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How safe is Oral Terbinafine?

This a question that crops up regularly when speaking to colleagues and patients alike. Terbinafine is an allylamine drug used in the treatment of onychomycosis. Despite the drug being available since the early 1990's, there has always been some hesitancy about its potential side effects particularly those affecting the liver when taken orally. In this article, I will have a look at the published safety data on its use.

Terbinafine, as a new antifungal, effectively was a game changer in the treatment of onychomycosis when it entered the UK market in the 1991 (Latterly 1998 in the USA). Before this time, the choices for treatment of fungal nails were limited. Topical treatments were often disappointing. Until this time, oral griseofulvin and ketoconazole were the drugs of choice indicated for dermatophyte nail infection orally but they were far from effective (1). They required long courses and had a narrow spectrum of activity. Many patients would give up due to the unpleasant side effects. So the idea of a new, modern antifungal drug was appealing with early studies suggesting it was much more effective than griseofulvin (2) with double the mycological cure rate. This was latterly shown to be the case with terbinfaine showing superiority in numerous studies (3).

The drug became widely used in the treatment of dermatophyte nail infections. Like many drugs, terbinafine is metabolised by the liver and excreted by the kidneys, consequently a reduction in function of either of those two organ systems could result in serious problems if prescribed to the wrong patient. The issue of liver disease (hepatotoxicity) with terbinafine has been long known, with the drug manufacturers highlighting that it should not be prescribed for patients with liver disease (Lamisil Monograph, Novartis 2013). Terbinafine, like nearly all classes of medications, has been shown to induce idiosyncratic liver injury or drug induced liver injury (DILI). The causes of DILI are diverse although pre-existing liver disease can play a part, in otherwise healthy individuals its aetiology is unclear although genetic susceptibility appears to play a role (4). Consequently, The British National Formulary consequently advises it should not be used in patient with known liver disorders and for those prescribed the drug, they should have liver function tests before commencing the drug and then periodically after 4–6 weeks of treatment (British National Formulary online) to assess liver function. The test monitors the levels of liver enzymes present in the bloodstream. Elevation of these enzyme levels can signal early disturbances in liver function.

There is a view that oral terbinafine is a particularly dangerous medication in relation to causing hepatotoxicity (5). The most common side effects in patients taking the drug include gastro-intestinal upset, taste disturbances, headache and rashes but liver problems may not be as common as perceived. In 1996 a British study (6), researchers reviewed 9879 patients who had taken the drug. Half of these had concurrent illnesses and were taking other medications at the same time. Of the cohort, 14% reported various side effects with only half of these thought to be related to the terbinafine as reported by their physicians. Liver problems were only reported in 0.1% of patients (14 cases) of which 10 cases were classified as minor and transient elevations in liver enzymes. In

addition, some of these patients were found to have pre-existing history of liver disease (gall bladder disease, alcohol related changes, hepatitis and cirrhosis. There were no terbinafine associated deaths.

The National Library of Medicine Liver Toxicity Database report on terbinafine (7) paints a similar picture reporting that less than one percent of patients see an increase in liver enzymes in the bloodstream and most resolve with stopping treatment. It estimates the probability of developing elevated liver enzymes levels requiring stopping treatment is about 0.31% for 2 to 6 weeks' treatment and 0.44% for treatment lasting longer than 8 weeks. It goes on to state that clinically apparent liver injury from terbinafine occurs rarely, in around 1 in 50,000 to 120,000 prescriptions.

So what are the symptoms of drug induced liver injury?

One final piece of research, worthy of a mention appeared in the British Journal of Dermatology (8). In this work 173 cases of terbinafine induced liver injury were reviewed. Interestingly, they discovered that terbinafine induced liver injury can occur at any time whilst taking the drug but most of these cases occurred on average at 30 days after commencing drug therapy. Patients typically reported symptoms such as jaundice, but include nausea, vomiting, abdominal pain, fatigue, anorexia, general itching and dark urine. Despite guidelines issued by the BNF of regular liver function monitoring for patients on terbinafine, none of these patient's liver damage was discovered by testing – it was all patient reported. However, others have highlighted cases where detection was made with blood tests in otherwise "healthy" patients (9).

Summary

As with most classes of drugs, terbinafine can potentially lead to liver problems. However, the data from the above suggests that oral terbinafine is safer than perhaps it is perceived, and minor side effects are far more likely for most patients than serious liver damage. Data from studies suggest the risk of serious liver injury to be between 1 : 50 000 – 1 : 120 000. Despite its rarity, patients taking terbinafine who exhibit any of the symptoms of liver problems (nausea, vomiting, abdominal pain, fatigue, anorexia, general itching and dark urine) should urgently be referred for further assessment.

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