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ORIGINAL REPORT

Association between terbinafine and arthralgia, fever and urticaria: symptoms or syndrome?

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SUMMARY

Purpose The antifungal agent terbinafine has been approved for marketing in The Netherlands since 1992. Adverse drug reactions (ADRs) may occur in about 10% of the patients, the majority gastrointestinal disorders and skin reactions. Since the introduction of terbinafine, the Netherlands Pharmacovigilance Foundation Lareb received eight reports of arthralgia during the use of this drug. In four reports the additional presence of skin reactions was mentioned, two of these reports concerned urticaria. Two patients who reported arthralgia also had a fever. These reports were described in more detail, and analysed statistically in order to determine whether symptoms are interrelated.
Methods All reports with known gender and a reporting date between 1 March 1992 and 1 January 1999, concerning patients older than 10 years, were included. The extent to which the symptoms urticaria, fever and arthralgia were interrelated was examined by logistic regression modelling.
Results Case series as well as the results of the statistical analysis show a clustering of symptoms among reports of patients using terbinafine. Both urticaria and arthralgia were statistically significantly associated with reports on terbinafine compared to all other reports in the database.
Conclusion The findings might point towards a clustering of these symptoms in patients using terbinafine. Possibly these symptoms have a shared aetiology, presumably an immunological reaction. Copyright © 2001 John Wiley & Sons, Ltd.

KEY WORDS — terbinafine; arthralgia; allergy; pharmacovigilance

INTRODUCTION

The orally and topically active allylamine antifungal agent terbinafine has been approved for marketing in The Netherlands since March 1992. The drug interferes with the ergosterol biosynthesis via specific and selective inhibition of fungal squalene epoxidase.[1]

Terbinafine is effective in the treatment of onychomycosis and several other types of dermatomycotic infections.[2,3] Its spectrum includes a broad range of dermatophyte and some yeast species. Adverse drug reactions (ADRs) may occur in about 10% of the patients treated with terbinafine, the majority being gastrointestinal disorders (5%), and skin reactions (2–3%).[4–6] Rarely, terbinafine has been associated with severe drug eruptions such as toxic epidermal necrolysis,[7,8] erythema multiforme[8–10] and Stevens Johnson Syndrome.[11]

In general, frequently occurring ADRs are usually detected in pre-marketing trials. In these trials, drugs are used by a well-defined group of a relative small number of patients for a limited time span.[12] After

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marketing, when the drug is used by a large number of patients under different circumstances, previously unknown ADRs are still being detected. An example is the detection of taste disorders associated with terbinafine, which was described for the first time in 1992, after the international marketing of the drug.[13,14] Reporting of ADRs by pharmacists or physicians to 'spontaneous reporting systems'(SRS) play an important role in the detection of ADRs. In most countries these systems are maintained by so-called 'national pharmacovigilance centres'. In the Netherlands, the Pharmacovigilance Foundation Lareb is responsible for collecting and analysing these reports. Since the introduction of terbinafine, Lareb received 294 reports of suspected adverse reactions to terbinafine. Eight reports concerned arthralgia. In four of these reports the reporting physician or pharmacist also mentioned the presence of skin reactions, including two reports of urticaria. Two patients who reported arthralgia also had a fever. The reports suggest a clustering of arthralgia, fever and urticaria. The association between terbinafine and arthralgia is not yet mentioned in the Dutch Summary of Product Characteristics, but will be in the future.

The objective of this article is to describe the clinical characteristics of these reports and to analyse the clustering of these symptoms statistically in order to determine the strength of the association. In case symptoms are interrelated, this might be an indication for the existence of a syndrome.

METHODS

Setting

The Netherlands Pharmacovigilance Foundation Lareb is the National Centre for spontaneous reports of suspected ADRs originating from health care professionals in the Netherlands.[15] These reports are considered to be a reflection of the ADRs that occur in daily practice, taking into account the various degrees of underreporting that are an inherent attribute of spontaneous reporting.[16–19] After being received by Lareb, the reported possible adverse drug reactions are evaluated and coded by a qualified assessor according to the WHO Adverse Drug Reaction Terminology.[20]

Case series

For all reports of terbinafine coded by 'arthralgia', additional information concerning the clinical details was retrieved from the reporter by means of a questionnaire. Special attention was paid to the symptoms involved, type and distribution of arthralgia or arthritis and accompanying symptoms such as fever, lympadenopathy, renal function and skin disorders. Furthermore, additional question were asked about the time of onset and course of the symptoms, a history of allergic or rheumatological disorders, liver or renal function disorders or a family history of rheumatological disorders. In the event an additional radiological examination or laboratory testing was carried out, a copy of the results was asked for. Questionnaires were sent to the reporting physician or pharmacist together with a copy of the data already present in our database. After 3 weeks, a reminder was sent. If there was no response after an additional period of 3 weeks, the reporting physician or pharmacist was contacted by telephone.

Analysis of clustering

Reports with a reporting date between 1 March 1992 and 1 January 1999 were eligible for enrolment in the study. Since terbinafine is rarely used in children and in our database no reports concerning patients younger than 13 years were present, only reports concerning patients older than 10 years of age were included. Reports were excluded where the gender of patients was not reported.

A report to a SRS can be considered as a set of data considering a single patient, in combination with one ore more drugs and one or more ADRs. Statistical methods, such as logistic regression analysis can be used to provide evidence for a possible underlying relationship between these different covariates. In the SRS databases the strength of the association between a drug and ADR can be studied by calculating reporting odds ratios.[21,22] To study a possible relationship between fever, urticaria and arthralgia, the ADRs were considered to be covariates and the presence of terbinafine as the suspected drug on the report form to be the dependent variable. The extent to which the covariates are interrelated can be examined by using statistical 'interaction terms' in a logistic regression model. Since we were interested in expressing the presence of terbinafine as a function of arthralgia, fever and urticaria, cases were defined as reports on which terbinafine (oral administration) was mentioned as the suspected medication, non-cases were defined as all other reports. Reporting odds ratios (ROR) were calculated, which were adjusted for age and gender of the patients, source of the reports and year of reporting. In the logistic regression analysis a forward stepwise approach was applied. SPSS 8.0 was used for all statistical assessments.

RESULTS

Case series

Cases involved five men and three women. All patients were treated with terbinafine 250 mg once daily. The median age was 42 years (range 34–66 years). Time of onset of the reaction ranged from a 1 or 2 days to 18 days. Seven physicians and one pharmacist submitted the reports. Additional information was received with regard to six out of the eight cases of arthralgia. One patient had moved so additional information could not be provided. Clinical details of these patients (A–H) are presented in Appendix 1/Table 4. No clear pattern could be recognized in the type of joints involved and the distribution of the arthralgia. Polyarthralgia was present in all eight cases. Only patient B had a history of backache. Patients A–F and H were treated for onychomycosis. The indication for use of patient G was not received. Patients A,B,D–F and H had no history of joint disorders, traumata, liver or kidney function disorders, rheumatological or allergic disorders. There were no joint disorders in the family history of any of the patients concerned. These data could not be retrieved for patients C and G. In none of the patients a rechallenge was carried out.

Analysis of clustering

Between 1 March 1992 and 1 January 1999, a total number of 16,776 reports were received by the Netherlands Pharmacovigilance Foundation. Of 98 patients sex or age was not known and 649 reports were excluded because the patients were younger than 10 years of age. A total of 16,127 reports were included in the analysis, of which 294 reports mentioned terbinafine as the suspected medication. Joint complaints were reported 154 times, of which eight were associated with terbinafine. The distribution of the ADRs urticaria, fever and arthralgia on reports concerning terbinafine and other reports are presented in Table 1. Both urticaria (adjusted ROR 1.72 (95% CI 1.35–2.18)) and arthralgia (adjusted ROR 3.14 (95% CI 1.52–6.47)) were significantly associated with reports on terbinafine (Table 2). The covariates being the best predictors of the dependent variable were urticaria (adjusted ROR 1.66 (95% CI 1.29–2.14)) as well as the interaction terms arthralgia*fever (adjusted ROR 2.35 (95% CI 1.32–4.17)) and arthralgia*urticaria (adjusted ROR 3.33 (95% CI 1.03–10.73)). The odds ratios and corresponding 95% confidence intervals are shown in Table 3.

Table 1. Distribution of ADRs: urticaria, arthralgia and fever on terbinafine versus all other drugs

	Reports on terbinafine *n* (%)	Reports on other drugs *n* (%)
Only arthralgia reported	5 (1.7%)	142 (0.9%)
Only urticaria reported	17 (5.8%)	345 (2.2%)
Only fever reported	2 (0.7%)	161 (1.1%)
Both arthralgia and urticaria reported	1 (0.3%)	2 (0.01%)
Both arthralgia and fever reported	1 (0.3%)	2 (0.01%)
Both fever and urticaria reported		2 (0.01%)
Urticaria, fever and arthralgia reported	1 (0.3%)	
No arthralgia, urticaria of fever reported	267 (90.8%)	15,179 (95.9%)
Total	294	15,833

Table 2. Association between arthralgia, fever, urticaria and terbinafine

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Fever	1.06 (0.83–1.37)	1.06 (0.83–1.36)
Urticaria	1.75 (1.38–2.22)	1.72 (1.35–2.18)
Arthralgia	3.00 (1.46–6.18)	3.14 (1.52–6.47)

*Odds ratio adjusted for year of reporting, source of the reports, age and gender of the patient.

Table 3. Association between terbinafine and arthralgia, fever and urticaria. Results of logistic regression (forward stepwise approach)

	Odds ratio (95% CI)
Arthralgia * fever	2.35 (1.32–4.17)
Arthralgia * urticaria	3.33 (1.03–10.73)
Urticaria	1.66 (1.29–2.14)

DISCUSSION

The case series as well as the statistical analysis suggest a clustering of fever, arthralgia and urticaria in association with the oral antifungal drug terbinafine. In general, ADRs to terbinafine are often mild. The reported overall incidence of ADRs in a large post-marketing study involving 25,884 patients was 10.5%. Of all events 55.9% were considered to be probably related to terbinafine. The majority involved the gastrointestinal system and the skin.[5] Nevertheless more serious reactions may occur. Liver and kidney function disorders may decrease the elimination of

Table 4. Clinical details of eight reports concerning arthralgia during use of terbinafine

Patient; gender; age (years)	Indication for use	Concomitant medication	Description of suspected ADR	Time for the ADR to occur	Remarks
A; F; 44	Onychomycosis	Doxycycline 100 mg during 7 days (1 week after start of terbinafine) Ethinylestradiol/ desogestrel	Arthralgia of right wrist, 1 week later followed by right knee. ADL impaired	18 days after start	Fully recovered after stopping terbinafine complaints. ESR, C-reactive protein levels, streptococcal antibody titre or rheumatoid factors not increased. Treated with ibuprofen 400 mg three times daily
B; M; 41	Mycosis	Ibuprofen 400 mg 3dd1, miconazole cream; Beclomethasone inhaler	Arthralgia of shoulders, hips and elbows. Symmetrical affected. No signs of arthritis. ADL impaired. Backache in history	10 days after start	Recovered after stopping terbinafine Lab: ESR, 5 mm; GGT, 11 mmol/l;Hb, 8.9 mmol/l; leukocyte count, 5.4×10^9/l, was treated with nabumetone 1 g twice daily
C; F; 42	Onychomycosis		Pain of hands and feet	'Couple of days' after start	No additional information received
D; M; 41	Onychomycosis		Arthralgia. Pain on flexion and extension of wrists and knees. No signs of arthritis	2 weeks after start	Recovered. No additional laboratory examination
E; F; 37	Onychomycosis		'Joint complaints', malaise, rash (pruritus, erythema)	10 days after start	Recovered after stopping terbinafine leukocyte count, 7.2×10^9/l; ALT, GGT not increased. In blood smear, some atypical lymphocytes. After 1 week re-examination of blood revealed no abnormalities
F; M; 66	Onychomycosis	Echinacea-containing drug	Urticarial rash, fever, headache, vomiting, arthralgia, diffuse No joints specified	2 weeks after start	Treated with terfenadine and prednisolone. Lab: Hb, ESR, leukocytes and blood smear within normal limits
G; M; 34	Unknown	Miconazole cream	Generalized urticaria and arthralgia. No joints specified	10 days after start	Treated with terfenadine, prednisolone and promethazine
H; M; 50	Onychomycosis	Budesonide inhaler	Pain in almost every joint and myalgia. No signs of arthritis. One week after the start of terbinafine, anorexia, vomiting, abdominal pain, smell and taste disorders, also rash, stomatitis and peeling of the skin developed. Fever of 39°C leukocyte count, 4.8×10^9 / l; ESR, 5 mm; Hb, 9.3 mmol/l; ALT, 1672 U/l; LDH, 869 U/l; GGT, 202 U/l; kidney function normal	'Couple of days' after start	Recovered. Treated with diclofenac and domperidone

All patients were treated with terbinafine 250 mg once daily. Patients indication for use of patient G was not known. Patients A, B, D–F and H had no history of rheumatological disorders, traumata, liver or kidney function disorders, rheumatological or allergic disorders. No rechallenge was carried out in either of these patients. These data could not be retrieved for patients C and G.

terbinafine.[23,24] These patients are more likely to experience ADRs due to an increase in plasma levels of terbinafine. For this reason we asked for liver and kidney function disorders in our questionnaire, but they were not observed. Complaints of the musculoskeletal system were reported in 0.8% in the postmarketing study mentioned.[24] In another postmarketing study among 10,361 patients, which were probably part of the previously mentioned postmarketing study, 10.9% of the patients had pre-existing musculoskeletal system disorders. In this study, musculoskeletal events were reported by 1.3% of the patients, of which only 25.2% were thought to be related to terbinafine treatment. Arthralgia occurred in 0.4% of the patients, myalgia in 0.2%. Half of the cases of arthralgia and myalgia occurred within the first 2 weeks of treatment, and were considered as being possibly related to the use of terbinafine. None of the musculoskeletal events was serious and there was no evidence that terbinafine exacerbated pre-existing muskuloskeletal symptoms. Dermatological events were reported by 341 patients (3.3%), of which urticaria was reported 47 times (0.4%).[25] Both studies had a descriptive character and no control groups were used. Details on the simultaneous occurrence of different symptoms were not provided.

In the literature anecdotal case reports have appeared, describing symptoms similar to those in our study. It is not yet clear if these reports represent distinct or related symptoms; in the latter case they might share a common aetiology. For instance, terbinafine has been associated with the clinical diagnosis of a serum sickness-like reaction in one case report. This concerned a well-documented case of an-81-year-old male, who developed exanthematous rash, fever, myalgia and arthralgia 6 weeks after the start of terbinafine therapy.[26] True serum sickness is caused by an immune complex-mediated reaction to a foreign serum protein occurring 1–3 weeks after exposure. Usually it presents with an urticarial rash, followed or accompanied by pain and swelling of the joints (knees, ankles and wrists) in a symmetrical distribution. Serum sickness-like reactions, with arthralgia or arthritis, skin reaction or fever may occur with many drugs, but penicillin is the most common cause.[27–29] The diagnosis of a true serum sickness-like reaction, however, requires information about complement factors C3 and C4. Since this is not a parameter commonly tested by general practitioners, this information was not available. For the majority of the reactions reported to Lareb, the time of onset is compatible with a serum sickness-like reaction. Patient A also used doxycycline, which was incidentally associated with a serum sickness-like reaction.[28,30] Involvement of doxycycline in this patient cannot be fully excluded. Alternatively, urticaria, joint pain and sometimes swelling of the joint can occur together as 'urticarial arthralgia', in which attacks of severe urticaria and joint pain occur coincidentally due to an urticarial reaction of the synovia. Usually it involves a type I hypersensitivity reaction, although some food allergy reactions also might be immune complex-mediated.[31] In another case history in the literature, terbinafine has been associated with a hypersensitivity syndrome consisting of fever, pruritic eruption, lymphadenopathy and hepatitis 10 days after the start of oral terbinafine.[32] No arthralgia was mentioned in this patient. Another hypersensitivity syndrome was described in a 66-year-old male who developed a cutaneous eruption, fever, lymphadenopathy and hepatic dysfunction after 4.5 weeks of therapy.[33] Our patient H also had abnormal liver function tests, and a skin reaction with erythema and peeling. Terbinafine has in incidental case reports also been associated with severe drug eruptions such as toxic epidermal necrolysis,[7,8] erythema multiforme,[8–10] Stevens Johnson Syndrome[11] and acute generalized exanthematous pustulosis.[34,35] Also, drug- induced psoriasis,[4,36] cutaneous lupus erythematosus[37,38] and the exacerbation of a systemic lupus erythematosus [39] have been reported. In our patients, the symptoms were not suggestive of a SLE-like syndrome, but this could not be ruled out, since no antinuclear antibodies were checked.

Other rare skin reactions, associated with the use of terbinafine are a fixed drug eruption[40] and an erythema anulare centrifugum-like psoriatic drug eruption.[41] The description of the symptoms of patient H might resemble a Stevens Johnson syndrome or erythema multiforme. Next to mucosal lesions, a Stevens Johnson syndrome may be accompanied by extracutaneous manifestations, such as arthralgia, liver and kidney disorders and fever.[42,43] In a Stevens Johnson syndrome, an immune mechanism might be involved in the process. Circulating antibody–antigen complexes and complement activation have been demonstrated in the blood and skin lesions of patients.[42] Not only terbinafine, but also other antifungal agents have also been associated with joint disorders. The antifungal antibiotic amphotericin B may cause severe pains in muscles and joints along with many other side-effects.[27] Itraconazole was also associated with a serum sickness-like reaction in a 53-year-old female.[44] As far as we know, there are no signs in mycotic infections that resemble the symptoms presented in our patients. Confounding by indication is therefore unlikely.

In an additional analysis the clustering of the separate symptoms was analysed in more detail. In logistic analysis, next to urticaria two interaction terms were found to be the strongest predictors of the dependent variable. This indicates a clustering of arthralgia and fever as well as arthralgia and urticaria in reports on terbinafine. In the control group, however, no report was present in which all three symptoms were mentioned together. For this reason, the corresponding interaction term indicating the clustering of all three symptoms could not be taken into account in the analysis. All eight patients in our analysis had 'arthralgia'. Because the distinction between arthralgia and arthritis is sometimes difficult to make, we also included the WHO term 'arthritis' in a separate analysis. Also in this situation the variables urticaria and the interaction term arthralgia*fever were statistically significant. The findings of the statistical analysis are in support of a clustering of the symptoms involved, but cannot be considered as conclusive evidence. For methodological reasons, suspicions of new or unexpected ADRs originating from reporting systems only have a signal generating value. In general, further epidemiological studies are necessary to confirm a possible causal relationship between a suspected drug and suspected adverse drug reactions.

Spontaneous reporting systems are primarily designed for the detection of individual symptoms in relation to drug use. These signals can be detected by means of the analysis of individual reports. Also more complex relationships can be studied in SRS databases, such as the signalling of possible drug–drug interactions.[45,46] When two or more adverse events occur in a patient, it is of major interest, but often difficult to determine whether both have been caused by the same or by a different pharmacological or pathological mechanism, i.e. if they are related (part of a syndrome) or coincidental. In this study we have used statistical reasoning to address the question of whether terbinafine-associated arthralgia, urticaria and fever are likely to be related or separate events. We propose that a similar approach may be more widely used in identifying drug-induced syndromes in spontaneous reporting databases.

CONCLUSION

Reports to the Netherlands Pharmacovigilance Foundation Lareb are suggestive of an association between the use of the antifungal agent terbinafine and the occurrence of arthralgia, fever and urticaria. Case series as well as the results of the statistical analysis show a clustering of symptoms among reports of patients using terbinafine. These findings might point towards a shared aetiology of these symptoms, presumably an immunological reaction. If arthralgia develops, it is important to inquire about involvement of other organ systems and to have additional laboratory examinations done. Considering the possibility of an immunological reaction, it is advisable that the use of terbinafine in these patients should be stopped.

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APPENDIX 1

Patient A is a 44-year-old woman who developed arthralgia of the right wrist 18 days after the start of terbinafine, 1 week later this extended to her right knee. Concomitant medication used was doxycycline 100 mg (indication for use unknown) 7–14 days after the start of terbinafine. An oral contraceptive ethinyl estradiol/desogestrel was used concomitantly. The complaints hampered her daily activities. Laboratory examination revealed no abnormalities. C-reactive protein levels, ESR, streptococcal antibody titre and rheumatoid factor were within normal limits. The use of terbinafine was stopped and she was treated with ibuprofen 400 mg three times daily. She fully recovered. There was no history of joint disorders, traumata, liver or kidney function disorders or rheumatological or allergic disorders. There were no joint disorders in the family history. No rechallenge was carried out. Terbinafine had not been used previously.

Patient B is a 41-year-old male who developed arthralgia of shoulders, hips and elbows, 10 days after the start of terbinafine. All joints were symmetrical affected. There were no additional signs of arthritis. There was no fever, lymphadenopathy or skin disorders. Laboratory examination revealed: ESR 5 mm, GGT 11 mmol/l, Hb 8.9 mmol/l, leukocyte count 5.4×10^9 / l. The use of terbinafine was stopped and he was treated with nabumetone 1 g twice daily. He fully recovered. Concomitant medication used was miconazole creme, beclomethasone nasal inhaler and ibuprofen 400 mg three times daily when needed. The latter drug was used because of chronic backache.

Patient C is a 42-year-old female, who developed pains of hands and feet 1–2 days after the start of terbinafine. She used no concomitant medication. Unfortunately, no additional information was received.

Patient D is a 41-year-old male who developed pain on flexion and extension of wrists and knees, 2 weeks after the start of terbinafine. There were no additional signs of arthritis. No additional laboratory testing was done. He fully recovered immediately after stopping the use of terbinafine.

Patient E is 37-year-old female, who developed signs of 'generalized' arthralgia (no joints specified), 10 days after the start of terbinafine. On physical examination no abnormalities were found. She was treated with ibuprofen 400 mg. On laboratory examination, the leukocyte count of 7.2×10^9/l, ALT and GGT had not increased. In the blood smear, some atypical lymphocytes were found. After 1 week re-examination of blood revealed no abnormalities. She fully recovered after 1 month.

Patient F is 66-year-old male who developed urticarial rash, fever, headache, vomiting and diffuse arthralgia (no joints specified) 2 weeks after starting terbinafine. He used a homeopathic drug as concomitant medication. He was treated with terfenadine and prednisolone. Laboratory examination revealed no abnormalities (Hb, ESR, leukocytes, and blood smear). After stopping terbinafine, he fully recovered.

Patient G is a 34-year-old male, who developed signs of arthritis (no joints specified) and generalized urticaria 10 days after he started using terbinafine. Concomitant medication used was miconazole cream. He was treated with terfenadine, prednisone and promethazine. Unfortunately, additional information could not be retrieved, since the patient had moved and his former GP did not have his present medical history.

Patient H is a 50-year-old male, who developed pains in almost joints and myalgia 1–2 days after the start of terbinafine. The arthralgia was symmetrically distributed. There were no signs of arthritis. One week after the start of terbinafine, he developed anorexia, vomiting, and abdominal pain and complained of smell and taste disorders. Also a rash, stomatitis and peeling of the skin developed. He had a fever of 39°C. Laboratory tests revealed the following abnormalities: leukocyte count, 4.8×10^9/l; ESR, 5 mm; Hb, 9.3 mmol/l; ALT, 1672 U/l; LDH, 869 U/l; GGT, 202 U/l; kidney function normal. Concomitant medication used was budesonide inhaler. He was treated with diclofenac and domperidone and fully recovered after 9 weeks.

All patients were treated with terbinafine 250 mg once daily. Patients A–E and H were treated for onychomycosis. The indication for use of patient G was not known. Patients A, B, D–F and H had no history of joint disorders, traumata, liver or kidney function disorders, rheumatological or allergic disorders. Neither were there any joint disorders in the family history of any of the patients. These data could not be retrieved for patients C and G. No rechallenge was carried out in any of the patients.

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