A systematic review and critical appraisal of famciclovir treatment of herpes zoster

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A systematic review and critical appraisal of famciclovir treatment of herpes zoster

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Foreword

The British Columbia Office of Health Technology Assessment (BCOHTA) was established on December 1, 1990 by a grant to The University of British Columbia from the Province, to promote and encourage the use of assessment research in policy, planning and utilization decisions by government, health care executives, and practitioners. It is important to note that the role of the Office is to appraise the scientific evidence only, without involvement in actual policy development for the requesting agency.

Assessments are performed in response to requests from the public sector such as hospitals, physicians, professional associations, health regions, government; private sector groups such as manufacturers; and individuals from the general public. One or more of the following criteria are used to determine the priority of an assessment and the level of analysis: (1) number of users and potential change in quality of life; (2) acquisition and operating costs to the health care system; (3) potential to influence provider and consumer behavior as a result of a review; and (4) availability of accurate information and appropriate research skills.

Electronic bibliographic databases and fugitive literature (that is, literature not indexed or distributed publicly) are searched using predefined inclusion and exclusion criteria based on the specific search strategy. The critical appraisal of the retrieved evidence includes the formulation of logical and defensible conclusions about the technology under study.

Health Technology Assessment projects are conducted by faculty and staff who are expert in systematic review methodology. Reports are reviewed internally, and then sent to experts from a variety of academic or clinical disciplines for external review. Comments and suggestions are considered before a final document is produced. Distribution of the reports is by request from the Office or through inclusion on our mailing list.

The strength of BCOHTA’s method of systematic review lies in the process of explicitly detailing the methodology and criteria used to produce recommendations which are based solely on the research evidence. This transparent and reproducible assessment process allows readers to review the evidence objectively for themselves. The ensuing reports are available for public distribution.

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Introduction to the Series

The Joint Heath Technology Assessment Series reports on projects initiated by the British Columbia Office of Health Technology Assessment (BCOHTA) and evidence-based medicine programs in BC. Dedicated to producing unbiased, systematic reviews of clinical efficacy and effectiveness evidence for health care providers, administrators, policy makers, and the general public, these programs currently include:

- Therapeutics Initiative (TI), Department of Pharmacology and Therapeutics, Faculty of Medicine, University of BC, Vancouver
- Technology Assessment Committee, Capital Health Region, Victoria
- Drug Benefit Committee, Pharmacare, and ad hoc Health Technology Assessment Committees, the Ministry of Health and Ministry Responsible for Seniors, Victoria
- Technology Assessment Committee, Workers' Compensation Board of BC, Richmond
- Population Testing Programs, Boundary Health Unit, South Fraser Health Unit, Surrey
- BC Research Institute for Child and Family Health, BC Women’s and Children’s Hospital, Vancouver
- Centre for Clinical Epidemiology and Evaluation, Vancouver Hospital and Health Sciences Centre, Vancouver
- Public Health Nursing, Boundary Health Unit, South Fraser Health Unit, Surrey

Topics reflect initiative and institutional needs. Priority is given to topics with significant impact on patient health and health care costs, and with issues in more than one context. The goal of the Series is both to demonstrate systematic review and critical appraisal skills, and to co-ordinate research efforts within contexts that are geographically separate and institutionally diverse.

The Series addresses two different types of evidence-based medicine issues:
1. Uncertainty regarding new technology;
2. Discrepancy between evidence and practice for established technology.

The Joint HTA Series will produce scientifically valid systematic reviews, supported by key individuals in each receptor site. These individuals are able to present and defend the systematic review conclusions during ongoing committee debates. This is an essential step if health policy and funding decisions are to be connected to the available efficacy and effectiveness evidence.
ABSTRACT

Objective: to determine the efficacy and effectiveness of famciclovir versus placebo for the treatment of herpes zoster.

Design: systematic review and critical appraisal of randomised trials comparing the efficacy of famciclovir with placebo in adults with herpes zoster.

Setting: outpatient clinics in the United States, Canada, and Australia.

Subjects: adults with uncomplicated herpes zoster.

Interventions: famciclovir 500 mg & 750 mg

Main outcome measure: incidence, severity and patient-days of post herpetic neuralgia.

Results: The one published report which met the inclusion criteria was of poor methodological quality. Data analysis was incomplete and incongruous. Famciclovir increased the incidence of post herpetic neuralgia from 38% in the placebo arm to 44% in the famciclovir 500 mg and 50% in the famciclovir 750 mg arms respectively. The difference was statistically significant (p<0.004) in the group of patients over age 50 in the famciclovir 750 mg arm. Patients over age 50 also had similar patient-days of neuralgia: 3689 days (35%) placebo versus 2867 days (27%) famciclovir 750 mg. This non-statistically significant 8% difference in patient-days contrasts with the dramatic 50% reduction in post herpetic neuralgia duration reported in the published study.

Conclusion: Evidence that famciclovir provides a therapeutic advantage over placebo for treatment of herpes zoster is incomplete, and inconclusive. The results demonstrate the importance of careful critical appraisal of published trial reports before acceptance, and the need for further trials in this area.
INTRODUCTION

The clearest and most clinically significant therapeutic benefit from treating herpes zoster with currently available antiviral medications - acyclovir, valacyclovir (a recent prodrug form of acyclovir) and famciclovir would be a reduction in the incidence of neuralgic pain. Post herpetic neuralgia, defined in this trial and elsewhere as "pain after (skin lesion) healing" is known to cause significant immediate disability lasting months, and sometimes an intractable chronic pain syndrome lasting years. Acyclovir has not been found to reduce the incidence of neuralgia versus placebo. Valacyclovir has no published clinical trial evidence establishing its benefit versus placebo for any parameter of neuralgia, including incidence. Clinical evidence supporting valacyclovir consists of one published trial comparing it with acyclovir. This trial, which was subjected to critical appraisal and reported elsewhere concluded that valacyclovir did not influence the incidence of post herpetic neuralgia.

Significantly reducing neuralgic pain severity would confer almost as much therapeutic benefit as reducing its occurrence (incidence) altogether. In contrast to duration, discussed below, evidence that neuralgic pain severity is reduced would confer therapeutic benefit independent of pain duration, assuming that duration was not increased. No published reports to date have claimed that acyclovir or valacyclovir reduce the severity of neuralgic pain. In fact, study authors have concluded that acyclovir has no effect on pain severity.

Neuralgic pain duration is the weakest and most problematic measure of treatment effect. First, clinical interpretation of pain duration, however measured, depends on knowledge of pain severity. For example, treatment effect to shorten the duration of neuralgia may or may not be desirable if pain intensity is increased.
While duration of neuralgia is a controversial outcome measure, Tyring et al.\textsuperscript{10} make a striking efficacy claim for famciclovir in the treatment of patients over age 50 with herpes zoster:

\textit{The median times to resolution of post herpetic neuralgia in these older patients [over age 50] were 63 days for the 500mg famciclovir group, 61 days for the 750mg famciclovir group, and 163 days for the placebo group.... No benefit was seen for patients younger than 50 years.}\textsuperscript{10} p.92

If post herpetic neuralgia is actually reduced in the treatment group as much as the quotation suggests, then famciclovir treatment of herpes zoster would clearly be justified. However, before clinicians accept that famciclovir provides a clinically significant benefit to patients with herpes zoster, several important questions need to be addressed: What is the influence of famciclovir on other parameters of post herpetic neuralgia beyond its duration, most notably its incidence and severity? In particular, clinicians need to note that a 50\% reduction in duration of post herpetic neuralgia averaged over an entire treatment group may not translate into any reduction in patient suffering if the incidence doubles.

In addition, clinicians also require assurance that trial results are valid, generalisable and replicable. Has this trial been repeated, with results confirmed by other investigators?
METHODS

The following electronic bibliographic databases were searched from 1993 to Jan 1998: MEDLINE, Current Contents, EMBASE, Cochrane Controlled Trials Registry, Life Sciences Collection, OCLC FirstSearch(Article1st), and Outcomes Activities Database. Key search terms used were "famciclovir" and "herpes zoster". The Current Contents database was searched to December 1997. The reference lists from retrieved articles were scanned. No data were obtained from the manufacturer of famciclovir despite repeated requests. Studies were selected that randomized patient allocation, blinded patients and clinicians, and included famciclovir and placebo treatment arms.

The methodology of Chalmers TC et al.\textsuperscript{11} was used to critically appraise trial quality. In addition, various numerators and denominators were extracted from the published results to calculate incidence. Calculated post herpetic neuralgia incidence was then combined with duration of post herpetic neuralgia to form a 'patient-day' unit. A patient-day unit has an advantage over the "median duration of post herpetic neuralgia" unit, because it measures post herpetic neuralgia in relation to all patients in the treatment arm. In contrast, for post herpetic neuralgia duration the denominator is the sub-group of patients with post herpetic neuralgia.

A Standard Pearson Chi-Square test for categorical data was used for tests of significance.
RESULTS

One published report, Tyring et al\textsuperscript{10}, met the inclusion criteria: 419 patients were randomized into one of three treatment arms: famciclovir 500 mg, famciclovir 750 mg or placebo three times a day for 7 days. Tyring et al\textsuperscript{10} provide the only published efficacy evidence, from a randomized control trial, supporting famciclovir treatment of herpes zoster versus placebo (one earlier trial compared famciclovir to acyclovir, but did not include a placebo treatment group\textsuperscript{12}).

**Key critical appraisal findings**

**Loss of blinding**

The validity of this study's claims regarding post herpetic neuralgia depends on maintenance of blinding as to patient allocation. Loss of blinding is strongly suggested in Tyring et al\textsuperscript{10} by close scrutiny of the intention to treat versus efficacy evaluable groups described in relation to assessment of acute pain <\textsuperscript{10} p.91-92>. The intention to treat group is defined as patients who took at least one dose of study medication, the efficacy evaluable group is defined as patients who completed 80% of the study protocol. While the subgroup of patients with severe rash ( >50 vesicles) in the famciclovir 500 mg and 750 mg arms maintained exactly the same median duration of pain resolution in moving from intention to treat to the efficacy evaluable calculations (remaining at 20 and 27 days respectively), the median duration of acute pain resolution nearly doubled for the placebo group (from 30 to 53 days). This difference in pain duration suggests a selective loss of less severely afflicted patients from the placebo group. The importance of the shift from intention to treat to efficacy evaluable groups becomes clear when it is appreciated that adding as few as 12 mildly afflicted individuals to the placebo group would result in the same median duration of post herpetic neuralgia as found in the famciclovir groups, by itself negating the authors' most substantive efficacy claim.
Re-analysis of reported findings

The validity of this study's claim that famciclovir shortens the duration of post herpetic neuralgia cannot be interpreted without knowledge of incidence and pain severity.

Incidence of post-herpetic neuralgia:

The incidence of post herpetic neuralgia was calculated from the published trial results (Table 1). The calculation suggests that famciclovir increased the incidence of post herpetic neuralgia from 38% placebo to 44% in the famciclovir 500 mg arm and 50% in the famciclovir 750 mg arms respectively. Furthermore, it suggests that the higher the dose of famciclovir, the higher the incidence of post herpetic neuralgia. The difference becomes statistically significant (p<0.004), comparing patients over age 50 in the famciclovir 750 mg versus placebo groups, arguably the age group of greatest clinical concern due to higher risk of severe post herpetic neuralgia.2

Total patient-days of neuralgia

In total, 22192 patient days of data is available from the Tyring et al10 trial (Table 2). Patients in the famciclovir 750 mg group experienced 4148 (20%) patient-days of neuralgia compared to 6664 (30%) in the placebo group. In the over 50 age group a total of 10640 patient-days of data are available. Patients in the famciclovir 750 mg group experienced 2867 (27%) patient-days of neuralgia compared to 3689 (35%) in the placebo group.

These values, while showing an 8% absolute reduction in post herpetic neuralgia patient-days for the famciclovir 750 mg group, should be viewed skeptically owing to an incongruous value found in the text<10 p.92> and Table 4. The authors report the "median duration" of post herpetic neuralgia in patients over age 50 in the placebo group as 163 days. This total, 163 days, exceeds the total defined post herpetic neuralgia study period by 11 days.

Assuming that the discrepancy regarding median duration of post herpetic neuralgia in the placebo group can be explained, the best clinicians can hope for is that, at the end of 6 months,
patients over age 50 treated within 72 hours of onset of herpes zoster rash with famciclovir 750 mg three times a day for 7 days will have 8% fewer days of post herpetic neuralgia. This means that for every 100 days that patients taking placebo have post herpetic neuralgia, patients taking famciclovir 750 mg will have 92. The point is not to present these values as conclusive. Rather, it is to contrast a non-statistically, and arguably non-clinically, significant 8% difference in patient-days with the dramatic 50% reduction in post herpetic neuralgia duration reported by Tyring et al.\textsuperscript{10}

**Pain severity**

With remarkably similar patient-days of suffering in the famciclovir 750 mg treatment arm, pain intensity becomes crucial for interpreting trial findings. Tyring et al\textsuperscript{10} report pain severity at trial onset, albeit measured using a four point scale that has not been validated. The authors incongruously do not report post herpetic neuralgia severity for the remaining assessments during the study. The drug manufacturer refused repeated requests to supply this crucial data. Therefore, there is no way of knowing whether patients receiving famciclovir 750 mg had more painful as well as more frequent post herpetic neuralgia.
Table 1. Incidence of post-herpetic neuralgia calculated from the raw data reported by Tyring et al\textsuperscript{10} 1995

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Overall incidence</th>
<th>Subgroup analysis</th>
<th>Incidence in subgroup over age 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo:</td>
<td>56/146 = 38%</td>
<td>over age 50:</td>
<td>31/70 = 44%</td>
</tr>
<tr>
<td>famciclovir 500 mg:</td>
<td>61/138 = 44%</td>
<td>over age 50:</td>
<td>41/69 = 59%</td>
</tr>
<tr>
<td>famciclovir 750 mg:</td>
<td>68/135 = 50%</td>
<td>over age 50:</td>
<td>47/69 = 68%</td>
</tr>
</tbody>
</table>

The top line of Table 4 \textsuperscript{10} p.93 provides the (intention to treat) numerator: 61 (famciclovir 500 mg), 68 (famciclovir 750 mg), and 56 (placebo) patients developed post herpetic neuralgia. The top line of Table 1\textsuperscript{10} p.91 provides the denominator: 138 (famciclovir 500 mg), 135 (famciclovir 750 mg), 146 (placebo). These tables also provide data for people over age 50.

Table 2. Total patient-days of neuralgia calculated from the raw data reported by Tyring et al\textsuperscript{10} 1995

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Calculation of total patient days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>56 patients x 119 days (median duration PHN) = 6664 patient-days</td>
</tr>
<tr>
<td></td>
<td>= 6664/22192 total</td>
</tr>
<tr>
<td></td>
<td>= 30% patient-days</td>
</tr>
<tr>
<td></td>
<td>over age 50 = 31 x 119 = 3689/10640 = 35% patient-days</td>
</tr>
<tr>
<td>famciclovir 750 mg:</td>
<td>68 patients x 61 days (median duration PHN) = 4148 patient-days</td>
</tr>
<tr>
<td></td>
<td>= 4148/20520(total)</td>
</tr>
<tr>
<td></td>
<td>= 20% patient-days</td>
</tr>
<tr>
<td></td>
<td>over age 50 = 47 x 61 = 2867/10488 = 27% patient-days</td>
</tr>
</tbody>
</table>

The total number of days in the "post-herpetic" neuralgia period was taken as 5 months (approximately 152 days) based on the stated study definition: "After the lesions had healed, patients were assessed for the presence of post herpetic neuralgia for an additional 5 months"\textsuperscript{10} p.90. This sample calculation is inaccurate because only "median" as opposed to "mean" duration of post herpetic neuralgia data was available (Tables 1 and 4).
DISCUSSION

As detailed above, famciclovir, if anything, increases the incidence of neuralgia for patients over age 50, arguably the patients of greatest clinical concern. Furthermore, Tyring et al.\(^\text{10}\) did not report on the influence of famciclovir on pain severity. Instead, Tyring et al.\(^\text{10}\) limit their discussion of treatment effect to an analysis of post herpetic neuralgia duration.

The problem with using neuralgic pain duration to assess treatment effect is that its measurement remains controversial.\(^\text{2,8}\) Many studies, starting with the early studies of acyclovir, measured post-herpetic neuralgia, that is, pain after a certain period of time (i.e. 30 days), usually corresponding to skin lesion healing. Neuralgic pain before lesion healing was termed acute phase pain and considered clinically distinct from post herpetic neuralgia. However, distinguishing between acute phase pain and post herpetic neuralgia has no pathophysiological basis and can lead to bias. For example, exclusively assessing patients with post herpetic neuralgia is a sub-group analysis of non-randomised groups of patients.

Some authors have argued for measuring all herpes zoster pain together, that is, combining acute phase pain with post herpetic neuralgia.\(^\text{1}\) Termed zoster associated pain, this measurement method, in contrast to post herpetic neuralgia, keeps almost all patients in the analysis of treatment effect, since almost all patients have some degree of pain, at least in the acute phase. As demonstrated above in the patient-day calculation of famciclovir, this type of approach does provide some sense of the overall population treatment effect, lost by post herpetic neuralgia duration calculations.

Authors have made several claims and counter-claims regarding the effect of antiviral medications on the duration of neuralgia. None, however, has related their duration claims to valid assessments of pain severity and/or incidence. The study comparing valacyclovir to acyclovir, for example, claimed that valacyclovir reduces zoster associated pain versus acyclovir, 41 and 51 days (median), respectively.\(^\text{8}\) This measure is not interpretable, as the authors do not
report on pain severity. Tyring et al\textsuperscript{10} similarly reported on a reduction of post herpetic neuralgia duration without discussing pain severity. In addition, Tyring et al\textsuperscript{10} give clinicians and patients the unwelcome decision whether to opt for treatment with famciclovir, which may increase their chance of developing post herpetic neuralgia, but when it does occur may decrease the duration of pain.
SUMMARY AND CONCLUSION

Tyring et al\textsuperscript{10} provide the only published efficacy evidence that famciclovir treatment of herpes zoster benefits patients versus placebo. Shortcomings in the methodology and conclusions of this single randomized clinical trial, and evident omissions in its report are noted here with concern. Critical appraisal and re-analysis of this trial report demonstrate that the efficacy claims of these authors are questionable. The sub-group analysis of patients over age 50 demonstrating an increased incidence of post herpetic neuralgia with famciclovir is not meant as conclusive. In fact, it is equally possible that famciclovir does or does not actually provide patient benefit.

The purpose of this critical appraisal is to draw attention to the limitation of the original trial report, and to fuel debate as to whether currently published trial evidence is sufficient to support use of this drug for the treatment of herpes zoster. The results demonstrate the importance of careful critical appraisal of published trial reports before acceptance, and the need for further trials in this area.
REFERENCES


