



Newer drugs and overall costs of treating onychomycosis

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Onychomycosis is caused by dermatophytes, yeasts, and non-dermatophytic fungi and the frequency of each group of fungi responsible for the infection varies across the world. These differences primarily arise due to the differences in geographic and climatic conditions, and in some instances due to the different clinical types of onychomycosis included or reported in the studies [1]. Published European and United States prevalence of onychomycosis ranges lie within 3-22% [2-4]. The period and point prevalence of dermatophyte onychomycosis in Spain was 2.6% and 1.7% in 1992-93, with women and older age group individuals having higher prevalence than men and 55 years and younger individuals [5]. This study further estimated that only 38.6% of those who suffered from dermatophyte onychomycosis sought medical advice, and only 14% of those who did, consulted a dermatologist. Treatment for onychomycosis has changed from nail avulsion to pharmacotherapy with nail lacquer and oral anti-fungal agents. With newer oral antifungal agents available now in most parts of the world, if therapy is initiated at an early stage, complete cure of this fungal infection is possible. However, the acquisition costs of most of these newer anti-fungal drugs are greater than the traditional therapies. It is therefore of no surprise to see a sudden interest and rise in pharmacoeconomic evaluations in this therapeutic field [6]. The goal of a pharmacoeconomic evaluation is to meet the objectives of allocative and technical efficiency. Allocative efficiency is concerned with the allocation of resources between types of services within the health sector, in a way that results in greatest gain. Whereas, technical efficiency is concerned with the optimal use of these health care resources in a way that maximizes output (at a given level of resources) or minimizes expenditure (for a given level of output) while maintaining adequate quality of services. The purpose of this paper is to summarize the economic impact of the newer antifungal agents available for treating onychomycosis. Only original pharmacoeconomic research studies published in the English literature that included onychomycosis cases will be discussed in this paper.

Oral antifungal pharmacotherapy

Griseofulvin and ketoconazole were the first generation oral antifungal agents that were approved to treat onychomycosis and other dermatomycoses in humans. However, since the 1990s, the introduction of terbinafine, itraconazole, and fluconazole, has made the first generation of antifungal agents a less preferred choice. Reasons for this change in treatment pattern included higher mycological and clinical cure rates, lesser relapse rates, better tolerability, and shorter duration of therapy with the newer agents. Nevertheless, these new oral antifungals have a premium price compared to the first generation oral antifungals. For example, the 2002 retail price (cash paying patient) in the United States for 100 tablets of griseofulvin (250 mg), ketoconazole (200 mg), terbinafine (250 mg), and itraconazole (100 mg), is \$58.87, \$81.00, \$896.87, and \$941.87, respectively. These prices would however vary depending on one's health insurance status (e.g. Medicare vs. private managed care organizations) and prescription plan (e.g. co-pay for generics vs. brand-names). In the United States, itraconazole and terbinafine are currently available only in the brand-name form.

Pharmacoeconomic evaluations

One of the first pharmacoeconomic studies published in the English literature was conducted by the Onychomycosis Study Group [7]. This study was a multinational cost-effectiveness analysis comparing two older (griseofulvin and ketoconazole) and two newer generation oral treatments (terbinafine and itraconazole) for finger and toenail onychomycosis, conducted from a government's perspective. The pharmacoeconomic decision analytic model included all relevant factors affecting costs, namely drug acquisition cost, drug administration cost, routine medical care, laboratory tests, and adverse drug reaction management costs in 13 countries: Austria, Belgium, Canada, Finland, France, Germany, Greece, Italy, The Netherlands, Portugal, Spain, Switzerland and the U.K. Clinical end-points, namely clinical success rates, relapse rates, and adverse effect rates were derived from a worldwide meta-analysis of published studies. Although relapse rates, and adverse effect rates were not reported, terbinafine had the highest success rate of the four clinical comparators for primary treatment of onychomycosis of the finger (95%) and toe (78.3%). Terbinafine was associated with the highest effectiveness (defined as disease-free days) in relation to cost for all countries, or in other words possessed the lowest cost-effectiveness ratio. A rank order stability analysis, a form of threshold analysis, showed that the results were robust over the provided ranges (elasticities were less than 1). Canadian specific results from this multinational study

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were reported as an independent study appearing in the same issue of the journal [8]. The pharmacoeconomic conclusions for Canada remained the same as the previous. The same group of researchers, using the same clinical and cost data as the previous study carried out a second study [9]. The addition to the later study was indirect costs associated with finger and toenail onychomycosis. Indirect costs were those associated with receiving therapy, including assessments and follow-up visits for monitoring or for treatment of adverse drug reactions, in the form of expenses as transportation and lost wages due to time away from work. Therefore the cost-effectiveness ratios remained the same as the previous study [8] when the perspective was that of the Canadian government payer. The order of results remained the same even when indirect costs (or a patient's perspective) were included because patients treated with terbinafine required less medical care and had substantially lower indirect costs compared to the other two comparators that required close monitoring to avoid toxicity and undesirable side effects.

In addition a relative cost-effectiveness study of the most commonly prescribed antifungal therapies in Germany, that is, oral itraconazole (continuous, and pulse), oral terbinafine, and a topical ciclopirox nail varnish was conducted [10]. The time horizon selected for this analysis was 1.3 years (15 months), as compared to previous studies where it ranged from 2-3 years depending on the site of infection. Cost and efficacy data were collected from interviews carried out with dermatologists and meta-analyses, respectively. Itraconazole (pulse dosing) was most cost-effective followed by oral terbinafine, ciclopirox nail varnish, and itraconazole (continuous dosing). However, sensitivity analysis indicated that itraconazole (pulse dosing) and terbinafine had similar cost-effectiveness ratios.

Marchetti *et al.* [11] performed the first U.S. based pharmacoeconomic evaluation comparing oral griseofulvin, itraconazole, ketoconazole, and terbinafine using the previously constructed decision-analytic model by the Onychomycosis Study Group. Clinical management patterns were assessed to identify and quantify medical resource use for treating both toe and fingernail onychomycosis. Treatment efficacy data and costs for physician fee were derived from a meta-analysis and New York Metropolitan Medicare charge data respectively. Sensitivity analysis confirmed that terbinafine was the economical and cost-effective treatment for patients, supporting the multinational and Canadian studies. Gupta performed a pharmacoeconomic evaluation of toenail dermatophyte onychomycosis on a similar set of drugs as the Onychomycosis Study Group (fluconazole was used instead of ketoconazole) [12]. A 5-step approach was used in this study. The first step was to identify the comparator drugs and their dosage regimens. Step two was to identify the medical practice and resource-consumption patterns associated with the treatment. Step three was to perform a meta-analysis of the efficacy literature that met specified criteria. In step four the treatment algorithm for the management of onychomycosis was constructed for each drug and cost-of-regimen analysis, and cost-effectiveness analysis were calculated. In step five, a sensitivity analysis was performed. In contrast to the previous analyses, terbinafine had the lowest cost-effectiveness ratio. The main advantage of this study, however, compared to the previous pharmacoeconomic studies was the inclusion of itraconazole pulse therapy as a treatment option. Due to the previous relative lack of data on itraconazole pulse therapy, researchers had voluntarily excluded this treatment regimen.

The majority of older pharmacoeconomic studies evaluated the role of newer oral antifungals versus the older antifungals. All of these studies showed that the newer generation oral antifungal, namely terbinafine, was more cost-effective when compared to griseofulvin, or ketoconazole. More recently, published pharmacoeconomic studies have focused on assessing the cost and outcomes between the newer oral antifungals themselves. A cost-effectiveness analysis was performed using the data from terbinafine versus itraconazole in a onychomycosis randomized clinical trial study [13]. The results of the trial itself had concluded that terbinafine was more effective than itraconazole with cure rates of 45.8% vs 23.4%. Cost calculations were estimated for six European countries that included costs for medication, physician visits, laboratory tests, and management of adverse events and relapse. In five out of six countries, the costs for terbinafine were significantly lower than those for itraconazole, indicating that terbinafine was the dominant strategy (i.e. less expensive and more effective), thus not necessitating a formal economic analysis. In Finland, however, the total cost of managing onychomycosis with terbinafine (FMK 3665, FMK 5132) was greater than that for the itraconazole (FMK 2955, FMK 3649), at the end of 12 weeks and 16 weeks, respectively.

Table 1. Comparison of relative cost-effectiveness ratios between the newer generation oral antifungal agents.

Pharmacoeconomic Study	Terbinafine	Itraconazole	Itraconazole pulse therapy
Arikian <i>et al.</i> 1994 [7]*	1.00	1.59	-
Van Doorslaer <i>et al.</i> 1996 [10]	1.11	2.22	1.00
Marchetti <i>et al.</i> 1996 [11]	1.00	1.63	-
Angello <i>et al.</i> 1997 [27]**	1.67	4.75	2.20
Gupta 1998 [12]	1.02	1.73	1.00
Bootman JL 1998 [28]	1.00	1.62 and 1.58	-
Gupta <i>et al.</i> 1999 [29]	1.01	1.94	1.21
Gupta 2000 [30]***	1.27	2.08	1.19
Average Relative CE Ratio	1.14	2.19	1.32

* An average across all countries' relative cost-effectiveness ratio for the toenail onychomycosis is reported.

** This was the only study identified by the authors that evaluated the pharmacoeconomic outcome of terbinafine-pulse therapy that had the lowest cost-effectiveness ratio compared to its comparators.

*** The drug comparators in this study included ciclopirox 8% nail lacquer that had the lowest cost-effectiveness ratio compared to the oral antifungal therapies.

The newer oral antifungal agents (e.g. terbinafine) are fungicidal, whereas the traditional oral antifungal agents (e.g. griseofulvin) are fungistatic. This accounts for the shorter treatment regimens for the newer antifungal agents. Thus, with excellent cure rates both short and long term treatment [14, 15], tolerability profile, and the lowest cost-effectiveness ratio, the pharmacoeconomic literature supports terbinafine to be the drug of choice for the treatment of onychomycosis. Table 1 summarizes the pharmacoeconomic outcomes of terbinafine and itraconazole that have been published in the English literature. Compliance with medications, especially when pharmacotherapy is for a long duration, is an important issue and has to be included in any pharmacoeconomic analyses. However, although all studies assumed 100% compliance, the final pharmacoeconomic result may not change as rigorous sensitivity analyses were performed. Pharmacoeconomic analyses of the newer oral antimycotic agents have thus demonstrated that a more expensive per unit drug can be the most cost-effective therapeutic alternative.

Health-related quality of life impact

Recently, several studies have documented the impact of onychomycosis on patients' health-related quality of life (HR-QOL) [16-20]. Collectively, these studies concluded that onychomycosis is not a mere cosmetic problem, but is associated with significant degree of psychosocial morbidity for a large proportion of patients [21]. Although results of one particular study [20] suggested that oral antifungal treatment may provide a greater HR-QOL benefit than traditional surgical remedies, further evidence in the form of a formal study is needed to determine the differential effects of the new generation oral antifungal regimens on patient HR-QOL in the general (i.e. outside the clinical trial setting) as well as special populations (e.g. diabetes or immunocompromised individuals).

Discussion and conclusion

Despite having greatly improved pharmacotherapy for onychomycosis, 20% treatment failure rates (sometimes up to 20-50%) have been observed with the newer antifungal agents [22]. Treatment success is depen-

dent on numerous factors, including patient compliance, lack of drug penetration, drug interactions, and finally fungal resistance [23]. Current studies have proposed the use of combination therapy, as a new treatment strategy to overcome this problem [24]. The hypothesis is that a combination treatment (e.g. concomitant use of an oral and a topical drug would produce synergistic activity) would achieve higher cure rates as compared to monotherapy with a single antimycotic agent, especially in treating the severe form of the disease [25]. A pilot pharmacoeconomic analysis was included as a part of the previous investigation [26]. The cost-per-cure assessment for a 12-week regimen was least (≈357.8) for the combination therapy (oral terbinafine + amorolfine lacquer) when compared to treatment with oral terbinafine alone (≈458.4). However, the authors did not describe in detail the pharmacoeconomic methodology (e.g. types of costs used, or performing a sensitivity analysis), making the results of the study less robust. Future pharmacoeconomic studies need to substantiate the conclusions of the above-mentioned study, and determine whether combination therapy is cost-effective compared to monotherapy with newer generation antifungal agents not only in the short run but also more importantly in the long-term.

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