Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Skin reactions associated with the use of oral terbinafine

Introduction

The orally and topically active allylamine antifungal agent terbinafine (Lamisil®) has been approved for the Dutch market in 1991. Terbinafine is indicated for *the treatment of tinea capitis and* fungal infections of the skin, for the treatment of tinea corporis, tinea cruris and 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 treatment of onychomycosis may take up to 12 weeks[1].
The Netherlands Pharmacovigilance Centre Lareb received a number of reports of adverse skin reactions associated with use of oral terbinafine which are not mentioned in the Dutch Summary of Product Characteristics.

Reports

The reports on photosensitivity reactions (table 1) and psoriasis (table 2) are highlighted separately in the following. Adverse reactions which are reported ≥ 3 times and have a reporting odds ratio (ROR) with a lower 95% confidence limit ≥ 1 are listed in table 3. Lareb recently reported on lupus erythematosus and terbinafine, therefore these reports are not included in this review.

A. Reports of photosensitivity reactions

Table 1. Reports of photosensitivity reaction associated with the use of terbinafine 1dd 250 mg received by the Netherlands Pharmacovigilance Centre.

Patient, gender age	Comedication	Time to onset	Additional remarks
A, F, 44	pravastatin, nicotinell	1 month	
B, M, 45	none reported	9 weeks	exposure in France
C, F, 54	fenoterol/ipratropium	8 weeks	
D, F, 39	iron	16 weeks	
E, F, 52	none reported	2 weeks	de- and rechalenge positive
F, F, 62	triamtereen / hydrochlorothiazide	not reported	
G, M, 45	none reported	not reported	exposure in Italy
H, F, 39	triamcinolon creme	4 weeks	
I, F, 27	ethinylestradiol/levonor-gestrel, diclofenac	3 hours	exposure in solarium

The time of onset of the skinreaction on the exposed skin varies but in most reports is longer than 4 weeks after start of treatment with 250 mg terbinafine 1dd. One report (D) with a shorter latency concerns a patient with a recurrent reaction and one report (I) concerns intense exposure to UV-light in a solarium.

Other sources of information on photosensitivity reactions

Literature

A search in the Medline database revealed no publications concerning the occurrence of terbinafine associated with photosensitivity or photodermatitis.

Databases

A total number of 692 reports on terbinafine have been reported to Lareb. In our data set terbinafine was disproportionately associated with photosensitivity reaction. The reporting odds ratio (ROR) of the association between terbinafine and photosensitivity reaction (n=8) is 2.3 (95% CI 1.1 – 4.6)

At the end of the second quarter of 2004 the reporting odds ratio of the association between terbinafine and photosensitivity reaction (n=126) in the combination database of the WHO Monitoring Centre was 1.96 (95% CI 1.65 – 2.34).

Mechanism

The patho-physiology of photosensitivity associated with terbinafine in not clear but perhaps patients with known lupus erythematosus or photosensitivity are predisposed to drug-induced or drug-exacerbated disease. Lareb recently reported on lupus erythematosus and terbinafine [2].

B. Reports of psoriasis

Table 2. Reports of (exacerbation of) psoriasis associated with the use of terbinafine 1dd 250 mg received by Lareb.

Gender age	Comedication	Time to onset	Additional remarks
J M, 59	none reported	25 days	psoriasis treated with calcipotriene
K F, 53	amiloride/ hydrochlorothiazide	? days	exacerbation of psoriasis
L F, 78	miconazol creme	11 days	psoriasis treated with betamethasone en hydrocortisone

Other sources of information on psoriasis

Literature

A search in the Medline database revealed several publications concerning the association of terbinafine with both exacerbations of pre-existing psoriasis, as well as de novo development of psoriasis. The skin lesions generally resolved within one month of terbinafine discontinuation, sometimes with psoriasis treatment.[3-5]

Databases

A total number of 692 reports on terbinafine have been reported to Lareb. In our data set terbinafine was disproportionately associated with psoriasis. The ROR of the association between terbinafine and psoriasis (n=4) is 2.0 (95% CI 0.7– 5.3)

At the end of the second quarter of 2004 the reporting odds ratio of the association between terbinafine and psoriasis in the data set of the WHO Monitoring Centre(n=16) was 5.2 (95% CI 3.2–8.6) and of psoriasis aggravated (n=25)was 4.3 (95% CI 3.4–7.4) .

C. Reports of other skin reactions

Table 3. number of reports of skin reactions associated with the use of terbinafine 1dd 250 mg. Lareb recently reported on lupus erythematosus and terbinafine, therefore these reports are not included in this review

	Number of Lareb reports	ROR	ROR- 95 CI	ROR+ 95 CI	Listed in Dutch SPC
erythema multiforme	9	19.10	9.06	40.28	Yes (rare)
toxic epidermal necrolysis	5	12.58	4.82	32.86	Yes (rare)
dermatitis exfoliative	10	5.57	2.91	10.68	No
urticaria	42	3.07	2.23	4.22	Yes
exanthema	8	3.36	1.64	6.87	#
alopecia	26	2.14	1.44	3.19	Yes (rare)
rash	48	1.85	1.38	2.49	#
nail disorder	3	4.25	1.32	13.71	No
rash erythematous	22	1.95	1.27	3.00	#
rash maculo-papular	9	2.25	1.15	4.39	#
pruritus	22	1.56	1.01	2.39	No

in the Dutch SPC “erytheem” is listed

Prescription data

The use of terbinafine expressed as number of prescriptions and the total number of ADR reports in the Netherlands over time are shown in figure 1.

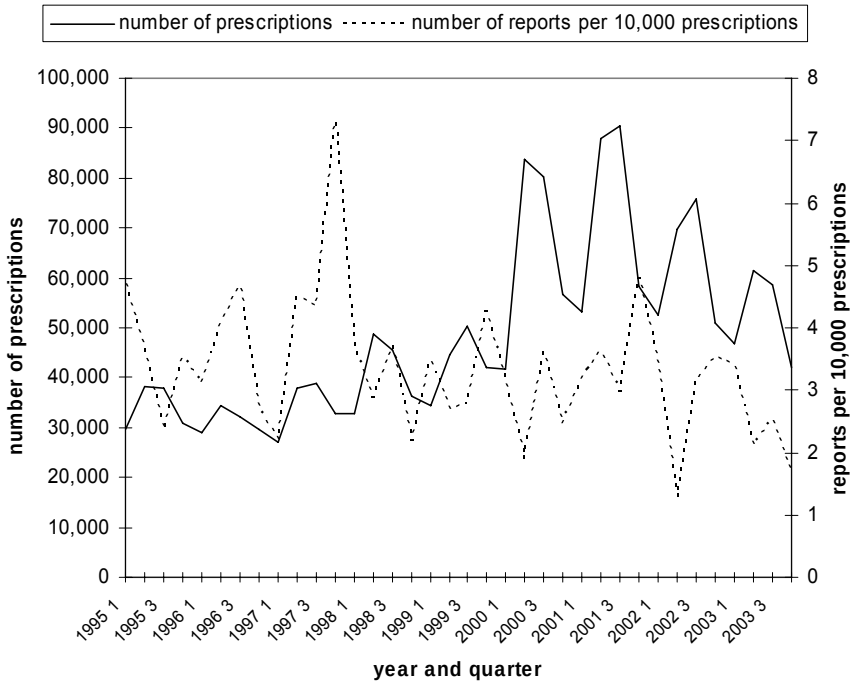

Figure 1. Total number of prescriptions and all reports per prescriptions per quarter since 1995 (Source: GIP College voor Zorgverzekeringen, Diemen).

Conclusion

Skin reactions are prominently listed in the the Dutch Summary of Product Characteristics. Nevertheless reports to the Netherlands Pharmacovigilance Centre indicate additional skin reactions that can be considered being related to the use of terbinafine. A causal relationship between the use of terbinafine and photosensitivity reactions and (exacerbation of) psoriasis is supported by disproportionality analysis of the WHO-database.

References

1. Dutch SPC Lamisil®. (version date 19-4-2001) http://www.cbg-meb.nl/IB-teksten/14841-14842.PDF.
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4. Pauluzzi P, Boccucci N. Inverse psoriasis induced by terbinafine.Acta Derm Venereol. 1999 Sep;79(5):389.
5. Wilson NJ, Evans S. Severe pustular psoriasis provoked by oral terbinafine. Br J Dermatol. 1998 Jul;139(1):168