Cost Effectiveness of Newer Antiviral Agents for Herpes Zoster: Is the Evidence Spotty?

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Famciclovir and valaciclovir were approved for use in the treatment of herpes zoster despite controversy over antiviral therapy in zoster due to high costs and uncertain benefits. To explore these issues, a Markov decision model was developed, and the incremental cost effectiveness of antiviral treatment for herpes zoster was estimated using these agents compared with no antiviral therapy. A third-party payer perspective was taken. Sensitivity analyses were performed, modeling differences in antiviral efficacy, postherpetic neuralgia (PHN) risk, and other illness parameters. Treatment of severely symptomatic acute zoster was found reasonable from a cost-effectiveness standpoint in base-case and worst-case scenarios. Treatment of mildly symptomatic acute zoster was more expensive but would likely be considered cost effective in scenarios where PHN risk was higher, PHN duration longer, or antiviral shortening of PHN greater. Further research comparing antiviral efficacy in herpes zoster is needed.

Famciclovir and valaciclovir were recently released, joining acyclovir as US Food and Drug Administration–approved drugs for the treatment of herpes zoster (HZ). However, controversy still surrounds antiviral therapy for immunocompetent patients with zoster, due to the relatively high costs and uncertain benefits from antiviral use [1–4]. Whether these newer agents offer any clinical advantages over acyclovir for zoster is unclear [5].

Antiviral therapy decreases the severity and duration of acute zoster symptoms, and all agents seem equally effective for this purpose [5]; however, the effects of antivirals on postherpetic neuralgia (PHN) are mixed. Several studies using oral acyclovir showed inconsistent reduction of PHN [6–12]. One study found reduced duration of PHN with famciclovir compared with a placebo [13], while another showed no reduction in comparison with acyclovir [14]. In another study, the duration of PHN was reduced in patients given valaciclovir compared with those given acyclovir [15]. Studies showing reduction in PHN with antiviral therapy found no change in PHN risk but did note decreased PHN duration. There are no studies as yet comparing famciclovir to valaciclovir.

To explore the economic implications of using these newer antiviral agents, we developed a computerized decision model. We used this model to estimate the cost effectiveness of famciclovir and valaciclovir treatment for immunocompetent patients with HZ and to identify the clinical and cost parameters that would most affect the decision to treat with antiviral agents.

Methods

Using standard decision-analysis computer software (Decision Maker 7.01; Pratt Medical Group, Boston), we developed a Markov decision model to estimate the incremental cost per quality-adjusted life year (QALY) gained by treating HZ patients with either famciclovir or valaciclovir compared with no antiviral. We did not compare the drugs to one another due to the lack of direct comparison data. A third-party payer perspective was taken, considering only the direct medical costs of illness [16].

QALYs are derived by multiplying years of life by the quality-of-life utility values associated with those years. For example, 10 years of life in a health state with a quality-of-life utility value of 0.8 (on scale of 0.0–1.0) is equivalent to 8 QALYs.

Incremental costs per QALY gained are calculated by dividing the difference in costs between two interventions by the difference in QALYs associated with the interventions. If a patient with a life expectancy of 10 years at a utility of 0.8 had a treatment costing $1000 that increased the utility of those 10 years to 0.85, then 0.5 QALYs [(0.85 × 10 years) – (0.80 × 10 years)] would be gained, and the incremental cost per QALY gained for the treatment compared with no treatment would be $2000 ($1000/0.5 QALY).

The model. Markov models estimate cost effectiveness by tracking the health states of hypothetical patients over time, and they calculate costs and effectiveness on the basis of time spent in each state of health [17]. Patients may change health states or remain in the same state during each time period (or cycle) of the model on the basis of the probability of a change in health status during that time. Our base case analysis considered 2 hypothetical cohorts of identical immunocompetent 70-year-old patients seen within 72 h of onset of HZ rash: One cohort was treated with an antiviral agent, and the other was not treated. In the model, we
considered patients to be in one of four health states: with PHN, no PHN, hospitalized for acute zoster symptoms, dead due to causes unrelated to zoster (no patients died of zoster or zoster symptoms). The Markov cycle length was 1 month. We assumed that antiviral treatment might shorten the duration of PHN but would not modify the probability of its occurrence. Hospitalization was due only to acute zoster symptoms and was not modified by antiviral treatment. We also assumed that PHN began during the month after HZ onset. Side effects of antiviral therapy were not explicitly modeled, due to their relative rarity and mildness [1, 13–15].

Patients entered the model in the no-PHN health state, the PHN state, or the hospitalized state, as determined on the basis of the probability of these occurrences. Patients hospitalized due to acute zoster entered the PHN state or the no-PHN state, or they died of other causes during the next monthly cycle. Those in the PHN state either remained in that state, changed to the no-PHN state (on the basis of the median duration of PHN), or died of other causes during ensuing cycles of the model. Patients in the no-PHN state remained in that state or died of other causes. The model cycled until all patients were dead.

Probabilities, utilities, and costs were obtained from published literature, when available. When values for parameters were not available in the literature, estimates were used.

**Probabilities.** Hospitalization for acute HZ symptoms was estimated to occur in 0.1% of the cases. PHN occurred in 20% (range, 10%–30%) of HZ patients [18–21] regardless of treatment. Age-specific probabilities for dying of other causes were derived from standard mortality tables [22].

**Utilities.** Patients receiving antiviral treatment had 1.6 fewer days of acute zoster symptoms and 50% relief during symptomatic days compared with patients receiving no treatment [7, 8, 13]. Untreated patients who developed PHN had a median PHN duration of 90 days in the baseline analysis [7, 8, 12, 13]. We examined the effect of antiviral treatment if it reduced the duration of PHN by 0%, 10%, or 20% in the base case analyses and modeled up to 60% reduction in sensitivity analyses.

Quality-of-life utility values may vary from 0.0 to 1.0, with 0.0 being equivalent to death and 1.0 denoting perfect health. We modeled two scenarios for acute zoster symptoms: a utility value of 0.7 for patients with severe symptoms and a utility of 0.9 for those with mild symptoms. Patients with PHN had an average utility of 0.9, and those hospitalized with acute zoster had a utility of 0.3. These utility values were derived from two studies describing quality-of-life utility values given by general population groups for other medical conditions [23–24]. Both famciclovir and valaciclovir were assumed to have equal effects on acute zoster and PHN symptoms [5].

**Costs.** As determined using the average wholesale prices from December 1995, a 1-week course of famciclovir (500 mg three times daily) cost $129.15, and 1 week of valaciclovir (1 gm three times daily) was $96.60 [25]. The monthly direct costs of PHN were $33.75, assuming the use of generic pain medications and one physician visit every 3 months (range, 0–2 visits/month in the sensitivity analysis). Hospitalizations were estimated to cost $4000 on average. All costs and benefits were discounted at 3%/year [26].

**Sensitivity analysis.** One-way sensitivity analyses were performed on all parameters, with closest scrutiny placed on those values not obtained from the literature. Those parameters that, with variation, crossed the $50,000/QALY-gained threshold were then studied in multiway analyses, varying two or more parameters simultaneously. An incremental cost of $50,000/QALY gained is a commonly used reference point [26, 27] but should not be interpreted as an absolute cost-effectiveness criterion since no such criterion exists [26]. However, in the literature, costs per QALY much above $50,000 are unlikely to be considered cost effective, while costs < $50,000 are typically judged favorably [27].

**Results**

In severely symptomatic acute HZ, the incremental cost per QALY gained by famciclovir treatment was $28,100 if treatment decreased PHN duration by 0%, $23,900 if PHN duration decreased 10%, and $20,700 if PHN duration decreased 20%. For valaciclovir, the respective values per QALY gained were $21,000, $17,800, and $15,300.

Treating mild acute HZ was more expensive. The cost per QALY gained for famciclovir was $84,300 if PHN duration was unchanged, $57,100 if PHN duration decreased 10%, and $42,700 if PHN duration decreased 20%. The respective values for valaciclovir were $63,000, $42,400, and $31,400.

**Sensitivity analysis—severe acute HZ scenario.** Antiviral treatment of severe acute zoster cost ≤ $50,000/QALY gained compared with no treatment when all parameters were varied within clinically plausible ranges. In worse-case scenarios, in which acute symptom relief was low and PHN was mild, of short duration, and unaffected by treatment, cost per QALY gained was $48,200 for famciclovir treatment and $36,100 for valaciclovir.

Similarly, treatment of severe acute zoster was not sensitive to variation of antiviral agent costs. Cost per QALY gained remained ≤ $50,000 if antiviral costs were ≤ $266 per treatment course.

**Sensitivity analysis—mild acute HZ scenario.** Antiviral treatment of mild acute zoster was sensitive to variation of some parameters, as shown in table 1. The number of values ≤ $50,000 did not change when hospitalization probability, shortened duration of acute zoster, patient age (as an independent variable), hospitalization cost, or monthly PHN cost (including increasing physician visits to twice monthly) were varied; therefore these parameters are insensitive to variation. Median PHN duration was only mildly sensitive to variation. Results were more sensitive to variation of PHN risk, PHN utility values, and degree of symptom relief in acute zoster.

Treating mild acute zoster was sensitive to antiviral cost, but cost per QALY would have been ≤ $50,000 if antiviral costs had been ≤ $76.64 under baseline conditions, assuming no antiviral impact on PHN duration.

Multiway analyses for famciclovir and valaciclovir treatment in mild acute zoster are shown in figure 1. In these analyses, two of the most sensitive parameters, the PHN quality-of-life utility value and the risk of PHN, were simultaneously varied.
Table 1. Sensitivity analysis for treatment of mildly symptomatic acute herpes zoster in patients treated with famciclovir or valaciclovir.

<table>
<thead>
<tr>
<th>Baseline value</th>
<th>Change value</th>
<th>Cost* of famciclovir for patients with a decrease in PHN duration of</th>
<th>Cost* of valaciclovir for patients with a decrease in PHN duration of</th>
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<tbody>
<tr>
<td></td>
<td>0%</td>
<td>10%</td>
<td>20%</td>
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<td>Baseline analysis</td>
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<td>1%</td>
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<td>Shortened duration of acute zoster</td>
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<td>0 days</td>
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<tr>
<td></td>
<td>2 days</td>
<td>2 days</td>
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<td>Relief of acute symptoms</td>
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<td>80%</td>
<td>80%</td>
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<td>Duration of PHN (median)</td>
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<td></td>
<td>120 days</td>
<td>120 days</td>
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<tr>
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<tr>
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NOTE. Bold data denote costs < $50,000. PHN = postherpetic neuralgia.
* Cost per quality-adjusted life year gained in thousands of dollars.

along with the antiviral reduction of PHN duration, using the $50,000/QALY-gained threshold. For example, if an average PHN utility value of 0.85 was used (rather than the baseline value of 0.9) and the reduction in PHN duration with antiviral therapy was 10%, the point denoting those values would fall within the lightly shaded area on the famciclovir graph in figure 1. Therefore, the cost per QALY gained for famciclovir treatment would be ≤ $50,000 if the risk of PHN was ≥ 20%, but the cost would be > $50,000 if PHN risk was ≤ 10%. Using the same values in the valaciclovir graph in figure 1, that point falls into the unshaded area; therefore the cost per QALY gained is ≤ $50,000 if PHN risk is ≥ 10%.

In mild acute zoster, famciclovir treatment would always cost ≤ $50,000/QALY gained if it reduced PHN duration by ≥ 52.9%, given a PHN utility of ≤ 0.95 and a PHN risk of ≥ 10%. If we used the same values, valaciclovir would cost ≤ $50,000/QALY if it decreased PHN duration by ≥ 20.2%.

Costs > $50,000/QALY gained are seen in the hatched area of each graph in figure 1. If PHN duration were to be reduced ≤ 4% by famciclovir or ≤ 2% by valaciclovir, antiviral treatment of mild acute zoster would cost > $50,000/QALY, unless the probability of PHN was > 30%.

If the degree of acute symptom relief were to be substituted for PHN risk in the multiway analysis, similar areas of cost effectiveness for famciclovir and valaciclovir would be seen.

Discussion

In our analysis, treatment of severely symptomatic acute HZ cost ≤ $50,000/QALY gained through a broad range of clinical and cost parameters. Our study supports recommendations for antiviral treatment of severe acute zoster in patients ≥ 50 years old within 72 h of rash onset [5]. Treatment of patients < 50 years old with severe acute zoster is also recommended [5] and would likely be cost effective on the basis of acute symptom relief alone. It is unclear if antiviral treatment of severe acute zoster begun > 72 h after rash onset is cost effective, but further research in this area is warranted.

Treatment of mildly symptomatic acute zoster is more expensive, with cost effectiveness most sensitive to variation of PHN risk, symptom severity during PHN, drug costs, and drug effectiveness in PHN and acute zoster. When a patient presents with mild acute zoster, questions should be answered to allow a cost-effective decision to be made regarding the use of antiviral therapy.

The first question is whether antiviral drugs change the course of PHN and, if they do, which one is most effective? Both famciclovir and valaciclovir have shown benefits for patients with PHN [13, 15], and acyclovir is probably beneficial also [28, 29]. However, no agent changes the probability or severity of PHN; only the duration is affected [6–15]. Antivi-
rals may reduce PHN duration more than the 20% used in the analysis, with recent data suggesting a 50% reduction [13, 28, 29]. If further studies confirm this, antiviral therapy would likely be considered cost effective in all patients >50 years old, regardless of acute zoster severity. On the basis of available data, one agent cannot be declared superior to another for HZ. Hence, in this increasingly cost-oriented era, drug costs may become a major factor in treatment choice. Using average wholesale prices from December 1995, we determined that a course of valaciclovir costs ~$32 less than famciclovir, and the cost of famciclovir ($129.15) was comparable to that for acyclovir ($128.95) [25]. If no difference in drug effectiveness can be distinguished, the least expensive drug is most cost effective. More and better data comparing antiviral agents in PHN are needed to allow the best medical decision, which is not necessarily the most frugal one.

The second question is whether there are clinical characteristics that predict the risk, severity, and duration of PHN in mild acute zoster. Patient age is perhaps the best predictor. Age as an independent variable in our analysis was not a sensitive parameter, but increasing age is known to increase the probability, severity, and duration of PHN [2–5, 18–20]. Our model suggests that treating mild acute zoster in patients over the age of 70 or 80 would be cost effective because the risk of PHN approaches ≥30% in that age group [2–5, 18–20]. The cost effectiveness of treating younger patients, in whom PHN is rarer and less severe, depends more on the effect of treatment on PHN duration. Clarification awaits further investigation, but
beneficial effects in patients <50 years old have not been seen [13]. Patients with mild acute zoster in an ophthalmic distribution should also receive antiviral therapy to prevent ophthalmologic complications and because of the higher risk for PHN [5, 11]. Premonitory dysesthesia [30] or later development of severe acute pain [31] may also predict a more complicated course.

Finally, one must question whether the antiviral drugs used for zoster cause harm. Side effects are rare and usually mild [1, 13–15]. Cautious clinicians may also avoid antiviral use for fear of creating drug-resistant viruses. Varicella-resistant acyclovir has been described but only in immunocompromised patients receiving chronic acyclovir treatment [1, 32, 33]. Development of antiviral resistance after the usual course of treatment for HZ has not been described.

Antiviral treatment costs remain a stumbling block for many physicians and patients [34, 35], and they are a major factor in our cost-effectiveness calculations. However, drug costs tend to diminish over time. If costs for a course of antiviral therapy decrease to €76, treating HZ of any severity in patients ≥50 years old will cost €50,000/QALY gained in almost all plausible clinical scenarios.

There are several limitations to this analysis. Indirect costs of illness, such as lost wages or productivity, were not included in our model. Consideration of those costs as well as direct costs would change the perspective of the analysis from that of a third-party payer to that of society [16]. However, it is unclear if third-party payers will incorporate societal costs into their coverage decisions. Due to the scarcity of data, the baseline analyses depend on many estimates; for example, utility values were not obtained from patients, but were derived from other sources. At the same time, sensitivity analyses examined clinically plausible ranges for all parameters, allowing cautious interpretation of the available data while awaiting more definitive data from future investigations. Most important, antiviral costs can vary greatly from place to place. Valaciclovir appears more cost effective in this analysis only because its average wholesale price was lower than that for famciclovir at the time studied; the lower cost was not due to any proven benefit of one drug over the other. Physicians should be aware of the cost of antivirals so that they can make informed treatment choices while awaiting comparative efficacy data.

In conclusion, treating severely symptomatic acute HZ with antiviral drugs seems reasonable from a cost-effectiveness standpoint. Treatment of mild acute zoster is less well supported by the available evidence but would likely be considered cost effective in those patients whose age or other clinical characteristics would predict greater PHN risk, PHN severity, or treatment effect on PHN duration. Further research is needed to obtain much of this predictive data. In the absence of further data, cost may become a major factor in antiviral choice.

References


