygomatic area and right little finger, **(c)** Keratinous content protruding through the capsule of the cyst.

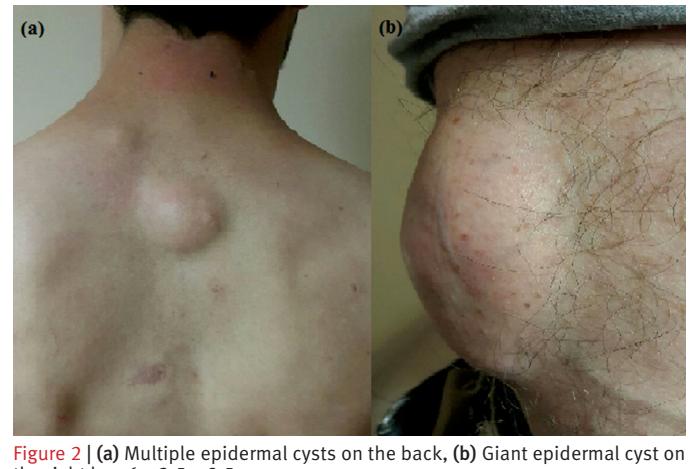

Figure 2 | **(a)** Multiple epidermal cysts on the back, **(b)** Giant epidermal cyst on the right leg, 6 × 3.5 × 2.5 cm.

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To the best of our knowledge, this is the first report of multiple widespread epidermal cysts of the skin ranging from 1.5 to 6 cm. Therefore, we wished to share this unusual presentation with our colleagues.

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Giant subcutaneous Angiofibrolipoma: successful surgical approach in a Bulgarian patient

Georgi Tchernev[1] ✉, Anastasiya Atanasova Chokoeva[2], James W. Patterson[3]

Received: 5 April 2016 | **Returned for modification:** 6 May 2016 | **Accepted:** 10 May 2016

To the Editor:

We report on a 37-year-old male patient that presented to our dermatological polyclinic with complains of moderate pain and discomfort provoked by a tumor-like formation on the left shoulder blade region. The lesion had begun 3½ years prior to his clinic visit. Clinical examination revealed a large subcutaneous tumor with a soft consistency and sharply demarcated borders located on the patient's back and covering almost the entire left scapula. The mass appeared to be encapsulated and moderately mobile, and it lacked clinical evidence of infiltration of the surrounding tissues. There was a moderate degree of pain on palpation. Clinically, it resembled a large lipoma (Fig. 1a). Laboratory blood tests and diagnostic imaging procedures, including abdominal/cutaneous ultrasonography and chest X-ray, failed to reveal any other significant abnormalities. After testing to ensure a negative allergic reaction to local anesthetic agents, we performed a total surgical excision of the formation and closed the wound with multiple single stiches (Figs. 1b, c).

Histopathologic findings included a fibrous capsule, numerous

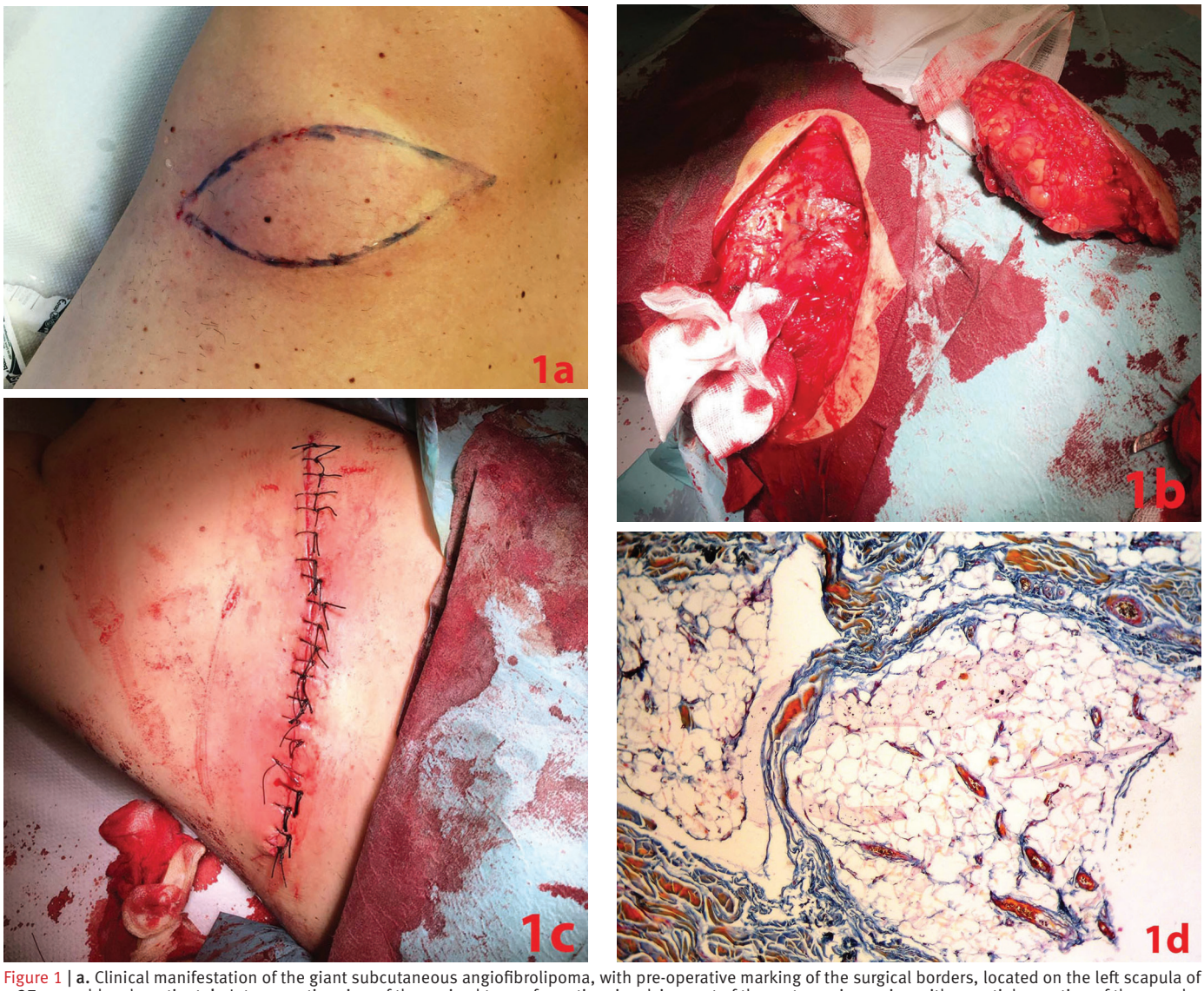

Figure 1 | **a.** Clinical manifestation of the giant subcutaneous angiofibrolipoma, with pre-operative marking of the surgical borders, located on the left scapula of a 37-year-old male patient. **b.** Intraoperative view of the excised tumor formation, involving part of the m. trapezius major, with a partial resection of the muscle. **c.** Postoperative clinical manifestation immediately after the procedure. The surgical defect was sutured layer by layer with application of subcutaneous absorbable sutures to achieve optimal low voltage on the following dermal stitches. **d.** Histopathological findings established the presence of mature adipocytes, blood vessels, and dense collagenous tissue.

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thin-walled vessels engorged with erythrocytes, nests of lipocytes (Fig. 1d), and prominent strands of fibrous connective tissue. The histopathological findings verified the diagnosis of subcutaneous angiofibrolipoma.

Angiofibrolipoma has been described as one of the rarest histopathological variants of lipoma, with occurrence most often in thehead and neck region (1, 2). Clinically, it is similar to conventional lipoma because it usually presents as a solitary, subcutaneous, well-circumscribed lesion (3). Lipomas are typically composed of mature adipocytes and arise from subcutaneous tissues of the trunk, neck, and proximal extremities. However, there are also numerous histopathologic variants, including spindle cell, atypical or pleomorphic, sclerotic, glandular, fibrohistiocytic, and chondroid lipomas (4), myxolipomas (5), fibrolipomas, angiolipomas, angiomyolipomas, and infiltrating angiolipomas; these are categorized according to their content of fat, muscle, blood vessel, connective tissue, or other structures (3). In contrast to an angiomyolipoma, which is composed of blood vessels, smooth muscle cells, and adipocytes, an angiofibrolipoma shows a different combination of elements; namely, a combination of mature adipocytes and blood vessels with dense collagenous tissue (as in our case) (3). Angiofibrolipomas have most often been reported in non-cutaneous locations, including the intranasal cavity (1), larynx (2), spermatic cord (3), greater omentum (6), pericardium (7), tonsils (8), and kidney (9). Only two reports appear to describe this lesion in subcutaneous tissues: one in the calf (10) and another in the foot (11). To the best of our knowledge, this is the first reported case of a giant subcutaneous angiofibrolipoma located on the back of an adult patient.

Total surgical excision and a 5-year postoperative follow-up are recommended in order to assess the possibility of recurrence or malignancy (2).

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Predictive value of a negative oral provocation test in patients with hypersensitivity to analgesics

Maja Jakič[1*], Miha Jager[1*], Mitja Košnik[1,2] ✉

Abstract

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) take first or second place as the cause of drug-induced hypersensitivity reactions. The oral provocation test (OPT) is a gold standard for the diagnosis of NSAID hypersensitivity. We investigated which analgesics patients took after a negative OPT and determined the proportion of patients that experienced a hypersensitivity reaction despite a negative OPT.

Methods: We selected 115 patients (67.8% female, age 54.9 ± 16.7 years) with a negative aspirin OPT and a convincing history of immediate hypersensitivity to aspirin or NSAIDs. In a telephone survey, we identified the analgesics taken after the OPT and possible adverse events.

Results: The mean follow-up time was 5.1 ± 2.0 years. All subjects needed at least one analgesic drug. Despite the negative outcome of the aspirin OPT, only 33.9% of subjects took aspirin and 0.9% had a hypersensitivity reaction. The negative predictive value (NPV) of the aspirin OPT was 97.4%. Overall, 16 (13.9%) subjects experienced a hypersensitivity reaction, 12 of which occurred after taking a drug not tested with the OPT. The NPV of the OPT for all NSAIDs was 96.4%.

Conclusion: Our results support the available data that most subjects do not re-take the tested drug regardless of the high NPV of the OPT.

Keywords: aspirin, hypersensitivity, negative predictive value, NSAIDs, oral provocation test

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Introduction

Hypersensitivity to analgesics affects approximately 3% of the general population (1–6). The vast majority of hypersensitivity reactions are non-immunologic (non-allergic) due to cyclooxygenase 1 (COX-1) inhibition by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) (7, 8). Symptoms develop because of leukotriene overproduction. In addition, decreased levels of PG E2 and PG D2 enhance histamine release from mast cells (9, 10). This mechanism is involved in NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated chronic urticaria (NECD), and NSAID-induced urticaria-angioedema (NIUA) (8, 11, 12). Symptoms occur within 1 to 4 hours after NSAID intake. There is marked cross-reactivity among COX-1 inhibitors (7). These patients most often tolerate weak COX-1 inhibitors and COX-2 inhibitors (3, 11, 13, 14).

In some patients, urticaria or even anaphylaxis occurs in the 1st hour after ingestion of only a single NSAID or a few NSAIDs belonging to the same chemical group (single NSAID-induced urticaria, angioedema, or anaphylaxis, SNIUAA). This type of reaction is suggestive of an immune-mediated type I reaction, although IgE and skin tests are rarely positive (15, 16). Nine cases of diclofenac-induced anaphylaxis were reported to the Allergy Vigilance Network in France (17).

Cell-mediated hypersensitivity reactions occur within days of taking a single NSAID (4).

Drug provocation is a gold standard in the diagnosis of NSAID hypersensitivity (3, 11). If the challenge with aspirin is positive, the patient is diagnosed as intolerant to COX-1 inhibitors. If the challenge is negative, the patient might have a selective NSAID allergy or be NSAID-tolerant. Provocation with the culprit drug is warranted in cases with an unclear history (4).

However, a negative oral provocation test (OPT) result does not completely exclude hypersensitivity to NSAIDs (11). False negative results might occur due to the absence of co-factors in the OPT, such as viral infection, co-medication, and physical exercise (3, 18). In addition, there is a concern that slowly increasing doses during the OPT might induce transient desensitization and thus result in a false negative test (19, 20).

We analyzed a group of patients that were OPT-negative for aspirin. We investigated the analgesics the patients took after the negative OPT and determined the proportion of patients that experienced a hypersensitivity reaction.

Methods

This study was approved by the national ethics committee (study no. 72/02/15). We identified patients from an OPT database that were tested for hypersensitivity to aspirin, other NSAIDs, or paracetamol between 2004 and 2014. An OPT was started with one-hundredth of the therapeutic dose. Then, one-tenth, half, and a full dose were administered at intervals of 60 to 90 minutes. The test was considered positive if the peak expiratory flow decreased by at least 20% or if urticaria, angioedema, nasal stuffiness, or anaphylaxis developed.

We reviewed the medical files of patients that were subjected to an OPT for aspirin between 2007 and 2011 and in 2013. We gathered information concerning the reaction that was the reason for the diagnostic workup (index reaction), including the clinical presentation, the NSAID causing the hypersensitivity, and the possible diagnosis of asthma, nasal polyposis, and/or chronic urticaria. We obtained data for the OPT results and the NSAIDs that were identified to be safe for use after the OPT. We selected patients with a convincing personal history of immediate hyper-

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sensitivity to aspirin or NSAIDs and a negative OPT to aspirin. The criteria for a convincing history were a reaction occurring up to 4 hours after taking the drug and patients presenting with urticaria, angioedema, nasal stuffiness, dyspnea, or anaphylaxis that could not be explained by an alternative cause. We investigated whether the discharge letter clearly advised which drugs the patient should take and whether aspirin was listed among the drugs advised.

In a telephone survey, we evaluated patients' analgesic needs after the testing. We specifically asked whether they had taken aspirin and NSAIDs that had been negative on the OPT. Patients that did not take drugs that were negative on the OPT were asked the reason for not taking that drug.

Statistical methods

The data were statistically analyzed using the statistics software SPSS (Statistical Package for the Social Sciences version 22, International Business Machines Corp., Armonk, NY). The data are shown as the average and standard deviation. To compare the differences between groups, we used a *t*-test and chi-square test. The negative predictive value (NPV) of the OPT for NSAIDs and aspirin was calculated based on all patients that retook the same drug after a negative OPT.

Results

The study group

In a 6-year period, 664 subjects (68.7% female; age 52.3 ± 16.2 years, range 19 to 92) were subjected to OPTs with analgesics. We excluded 205 subjects (30.9%) that were not tested with aspirin and 45 (6.8%) subjects with a positive outcome of the OPT. A total of 254 subjects (38.3%) had a vague clinical history. Out of the remaining 160 subjects, we were unable to contact 36 patients and nine did not want to participate (response rate was 71.9%).

A total of 115 subjects (67.8% female, 54.9 ± 16.7 years) participated in the survey. The sex and age distribution of the patients participating in the survey were the same as the distribution in the initial unselected group, confirming that the selection of patients for the survey was not biased. Six (5.3%) subjects had asthma, one (0.9%) had asthma and nasal polyps, one (0.9%) had asthma and chronic urticaria, and nine (7.4%) had chronic urticaria.

Index hypersensitivity reactions

The characteristics of the index hypersensitivity reactions are presented in Table 1. The most common presentation was urticaria and angioedema (72.0%). Among the patients, 51.6% reacted to multiple COX-1 inhibitors and 13.9% convincingly reacted to a single drug (aspirin, pyrazolones, or diclofenac).

Drugs taken after the OPT

The mean follow-up time after a negative aspirin OPT was 5.1 ± 2.0 years. Paracetamol was an efficient analgesic for 20.0% of subjects, and the others needed stronger analgesic therapy. Table 2 shows the details of the drugs that the subjects took after the negative OPT and whether they experienced any reaction to those drugs. Sixteen patients reported hypersensitivity reactions; however, 12 of these occurred after taking a drug that was not tested in the OPT. The most common hypersensitivity reactions were urticaria and angioedema (12 subjects, 75%). The hypersensitivity reaction most commonly occurred after paracetamol or pyrazolones. Hypersensitivity reactions occurred in four subjects despite a negative OPT with a particular analgesic (two paracetamol, one

Table 1 | Distribution of hypersensitivity types according to non-steroidal anti-inflammatory drugs in the index reaction.

Drug	Hypersensitive reaction					SUM	No. of patients tested with that drug as culprit drug
	Asthma exacerbation	Rhinitis	Urticaria, angioedema	Anaphylactic reaction	Other*		
Aspirin	0 (0.0%)	2 (1.7%)	55 (47.8%)	2 (1.7%)	17 (14.8%)	76 (66.1%)	76 (100%)
Paracetamol	0 (0.0%)	1 (0.9%)	19 (16.5%)	2 (1.7%)	5 (4.3%)	27 (23.5%)	22 (81.5%)
Naproxen	0 (0.0%)	0 (0.0%)	13 (11.3%)	0 (0.0%)	1 (0.9%)	14 (12.2%)	6 (42.9%)
Diclofenac	0 (0.0%)	1 (0.9%)	27 (23.5%)	7 (6.1%)	6 (5.2%)	41 (35.7%)	8 (19.5%)
Ketoprofen	0 (0.0%)	1 (0.9%)	5 (4.3%)	0 (0.0%)	1 (0.9%)	7 (6.1%)	2 (28.6%)
Pyrazolone	0 (0.0%)	0 (0.0%)	11 (9.6%)	2 (1.7%)	3 (2.6%)	16 (13.9%)	0 (0.0%)
Ibuprofen	0 (0.0%)	0 (0.0%)	4 (3.5%)	0 (0.0%)	0 (0.0%)	4 (3.5%)	3 (75.0%)
SUM**	0	5	134	13	34	115 (100%)	117 (62.9%)

*erythema, maculopapular rashes, itching without a rash, and history of weakness or faintness
**Hypersensitivity reactions occurred after more than one drug in some individuals

Table 2 | Distribution of non-steroidal anti-inflammatory drug consumption after the oral provocation test and outcome. The data were obtained by a telephone survey.

Substance	Reaction to drug			No. of subjects that took drug
	No reaction	Predictable adverse effect*	Hypersensitivity reaction	
Paracetamol	79 (68.7%)	0 (0.0%)	4 (3.5%)**	83 (72.2%)
Central analgesics	11 (9.6%)	0 (0.0%)	2 (1.7%)	13 (11.3%)
Meloxicam	2 (1.7%)	0 (0.0%)	0 (0.0%)	2 (1.7%)
Aspirin, 100 mg only	13 (11.3%)	1 (0.9%)	1 (0.9%)	15 (13.0%)
Aspirin, 500 mg	23 (20.0%)	1 (0.9%)	0 (0.0%)	24 (20.9%)
Diclofenac	17 (14.8%)	4 (3.5%)	3 (2.6%)	24 (20.9%)
Pyrazolone	4 (3.5%)	0 (0.0%)	4 (3.5%)	8 (7.0%)
Other NSAIDs***	40 (34.8%)	1 (0.9%)	2 (1.7%)	43 (41.0%)
SUM****		8 (7.0%)	16 (13.9%)	115 (100%)

*The predictable adverse effects were nausea, vomiting, shivering, and nosebleed.
**None of the subjects had chronic urticaria.
***Thirty-three (28.7%) subjects took naproxen, eight (7.0%) subjects took ibuprofen, and two (1.7%) subjects took ketoprofen. The predictable adverse effects were reported by a subject taking naproxen, and two subjects reported hypersensitivity reactions after taking naproxen and ibuprofen, respectively.
****Some subjects took more than one type of drug.

aspirin 100 mg, one diclofenac). The NPV of the OPT for all analgesics was 96.4%. The NPV of the OPT for aspirin was 97.4%.

During the review of the hospital discharge letters, we found that 60 (52.2%) subjects did not receive specific information concerning which analgesics were safe for them to use. Only 27.8% were told that aspirin was a safe drug for them to use.

Out of 115 subjects with a negative OPT for aspirin, 76 (66.1%) did not retake aspirin over the next few years. The most common reasons were as follows: 30 (39.5%) subjects did not need this particular drug, 28 (36.8%) subjects feared a drug hypersensitivity reaction, and four (5.3%) subjects were discouraged by their personal physician from re-administration due to an unclear instruction in the discharge letter. We did not obtain this information for 14 (18.4%) subjects.

Discussion

A good concordance (86%) was reported between the OPT with NSAIDs and the patients' history, at least for NERD (21). We were surprised to find a low number of positive OPTs in our cohort, particularly because we analyzed 115 selected subjects with a convincing medical history of hypersensitivity. It is possible that clinical history is good predictor of a positive OPT in patients with NERD and not in patients with NIUA or anaphylaxis, as were the vast majority of our patients. Indeed, several studies showed that the majority of patients with a convincing history of NSAID hypersensitivity were actually NSAID-tolerant. In a study by Zisa et al. of 159 patients with a clinical history of urticaria/angioedema apparently related to NSAIDs, only 10.7% were positive on the OPT with the suspected drugs (22). Half of these were single-NSAID reactors. Indeed, 37.1% of our patients were not challenged with the culprit drug but only with aspirin, which excluded intolerance to COX-1 inhibitors but not selective hypersensitivity to a single NSAID. As shown in a study performed by Chaudhry et al., 43% of homologous NSAID challenges but only 25% of heterologous NSAID challenges were positive in patients with a history of NSAID hypersensitivity (64% had cutaneous reactions and 36% had anaphylaxis) (23). Patients with anaphylaxis and those that reacted to diclofenac were most likely to have a positive challenge.

There are only a few reports in the literature on the NPV of OPTs with aspirin and NSAIDs. A French study published by Defrance et al. found that 53.3% of 260 patients followed up for a median time of 2.75 years re-took the tested drug; a hypersensitivity reaction was reported in 3.1%, resulting in an NPV of the OPT of 98.6% (18). Our study covered an extended period of time (5.1 years) and found a similar NPT (96.4%). We could speculate that many urticarial reactions following analgesic ingestion were not due to analgesic hypersensitivity but were provoked by the same underlying cause that was the reason for taking the analgesic drug (i.e., viral infection). This speculation is supported by the fact that half of the reactions in our study occurred after paracetamol ingestion, which is commonly taken to treat symptoms of viral infections and is generally well tolerated in patients with COX-1 inhibitor hypersensitivity. A similar NPV was reported by Waton et al. (24). In this study, 65 patients with cutaneous symptoms during NSAID therapy were negative in the NSAID OPT. Eighteen (28%) took the NSAID again and two reported hypersensitivity reactions, leading to a high NPV for the OPT.

In patients with a history of only cutaneous reactions and a negative OPT with NSAIDs, Bommarito et al. found that 47.7% did not re-take the tested NSAID (3). The main reason was fear of hypersensitivity reaction (70.8%). In our study, the percentage of subjects that did not take the tested drug was even higher; one important reason for this was that the GPs discouraged the use of the NSAID due to the unclear discharge letter.

The mean provocative dose of oral aspirin that triggered respiratory reactions in people with asthma is 85.8 mg (25). The threshold is even higher in patients with NSAID-induced urticaria/angioedema. The majority reacted only with a full therapeutic dose (22). One of the obstacles in the NSAID challenge test is desensitization, which might influence the OPT in such a way that the outcome can be a false negative (19, 20). Namely the protocol used for aspirin desensitization also uses a gradual increase in the dosage (doses are approximately doubled) at 90-minute intervals until a 500 mg dose is reached.

Some subjects in our study re-took the culprit drug although it was not specifically tested with the OPT. This is particularly dangerous for diclofenac and pyrazolones, which are typical representatives of drugs that induce SNIUAA and should therefore be discouraged from re-administration unless a negative OPT with the culprit drug is reported (17, 26–29). In patients with hypersensitivity reactions to only one NSAID, alternative strong COX-1 inhibitors should be tested to determine whether the patients are single reactors and which NSAIDs are safe for them (30).

In conclusion, despite the negative OPT outcome, only 33.9% of subjects took aspirin. Only 0.9% experienced a hypersensitivity reaction with a drug that was negative in the OPT. In addition to performing the OPT, a clear explanation of the results is necessary in the discharge letter to ensure the safe use of analgesics by the patient.

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Frequency of detection of Gardnerella vaginalis in vaginal smears in the Upper Carniola region

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Abstract

Introduction: Bacterial vaginosis is of clinical interest because of its possible causal relationship with complications during pregnancy, postpartum, and complications after surgery.
Methods: Gram stain for clue cells and *Gardnerella vaginalis* culture methods were evaluated retrospectively in a microbiological medical laboratory for the first half of 2015. We were interested in the proportion of *G. vaginalis* bacteria isolated from genital samples, correlation with Gram-staining presence of clue cells, referral clinical diagnosis, and pregnancy.
Results: In the first half of 2015 we received 358 vaginal specimens; 82% of them had a referral clinical diagnosis of colpitis, cervicitis, or vaginal discharge; 40% were pregnant women. *G. vaginalis* was isolated from 14% of vaginal specimens, and 52% of these came from pregnant patients. Gram stain clue cells and isolation of *G. vaginalis* matched in 86%.
Conclusion: For diagnosing bacterial vaginosis in clinical practice, standard clinical criteria, Gram staining of vaginal discharge smear, and/or isolation of *G. vaginalis* are used. Isolation of *G. vaginalis* without clue cells is reported only in cases in which bacterial growth is predominant. The results of our studies confirm that isolating *G. vaginalis* helps confirm the diagnosis of bacterial vaginosis.

Keywords: *Gardnerella vaginalis*, vaginal smears, Gram staining, culture, bacterial vaginosis

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Introduction

Gardnerella vaginalis is the only species of the genus *Gardnerella*. It consists of facultatively anaerobic, oxidase- and catalase-negative, nonsporing, nonencapsulated, nonmotile, pleomorphic, Gram-variable rods (1). It grows slowly on standard cell culture medium and is difficult to distinguish from other bacteria in the vagina. It grows on sheet blood agar in the form of tiny colonies, either anaerobic or in 5% CO2. A suitable growth medium is Columbia Blood Agar Base, on which bacteria forms a beta hemolysis. *G. vaginalis* is found in the vagina of 15% to 69% of asymptomatic women and 13.5% of girls.

G. vaginalis is almost universally present in the vagina of women with bacterial vaginosis (BV), where it is found with mixed anaerobic flora (2). BV is a condition in the vagina in which the normally present lactobacilli are replaced by anaerobic bacteria. Patients with BV most often complain of odor and discharge, which tends to be gray and homogenous. Vulvovaginal irritation is usually not a prominent symptom, hence the use of term *vaginosis* rather than *vaginitis* (3). BV represents a serious public health problem because it is connected with premature births, premature rupture of membranes, chorioamnionitis and neonatal meningitis, endometritis, transmission of the human immunodeficiency virus (HIV) and other sexually transmitted diseases (4, 5). Bacterial vaginosis is triggered by sexual transmission of the bacteria *G. vaginalis*, which has virulent agents that enable attachment to epithelial cells of the host, creating a biofilm (4). Numerous researchers have found statistically significant links between BV and infection with the herpes simplex virus and also with infection with human papillomavirus (6, 7).

Due to broad diversity in selection of patients' material, methods, and criteria for diagnosis of BV, in various studies the isolation rate of *G. vaginalis* varies from 6 to 94% (8).

Direct examination of vaginal secretions is the gold standard for diagnosis of BV because a positive culture of *G. vaginalis* can also be recovered from healthy women. The typical smear of vaginal discharge from BV patients shows clue cells (bacteria covering epithelial cell margins) together with mixed flora consisting of large numbers of small rods and coccobacilli: gram-negative *Prevotella* and *Porphyromonas* spp. and gram-variable *G. vaginalis)* coccobacilli. Lactobacilli are almost always absent. It is recommended that a standardized Gram staining interpretative scheme be used in order to improve the reproducibility of this method (9).

Gram-stained vaginal smears are the least expensive and fastest among the laboratory methods. However, high intracenter variability has been shown using the Gram stain for diagnosis of BV (10).

This study compares two laboratory methods for detecting *G. vaginalis*: the Gram stain for clue cells and the *G. vaginalis* culture methods.

Patients and methods

We performed a retrospective analysis of the microbiological results of vaginal swabs sent in the first half of 2015 to the Kranj department of the microbiological laboratory at the National Laboratory of Health, Environment, and Food (NLZOH), which covers approximately one-tenth of the Slovenian population with its microbiological services.

The samples were sent from the gynecological clinics of healthcare centers in Upper Carniola and from the general hospital in Upper Carniola.

Microbiological analysis: *G. vaginalis* was detected using two tests. The first was the Gram stain, with which we were looking for epithelial clue cells. The second method was isolation of *G. vaginalis* on human blood agar incubated in an anaerobic or CO2 atmosphere. Mass spectrometry using MALDI TOF technology

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(Bruker, Billerica, MA) was used to identify *G. vaginalis*, the enterobacteria, *Streptococcus agalactiae* and *Candida* spp.

Statistical methods

Matching of the results of clue cells in the Gram stain and isolation of *G. vaginalis* was statistically analyzed for significance using a chi-square test. The analysis was performed by Microsoft Excel. $P < 0.05$ was taken as significant.

Results

Out of 358 patients included in this study, 148 (41%) had no pathogenic bacteria in the vaginal swab, 67 (19%) had yeasts, 46 (13%) had enterobacteria, 47 (13%) had *S. agalactiae* and other streptococcus, and 50 (14%) had isolates of *G. vaginalis*. The number of genital samples of pathogenic bacteria received, the number (%) of isolates of *G. vaginalis*, Gram stain matching with bacterial vaginosis (%), clinical diagnosis (%), and pregnancy (%) are presented in Table 1.

Matching of results of clue cells and isolation of *G. vaginalis* was 86% (Table 2). The difference between methods was statistically significant (chi-square; $p < 0.01$; Table 2). Using both methods, the detection rate of *G. vaginalis* increases from 50 to 57 out of 350 samples (from 14.3% to 16.3%).

The frequencies of bacteriological isolates in each clinical condition are presented in Table 1. We found no statistically significant differences between the proportions of written clinical diagnosis on the referral letters between smears positive and negative for *G. vaginalis*.

Discussion

The term *bacterial vaginosis* (BV) was introduced by a group of researchers from Washington University that established that non-specific vaginitis is connected with large changes in the vaginal flora, proving this through the molecular method of 16s RNA sequencing. This group also defined the clinical criteria for BV as follows: white milky secretion, pH of the vaginal excrement over 4.5, fishy smell after adding 10% KOH to the vaginal secretion, and at least 20% of vaginal epithelial cells covered with tiny coccobacilli (clue cells). Coccobacilli are best appreciated at the edges of the cell: when they abound, they partially obscure the nucleus. Not all cells in the specimens are clue cells, but some clue cells are seen in more than 90% of patients with BV (9). For a clinical diagnosis of BV, at least three of four criteria must be met (11).

Soon after the introduction of these criteria, Nugent et al. changed the Gram stain criteria. They proposed using a combination of most reliable morphotypes detected in the vaginal smear; namely, *Lactobacillus* spp. (Gram-positive bacilli), *G. vaginalis* (Gram-negative coccobacilli), and *Mobiluncus* spp. (Gram-negative bent bacilli). A weighted score of 0 to 3 is characteristic for normal flora (prevailing lactobacilli), and 7 to 10 for BV (absence of lactobacilli, two bacterial species prevailing). The weakness of this method is that it is time-consuming and demands trained staff (11, 12). Mota et al. found that both Amsel's and Nugent's methods have comparable diagnostic efficacy for diagnosing BV (13).

In our retrospective analysis, we identified the presence of *G. vaginalis* in 14% of vaginal swabs. We were aware that *G. vaginalis* can also be found in women without clinical signs of infection. It has to be taken into consideration that gynecologists decide on microbiological testing of the vaginal tract only in cases of clinical complaints. In our study, clinical data (clinical diagnosis, pregnancy) were obtained from referral letters. The difference between the results of the Gram stain and isolation of *G. vaginalis* was statistically significant. The most probable reason is that the Gram stain criteria are not uniform among our laboratory personnel.

Our data are fairly comparable with another Slovenian study, in which bacterial vaginosis was determined clinically and microbiologically in women in three hospital wards of the Ljubljana Gynecology Clinic. A diagnosis of BV was established in 5.5% of 75 pregnant women at the Pathological Pregnancy Clinic, in 14.0% of 100 women before therapeutic abortion at the Day Clinic, and in 23.0% of 13 women at the Sexually Transmitted Disease Clinic. A correlation was found between bacterial vaginosis and sexual behavior. Due to the small number of women investigated, a correlation could not be confirmed between bacterial vaginosis and premature birth (14).

At the Slovenian microbiological laboratory, we confirm BV by detection of clue cells and the absence of lactobacilli in direct Gram stain and with isolation of *G. vaginalis*. We do not use the Nugent score system. In our study, Gram-stained clue cells and isolation of *G. vaginalis* matched in 86% of samples. A significant association was found between clue cells and *G. vaginalis*, which was in line with earlier studies (15).

Kelsey et al. showed that isolation of *G. vaginalis* and anaerobes helps confirm the diagnosis of BV and distinguish it from other pathology. Compared to healthy women, the isolation of *G. vaginalis* was the most sensitive indicator of BV (100%), although

Table 1 | Number of genital samples for pathogenic bacteria received and number (%) of isolates of *G. vaginalis* in the first half of 2015 at the medical microbiology laboratory in Kranj, Slovenia.

	Genital samples analyzed for pathogenic bacteria	Isolates of *G. vaginalis* (%)	Isolates of *S. agalactiae* (%) and streptococci	Isolates of *C. albicans* (%) and other *Candida* spp.	Isolates of enterobacteria (%)	No pathogenic bacteria/yeast isolated (%)
No. of genital samples	358 (100%)	50 (14%)	47 (13%)	67 (19%)	46 (13%)	148 (41%)
Pregnancy	144 (40%)	26 (52%)	20 (42%)	29 (43%)	10 (22%)	77 (52%)
Diagnosed	295 (82%)	38 (76%)	40 (85%)	55 (82%)	39 (85%)	121 (82%)
Cervicitis	159 (44%)	14 (28%)	22 (47%)	36 (54%)	25 (54%)	65(44%)
Vaginal discharge	65 (18%)	12 (24%)	6 (13%)	11 (16%)	5 (11%)	31 (21%)
Vaginitis/vaginosis	37 (10%)	10 (20%)	8 (17%)	3 (4%)	7 (15%)	9 (6%)
Preterm labor	29 (8%)	2 (4%)	4 (9%)	5 (7%)	2 (4%)	16 (11%)
No diagnosis	68 (18%)	12 (24%)	7 (15%)	12 (18%)	7 (15%)	27 (18%)
Clue cells	50 (14%)	43 (86%)	1 (2%)	1(1%)	(0%)	5 (3%)

Table 2 | Matching of results of clue cells in Gram stain and isolation of *G. vaginalis* at the clinical microbiology department in Kranj, Slovenia. The difference between methods is statistically significant (chi-square; $p < 0.01$).

Clue cells	Isolation of *G. vaginalis*		
	Positive	Negative	Total
Positive	43	7	50
Negative	7	293	300
Total	50	300	350

it was not very specific (77.4%). Anaerobes were more specific (93.2%). Anaerobes in vaginal culture were a better predictor of BV (30.8%) than isolation of *G. vaginalis* (18.9%) (16).

Spiegel noted an inverse relationship between the quantity of the *Lactobacillus* morphotype and the *Gardnerella* morphotype on the Gram stain. When the *Lactobacillus* morphotype predominates (3 to 4+) with or without the *Gardnerella* morphotype, the Gram stain can be interpreted as normal. When the Gram stain shows mixed flora with few or no *Lactobacillus* morphotype (0 to 2+), the Gram stain is suspicious for BV (11).

Schwebke et al. studied the prevalence of *G. vaginalis* in healthy women. Vaginal specimens were self-collected daily for 30 days and analyzed by PCR. In half of the women, at least one specimen was positive for *G. vaginalis* (17).

Metronidazole is successfully used to treat bacterial vaginosis, highlighting the significance of anaerobic bacteria. Routine treatment of the sexual partner is not recommended. It is recommended to search for and treat bacterial vaginosis in women liable to premature birth, women before abortion, and women before hysterectomy (18).

With bacterial vaginosis, changes in the species of the lactobacilli can also be observed. *Lactobacillus iners* is present with bacterial vaginosis, and *Lactobacillus crispatus* prevails in the vaginal flora of women without BV symptoms. New laboratory methods allow more frequent identification of *G. vaginalis* and *Atopobium vaginae*, thus making it possible to identify pregnant women with BV and in this way provide therapy and prevent the risk of premature birth. Antibiotic treatment in preventing BV recurrence is not particularly effective because recurrences appear often. A better effect is expected with the use of new antibiotics (19).

Bacterial vaginosis is more common among homosexual women (20). Infections with *G. vaginalis* in children are rare. Invasive infections appear only in newborns (5).

Conclusion

Bacterial vaginosis affects a large number of women and has been associated with premature birth, chorioamnionitis, and postcesarean endometritis. Combining Gram-stained vaginal smears and isolation of *G. vaginalis* increases the diagnostic sensitivity for BV.

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NATIONAL SUCCINT STATEMENT

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

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

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A suspected case of lymphogranuloma venereum (LGV) suggests underdiagnosed LGV infection among Slovenian men who have sex with men

Boštjan Mlakar[1], Ana Ramšak[1] ✉

Abstract

Lymphogranuloma venereum (LGV) is sexually transmitted infection caused by serovars of *Chlamydia trachomatis*, mostly seen among HIV-positive men who have sex with men. The first three reports of possible LGV in Slovenia were from April to June 2015, followed by a confirmed case of LGV in August 2015. We present the case of an HIV-positive MSM that presented with an anorectal abscess, discharge, lymphadenopathy, and unusual perianal plaque. Gonococcal proctitis was assumed and he received empirical antibiotic treatment, after which only intermittent improvement occurred. After a positive test result for chlamydial infection, but without a response to azithromycin treatment, LGV was suspected. Treatment according to the guidelines was introduced. When doxycycline therapy started, rapid improvement was observed, and it was therefore assumed that the LGV infection had been successfully treated. Two similar cases with an unusual anorectal presentation and an excellent response to antibiotic therapy for LGV were observed at the same center shortly thereafter. While pointing out possible delays and limitations in diagnostic procedures at self-pay facilities, the need for better access to high quality STI management in public and in private services is emphasized. Enhanced surveillance and testing guidelines could reveal a hidden LGV epidemic among MSM in Slovenia.

Keywords: dermatology, proctology, lymphogranuloma venereum, MSM, private practice limitations

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Introduction

Lymphogranuloma venereum (LGV) is a sexually transmitted infection (STI) caused by L1, L2, and L3 serovars of *Chlamydia trachomatis* (CT), and in most cases in developed and European countries it is seen among white HIV-positive men who have sex with men (MSM) (1). Patients commonly present with symptoms of proctitis (i.e., rectal pain, discharge, bloody stools, constipation, and tenesmus) (1), although reports from the UK, the Netherlands, and Germany show that approximately one-third of LGV cases are asymptomatic (2).

Since 2003, when an LGV outbreak among MSM was first reported in the Netherlands, (3) LGV has spread across other western European countries (4, 5). The first laboratory-confirmed case of LGV in Slovenia was diagnosed at the STI outpatient clinic at the Clinic for Infectious Diseases and Febrile Illnesses at the Ljubljana University Medical Center and was reported to the National Institute of Public Health (NIPH) in August 2015 (6). In addition, three possible LGV cases among HIV-positive MSM were reported to the NIPH in 2015, all treated at the private clinic Zdrav Splet for self-pay patients from April to June 2015.

Case report

A 39-year-old HIV-positive MSM, who was not on anti-retroviral therapy (ART), was referred to our clinic by an infectologist. He had had one unprotected episode of receptive anal intercourse with one unknown HIV-positive partner 2 months earlier, and the first signs of anal discomfort were noticed 2 weeks after sexual intercourse.

At the first visit he underwent an urgent operation for a perianal abscess on the right side of the anal verge. On his left perianal region he had an unusual condylomatous plaque (Fig. 1) and bilateral inguinal lymphadenopathy was noted. Drainage of the abscess was performed and the pus was sent to the National Laboratory for Health, Environment, and Food in Maribor for a PCR test for CT and *Neisseria gonorrhoeae* (NG) and also for isolation and culture of NG. Suspecting a gonococcal infection, we started treatment with 2 g of azithromycin orally. A rapid blood test for syphilis, an immunoassay detecting antibodies against *Treponema pallidum* (TP) (Biomerieux, France), was negative, and testing for other STIs was refused by the patient. We received the microbiology results after a few days and they were positive for CT and negative for NG. The patient did not consent to paying for suggested microbiological examinations for LGV.

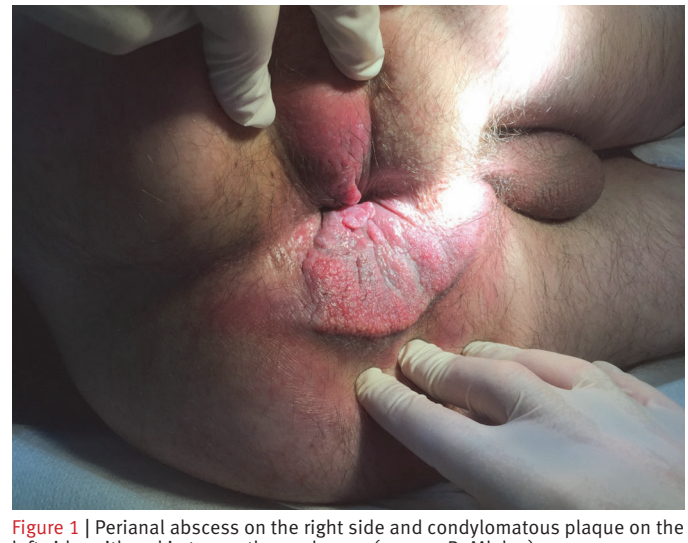

Figure 1 | Perianal abscess on the right side and condylomatous plaque on the left side, with a skin tag on the anal verge (source: B. Mlakar).

At the first follow-up after 14 days, the patient noticed only minor improvement (Fig. 2), probably mostly because the perianal abscess was drained. During a proctoscopy we found inflamed rectal mucosa with a whitish-yellow discharge, and we decided to treat him as an LGV case. We prescribed doxycycline 100 mg orally twice daily to him for 21 days in line with

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the 2013 European guidelines on the management of LGV (7). We also recommended that the infectologist start ART prior to surgical removal of the perianal condylomatous plaque.

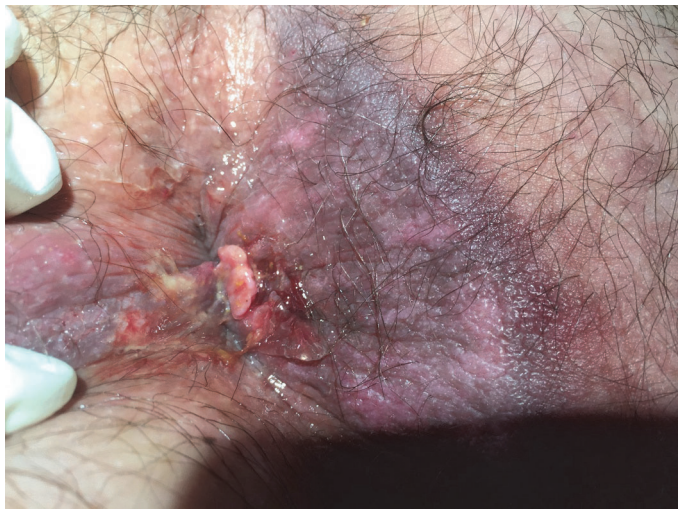

Figure 2 | Hyperpigmented perianal condylomatous plaque, a skin tag on the anal verge, and presence of purulent and bloody anal discharge (source: B. Mlakar).

At the second follow-up visit, 4 weeks later, the patient was almost asymptomatic, and he reported no pain, normal bowel movements, and no anal discharge. However, during the proctoscopy we found a white coating on the rectal mucosa, and therefore we repeated PCR tests for NG and CT, and also for other pathogen bacteria and fungi. Only *Candida albicans* was positive, and fluconazole capsules 100 mg twice daily for 14 days were prescribed. Three weeks later, the rectal mucosa were normal at proctoscopy and the perianal plaque had also almost disappeared. The condylomatous regression was probably a result of the HIV therapy he had started 6 weeks earlier. We decided to use cryotherapy to remove the remains of this plaque instead of surgery. Later on, the patient was without signs and symptoms of an STI.

In the short period of 3 months, two additional MSM patients visited our clinic with complaints of anal pain, discharge, and lymphadenopathy. The first patient was HIV-positive and was receiving ART. In the second patient, coinfections with HIV and syphilis were discovered. The syphilis was treated at our clinic, and he was referred to an infectologist for induction of ART. Both had had anal intercourse within 1 month prior to examination. The examination revealed anal discharge and mucosal inflammation. We assumed gonococcal proctitis, and rectal swabs for PCR and culture for NG were taken; both patients received immediate antibiotic therapy with azithromycin and ceftriaxone. There was only mild clinical improvement and the microbiological results for NG were negative. They were offered additional testing for CT and LGV, but both of them, because they were self-pay patients, refused. Because of the persistence of lymphadenopathy and discharge, they were empirically treated with doxycycline for probable LGV infection. After the treatment, both had no further anorectal symptoms and signs, and their lymph nodes reduced to normal size.

Discussion

We report on a possible LGV case suspected in an HIV-positive MSM that presented with common clinical manifestations for LGV and responded well to the treatment for LGV. A laboratory test for CT was performed and was found to be positive, but LGV was not laboratory-confirmed because the self-pay patient did not consent to paying for suggested additional microbiological examinations. Because the anorectal signs and symptoms were a common clinical manifestation of LGV and reacted only to antibiotic therapy, as prescribed according to the 2013 European guideline on the management of LGV (7), we concluded that LGV infection was probable and had been treated successfully. In addition, two additional suspected cases presented and were successfully treated at our clinic as LGV, even though LGV infection was not confirmed. All three cases were reported to NIPH as probable LGV in 2015. That same year, the only laboratory-confirmed and first proven case of LGV in Slovenia was reported from a public STI outpatient clinic (6).

Our report shows how long the diagnostic and therapeutic process can be when there are limitations on microbiological diagnosis because self-pay patients with signs and symptoms of STI do not consent to paying for testing for all of the most common STIs. Because our outpatient facility is known to be MSM-friendly, patients often do not want to be referred to the public outpatient STI clinics, where appropriate diagnosis, including necessary microbiological examinations, and relevant treatment can be provided and paid for within mandatory health insurance coverage.

For better access to high-quality STI case management, access to public and private specialized STI outpatient services without a referral from a primary healthcare level should be considered when the future sexual and reproductive national health strategy is prepared. Moreover, some reports of one-third of LGV cases being asymptomatic (2) should concern us, along with the fact that in most cases the sexual partners of infected patients remain unidentified. Therefore, enhanced LGV surveillance, together with national LGV testing guidelines, might reveal a hidden LGV epidemic among MSM in Slovenia.

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

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Kontraindikacije Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov.

Posebna opozorila in previdnostni ukrepi

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

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

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

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

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

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

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

Plodnost, nosečnost in dojenje

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

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

Plodnost Študij plodnosti z ingenol mebutatom niso izvedli.

Neželeni učinki

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

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

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

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

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

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

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

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

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

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

Preglednica 1 Neželeni učinki po organskih sistemih v skladu z MedDRA

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

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

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


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

Vir: 1. Humira Povzetek glavnih značilnosti zdravila

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Stelara® (ustekinumab)

SUMMARY OF PRODUCT CHARACTERISTICS

Name: STELARA 45mg/90 mg solution for injection in pre filled syringe. **Composition:** Each pre-filled syringe contains 45 mg ustekinumab in 0.5 ml or 90 mg ustekinumab in 1.0 ml. **Excipients:** Sucrose, L histidine, L histidine monohydrochloride monohydrate, polysorbate 80, water for injections. **Therapeutic Indications:** Plaque psoriasis adults: Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, MTX or PUVA. Plaque psoriasis paediatrics: Moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Psoriatic arthritis: Alone or in combination with MTX for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease modifying anti rheumatic drug (DMARD) therapy has been inadequate. **Posology and Method of Administration:** Under the guidance and supervision of a physician experienced in diagnosis and treatment of psoriasis or psoriatic arthritis. Avoid areas with psoriasis. Self injecting patients or caregivers ensure appropriate training. Physicians are required to follow-up and monitor patients. Plaque psoriasis adults & elderly: Initial dose is 45 mg s.c., followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. For patients with a body weight > 100 kg the initial dose is 90 mg s.c. at week 0, followed by a 90 mg dose at week 4, then every 12 weeks thereafter. Plaque psoriasis paediatrics (12 years and older): The recommended dose is based on body weight and should be administered at weeks 0 and 4, then every 12 weeks thereafter. *Patients<60 kg*: 0.75 mg/kg at week 0, followed by 0.75 mg/kg at week 4 then every 12 weeks thereafter. *Patients≥ 60-≤ 100 kg*: 45 mg at week 0 followed by 45 mg at week 4, then every 12 weeks thereafter. *Patients>100 kg*: 90 mg at week 0, followed by 90 mg at week 4, then every 12 Weeks. Psoriatic arthritis, adults & elderly: 45 mg at week 0, followed by a 45 mg dose at week 4, then every 12 weeks. Alternatively 90 mg may be used in patients with a body weight >100 kg. Consider discontinuation if no response in 28 weeks. Children <12 years: Not recommended. Renal & hepatic impairment: not studied. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, clinically important, active infection. **Special Warnings and Precautions for Use:** Infections: Potential to increase the risk of infections and reactivate latent infections. Caution in patients with a chronic infection or a history of recurrent infection, particularly TB. Patients should be evaluated for tuberculosis prior to initiation of STELARA. Consider anti-tuberculosis therapy prior to initiation of STELARA in patients with past history of latent or active tuberculosis. patients should seek medical advice if signs or symptoms suggestive of an incevtion occur. If serious infection develops, they should be closely monitored and STELARA should not be administered until the infection resolves. Malignancies: Potential to increase the risk of malignancy. No studies in patients with a history of malignancies or in patients who develop malignancy while receiving STELARA. Monitor all patients, in particular those older then 60, patients with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment for non-melanoma skin cancer. Concomitant immunosuppressive therapy: Caution, including when changing immunosuppressive biologic agent. Hypersensitivity reactions: Serious hypersensitivity reactions (anaphylaxix and angioedema) reported, in some cases several days after treatment. If these cases occur appropriate therapy should be instituted and STELARA discontinued. Latex sensitivity: Needle cover contains rubber (latex), may cause allergic reactions. Immunotherapy: Not known weather STELARA affects allergy immunotherapy. Serious skin conditions: Exfoliative dermatitis has been reported following treatment.. Discontinue STELARA if a drug reaction is suspecte. **Interactions:** In vitro, STELARA had no effect on CYP450 activities. Vaccinations: Live vaccines should not be given concurrently with STELARA, and should be witheld for at least 15 weeks after last dose of STELARA. STELARA can resume at least 2 weeks after such vaccinations. No data on secondary transmission of infection by live vaccines in patients receiving STELARA. Concomitant immunosuppressive therapy: Psoriasis: The safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated.. **Fertility, Pregnancy and Lactation:** The effect of ustekinumab on human fertility has not been evaluated. STELARA should be avoided during pregnancy. Women of childbearing potential should use effective methods of contraception during treatment and up to 15 weeks post treatment. Because of the potential for adverse reactions in nursing infants from ustekinumab, a decision on whether to discontinue breast feeding during treatment and up to 15 weeks after treatment or to discontinue therapy with STELARA must be made taking into account the benefit of breast feeding to the child and the benefit of STELARA therapy to the woman. **Undesirable Effects:** Dental infections, upper respiratory tract infection, nasopharyngitis, dizziness, headache, oropharyngeal pain, diarrhoea, nausea, pruritus, back pain, myalgia, arthralgia, fatigue, injection site erythema, injection site pain, antibodies to ustekunumab, cellulitis, serious hypersensitivity reactions (including anaphylaxis, angioedema), skin exfoliation, exfoliative dermatitis. Studies show AE reported in ≥12 years olds with plaque psoriasis were similar to those seen in previous studies in adults with plaque psoriasis. **Refer to SmPC for other side effects. Incompatibilities:** STELARA must not be mixed with other medicinal products. **Marketing Authorisation Holder (MAH):** Janssen-Cilag International NV, Turnhoutseweg 30, 2340 Beerse, Belgium **Local Representative of the MAH:** Johnson & Johnson d.o.o., Šmartinska cesta 53, Ljubljana **General Classification for Supply:** RP/Spec. **Date of last Revision:** 22. 06. 2015

For Summary of Product Characteristics with detailed information please contact Local Representative of the MAH.

* adalimumab and etanercept: (HR=4.16 and HR=4.91, respectively [p<0.0001])

§ Setting of medication administration (clinic vs. self-administration) was not factored into this analysis.

1. Manter A et al. Poster presented at Annual Meeting of the American Academy of Dermatology 2015, San Francisco, CA, USA.

STE-SLO-A-201-080316

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