Treatment of Acute Herpes Zoster: Effect of Early (<48 h) versus Late (48–72 h) Therapy with Acyclovir and Valaciclovir on Prolonged Pain

M. J. Wood, S. Shukla, A. P. Fiddian,* and R. J. Crooks

Department of Infection, Heartlands Hospital, Birmingham, and Glaxo Wellcome Research and Development, Uxbridge, United Kingdom

The efficacy of early versus late treatment with acyclovir and valaciclovir on zoster-associated pain was assessed from two databases (1076 patients) that were compiled from randomized trials. Early treatment was started <48 h and late treatment was started 48–72 h after the onset of cutaneous herpes zoster. Median times to complete resolution of zoster-associated pain were 28 and 62 days, respectively, for patients (≥18 years of age) treated with acyclovir and placebo within 48 h (hazard ratio [HR], 1.68; 95% confidence limit [95% CL], 1.19, 2.38) and 28 and 58 days, respectively, for those treated later (HR, 2.20; 95% CL, 1.03, 4.71). In the valaciclovir versus acyclovir study (in patients ≥50 years of age), the corresponding figures were 44 and 51 days for patients treated early (HR, 1.28; 95% CL, 1.03, 1.60) and 36 and 48 days for those treated later (HR, 1.40; 95% CL, 1.04, 1.87). Acyclovir significantly shortened the time to complete resolution of zoster-associated pain compared with placebo (and valaciclovir was superior to acyclovir in this regard) even when therapy was delayed up to 72 h after rash onset.

Herpes zoster (HZ) results from reactivation of varicella-zoster virus (VZV) in the dorsal root ganglion and is the most common sensory neurologic disease in the elderly. Although the disease can occur at any age, in the otherwise immunocompetent individual the risk of developing HZ substantially increases over the age of 50 years: it has been estimated that 50% of persons who reach the age of 85 years will have suffered at least one attack of HZ [1].

The most troublesome symptom of HZ is pain, which occurs in most patients and, particularly in the elderly, often persists after the cutaneous manifestations of the disease have healed. The pathophysiology of the pain of HZ is complex. Replication of VZV within the neurons causes an acute neuritis, and this, in turn, initiates changes within the central nervous system, leading to potentially chronic neuralgia. Because the nerve damage or malfunction (or both) triggered by VZV replication occurring early in acute HZ is responsible for the pathophysiology of the more persistent pain, therapy with antivirals to limit the subsequent pain of HZ must be started during the period of viral replication [2]. Prompt presentation and diagnosis is therefore critical for effective relief of symptoms and for stopping further virus replication. This is often not achieved since most patients and their medical attendants do not recognize the prodromal pain of HZ for what it is and only present or diagnose the condition once the rash appears.

Most controlled clinical trials of antiviral drugs for HZ in otherwise immunocompetent individuals have enrolled patients within 72 h from rash onset [3–9]. The efficacy of acyclovir on rash healing was shown to be most marked when treatment was started within 48 h of rash onset [4]; however, given the complex pathophysiology of acute pain and the postherpetic neuralgia of HZ and the possibility of differing degrees of penetration of antiviral agents into dermatologic and neurologic tissues, the time course for antiviral efficacy on rash and on pain should not be assumed to be comparable. It is possible, therefore, that limiting antiviral usage to early in the course of the rash may deny patients potential benefits on pain resolution.

Although patients who experience chronic pain will also have suffered acute pain (of a different pathophysiology), these overlap to a considerable extent; thus, patients regard their pain as a continuum. For this reason and also because it avoids a possibility of introduction of inherent bias, many have adopted the term zoster-associated pain for the primary pain end-point measurement in clinical trials evaluating antiviral agents in HZ [10]. Two large databases (1076 patients) have been generated from the controlled clinical trials of acyclovir and valaciclovir in the treatment of acute HZ. The trials measured the duration of zoster-associated pain as a primary end point [9, 11].

The first database comprised results for all patients in the three placebo-controlled studies of oral acyclovir in which the recommended doses (800 mg five times daily) were used and the time to complete cessation of pain was assessed. The results showed that acyclovir was significantly better than a placebo in speeding resolution of zoster-associated pain (hazard ratio [HR], 1.79; confidence limit [95% CL], 1.43, 2.39; P < .001) and that this benefit was most marked in patients aged ≥50 years old (HR, 2.13; 95% CL, 1.42, 3.19; P < .001) [11].

Key findings from the second database (valaciclovir vs. oral acyclovir) showed that valaciclovir was significantly better than acyclovir in speeding resolution of zoster-associated pain (HR, 1.34; 95% CL, 1.12, 1.60; P = .001) [9].
In the present study, these databases were analyzed further to determine the efficacy of acyclovir or valaciclovir therapy on the duration of zoster-associated pain when either was given early (<48 h) or late (48–72 h) after onset of the HZ rash.

**Methods**

The randomized patients in each contributing study were otherwise healthy adults who began treatment within 72 h of onset of the characteristic HZ rash. The acyclovir dataset (study 1) comprised the three placebo-controlled trials that evaluated the recommended oral dose (800 mg five times daily) in patients aged ≥18 years and which were designed to determine the time to final cessation of zoster-associated pain during the follow-up period of 6 months [3, 5, 12]. Time to complete cessation of pain (and other pain end points) was measured for each patient. Timings of clinical assessments differed within each study, but all patients were followed for 6 months.

In the fourth placebo-controlled, double-blind trial of the recommended dose of acyclovir [4], data for most patients were not available for ≥6 months because the patients were discharged from follow-up when they became free of pain for 1 month. Details of the timings and type of pain assessments in these trials and the way in which times to complete cessation of pain were determined for the present analysis have been provided elsewhere [11].

The valaciclovir dataset (study 2) was from a large multicenter international study in which patient entry was restricted to adults aged ≥50 years old and treatment was with oral valaciclovir (1000 mg three times daily) for 7 or 14 days or with oral acyclovir (800 mg five times daily) for 7 days [9]. The primary pain end point was time to complete cessation of zoster-associated pain, and all patients were followed for 6 months.

Subgroup analyses were done that estimated treatment differences for patients beginning treatment within 48 h of and those beginning treatment 48–72 h after rash onset. The distribution of time to loss of zoster-associated pain was estimated by the Kaplan-Meier product limit survival method [13]. Differences between treatments were determined by use of Cox’s proportional hazards models, adjusting for important prognostic factors influencing HZ pain and routinely taking into account any differences in demographic variables between treatment groups [14].

For the acyclovir versus placebo studies, Cox models were adjusted for age (continuous variable), sex (male vs. female), pain severity at presentation (≥ moderate vs. none or mild), and duration of prodromal symptoms (≥48 h vs. <48 h). For the valaciclovir versus acyclovir studies, the same factors were fitted into each Cox model, but prodromal symptoms were simply categorized as absent versus present.

Since valaciclovir at 1000 mg three times daily for 7 days is now the recommended dosage registered in many countries for treatment of HZ, only the data for this regimen in relation to the findings for acyclovir are analyzed here.

**Results**

Three hundred sixteen patients were in the acyclovir versus placebo dataset (study 1) and 760 in the valaciclovir versus acyclovir dataset (study 2). The mean age of patients was 52 years in study 1 (although >90% were ≥50) and 68 years in study 2. At least 60% of patients in each dataset began treatment within 48 h of rash onset. No major differences between treatment groups were evident within the studies or overall (data not shown).

**Acyclovir versus placebo.** Kaplan-Meier plots for time to complete cessation of zoster-associated pain after early and late treatment are illustrated in figure 1A. HRs, 95% CLs, and median values for duration of zoster-associated pain for early and late treatment are given in table 1. The HRs were statistically significant, indicating that acyclovir treatment significantly accelerated pain resolution compared with placebo in both subgroups, with no evidence for loss of efficacy in the 48–72 h subgroup.

**Valaciclovir versus acyclovir.** The superiority of valaciclovir over acyclovir in speeding resolution of zoster-associated pain was evident in patients starting treatment within 48 h and 48–72 h after rash onset (figure 1B). HRs, 95% CLs, and median duration values for zoster-associated pain for early and late treatment are given in table 1; these ratios were also statistically significant, with similar benefits of valaciclovir over acyclovir in speeding pain resolution in each subgroup.

**Discussion**

The intent-to-treat analyses of the duration of zoster-associated pain in the individual datasets previously demonstrated the efficacy of oral acyclovir treatment of acute HZ in accelerating the resolution of zoster-associated pain [11] and that the greater systemic acyclovir exposure provided by valaciclovir resulted in further speeding of its resolution [9]. The results of the present analysis of the subgroups of patients within these studies treated within 48 h or 48–72 h after onset of their rash are consistent with the intent-to-treat analysis for zoster-associated pain resolution of the individual datasets and extend these results to show that the further benefit of valaciclovir over that of acyclovir in speeding pain resolution in HZ still occurs when therapy is delayed up to 72 h after rash onset.

Placebo-controlled trials of oral acyclovir for the treatment of HZ have demonstrated the enhanced benefit of treatment within 48 h of rash onset in hastening healing of the rash [4]. That this is not the case for the effect of certain antiviral therapies on zoster-associated pain should not be surprising. The time course of viral replication within neurologic tissues (a factor that seems to be of considerable importance both in the pathophysiology of pain during acute HZ and in triggering the central nervous system changes responsible for the prolonged pain after healing of the rash) is unknown and not necessarily the same as the duration of replication within the skin lesions. Since it is the replication within neurons that needs to be minimized in order to influence pain, the penetration and activity of antiviral agents within neurons is likely to be of paramount importance in determining their potential for hastening pain resolution.
Figure 1. Kaplan-Meier plots for time to complete cessation of zoster-associated pain (ZAP) after initiation of treatment <48 h or 48–72 h of herpes zoster rash onset. A, Acyclovir (○) vs. placebo (●) dataset. B, Valaciclovir (○) vs. acyclovir (●) dataset.

Results from the present analysis, as well as the finding from a large comparative controlled trial of acyclovir versus netivudine [15], which failed to show an effect of rash duration before treatment on pain duration, indicate that treatment with acyclovir remains appropriate for patients presenting up to 72 h after rash onset. The present study also shows that the greater concentrations of acyclovir achieved after valaciclovir exposure continue to be an advantage on pain duration even when

Table 1. Hazard ratios (Cox’s proportional hazard model) and median number of days to complete cessation of zoster-associated pain in patients treated early or late after onset of rash with acyclovir versus placebo or valaciclovir versus acyclovir.

<table>
<thead>
<tr>
<th></th>
<th>Acyclovir vs. placebo</th>
<th>Valaciclovir vs. acyclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain duration (median days)</td>
<td>Hazard ratio (95% CL)</td>
</tr>
<tr>
<td>Early (&lt;48 h)</td>
<td>28 vs. 62</td>
<td>1.68 (1.19, 2.38)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .005</td>
<td></td>
</tr>
<tr>
<td>Late (48–72 h)</td>
<td>28 vs. 58</td>
<td>2.20 (1.03, 4.21)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> = .04</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. CL = confidence limit.
therapy is delayed up to 72 h. This is in apparent contrast with famciclovir: A controlled trial of famciclovir for the treatment of HZ did not demonstrate improvement over acyclovir when therapy was initiated 48–72 h after rash onset [8].

These data have important clinical implications for patients who may not immediately recognize HZ. The prodromal pain of HZ is nonspecific and, even if a doctor is consulted at this stage, may not be recognized for what it is. The rash of HZ often starts proximally within the affected dermatome and, particularly if this is on the trunk, may not be noticed by the patient for a day or two. For patients whose rash is recognized rapidly, consultation with a primary care physician might be impractical (e.g., on weekends), and presentation after 48 h may be considered, out of tradition, too late for initiation of effective antiviral therapy.

A further controlled trial is in progress to determine whether and for how long this “window of opportunity” for deriving clinical benefit of valaciclovir on pain in HZ extends beyond 72 h.

References