

Serious Adverse Events Reporting on Systemic Terbinafine: A Danish Register-based Study

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Accepted October 14, 2010.

Terbinafine is an antifungal medication used mainly for the treatment of dermatophyte skin, hair and nail infections. The use of topical and systemic terbinafine antifungal medication has increased over the past ten years. This increase is due mainly to an increased level of treatment of onychomycosis, as people have become less tolerant of nail changes, and with increased exposure to advertising for antifungals (1).

An increased number of patients now receive systemic terbinafine, which is generally well tolerated (2, 3) but can cause adverse reactions, some of which are severe and life-threatening (4). It is important for doctors prescribing systemic terbinafine to be familiar with the severe adverse reactions (SAEs) related to the drug, in order to be able to evaluate the risk against the possible benefits of the product and inform patients accordingly. The objective of this study was to describe SAEs due to systemic terbinafine reported to the National Danish Adverse Reaction Database over a 10-year period. The study design gives a safety profile of the agent in actual clinical practice, in an uncontrolled setting and without patient exclusions.

MATERIALS AND METHODS

National Adverse Reaction Database

Physicians in Denmark are obliged to report all serious or unexpected adverse reactions due to pharmaceutical products. Physicians are also obliged to report known or non-serious adverse reactions during a pharmaceutical product's initial 2 years on the market. The reports are registered in a National Adverse Reaction Database managed by The Danish Medicines Agency.

A SAE is characterized by an incident related to the use of a pharmaceutical product, which involves hospitalization or prolonged hospitalization, causes significant disability or incapacity, causes a life-threatening condition or causes congenital abnormality. All reports of adverse events related to terbinafine from 30 April 1998 to 30 April 2008 were extracted from the register according to Anatomical Therapeutic Chemical (ATC) code D01BA02.

National Register of Medicinal Product Statistics

The National Register of Medicinal Product Statistics (NRM) was established in Denmark in 1994 and is available for research purposes. Information in the NRM is categorized according to ATC codes. The information that can be extracted includes name, trade name, dose, number of packages and defined daily doses (DDD), as set by the World Health Organization (WHO). We extracted the consumption of the individual pharmaceutical products, measured in DDD, which is the average adult dose used for the main indication. The DDD for terbinafine is 0.25 g. The total consumption from the primary and secondary health care sectors was extracted. The figure was derived by use of the aforementioned ATC code.

RESULTS

In the 10-year period studied, 263 patients reportedly experienced an adverse event due to terbinafine (females 140, males 123); of these 78 (26%) patients experienced a SAE (46 females, 32 males). The mean age of patients experiencing a SAE was 52.9 years (age range 17–87).

The distribution of reports is shown in Fig. 1. Although the number of patients experiencing a SAE varied from year to year, over time there is a trend towards an increased number of such reports. Thus, only 32% (25/78) of all reported SAE cases are in the first 5 years compared with 68% (53/78) in the last 5 years. However, the prescription of terbinafine has also increased over time (see below).

Since most patients represented more than one adverse event, the total number of adverse events reported in the period was 493, of which 197 were considered serious.

Reported SAEs were divided into system organ classes. The most prominent category of SAE was "skin and subcutaneous tissue disorders" (30%, $n=60$) followed by "nervous system disorders" (13%, $n=26$). "Ageusia", the inability to taste, accounted for a large proportion of the nervous system disorders (38.5%, 10 of 26). The category of "skin and subcutaneous disorders" comprised both less serious disorders, such as subacute cutaneous lupus erythematosus ($n=4$), and extremely serious and life-threatening adverse events, such as erythema multiforme ($n=8$), exfoliative dermatitis ($n=8$), Steven–Johnson's syndrome ($n=2$) and toxic epidermal necrolysis (TEN) ($n=2$).

Hepatobiliary disorders ($n=7$) and increases in liver enzymes ($n=22$) together accounted for 15% of the reports. Gastrointestinal disorders ($n=17$) and general disorders ($n=17$) each accounted for 9%. Blood and lymph, cardiac, congenital infectious, metabolic, psychiatric, respiratory and vascular disorders were all represented, but with fewer

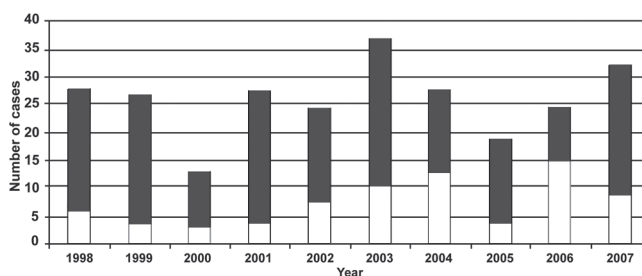


Fig. 1. Number of patients in Denmark reported to have experienced an adverse event related to systemic terbinafine between 1998 and 2008. The number of patients reported to have experienced a serious adverse event are shown in white.

than ten cases each. One case of death was reported during the period studied: an 86-year-old man died of pancytopenia on receiving treatment for fungal skin infection.

The level of consumption of the product in the primary health system and hospitals, as measured by DDD rose steadily in the period studied, from 929,000 DDD in 1998 to 3,132,000 DDD in 2007. The number of SAE cases correlated to the DDD of terbinafine for the whole period was 0.0042 (78 SAE cases/18,534 DDD). The figures were similar in the first and second half of the period viz. 0.38×10^5 (25 SAE cases/6,477,000 DDD) and 0.44×10^5 (53 SAE-cases/12,057,000 DDD), respectively.

DISCUSSION

This descriptive register study provides insight into SAEs, including deaths, related to systemic terbinafine treatment. The study is based on data from The National Adverse Reaction Database, which is used by the Danish Medicines Agency to keep pharmaceutical products under surveillance. This design provides a safety profile of the agent in actual clinical practice. Some data limitations should be mentioned. Any incident suspected to be related to terbinafine can be reported, but cause-relations analysis is not necessarily made and the adverse events may only be temporally, but not causally, related to the intake of terbinafine. This would overestimate the prevalence of adverse events. On the other hand, some actual adverse events may go unnoticed, including symptoms occurring years after initiation of systemic therapy, leading to an underestimation of the prevalence. Well-known adverse events related to terbinafine, which has been on the market for more than 2 years, are less likely to be reported.

There was limited information available relating to the indication for which terbinafine was subscribed. More than 50% of the SAEs reported occurred during treatment for the indication onychomycosis. The actual proportion is thought to be even higher, as, in Denmark, the frequency of dermatophyte infections in hair is lower than in nails (1), and as oral treatment of dermatophyte infection of the skin is indicated only when the infection is severe. Furthermore, the duration of treatment of onychomycosis is longer (12 weeks compared with 2–4 weeks for skin lesions) making drug exposure time in each case longer. The mean age of all patients treated with terbinafine was relatively low (approximately 50 years). This indicates that the increase in terbinafine use is due not only to an increased elderly population, at greater risk of tinea unguium, but also to increased awareness and lack of tolerance of nail infections among the general public, associated with increased exposure to advertising for antifungal treatment.

We related the number of SAE-cases to consumption, measured in DDD. The result shows that the high number of SAE-cases in the second half of the observed period could be explained by an increase in

consumption of terbinafine. Safety reports from clinical trials, as well as surveillance studies, have proven good safety records for terbinafine (5–7). In our study, hepatobiliary disorders and the category “Investigations”, which mostly covered an increase in liver enzymes, were among the three most prevalent SAEs reported, indicating a potential risk of hepatic dysfunction in the use of terbinafine. The increase in liver enzymes is usually reversible.

In accordance with former findings, the categories “gastrointestinal disorders” and “skin and subcutaneous tissue disorders” were well represented (2, 3), including life-threatening diseases.

When reviewing the risk of SAEs related to a pharmaceutical product, it is reasonable to take into account the indication for which the product is given. One should consider how the disease affects the patient’s life, the likely benefit that can be obtained, and whether alternative treatments exist. In terms of harmless diseases, as in the case of onychomycosis, it is difficult to accept that treatment may result in life-threatening SAEs, even though these are relatively rare.

In conclusion, prescription guidelines must be observed with care, such treatment being restricted to microbiologically proven mycosis only, and patients must be properly informed of the risks involved.

Conflicts of interest: Ditte Marie Saunte received honorary payments for speaking/reimbursement of travel expenses from Galderma, Medinor A/S, Schering-Plough and Swedish Orphan.

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