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Terbinafine and exacerbation of lupus erythematosus

Introduction

Terbinafine (Lamisil[®]) is an antifungal agent approved for the Dutch market in 1991. Terbinafine is indicated for *the treatment of tinea capitis and dermal fungal infections by tinea corporis, tinea cruris or tinea pedis, and for treatment of onychomycosis, caused by dermatophytes* [1].

The most frequent adverse drug reactions mentioned in the SPC are: gastro-intestinal symptoms, non-serious skin reactions (erythema, urticaria) and musculoskeletal reactions (arthralgia, myalgia). Rare cases of Erythema Multiforme, Stevens Johnson syndrome, Toxic Epidermal Necrolysis, anaphylactic reactions and of taste alterations, hepatic effects, hematologic disorders and alopecia are described as well. The SPC does not mention Lupus Erythematosus (LE) as a possible adverse drug reaction [1].

Lupus Erythematosus refers to a chronic autoimmune disease with unknown etiology and a variety of symptoms. It is characterized by the presence of anti-nuclear antibodies (ANA). Most commonly seen symptoms are fatigue, arthritis, muscle pain and skin rashes.

Reports

Up to December 2003, the Lareb database contains a total of 22 reports of Lupus Erythematosus as a suspected adverse drug reaction. Four reports refer to a LE-like skin reaction, associated with the use of terbinafine (Table 1).

Patient A is a 34-year-old female, with a medical history of SLE. She used terbinafine for the treatment of hallux mycosis. After 3 months she developed itchy red spots on chest, back and arms, specified as: blurry bounded, lenticular to numular, big erythematous lesions. Immunofluorescence tests were indicative for exacerbation of existing LE. Upon discontinuation of terbinafine and local treatment with clobetasol the patient recovered from this skin reaction. Extensive concomitant medication was used.

Patient B is a 70-year-old female. She used terbinafine for 2 months and then developed a LE like skin reaction, first on the chest, later also on trunk, extremities and face. Immunofluorescence tests were indicative for SCLE (subacute cutaneous LE). Upon discontinuation of terbinafine and local treatment with clobetasol patient improved. In retrospect, the patient had possibly had similar symptoms (not related to terbinafine) several years before.

Patient C is a 26-year-old female with SLE. After 6 weeks of terbinafine use for onychomycosis, she developed a SCLE-like skin reaction, described as slightly raised erythematous spots spread over the whole body; lenticular to numular erythematous-papular plaques. Pathological anatomical examination confirmed the assumption of SCLE luxation. Terbinafine was discontinued and the patient was at first treated with cetirizine, followed by prednisone, whereafter the symptoms disappeared.

Patient D is a 24-year-old female, who used terbinafine for onychomycosis. After 3 months she developed CDLE(chronic discoid LE)-like skin disorders. Additional histological examination (including immunofluorescence) demonstrated an image consistent with LE. After discontinuation of terbinafine and treatment with hydroxychloroquine and (locally applied) clobetasol the patient partly recovered. Upon inquiry it appeared that she had also experienced LE-like skin reactions (not related to terbinafine) in the past.

Table 1. Reports of Lupus Erythematosus associated with the use of terbinafine.

Patient, Sex, age	Drug Dose, indication	Concomitant medication	Reported adverse drug reaction	Time to onset, outcome
A F, 34	Terbinafine 250 mg od Hallux mycosis	Diclofenac, colecalfiferol/calciumcarbonate, acenocoumarol, omeprazol, prednison	SLE exacerbation: skin reaction in patient with known SLE	3 months, recovered
B F, 70	Terbinafine 250 mg od Indication unknown	Colecalciferol, atenolol, hydrochlorthiazid	SCLE like skin reaction	2 months, recovering
C F, 26	Terbinafine 250 mg od onychomycosis	none	SCLE like skin reaction in patient with known SLE	6 weeks, recovered
D F, 24	Terbinafine 250 mg od Onychomycosis	none	CDLE like skin reaction	3 months, partly recovered

Other sources of information

Literature

Several case reports describe the association between use of terbinafine and either induction or exacerbation of (SC)LE e.g.[2-4].

Databases

The database of the WHO Monitoring Centre contains 11,154 possible ADRs during the use of terbinafine. An association between terbinafine and LE rash was suggested in 19 reports, resulting in a ROR of 10.2 (95% CI 6.5-16.2).

Terbinafine was associated with LE syndrome in 48 reports. The ROR of this combination is 3.4 (95% CI 2.6-4.6). The association between terbinafine and aggravated LE syndrome was not statistically significant disproportional.

Mechanism

The underlying pathogenesis of drug-induced LE is still unresolved. One of the hypotheses is based on the assumption that drug-induced LE is not caused by the drug itself, but by reactive drug metabolites. In a first process the drug is transformed by neutrophil-mediated oxidation into an active metabolite. This metabolite then causes an (auto-)immune reaction [5].

Another theory assumes that the suspect drug mediates apoptosis in human lymphoblasts. It acts by activation of intracellular proapoptotic signaling cascades. An increased rate of apoptosis could lead to an overflow of the phagocytic system with apoptotic cell bodies. The inflow of apoptotic break-down products may lead to induction of auto-immunity against nuclear components [6].

Conclusion

Four cases in the database of the Netherlands Pharmacovigilance Centre Lareb show an association between terbinafine and Lupus Erythematosus skin reactions. In all four cases the patient either had LE in her medical history or had had a similar reaction before. In the WHO database the association between terbinafine and LE-rash and LE-syndrome (but not aggravated LE) was shown to be disproportionally present.

Case reports in literature support the association between terbinafine and both induction and exacerbation of (SC)LE.

References

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