

Modeling the Cost-Effectiveness of Oral Therapy for Nail Fungus

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Abstract

Onychomycosis (fungal infection of the nails) affects 15% to 20% of all adults and can result in pain, disfigurement, and decreased quality of life. A clinical decision-analysis model was developed to compare the costs and outcomes of itraconazole, an antifungal agent recently approved by the Food and Drug Administration for the treatment of onychomycosis, with those of standard therapy with griseofulvin. Data were derived primarily from a random-effects meta-analysis of published studies and from a clinical panel of experts. Outcomes included adherence to therapy, adverse events and their treatment, clinical response, and occurrence of relapse. The model also accounted for a repeated course of therapy and switches to an alternative therapy. Relative to griseofulvin, itraconazole was consistently associated with less discontinuation of therapy, fewer adverse events, and higher cure rates. Itraconazole was shown to be highly cost-effective compared with griseofulvin, with a marginal cost of \$1.56 per additional disease-free day for fingernail infections and a marginal cost saving of \$0.30 per additional disease-free day for toenail infections.

(Am J Man Care 1996;2:59-66)

Onychomycosis (fungal infection of the nails) is the most common type of nail infection, with estimates of its incidence ranging from 2% to 13%.¹ It is more common in adults, among whom the incidence is 15% to 20%, than among children. Although onychomycosis is not life threatening, it can result in pain, disfigurement, and a decreased quality of life.²

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This study was funded by Janssen Research Foundation, 1125 Trenton-Harbourton Road, Titusville, NJ 08560-0200.

For years, griseofulvin was the only drug approved by the Food and Drug Administration (FDA) for onychomycosis and has been the drug used most commonly for treatment of this disease. However, a high percentage of patients administered griseofulvin experience adverse events, and the therapy has low efficacy.^{2,3} Itraconazole, an antifungal agent recently approved by the FDA for the treatment of onychomycosis, has been shown to have significant efficacy and a potentially more-favorable adverse-event profile for onychomycosis patients, although its unit cost is higher than that of griseofulvin.

In the current era of healthcare cost containment, the costs of new technologies relative to their health outcomes must be examined. Therefore, we have developed a clinical decision-analysis model to compare the costs and outcomes of itraconazole with those of griseofulvin for treatment of onychomycosis.

... METHODS ...

A decision model was developed to compare the costs and outcomes of itraconazole with those of griseofulvin for the treatment of onychomycosis. Development of the model involved review of published literature relevant to the treatment of onychomycosis, to obtain information on treatment patterns and outcomes. A questionnaire was then developed to elicit additional data on onychomycosis therapy from a group of seven clinical experts. Both the data obtained from the clinical experts and data from the published literature were synthesized and incorporated into the decision model. Separate components of the model were produced for the treatment of fingernail infections and the treatment of toenail infections.

The model compares the costs and outcomes of onychomycosis therapy with itraconazole versus griseofulvin. Standard national values were used to assign costs to treatment events. Cost-effectiveness was expressed as the marginal cost per additional disease-free day gained within a 2-year period starting

at treatment initiation. Outcomes include adherence to therapy, occurrence of adverse events and their treatment, clinical response, and occurrence of relapse.

Structure of the Model

The basic model structure is represented in the Figure, which applies to each of the two therapeutic agents. The parameter values associated with each node of the decision tree were derived from the literature or from responses obtained from the clinical experts, or both (see Model Parameters).

At node 1 in the decision tree, patients who have begun onychomycosis therapy with a given agent may experience adverse events. A proportion of the patients who do not experience adverse events discontinue therapy as a result of nonadherence (node 2); the remainder adhere to their initial therapy. Patients discontinuing therapy as a result of nonadherence receive no further treatment and reach an end point in the model. Of those adherent to initial therapy and who are cured (node 3), a proportion remain cured (node 4) and reach an end point in the model. Those who relapse at node 4 receive an additional course of the same drug, discontinue treatment, or receive a course of a different drug (node 5). At this point in the model, patients switching to a different drug are placed on the comparator medication (ie, griseofulvin patients switch to itraconazole and vice versa). The costs and outcome probabilities for patients receiving a repeat course of the same drug or switching to the alternative drug are the same as those for patients initially receiving that therapy. Patients who are adherent to therapy but who are not cured (node 3)

receive an additional course of the same drug, discontinue treatment, or switch to the alternative drug (node 6).

Patients experiencing adverse events (node 7) receive medical care for the adverse events and then either continue with their drug or discontinue therapy (node 8). Those who stop therapy may terminate treatment altogether or switch to the alternative drug (node 9). Patients who continue their initial drug or receive the alternative drug follow subsequent branches (not shown in the Figure) that are identical from node 2 on for the remainder of that course of therapy.

Data Sources for the Model

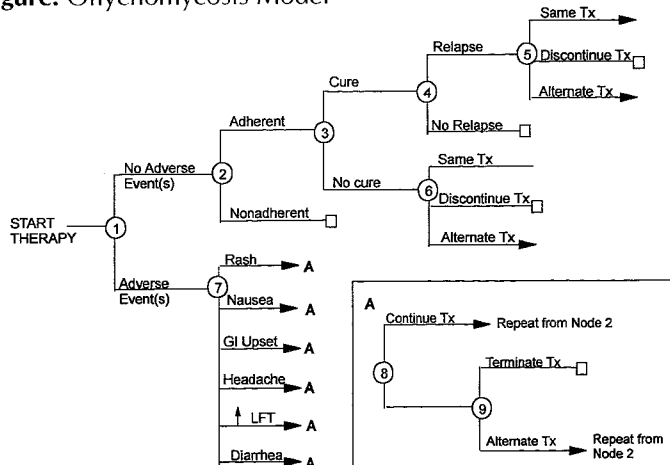
Some of the information used to develop the treatment patterns and probabilities for the decision model was obtained from the published literature. Articles and reports were assessed for quality and appropriateness of research methodology. Only findings from scientifically credible studies were included from articles specifying inclusion and exclusion criteria, treatment protocols, types of infections, outcome measures, and results for all patients enrolled in the study.

Patients were classified as having been successfully treated if published reports stated that they were "cured." Criteria for "cure" were the absence of clinically abnormal nails and negative mycology findings, by culture, microscopy, or both. Patients achieving outcomes indicating less-than-complete resolution of onychomycosis, such as "partial cure" or "marked improvement," were not considered to have attained successful outcomes.

Parameter values obtained from documented sources included probabilities of the following: occurrence of any adverse event, occurrence of specific adverse events, adherence to therapy, clinical response, and occurrence of relapse. Random-effects meta-analysis⁴ was used to combine efficacy data from 13 identified studies.^{3,5-16} When more than one source of data was available for other model parameters, a weighted point-estimate was used.

Expert opinion was used as a data source only when information required by the model could not be obtained in some other way. Examples of such parameters include the types and frequencies of diagnostic tests conducted during onychomycosis therapy; treatment patterns and

Figure. Onychomycosis Model



probabilities after occurrence of adverse events; and the probabilities of receiving an additional course of the same drug, discontinuing therapy, or receiving the alternative drug in the event of clinically ineffective treatment, relapse, or discontinuation of therapy after adverse events.

Seven clinical experts in the United States were selected to participate in the study on the basis of their experience with treatment of onychomycosis, diversity of practice setting (managed care organization, private practice, and tertiary care setting), and geographic diversity. A mail questionnaire was developed specifically for this study to elicit expert opinion on the necessary parameters. Information from returned questionnaires was used to determine median parameter values, for formulation of general treatment patterns for the model.

Parameters of the Model

Table 1 presents the major parameters and values used in the decision model. The probabilities of clinical events (eg, adverse events, adherence to therapy) were derived from published literature, as described. The efficacy data were derived from the meta-analysis. The studies in the meta-analysis included diverse patient populations. Some of the studies used a dose of itraconazole for some patients during the initial weeks of treatment that was lower than the labeling dose used for modeling (200 mg/day). The majority of the studies that included griseofulvin used a dose of 500 mg/day, rather than the labeling dose of 750 mg/day selected for this model. For consistency, current labeling information was used to determine the dosage for both drugs in the model. The somewhat lower doses in the published studies imply that drug efficacy and the probability of adverse events for both drugs included in the model are conservative estimates. Probabilities relating to the course of therapy after adverse-event-induced discontinuation, inadequate clinical response, or

relapse were based on information provided by the clinical experts.

Table 1 shows the incidence of specific adverse events among individuals who experienced any such event. Incidence rates were derived from published literature, and only adverse events reported in more than one report were included in the model. The probability of receiving treatment for specific adverse events ranged from 10% (eg, headache, changed sleep patterns) to 100% (eg, gastrointestinal upset, diarrhea, increased liver function test values); the probability of continuing treatment after occurrence of these events ranged from 10% (eg, skin rash) to 90% (eg, headache). These probabilities were obtained from the clinical experts.

Resource Utilization and Costs

The clinical experts provided data on treatment patterns and outcomes after occurrence of adverse events. The model includes direct medical costs of

Table 1. Model Parameters and Probabilities

Parameter	Therapeutic Agent	
	Itraconazole (%)	Griseofulvin (%)
Probability of Any Adverse Event	18.9	37.0
If Any Adverse Event, Probability of:		
Skin Rash	10	12
Nausea	35	18
Gastrointestinal upset	25	18
Diarrhea	--	29
Headache	10	--
Changed sleep patterns	20	18
Increased liver function test values	--	6
Probability of Adherence to Therapy	94	85.1
Probability of Adequate Clinical Response		
Fingernail infection	82.9	58.5
Toenail infection	69.8	25.8
Probability of Relapse*	22.4	18.5
After Therapy Discontinuation Due to Adverse Events, Probability of:		
Termination of therapy	80	35
Repeat course of same therapy	0	0
Subsequent course of alternative therapy	20	65
After Inadequate Clinical Response, Probability of:		
Termination of therapy	75	40
Repeat course of same therapy	10	10
Subsequent course of alternative therapy	15	50
After Relapse, Probability of:		
Termination of therapy	30	50
Repeat course of same therapy	50	0
Subsequent course of alternative therapy	20	50

*Among those experiencing adequate clinical response.

treatment for onychomycosis and direct costs associated with treatment of adverse events, including costs for drugs, monitoring of tests, and physician visits. All costs were calculated in 1994 dollars, using the appropriate Consumer Price Index inflator where necessary. The model was developed from a societal perspective. Indirect costs are not included.

The cost of itraconazole was based on labeling information for dosage and therapy duration (200 mg/day for 12 weeks in the base case). Clinical trial data are not yet available for fingernail infections, which generally require a shorter course of therapy than do toenail infections. The same duration and cost of itraconazole therapy was used in the model for both sites of infection, resulting in a conservative estimate of therapy duration for fingernail infections. A sensitivity analysis was conducted using a 10-week course of itraconazole for fingernail infections.

For consistency, labeling information also was used to determine the average recommended dose for griseofulvin (750 mg/day), whereas therapy duration was determined by meta-analysis of the published literature (7.5 months of griseofulvin for fingernail infections and 9.4 months for toenail infections). Recent clinical reports suggest that griseofulvin should be administered for as many as 12 months for fingernail infections,¹⁷ and for 12 to 18 months for toenail infections.^{17,18} Therefore, a sensitivity analysis was conducted to include durations of therapy for griseofulvin that were longer than those indicated by the meta-analysis.

Costs for both drugs were based on the 1995 *Physician's GenRx*¹⁹ or *Red Book*²⁰ average wholesale prices.

The base-case cost of a full course of griseofulvin therapy was \$551.08 for toenail infections and \$440.05 for fingernail infections, compared with \$867.09 for a full course of itraconazole for either infection site.

Treatment patterns associated with both drug monitoring and adverse events were based on information supplied by the clinical experts. Monitoring costs include those for liver function tests (LFTs; \$13.62 per test) and complete blood counts (CBCs; \$9.33 per test). The American Medical Association Physician's Current Procedural Terminology (CPT) codes²¹ and corresponding Health Care Financing Administration (HCFA) resource-based relative value scale reimbursement rates were used to determine these costs. The expert clinicians recommended a baseline LFT for itraconazole therapy, with 50% of patients receiving monthly LFTs thereafter; patients receiving griseofulvin therapy were assumed to have received a baseline LFT and CBC, with repeated monitoring for all griseofulvin patients every 3 months. If increased LFT values were observed during routine monitoring, three additional LFTs were performed.

Each outpatient visit to a physician was assumed to be of short duration (15 minutes) and of low complexity. The cost of an outpatient visit for either a new patient or an established patient was \$42.12, based on HCFA reimbursement data. Each treated adverse event was assumed to prompt one visit to a physician. In addition, a 2-week course of the following drugs was included in total treatment costs: Benadryl (Warner Wellcome Health Care Products, Morris Plains, NJ) and Cortizone 5 (Thompson Medical Co,

Table 2. Base-Case Model Outcomes

Outcome	Fingernail Infection		Toenail Infection	
	Itraconazole (%)	Griseofulvin (%)	Itraconazole (%)	Griseofulvin (%)
Discontinue from Decreased Adherence	7.0	15.0	7.2	15.9
Experience Adverse Events	23.3	43.3	23.7	46.1
Discontinue After Adverse Events	8.4	14.5	8.5	15.4
Repeat Course of Same Therapy	9.6	3.1	9.5	5.5
Subsequent Course of Alternative Therapy	6.9	27.5	8.1	37.4
Cured During Initial Course of Therapy	72.6	43.7	61.1	19.3
Relapse After Initial Cure*	16.3	8.1	13.7	3.6
Cure After:				
Initial therapy (without relapse)	56.3	35.6	47.4	15.7
Repeated therapy (without relapse)	5.4	1.1	4.5	0.9
Alternative therapy (without relapse)	2.4	15.5	1.3	17.7
Overall cure**	64.2	52.2	53.2	34.3

*A greater proportion of itraconazole patients than griseofulvin patients were cured during their initial course of therapy, resulting in a greater proportion of the itraconazole population experiencing relapse after initial cure.

**Overall cure includes initial cure without relapse, repeated course of the same drug without relapse, and repeated course of the alternative drug (ie, itraconazole for griseofulvin patients and vice versa) without relapse.

Inc, West Palm Beach, FL), for skin rash; Maalox (Rhone-Poulenc Rorer Pharmaceuticals Inc, Fort Washington, PA), for gastrointestinal upset; and Lomotil (Searle, GD & Co, Chicago, IL), for diarrhea.

... RESULTS ...

Base-case outcomes are presented in Table 2. Unless otherwise indicated, these values reflect the percentage of patients experiencing each outcome over the entire model, rather than for initial therapy only. For example, 7% of patients with fingernail infections receiving itraconazole discontinued therapy as a result of nonadherence. This value represents the sum of patients who discontinued therapy during their initial course of itraconazole plus patients who discontinued therapy during a repeat course of itraconazole or a subsequent course of griseofulvin. Note that, given a 94% adherence rate for itraconazole (as presented in Table 1), at least 6% of patients should discontinue this medication. However, as shown in the figure, individuals experienced adverse events before potentially discontinuing treatment because of nonadherence. As some of the adverse events led to change or discontinuation of therapy, the 6% nonadherence rate was applied to less than the entire population.

Table 2 indicates that roughly 50% fewer individuals who were given itraconazole than were given griseofulvin discontinued the drug as a result of nonadherence, experienced adverse events, or discontinued therapy owing to adverse events. Fewer itraconazole patients received a subsequent course of the alternative therapy (griseofulvin), reflecting the lower incidence of unfavorable clinical outcomes associated with itraconazole. A greater proportion of itraconazole patients than of griseofulvin patients were cured during their initial course of therapy; consequently, a greater proportion of the itraconazole patients experienced relapse after initial cure. In gen-

eral, more favorable outcomes were associated with fingernail infections than with toenail infections.

"Overall cure" in Table 2 refers to the net proportion of patients cured over the entire model. The table shows the proportions of patients cured without relapse with their initial therapy, or cured after repetition of the same therapy or after a subsequent course of the alternative therapy. Because some patients given griseofulvin were switched to itraconazole, which has the higher cure rate, the resulting overall cure rate for griseofulvin increased; switching itraconazole patients to griseofulvin reduced the overall cure rate for itraconazole. Compared with griseofulvin patients, patients receiving itraconazole had an approximately 11% greater likelihood of cure for fingernail infections and an 18% greater likelihood of cure for toenail infections. For both drugs, cure rates for fingernail infections were greater than cure rates for toenail infections.

Table 3 presents the base-case average costs associated with onychomycosis therapy for each drug. Costs included those associated with therapy and treatment of adverse events, averaged for patients experiencing all possible treatment pathways in the Figure. Drug costs represented about 87% of total costs for itraconazole and about 72% of total costs for griseofulvin. The higher drug cost for itraconazole was offset by other costs of therapy, all of which were less for itraconazole than for griseofulvin. The average cost per patient for treatment of toenail infections was \$44 higher for griseofulvin than for itraconazole; fingernail therapy was \$188 higher when itraconazole was used. These amounts are shown as marginal costs in Table 4.

Because itraconazole therapy is associated with improved outcomes but higher costs, it is important to examine the cost-effectiveness of this therapy. Base-case cost-effectiveness results are presented in Table 4. The principle therapeutic outcome—cure—was used as the outcome measure for the cost-effec-

Table 3. Base Case: Average per Patient Cost Associated with Therapy

Cost Component	Average Cost per Patient* (\$)			
	Itraconazole		Griseofulvin	
	Fingernail Therapy	Toenail Therapy	Fingernail Therapy	Toenail Therapy
Drugs	917.61	928.99	618.80	812.41
Monitoring of Tests	38.41	40.24	80.69	98.97
Physician Visits for Therapy	91.52	94.62	153.39	188.88
Adverse Events	8.57	8.71	14.97	15.98
Total	1,056.10	1,072.56	867.85	1,116.25

*Costs were averaged for patients who completed their initial course of therapy, repeated a course of the same therapy, were switched to an alternative therapy, or discontinued therapy at any point during treatment.

tiveness analysis. Cure was expressed in terms of "disease-free days" calculated over a 2-year period starting with the initiation of therapy, as used in a decision-analysis model developed by Arikian et al²² to compare various agents for the treatment of onychomycosis.

"Disease-free days" may be considered a more comprehensive outcome measure than "patients cured." The measure disease-free days reflects the impact of cure rates *and* duration of therapy; if two treatments are equally efficacious, but one requires only half as many days of therapy to achieve a cure, then it should produce twice as many disease-free days. However, the relative number of disease-free days resulting from a given therapy will depend, in part, on the time frame of the analysis; examining the results of therapy over a longer period will result in more disease-free days. As discussed by Arikian et al, a 2-year time frame (rather than a 1-year time frame) allows standardization of results when a long duration of therapy is used.

For fingernail infections, initial therapy with itraconazole resulted in 384.7 disease-free days over 2 years, compared with 263.7 disease-free days for griseofulvin. For toenail infections, the corresponding values were 306.7 and 160.9 disease-free days. Table 4 shows the cost-effectiveness of each drug expressed as the *marginal*, or additional, cost per *additional* disease-free day. This cost-effectiveness ratio expresses the difference in cost between the two treatments divided by the difference in disease-free days between the two treatments, providing information on the added value of the "new" therapy compared with

that of "standard" therapy. The marginal cost per additional disease-free day was \$1.56 for fingernail infection therapy and -\$0.30 for toenail infection therapy. The negative value for toenail infection therapy indicates a cost saving of \$0.30 per additional disease-free day resulting from the lower average cost per patient for itraconazole (Table 3).

To explore the impact of certain parameters of the model on costs and outcomes, we used sensitivity analysis to examine further the cost-effectiveness of itraconazole (Table 4). The first pair of sensitivity analyses examined the impact of clinical efficacy (percentage cured) on cost-effectiveness. For the higher cure rate analysis, the base cure rates (see Table 1) for both itraconazole and griseofulvin were increased by their standard errors, as calculated during the random-effects meta-analysis. For the lower cure rate analysis, base cure rates were decreased by their standard errors. For fingernail therapy, the marginal cost ranged from \$1.43 to \$1.92 per additional disease-free day; for toenail therapy, the marginal cost ranged from -\$0.77 to \$0.45 per additional disease-free day.

A second pair of sensitivity analyses altered the rate of drug monitoring for itraconazole and griseofulvin. The base-case drug-monitoring utilization rates were doubled or halved, with corresponding changes in associated costs. These changes did not affect efficacy rates or other probabilities in the model.

The third pair of sensitivity analyses altered the duration of therapy. First, griseofulvin therapy was increased to 12 months for fingernail infections and to 15 months for toenail infections, with the base-case duration of therapy for itraconazole held constant.

Table 4. Cost-Effectiveness Ratios for Base Case and Sensitivity Analyses

	Fingernail Therapy			Toenail Therapy		
	Marginal Cost	Marginal Number of Disease-Free Days	Marginal Cost per Additional Disease-Free Day	Marginal Cost	Marginal Number of Disease-Free Days	Marginal Cost per Additional Disease-Free Day
Base Case	\$188.25	121.0	\$1.56	-\$43.69	145.8	-\$0.30
Sensitivity Analysis						
Clinical efficacy						
Lower	\$154.67	80.7	\$1.92	-\$123.72	161.5	-\$0.77
Higher	\$223.12	156.0	\$1.43	\$57.21	126.4	\$0.45
Monitoring cost						
Half	\$209.04	121.0	\$1.73	-\$14.80	145.8	-\$0.10
Double	\$146.67	121.0	\$1.21	-\$101.45	145.8	-\$0.70
Therapy duration						
Griseofulvin*	-\$115.38	183.5	-\$0.63	-\$427.05	190.2	-\$2.24
Itraconazole**	\$69.49	118.8	\$0.58	-\$43.69	145.8	-\$0.30

*Increase from 7.5 to 12 months for fingernail therapy and from 9.4 to 15 months for toenail therapy; itraconazole remained as in base case (12 weeks for fingernail and toenail therapy).

**Decrease from 12 to 10 weeks for fingernail therapy; all other durations for itraconazole and griseofulvin as in base case.

This change resulted in cost savings of \$0.63 and \$2.24 per additional disease-free day for fingernail infections and toenail infections, respectively. When the duration of itraconazole therapy was decreased from 12 weeks to 10 weeks for fingernail therapy, the added cost per additional disease-free day decreased from the base-case value of \$1.56 to \$0.58.

... DISCUSSION ...

To estimate the costs and outcomes associated with alternative therapies for onychomycosis, we developed a decision-analysis model. The development of a model was necessary because no published study has reported the full costs and outcomes associated with these comparative agents. Furthermore, any single study considers treatment efficacy in a select population. By using meta-analysis to combine efficacy data and performing sensitivity analysis on key parameters, we have been able to develop a greater appreciation for the impact of differential economic and clinical factors on cost-effectiveness outcomes.

The methodology used by Arikian et al²² in a previous study was similar to the methodology used here. Those researchers developed a basic model structure, gathered information on treatment patterns and outcome probabilities from clinical experts and through a review of the literature, assigned costs, and performed an economic analysis. However, there are a number of problems with the study by Arikian et al. that we attempted to address. The model used was essentially a "black box"; although values for treatment efficacy were provided, no other information on treatment patterns, types and rates of adverse events, relapse rates, or costs for medical resource utilization were provided. Thus, the construct of the model cannot be examined or critiqued. Moreover, the Arikian et al. model structure was incomplete, as patient discontinuation was not explicitly included despite a substantial fraction of individuals discontinuing therapy due to lack of adherence or following adverse events. Further, Arikian et al. performed rank-order stability analysis to examine the stability of the results, rather than traditional sensitivity analysis to examine the impact of changing model parameters on model outcomes.

We have attempted to address these problems in the development of our model by providing all major model parameters, including discontinuation of therapy due to nonadherence or adverse events, and by performing several sensitivity analyses. However, our model does contain certain limitations, the principle of which is uncertainty of data. Data on utilization of

diagnostic tests and physician visits, treatment patterns for adverse events, and alternative therapies after discontinuation or treatment failure were based on information obtained from clinical experts. Although we obtained this expert information from a broad range of clinicians, it may not represent general practice patterns.

Despite this limitation, the model described here used a traditional cost-effectiveness approach to estimate costs and outcomes of itraconazole therapy and griseofulvin therapy for onychomycosis. Itraconazole consistently was associated with less therapy discontinuation, fewer adverse events, and greater cure rates than was griseofulvin. The primary component of the cost of therapy for either drug was drug costs. The cost-effectiveness results provide us with important information about the added value of a new therapy, itraconazole, compared with a standard therapy, griseofulvin.

Sensitivity analysis indicated that the model was relatively robust with respect to altering clinical efficacy and monitoring costs. The model was most sensitive to changes in the duration of therapy for either drug. If fewer than 12 weeks of itraconazole medication proves to be effective for the treatment of fingernail infection, then the base case underestimates cost-effectiveness, as shown in the corresponding sensitivity analysis. In contrast, if griseofulvin therapy requires 1 year or more to be effective, then itraconazole may be a cost-saving therapy for the treatment of both fingernail infections and toenail infections. Note that the sensitivity analyses altered only the duration of therapy. Although increased length of therapy decreases adherence to therapy, adherence was held constant in these sensitivity analyses for lack of data, likely resulting in underestimates of the cost-effectiveness of itraconazole.

... CONCLUSION ...

The base-case results obtained by the decision-analysis model indicated that itraconazole was highly cost-effective when compared with griseofulvin. For fingernail infections, use of itraconazole rather than griseofulvin resulted in a marginal, or added, cost of \$1.56 per additional disease-free day over a 2-year period. Results were even more favorable for the treatment of toenail infections; in this case, itraconazole provided a marginal cost saving of \$0.30 per additional disease-free day.

Acknowledgment

We gratefully acknowledge the participation in this study of the following clinical experts: Drs. Neil Brody,

Mark Dahl, James DelRosso, Janet Hickman, Richard Odom, David Pariser, and Phoebe Rich. We also would like to thank Dr. Margaret Rothman, of Janssen Research Foundation, for her assistance.

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