Background: There is lack of consensus from randomized controlled trials on the efficacy of antivirals in the management of herpes zoster. Therefore, a systematic review and meta-analysis was undertaken to provide better understanding of effectiveness of antivirals in management of herpes zoster.

Methods: A total of 12 randomized controlled trials with 7,277 patients were included in the review. Trials compared one antiviral to another (aciclovir, valaciclovir, famciclovir or brivudin) for a minimum of 7 days in immunocompetent patients presenting with herpes zoster diagnosed within 72 h of symptom onset. Primary outcome was reduction in pain.

Results: Compared with aciclovir, valaciclovir showed significant reduction in herpes-zoster-associated pain up to 112 days. The largest risk reduction in pain (36%) was seen at 21–30 days (relative risk [RR] 0.64, 95% CI 0.59, 0.70) with number needed to treat to benefit (NNT) of 3 (95% CI 2.7, 3.8). Famciclovir was also superior to aciclovir with a 46% reduction in risk of pain at 28–30 days (RR 0.54, 95% CI 0.48, 0.68) with NNT of 3 (95% CI 2, 5). Time to lesion healing and adverse effect profile was comparable.

Conclusions: Evidence from quality trials have shown significant reduction in risk of pain with valaciclovir and famciclovir for management of herpes zoster including ophthalmicus. Valaciclovir or famciclovir should be preferred treatment options in patients with herpes zoster as they both provide significant reduction in risk of herpes-zoster-associated pain. Furthermore, the superior pharmacokinetics and more convenient dosing regimens with the use of valaciclovir and famciclovir clearly make them the preferred treatment option.

Introduction

Primary infection with varicella zoster virus (VZV; also known as chickenpox) results in viral latency in dorsal root, cranial and autonomic system ganglia [1]. Reactivation of the varicella virus, due to decreased cellular immunity, often associated with ageing, chemotherapy or immunosuppression, results in herpes zoster (HZ) infection, also known as shingles [2]. VZV migrates from a single ganglion to neural tissue of the affected segment and the corresponding cutaneous dermatome [1]. The migration and resultant neural inflammation result in altered sensation and pain (prodrome) to the dermatome, usually followed by development of fluid filled lesions, shallow ulcers and crusts. Ninety percent of primary infection with VZV occurs in children under thirteen years of age. Latent VZV is usually suppressed by a healthy immune system [2] although reactivation can occur through decreased cellular immunity [2]. The virus returns to the ganglion and latency. Viral multiplication within ganglionic nerve cells causes acute inflammation and neuronal necrosis, which, combined with neuritis following viral migration down sensory nerves, results in lasting pain known as post-herpetic neuralgia (PHN) occurring in approximately 20% of patients [3]. If VZV affects the ophthalmic division of the trigeminal nerve, ocular involvement may occur causing ocular manifestations including conjunctivitis, epithelial or stromal keratitis and ocular pain [4]. If corneal scarring occurs, visual loss may be irreversible.

Nucleoside analogues (for example, aciclovir [ACV], valaciclovir [VACV], famciclovir [FAM] and brivudin...
[BVDU]), are the mainstay of clinical treatment for HZ and are most effective if started within 72 h of prodromal symptoms (for example, altered sensation, tingling and rash) [4] and continued for a minimum of 7 days. ACV and FAM are nucleoside analogues that have higher affinity for viral DNA binding sites compared to viral deoxyguanosine [5]. Hence, ACV and FAM disable viral DNA by preventing viral replication once encoded in viral DNA. ACV is the standard treatment for HZ. However, due to its poor intestinal absorption ACV dosing needs to be high and frequent (800 mg, 5× daily) in order to maintain inhibitory plasma concentrations. The produrg of ACV is VACV, which is readily absorbed from the gastrointestinal tract and metabolized in the liver to produce ACV phosphate [6,7]. FAM is a produrg of penciclovir triphosphate, which is an acyclic guanosine analogue with a longer intracellular half-life than ACV or VACV [5] and, as a result, can be given less frequently than ACV and in lower doses than ACV or VACV, improving both patient compliance and maintenance of steady-state plasma concentration.

ACV and FAM, when used as 7-day treatments, improve patient outcomes (that is, pain reduction, shorter duration of viral activation and decreased PHN [8,9]. VACV has been found to be comparable to both ACV and FAM [10–12], with a decrease in ocular complications (for example, conjunctivitis, epithelial or stromal keratitis and ocular pain) also noted [13]. A systematic review in 1995 on primary care management of acute HZ [14] failed to identify significant benefit of ACV due to a paucity of randomized controlled trials. A recent narrative review on treatment of HZ suggested antiviral medication had marginal effects on relieving acute pain and rate of lesion healing [15]. A retrospective study comparing VACV, ACV and placebo for HZ found VACV significantly reduced incidence of PHN compared to ACV [16].

In the past 15 years, many clinical trials comparing antivirals against each other for HZ have been conducted with varying results. Studies found advantages of VACV over ACV for pain resolution, decreased incidence of PHN, and proportion of patients with pain 6 months after cutaneous healing [10,17]. However, other studies have reported no significant difference between the two drugs except a simpler dosing schedule [10,11]. There are also studies that have shown no clinical difference between FAM and ACV in the treatment of HZ [13,18]; however, one study reported a more favourable adverse effect profile with FAM [19]. Furthermore, a study by Tyring et al. [12] found no significant difference between VACV and FAM, and another [20] found BVDU to provide greater efficacy than ACV.

Although recommendations for the management of HZ have been published [21], due to lack of consensus from the many published trials on the efficacy of antivirals in the management of HZ there are no internationally accepted guidelines. Therefore, an up-to-date systematic review was warranted to provide a better understanding of the effectiveness of antivirals in the management of HZ. This systematic review compared the efficacy of ACV, VACV, FAM and BVDU in the management of immunocompetent patients with active HZ diagnosed within 72 h of symptom onset.

**Methods**

A systematic review was conducted using Cochrane Collaboration methodology and software from the Nordic Cochrane Centre (Rigshospitalet, Copenhagen, Denmark) [22] of randomized controlled trials in the management of HZ (diagnosed within 72 h of symptom onset) in immunocompetent patients >18 years of age comparing one antiviral to another (ACV, VACV, FAM or BVDU) treated for a minimum of 7 days.

Primary outcome was the proportion of patients with reduction in pain. Pain was defined as any degree of HZ-associated dermal discomfort ranging from mild discomfort to discomfort that prevents activities of daily life. Secondary outcomes included rate of lesion healing and adverse effects.

**Search strategy and selection criteria**

Trials were excluded if they were non-experimental in design, compared antiviral with placebo, involved patients who had acute retinal necrosis, progressive outer retinal necrosis, or herpes simplex type I or II.

The following databases were searched for potential studies with no language restrictions: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, BioMed Central, Trials Central, Clinical Trials, Controlled Clinical Trials, Web of Science and online relevant medical journal web sites. All databases were searched from the date of inception until May 2011. The reference lists of retrieved articles were searched to identify potential studies. Authors of identified trials and pharmaceutical companies producing antivirals were contacted for further published, unpublished or ongoing studies.

The search of databases was initially conducted by one reviewer (EMM), and two reviewers (EMM and FSFR) independently selected trials for inclusion and assessed all trials that appeared potentially relevant. Full articles retrieved were obtained and translated where necessary. A third reviewer (JdK) would have been invited to arbitrate if there was failure in resolving disagreement between the first two reviewers. Figure 1 details selection of trials with reasons for exclusions.

A five-point Jadad scale was used to assess methodological quality of included studies [23]. Allocation concealment was also assessed using the Cochrane
Collaboration scale [24]. Table 1 lists both methodological quality scores.

All data was analysed on an intention-to-treat basis. Mantel-Haenszel fixed-effect model analysis was used for all dichotomous data [25,26]. Data was analysed using weighted mean differences and 95% CIs for continuous outcomes and relative risks (RR) calculated for dichotomous outcome with 95% CI. Where appropriate, number needed to treat to benefit (NNT) and 95% CI was calculated [27].

Results

Trial selection and quality

An electronic search yielded 1,740 abstracts, 18 trials were identified as potentially suitable, 6 were excluded and the remaining 12 [9–13,17–20,28–30] with 7,277 patients included. There was full agreement between two reviewers on exclusion and inclusion of trials. Characteristics of included trials are shown in Table 1. Included trials were of good methodological quality with six trials scoring ‘A’ and six scoring ‘B’ for Cochrane allocation concealment rating. In addition, included trials had an average Jadad score of 3.58, which is considered to be of good methodological quality [23]. Details for outcome comparisons which included two or more trials are summarized in Table 2.

Figure 1. Flow diagram of selected and excluded trials based on the Quorom statement

- Potentially relevant RCTs identified and screened for retrieval (n=2,054)
-RTC excluded as not relevant (n=2,036)
-RTC retrieved for more detailed evaluation (n=18)
-RTC excluded with reasons (n=6)
  - Immunocompromised n=1
  - Patients did not have herpes zoster n=2
  - Not an RCT n=3
-RTC potentially appropriate RTCs to be included in meta-analysis (n=12)
-RTC excluded from meta-analysis with reasons (n=0)
-RTC included in meta-analysis (n=12)
-RTC excluded from meta-analysis with reasons (n=0)
-RTC withdrawn, by outcome, with reasons (n=0)
-RTC with usable information, by outcome (n=12)
  - Pain n=9
  - Lesion healing n=7
  - Adverse effects n=9
  - Abnormal sensation n=2
  - Ocular complications n=2

RCT, randomized controlled trial.
### Table 1. Characteristics of included trials with methodological quality scores

<table>
<thead>
<tr>
<th>Reference</th>
<th>Total number of participants in trial</th>
<th>Population</th>
<th>Interventions</th>
<th>Outcome</th>
<th>Trial quality score (Cochrane/Jadad)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beutner et al. [10]</td>
<td>1,141</td>
<td>Multinational study of patients aged ≥50 years presenting with HZ within 72 h. Mean age 68 years, 57% male, 43% female.</td>
<td>VACV 1,000 mg 3× daily for 7 days; VACV 1,000 mg 3× daily for 14 days; ACV 800 mg 5× daily for 7 days.</td>
<td>VACV accelerates resolution of pain, has simpler dosing regimen and comparable safety profile to ACV.</td>
<td>A/4</td>
</tr>
<tr>
<td>Colin et al. [11]</td>
<td>110</td>
<td>French study of patients aged ≥18 years presenting with HZO within 72 h. Mean age 62 years, 48% male, 52% female.</td>
<td>VACV 1,000 mg 3× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>VACV is comparable to ACV in pain resolution, preventing ocular complications and adverse event profile.</td>
<td>B/3</td>
</tr>
<tr>
<td>Degreef et al. [28]</td>
<td>545</td>
<td>Multinational study of patients aged ≥50 years presenting with HZ within 72 h. Mean age 51 years, 44% male, 56% female.</td>
<td>FAM 250 mg 3× daily for 7 days; FAM 500 mg 3× daily for 7 days; FAM 750 mg 3× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>All three doses of FAM are comparable to ACV for pain resolution, lesion healing and adverse event profile.</td>
<td>B/3</td>
</tr>
<tr>
<td>Lin et al. [17]</td>
<td>57</td>
<td>Taiwanese study of patients aged ≥18 years presenting with HZ within 72 h. Mean age 63 years, 65% male, 35% female.</td>
<td>VACV 1,000 mg 3× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>VACV accelerates resolution of pain, has simpler dosing regimen and comparable safety profile to ACV.</td>
<td>B/2</td>
</tr>
<tr>
<td>Shafran et al. [18]</td>
<td>559</td>
<td>Multinational study of patients aged ≥18 years presenting with HZ within 72 h. Mean age 55 years, 42% male, 58% female.</td>
<td>FAM 250 mg 3× daily for 7 days; FAM 500 mg twice daily for 7 days; FAM 750 mg 1× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>All three doses of FAM were comparable to ACV for lesion healing.</td>
<td>B/3</td>
</tr>
<tr>
<td>Shen et al. [19]</td>
<td>55</td>
<td>Taiwanese study of patients aged ≥18 years presenting with HZ within 72 h. Mean age 60 years, 65% male, 35% female.</td>
<td>FAM 250 mg 3× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>FAM is comparable to ACV for lesion healing but has a more favourable adverse event profile.</td>
<td>B/3</td>
</tr>
<tr>
<td>Tyring et al. [9]</td>
<td>419</td>
<td>Multinational study of patients aged ≥18 years presenting with HZ within 72 h. Mean age 50 years, 53% male, 47% female.</td>
<td>FAM 500 mg 3× daily for 7 days; FAM 750 mg 3× daily for 7 days.</td>
<td>Both doses of FAM accelerated resolution of pain and have similar adverse event profile. No difference between FAM doses.</td>
<td>A/3</td>
</tr>
<tr>
<td>Tyring et al. [12]</td>
<td>597</td>
<td>American study of patients aged ≥50 years presenting with HZ within 72 h. Mean age 69 years, 37% male, 63% female.</td>
<td>VACV 1,000 mg 3× daily for 7 days; FAM 500 mg 3× daily for 7 days.</td>
<td>VACV is comparable to FAM for resolution of pain, lesion healing and adverse event profile.</td>
<td>A/5</td>
</tr>
<tr>
<td>Tyring et al. [13]</td>
<td>454</td>
<td>Multinational study of patients aged ≥18 years presenting with HZO within 72 h. Mean age 58 years, 47% male, 53% female.</td>
<td>FAM 500 mg 3× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>FAM is comparable to ACV for ocular manifestations.</td>
<td>A/5</td>
</tr>
<tr>
<td>Wassilew et al. [20]</td>
<td>1,225</td>
<td>Multinational study of patients aged ≥18 years presenting with HZ within 72 h. Mean age 53 years, 44% male, 56% female.</td>
<td>BVDU 125 mg 1× daily for 7 days; ACV 800 mg 5× daily for 7 days.</td>
<td>BVDU accelerates lesion healing compared to ACV whilst having comparable adverse event profile.</td>
<td>A/5</td>
</tr>
<tr>
<td>Wassilew et al. [29]</td>
<td>2,027</td>
<td>Multinational study of patients aged ≥50 years presenting with HZ within 72 h. Mean age 63 years, 40% male, 60% female.</td>
<td>BVDU 125 mg 1× daily for 7 days; FAM 250 mg 3× daily for 7 days.</td>
<td>BVDU is comparable to FAM for resolution of pain, lesion healing and adverse event profile.</td>
<td>A/5</td>
</tr>
<tr>
<td>Xu et al. [30]</td>
<td>88</td>
<td>Chinese study of patients aged ≥18 years presenting with HZ within 72 h. Mean age and gender ratio not stated in translation.</td>
<td>FAM 250 mg 3× daily for 7 days; ACV 200 mg 5× daily for 7 days.</td>
<td>FAM accelerates resolution of pain and shortens length of inflammation compared to ACV.</td>
<td>B/2</td>
</tr>
</tbody>
</table>

*Cochrane study quality score (A= adequate, B= unclear, C= inadequate and D= unused); Jadad trial quality score (0–5). ACV, aciclovir; BVDU, brivudin; FAM, famciclovir; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; VACV, valaciclovir.
Antivirals for herpes zoster

There was no further reduction in risk of pain from 113 to 170 days and there was no data available beyond 170 days. Colin et al. [11] compared VACV to ACV in patients with HZ ophthalmicus (HZO) and found no difference in the incidence of ocular complications or use of analgesics (topical or systemic) for ocular pain.

FAM 250 mg three times daily was compared to ACV 800 mg five times daily in two studies [19,28] with 328 patients (Figure 3). Risk of pain was reduced by 46% (RR 0.54, 95% CI 0.43, 0.68) compared to ACV at 28 to 30 days post-treatment, with an NNT of 3 (95% CI 2, 5; Table 2). Three studies [18,19,28] comparing FAM to ACV found no difference in adverse effects or lesion healing.

Vesicles, lesions, crusts and adverse effects
There was no difference in median time to loss of vesicles, cessation of new lesions, full crusting or loss of crusts when VACV or FAM was compared to ACV at any of the doses used in the included trials (Table 2). There was no difference in risk of the adverse effects when VACV or FAM was compared to ACV (Table 3).

Comparisons/outcomes & Number of studies (subjects) & RR (95% CI) & P-value & NNT (95% CI)

<table>
<thead>
<tr>
<th>Comparisons/outcomes</th>
<th>Number of studies (subjects)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VACV 1,000 mg 3× daily versus ACV 800 mg 5× daily</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pain</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>At presentation</td>
<td>3 (927)</td>
<td>1.01 (0.99, 1.03)</td>
<td>0.41</td>
<td>–</td>
</tr>
<tr>
<td>1–10 Days</td>
<td>3 (927)</td>
<td>0.92 (0.88, 0.97)</td>
<td>0.004*</td>
<td>14 (9, 50)</td>
</tr>
<tr>
<td>11–20 Days</td>
<td>3 (927)</td>
<td>0.91 (0.84, 0.98)</td>
<td>0.02*</td>
<td>14 (8, 100)</td>
</tr>
<tr>
<td>21–30 Days</td>
<td>3 (927)</td>
<td>0.64 (0.59, 0.70)</td>
<td>&lt;0.00001*</td>
<td>3 (2.7, 3.8)</td>
</tr>
<tr>
<td>31–60 Days</td>
<td>2 (870)</td>
<td>0.85 (0.73, 0.99)</td>
<td>0.04*</td>
<td>14 (8, 100)</td>
</tr>
<tr>
<td>61–112 Days</td>
<td>2 (870)</td>
<td>0.79 (0.63, 0.98)</td>
<td>0.03*</td>
<td>17 (8, 100)</td>
</tr>
<tr>
<td>113–170 Days</td>
<td>2 (870)</td>
<td>0.61 (0.62, 1.05)</td>
<td>0.11</td>
<td>–</td>
</tr>
<tr>
<td>FAM 250, 500, 750 mg 3× daily versus ACV 800 mg 5× daily</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pain</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FAM 250 mg, 28–30 days</td>
<td>2 (328)</td>
<td>0.54 (0.43, 0.68)</td>
<td>&lt;0.00001*</td>
<td>3 (2, 5)</td>
</tr>
<tr>
<td>Loss of vesicles</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FAM 250 mg versus ACV 800 mg, 5–7 days</td>
<td>3 (605)</td>
<td>0.97 (0.93, 1.02)</td>
<td>0.31</td>
<td>–</td>
</tr>
<tr>
<td>FAM 500 mg versus ACV 800 mg, 5–6 days</td>
<td>2 (553)</td>
<td>0.98 (0.93, 1.03)</td>
<td>0.38</td>
<td>–</td>
</tr>
<tr>
<td>FAM 750 mg versus ACV 800 mg, 5–7 days</td>
<td>2 (555)</td>
<td>0.99 (0.95, 1.04)</td>
<td>0.74</td>
<td>–</td>
</tr>
<tr>
<td>Cessation of new lesions</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FAM 250 mg versus ACV 800 mg, 3 days</td>
<td>2 (550)</td>
<td>0.89 (0.76, 1.04)</td>
<td>0.15</td>
<td>–</td>
</tr>
<tr>
<td>FAM 500 mg versus ACV 800 mg, 3 days</td>
<td>2 (553)</td>
<td>0.93 (0.80, 1.09)</td>
<td>0.37</td>
<td>–</td>
</tr>
<tr>
<td>FAM 750 mg versus ACV 800 mg, 3 days</td>
<td>2 (555)</td>
<td>0.95 (0.81, 1.10)</td>
<td>0.47</td>
<td>–</td>
</tr>
<tr>
<td>Full crusting</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FAM 250 mg versus ACV 800 mg, 6–11 days</td>
<td>3 (605)</td>
<td>1.04 (0.97, 1.10)</td>
<td>0.26</td>
<td>–</td>
</tr>
<tr>
<td>FAM 500 mg versus ACV 800 mg, 6–7 days</td>
<td>2 (553)</td>
<td>0.99 (0.92, 1.06)</td>
<td>0.69</td>
<td>–</td>
</tr>
<tr>
<td>FAM 750 mg versus ACV 800 mg, 6–8 days</td>
<td>2 (555)</td>
<td>1.03 (0.97, 1.10)</td>
<td>0.37</td>
<td>–</td>
</tr>
<tr>
<td>Loss of crusts</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>FAM 250 mg versus ACV 800 mg, 20–27 days</td>
<td>3 (605)</td>
<td>1.02 (0.97, 1.06)</td>
<td>0.45</td>
<td>–</td>
</tr>
<tr>
<td>FAM 500 mg versus ACV 800 mg, 19–21 days</td>
<td>2 (553)</td>
<td>0.99 (0.95, 1.04)</td>
<td>0.73</td>
<td>–</td>
</tr>
<tr>
<td>FAM 750 mg versus ACV 800 mg, 20–21 days</td>
<td>2 (555)</td>
<td>1.00 (0.96, 1.05)</td>
<td>0.86</td>
<td>–</td>
</tr>
<tr>
<td>FAM 500 mg 3× daily versus FAM 750 mg 3× daily</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pain</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10 Days</td>
<td>2 (545)</td>
<td>0.83 (0.76, 0.91)</td>
<td>&lt;0.0001*</td>
<td>7 (5, 13)</td>
</tr>
<tr>
<td>20 Days</td>
<td>2 (545)</td>
<td>0.95 (0.83, 1.09)</td>
<td>0.42</td>
<td>–</td>
</tr>
<tr>
<td>30 Days</td>
<td>2 (545)</td>
<td>0.94 (0.81, 1.09)</td>
<td>0.40</td>
<td>–</td>
</tr>
<tr>
<td>60 Days</td>
<td>2 (545)</td>
<td>1.03 (0.85, 1.26)</td>
<td>0.74</td>
<td>–</td>
</tr>
<tr>
<td>110 Days</td>
<td>2 (545)</td>
<td>0.88 (0.63, 1.21)</td>
<td>0.43</td>
<td>–</td>
</tr>
</tbody>
</table>

*Statistically significant outcome. ACV, aciclovir; FAM, famciclovir; NNT, number needed to treat to benefit (computed only for significant outcomes); RR, relative risk; VACV, valaciclovir.

Table 2. Outcomes with two or more included studies comparing antivirals for herpes zoster
Study or subcategory | VACV, n/N | ACV, n/N | RR (fixed) 95% CI | Weight, % | RR (fixed) 95% CI
--- | --- | --- | --- | --- | ---
01 1–10 days | Beutner 1995 | 334/384 | 346/376 | 86.40 | 0.95 (0.90, 0.99)
Colin 2000 | 24/56 | 32/54 | 8.05 | 0.72 (0.50, 1.05)
Lin 2001 | 23/32 | 20/25 | 5.55 | 0.90 (0.67, 1.20)
Subtotal (95% CI) | 472 | 455 | 100.00 | 0.92 (0.88, 0.97)
Total events: | 381 (VACV), 398 (ACV) |
Test for heterogeneity: | $\chi^2$=2.46, df=2 ($P$=0.29) |
Test for overall effect: | Z=2.91 ($P$=0.004) |

02 11–20 days | Beutner 1995 | 288/384 | 301/376 | 87.00 | 0.94 (0.87, 1.01)
Colin 2000 | 19/56 | 27/54 | 7.86 | 0.68 (0.43, 1.07)
Lin 2001 | 17/32 | 16/25 | 5.14 | 0.83 (0.54, 1.29)
Subtotal (95% CI) | 472 | 455 | 100.00 | 0.91 (0.84, 0.98)
Total events: | 324 (VACV), 344 (ACV) |
Test for heterogeneity: | $\chi^2$=2.31, df=2 ($P$=0.31) |
Test for overall effect: | Z=2.36 ($P$=0.02) |

03 21–30 days | Beutner 1995 | 238/384 | 363/376 | 92.00 | 0.64 (0.59, 0.70)
Colin 2000 | 14/56 | 17/54 | 4.34 | 0.79 (0.44, 1.45)
Lin 2001 | 9/32 | 13/25 | 3.66 | 0.54 (0.28, 1.06)
Subtotal (95% CI) | 472 | 455 | 100.00 | 0.64 (0.59, 0.70)
Total events: | 261 (VACV), 393 (ACV) |
Test for heterogeneity: | $\chi^2$=0.74, df=2 ($P$=0.69) |
Test for overall effect: | Z=10.41 ($P$<0.00001) |

04 31–60 days | Beutner 1995 | 165/384 | 188/376 | 94.91 | 0.86 (0.74, 1.00)
Colin 2000 | 8/56 | 10/54 | 5.09 | 0.77 (0.33, 1.81)
Subtotal (95% CI) | 440 | 430 | 100.00 | 0.85 (0.73, 0.99)
Total events: | 173 (VACV), 198 (ACV) |
Test for heterogeneity: | $\chi^2$=0.06, df=1 ($P$=0.81) |
Test for overall effect: | Z=2.03 ($P$=0.04) |

05 61–112 days | Beutner 1995 | 100/384 | 120/376 | 93.71 | 0.82 (0.65, 1.02)
Colin 2000 | 3/56 | 8/54 | 6.29 | 0.36 (0.10, 1.29)
Subtotal (95% CI) | 440 | 430 | 100.00 | 0.79 (0.63, 0.98)
Total events: | 103 (VACV), 128 (ACV) |
Test for heterogeneity: | $\chi^2$=1.53, df=1 ($P$=0.22) |
Test for overall effect: | Z=2.12 ($P$=0.03) |

The mean value for each trial is indicated by a square box with the line through it representing the 95% CI. The size of the square represents the weight that the corresponding study exerts in the meta-analysis; this is the Mantel–Haenszel weight. Mean values left of the vertical line of no effect (value of 1) favour less risk of pain with valaciclovir (VACV) and values on the right favour less risk of pain with aciclovir (ACV). The solid diamond indicates the overall mean effect VACV has on pain with the lateral points indicating confidence intervals of this estimate. A percentage weighting, which is dependent on the precision and sample size of the estimation of the mean value for each randomized controlled trial, is allocated to each study. The $\chi^2$ and the degrees of freedom (df) values for each time point provide a measure of heterogeneity of the results. The Z statistic indicates the level of significance for the overall result. $P$-values ≤0.05 are considered statistically significant. RR, relative risk.
Antivirals for herpes zoster

Figure 3. Famciclovir 250 mg three times daily reduces risk of pain versus aciclovir 800 mg five times daily at 28–30 days

The mean value for each trial is indicated by a square box with the line through it representing the 95% CI. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The solid diamond indicates the overall mean effect FAM has on pain with the lateral points indicating confidence intervals of this estimate. ACV, aciclovir; df, degrees of freedom; FAM, famciclovir; RR, relative risk.

Table 3. Valaciclovir, aciclovir and famciclovir adverse effects for outcomes with two or more included studies

Comparisons/outcomes | Number of studies (subjects) | RR (95% CI) | P-value |
--- | --- | --- | --- |
VCV 1,000 mg 3× daily versus ACV 800 mg 5× daily | – | – | – |
Vomiting | 2 (870) | 1.38 (0.89, 2.12) | 0.15 |
Diarrhoea | 2 (817) | 0.83 (0.51, 1.34) | 0.44 |
Constipation | 2 (817) | 1.01 (0.57, 1.81) | 0.96 |
Dizziness | 2 (817) | 0.70 (0.39, 1.26) | 0.24 |
FAM 250 mg 3× daily versus ACV 800 mg 5× daily | – | – | – |
Headache | 2 (332) | 1.25 (0.72, 2.17) | 0.43 |
Constipation | 2 (332) | 0.83 (0.37, 1.88) | 0.66 |
FAM 500 mg 3× daily versus FAM 750 mg 3× daily | – | – | – |
Headache | 2 (555) | 1.02 (0.73, 1.43) | 0.91 |
Nausea | 2 (555) | 1.08 (0.68, 1.72) | 0.75 |

ACV, aciclovir; FAM, famciclovir; RR, relative risk; VACV, valaciclovir.

Figure 4. Famciclovir 500 mg three times daily reduces risk of pain versus FAM 750 mg three times daily at 10 days

The mean value for each trial is indicated by a square box with the line through it representing the 95% CI. The size of the square represents the weight that the corresponding study exerts in the meta-analysis. The solid diamond indicates the overall mean effect FAM 500 mg has on pain with the lateral points indicating confidence intervals of this estimate. df, degrees of freedom; FAM, famciclovir; RR, relative risk.
and 750 mg three times daily) of FAM were compared they all provided similar efficacy in reducing pain and lesion healing, with the exception of greater reduction in risk of pain at 10 days with FAM 500 mg, when compared to 750 mg.

Outcomes with a single included trial
A single study with 273 patients [28] demonstrated significant reduction in risk of pain with three doses of FAM (250, 500, 750 mg three times daily) from 1–170 days when compared to ACV (800 mg five times daily).

The following comparisons were also included in single trials: VACV 1,000 mg versus FAM 500 mg [12]; FAM 250 mg versus ACV 200 mg [30]; FAM 250 mg compared to FAM 500 mg and FAM 750 mg [28]; BVDU 125 mg compared to ACV 800 mg [20] and FAM 250 mg [29]. Meta-analysis of a single trial is nonsensical and uninterpretable; therefore these comparisons are not discussed in detail.

Discussion
This is the first study to show significant reduction in risk of HZ-associated pain with VACV and FAM compared to ACV. The three antivirals did not differ regarding time to lesion healing, cessation of new lesions, full crusting or loss of crusts at any of the doses used in the trials and all antivirals showed comparable safety profile. It is interesting to note that although VACV provides significant reduction in risk of pain compared to ACV, there is no difference in the rate of skin lesion healing. It is possible that VACV is present in greater concentrations in the dorsal root ganglion compared to ACV. Furthermore, as there was no difference in the rate of skin lesion healing it is plausible that there was no difference in drug concentration at the skin. However, this pharmacological difference needs to be evaluated in future studies.

Recommendations published on the management of HZ [21] are in agreement with the results of this systematic review, preferring VACV and FAM over ACV. VACV and FAM provide higher plasma concentrations of acyclic nucleoside analogue required for inhibition of VZV, reducing acute viral shedding and minimizing neural damage [21]. As the dosing schedule for VACV and FAM is three times daily as opposed to ACV five times daily, patient compliance with dosing regimes is likely to be higher.

There has been ongoing debate as to the best way to measure PHN. Studies have used differing methods such as HZ-associated pain, and cross-sectional comparisons at times varying from 30–120 days after onset of pain. The Shingles Prevention Study (SPS) [31] used 90 days to define PHN but also did comparisons at 30, 60 and 120 days. We have used a similar comparison to the SPS measuring pain at varying times from 1–170 days but did not use any specific time to define PHN. Due to the changing definition of PHN over the years, our approach was to accept the inclusion of subjects with HZ-associated pain, from presentation to study completion. Pain as an outcome was stratified in some studies to include degrees of pain both during the acute phase and after cutaneous healing, whereas in other studies only presence or absence of pain was described and pain was seen as a continuum from presentation to resolution. Included studies assessed pain in a variety of ways including Gracely scales (0= no pain to 5= pain that requires rest or bed rest), four-point 0–3 scales (0= no pain to 3= severe pain), and six-point pain scales (0= no pain to 5= unbearable). Although there is general consensus that antiviral zoster trials, particularly those that measure PHN, utilize pain severity scores, we chose to use the presence or absence of pain as our primary outcome measure to enable comparability between studies and utilized comparable time points without defining post-rash status. The effect of using this definition as our outcome measure would underestimate treatment effect as participants with mild pain were included in the pain group.

In any systematic review it may be possible that not all studies have been identified. However, a comprehensive search for published and unpublished studies was performed to decrease the chance of missing any potential studies. No language restriction was applied and in studies with insufficient data, authors were contacted for further details.

A single trial conducted on 454 patients with HZO demonstrated no difference in the incidence of ocular manifestations between FAM (500 mg three times daily) compared to ACV (800 mg five times daily) indicating no increased risk of ocular manifestations when FAM is used for HZO [13]. Another study in 88 patients [30] showed reduction in time to cessation of acute pain, by 3 days with FAM (250 mg three times daily) compared to ACV (200 mg five times daily). This study [30] also demonstrated that lesion healing occurred a day earlier with FAM (250 mg three times daily) compared to ACV (200 mg five times daily) and loss of crusts occurred 3 days earlier with FAM (weighted mean difference 2.93 days, 95% CI 1.02, 4.84). It is possible, however, that the subtherapeutic dose (200 mg five times daily) of ACV did not provide adequate plasma concentrations to inhibit VZV, thus skewing the results in favour of FAM.

A recent systematic review [32] investigating antiviral treatment for preventing PHN stated ACV provided significant reduction in risk of PHN 1 month after onset of acute herpetic rash. This result, however, was heterogeneous (P=0.01, I²=72%) and therefore a valid conclusion cannot be derived. The authors did not find significant difference between ACV and control groups.
in the incidence of PHN at 4 or 6 months following acute herpetic rash. However, they have stated that a limitation of their review is the lack of quality clinical trials hampering the robustness of their conclusions and found insufficient evidence from included trials to support the use of other antiviral agents in preventing PHN. Our review of high-quality randomized controlled trials addresses this gap in evidence by showing up to 36% reduction in risk of pain with VACV and 46% reduction in risk of pain with FAM.

FAM has been shown to be more effective than ACV in reducing risk of pain with comparable lesion healing and safety profile. FAM 500 mg three times daily has been shown to significantly reduce risk of pain at 10 days compared to FAM 750 mg three times daily with no difference in adverse effects. A single study comparing FAM 250 mg to 750 mg, and 250 mg to 500 mg found all doses to be comparable for pain, lesion healing and adverse effects. HZO was excluded from all trials comparing FAM to ACV for pain, lesion healing and adverse effects. Therefore, the results of this comparison need to be used with caution in patients presenting with trigeminal first nerve involvement. Further studies are required to confirm these findings and, until such time, the lowest effective dose of FAM should be used in the management of HZ. Further studies are required comparing FAM and ACV beyond 30 days for reduction in risk of pain, lesion healing and adverse effects, particularly in patients with HZO.

Due to the greater clinical effectiveness of VACV and FAM, as evidenced by significant reduction in risk of pain, superior pharmacokinetics and easier dosing schedule compared to ACV, it is recommended that VACV and FAM be the treatments of choice in the management of HZ.

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Disclosure statement

The authors declare no competing interests.

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