Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Imiquimod and severe skin disorders

Introduction

Imiquimod is an imidazoquinoline amine with antiviral and antitumour activity [1,2] which has been approved in 1998 for the European market for the topical treatment of *external genital and perianal warts (condylomata acuminata) in adults* [3]. In July 2004 imiquimod has also been approved for *small superficial basal cell carcinomas (sBCCs) in adults* [4]. In October 2006 the indication for imiquimod has been extended with *clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate* [5].

The Netherlands Pharmacovigilance Centre Lareb received four reports of severe local skin reactions with super infections or reactivated viral infections. These reactions are listed in the SPC of imiquimod. Section 4.4 of the SPC of imiquimod states that: *"Rarely, intense local inflammatory reactions including skin weeping or erosion can occur after only a few applications of imiquimod cream. Local inflammatory reactions may be accompanied, or even preceded, by flu-like systemic signs and symptoms including malaise, pyrexia, nausea, myalgias and rigors. An interruption of dosing should be considered"* [3].
Section 4.8 states that infections are common (frequency 1-10%) in external genital warts and in superficial basal cell carcinoma and uncommon (frequency 0.1-1%) in actinic keratosis. Herpes simplex, bacterial infection, and herpes zoster infection are not listed in the SPC for sBCC or AK. Application site erosion, bleeding and oedema are listed in section 4.8 [3].

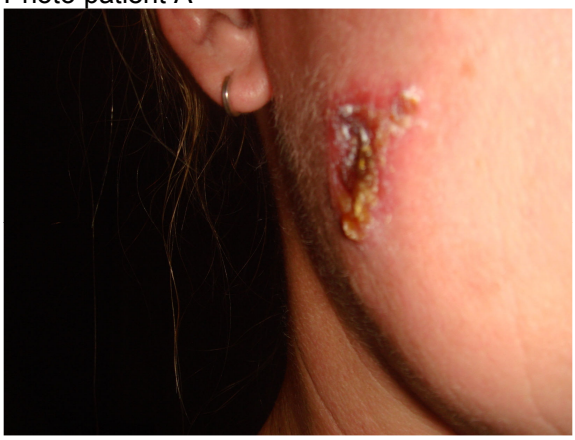
Although the reported local skin reactions are mentioned in the SPC, Lareb would like to pay attention to the reports, because the adverse drug reactions (ADRs) are more severe than expected.

Reports

Between October 30, 2006 and March 6, 2007 the Netherlands Pharmacovigilance Centre Lareb received four reports of severe local skin reactions with open wounds, bleeding and secondary infection.

Patient A (61824) is a female aged 38 years, who used imiquimod for actinic keratosis five days a week. After the eighth application she experienced face oedema and vesicles around the application site, which burst open. Also the pre-auricular lymph nodes were swollen at the side the vesicles were formed. After ten applications she stopped the treatment and applied a zinc preparation, as advised by her GP. The GP then prescribed silver sulfadiazine. Scabs were formed. Four months later the skin had almost completely recovered. Picture 1 shows the lesion. Not explicitly reported, but visible at the picture is a bacterial super infection. According to the reporter the prescribing dermatologist was not aware this adverse event could occur.

Photo patient A



Patient B is a female aged 59 years, who used imiquimod for multiple basal cell carcinomas on her thorax. Neither dosage nor application frequency were reported. Seven days after initiation the patient experienced papulovesicles, extensive redness, pain and bleeding in the area treated. Herpes simplex virology showed an infection: IgM <20 U/ml (negative) and IgG >4000 U/ml (positive). Imiquimod treatment was stopped because of these ADRs. Patient outcome is unknown. Concomitant medication was not reported.

Patient C is a female aged 86 years, who applied imiquimod on a facial wart on her left lower jaw. She experienced erythema, blisters, scabs and face oedema two days after initiation, which started at the right lower jaw and spread throughout the right half of the throat and the décolleté during the following seven to ten days. Every day a few new, large vesicles were seen. The vesicles burst open and formed large open wounds. The dermatologist prescribed valaciclovir, because of suspicion of herpes zoster, but this drug did not stop the formation of new vesicles. After cessation of imiquimod the lesions were recovering.

Patient D is a female aged 45 years, who used imiquimod for basal cell carcinoma five days a week on multiple lesions on her body and one lesion between her breasts. Two weeks after start patient experienced irritation and a burning sensation at and around the application sites. Between her breasts a lesion of several square centimetres occurred, which resembled a burn. The dermatologist prescribed fusidic acid cream. Imiquimod treatment was stopped. Five days after cessation of imiquimod amoxicillin capsule 3 dd 500 mg was started for an unknown indication. The reaction outcome is unknown.

Other sources of information

Literature

Three systematic reviews describe local skin reactions associated with topical imiquimod treatment.

Oldfield *et al.* describe local skin reactions associated with topical imiquimod treatment for superficial basal cell carcinoma. They performed a pooled analysis of two randomized, double-blind, multicentre trials, where patients with superficial BCC applied imiquimod 5% cream (n=184) or vehicle (n=178) five times per week for six weeks. The prevalence of severe local skin reactions in imiquimod treatment groups were: about 8% oedema, about 13% erosion, about 32% erythema, about 4% flaking or scaling, about 6% induration, 20% scabbing or crusting, about 6% ulceration and about 3% vesicles [1]. In the SPC of imiquimod severe erythema (31%) severe erosions (13%) and severe scabbing and crusting (19%) were very common in trials with imiquimod cream applied five times weekly for BCC [3].
In a systematic review of imiquimod for actinic keratosis Hadley *et al.* report particular severe local adverse effects as a percentage of imiquimod-treated patients: almost 30% erythema, over 20% scabbing or crusting, almost 10% flaking, scaling or dryness, over 5% erosion or ulceration, about 5% weeping or exudate and about 1% vesicles [2]. In the SPC of imiquimod severe erythema (24%) and severe scabbing and crusting (20%) were very common when used for AK [3].
Moderate to severe local reactions during treatment with imiquimod for genital warts were not pooled for several reasons [6]. In the SPC of imiquimod it is stated that most skin reactions were mild to moderate in severity and resolved within 2 weeks of treatment discontinuation. However, in some cases these reactions have been severe, requiring treatment and/or causing incapacitation [3].

Databases

Up to March 6, 2007 the Netherlands Pharmacovigilance Centre Lareb received eight reports with 23 ADRs on this product. Four reports concerning 13 ADRs are described in this report. The other reported ADRs were pruritus; syncope and headache; flu like symptoms; lymphadenitis with fever, malaise, leukocytosis, headache and flu.
Because of the diversity of the skin reactions, the associations do not allow the calculation of reporting odds ratios (RORs).
The database of the Uppsala Monitoring Centre of the WHO contains reports of the individual symptoms of the reported ADRs, most of which are disproportionally present. It is not possible to match the collection of skin reactions reported to Lareb with the associations in the WHO database.

Mechanism

Imiquimod, an imidazoquinoline amine, is an immunomodulating agent that affects both major divisions of the immune system: the innate and the acquired or adaptive immune system, resulting in cytokine release and co stimulatory molecule expression, followed by T-cell activation [7]. In superficial BCC this targeted immune response and apoptosis in BCC cells result in tumour destruction [1]. As a consequence of such an inflammatory reaction oedema will occur, as in patient B and C was reported.
Why super infections or reactivation of viral infections occurred during treatment with imiquimod is not clear. Perhaps the immune system is modulated in such a specific and demanding way that the herpes simplex infection in patient B, the

bacterial infection in patient A and the suspected herpes zoster infection in patient C could occur.

Prescription data

Prescription data were not available from the database of the 'College voor Zorgverzekeringen'.

Discussion and conclusion

Lareb received four reports of serious local skin reactions after topical application of imiquimod 5%. These ADRs were reported in a short period of time and after extension of the indication. In one report it was noted that the prescribing dermatologist was not aware these ADRs might take place. Also striking were the super infections in two patients and the possible reactivated infection in one patient. In patient A, who was treated with imiquimod for actinic keratosis, it was not clear whether other treatment options were contraindicated or less appropriate, according to the indications mentioned in the SPC. The reported indication for treatment in patient C was a wart. It is not clear whether this was a sBCC or AK. In literature and in the SPC of imiquimod these ADRs are noted. Nevertheless, it might be reasonable to repeat the strict indications for the use of this drug and to warn patients and health professionals more clearly that these ADRs can occur.

References
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