REVIEW ARTICLES

Oral Acyclovir Therapy Accelerates Pain Resolution in Patients with Herpes Zoster: A Meta-analysis of Placebo-Controlled Trials

M. J. Wood, R. Kay, R. H. Dworkin, S.-J. Soong, and R. J. Whitley

From the Department of Infection & Tropical Medicine, Birmingham Heartlands Hospital, Birmingham; and S-Cubed, Sheffield, United Kingdom; the Department of Anesthesiology, College of Physicians & Surgeons of Columbia University, New York, New York, USA; and the Biostatistics Unit, and the Departments of Pediatrics, Microbiology, and Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA

Meta-analysis of four double-blind, randomized, placebo-controlled trials of oral acyclovir (800 mg five times daily) for the treatment of herpes zoster was conducted to provide definitive assessments of the effect of acyclovir on the resolution of zoster-associated pain. The studies involved a total of 691 patients, and the analysis was performed on an intent-to-treat basis. A range of milestones of pain cessation were evaluated by means of Cox regression models with adjustment for relevant prognostic factors. The proportion of patients with postherpetic neuralgia at 3 and 6 months was also determined. Advancing age and more severe pain at presentation were associated with more prolonged pain. Acyclovir was clearly shown to accelerate pain resolution by all of the measures employed. Benefit was especially evident in patients 50 years of age or older. Fewer acyclovir recipients had postherpetic neuralgia at 3 or 6 months. Overall, the reductions of pain duration and prevalence were approximately twofold.

The pain associated with herpes zoster is the principal reason why patients seek medical care [1]. The pain of herpes zoster has been variably described [2, 3], although by any definition the prevalence decreases in the 6 months after acute zoster. Traditionally, pain present while the rash persists or in the first 30 days from the onset has been termed *acute pain.* Pain present after these time points is generally termed *postherpetic neuralgia.* However, for many patients who experience continuous pain, it may be impossible to regard it other than as a continuum. The term *zoster-associated pain* [1] has therefore been adopted for the analysis of clinical trials evaluating antiviral agents for the treatment of herpes zoster because it circumvents the need to select one of several arbitrary definitions of postherpetic neuralgia [4–6] and it facilitates application of statistical principles, including intent-to-treat analysis (i.e., the inclusion of all randomized patients). For instance, a definition of postherpetic neuralgia that depends on a start time related to rash healing introduces inherent bias because studies have consistently demonstrated the marked benefit of therapy in accelerating rash healing [7–9]. Postherpetic neuralgia is encompassed within zoster-associated pain and may be better defined as pain present 1, 3, or 6 months after rash onset.

Four placebo-controlled, randomized, double-blind trials evaluating the recommended dose of oral acyclovir (800 mg five times daily for 7–10 days) for the treatment of herpes zoster have been conducted [7–10]. Three studies [7, 8, 10] individually showed that acyclovir treatment reduces the prevalence of long-term pain, with the effect being most significant in the 3 months after rash onset. The fourth trial [9] did not detect a difference in prevalence overall.

Pain was a primary endpoint in each of the four placebo-controlled studies. Other similarities in the way that the studies were conducted included all patients starting treatment within 72 hours of rash onset and comparable evaluation of pain severity. However, three studies followed-up all patients for 6 months, while the fourth study only required assessments to continue until patients first reported that they were pain-free [11]. Despite other minor differences in study design, sufficient similarities allowed a formal meta-analysis of pain endpoints to be conducted.

Although analyses of the time to cessation of pain have previously been undertaken by other investigators [12, 13], they were less complete than the one reported here. In particular, we report estimates of the impact of therapy on a number of additional endpoints by providing hazard ratios and their 95% confidence intervals. Further, adjustment of treatment effects by

Received 14 June 1995; revised 1 September 1995.

Grant support: This work was supported by The Wellcome Research Laboratories, Beckenham, UK.

Reprints or correspondence: Dr. M. J. Wood, Department of Infection & Tropical Medicine, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5ST, United Kingdom.

Clinical Infectious Diseases 1996;22:341–7

1058–4838/96/2202–0022$02.00

taking into account the important demographic prognostic variables believed to influence pain outcome, particularly age and pain severity at presentation [14–16], increased the precision of these estimates. Since it has long been recognized that older patients are at higher risk for postherpetic neuralgia [17, 18], an evaluation of the efficacy of acyclovir therapy for this subgroup of patients provides information that is clinically relevant. This meta-analysis of all available data from double-blind, placebo-controlled, randomized trials of the recommended dose of oral acyclovir addresses each of these aspects and provides benchmarks for future trials.

Materials and Methods

Clinical Trial Databases

Four placebo-controlled, double-blind, randomized clinical trials of the recommended dose of oral acyclovir (800 mg five times daily) provided the databases on which all statistical analyses of individual trials and the combined meta-analysis were conducted [7–10]. In studies 1 and 3, treatment was for 10 days, while studies 2 and 4 evaluated a 7-day regimen.

Following screening and completion of enrollment procedures, all patients commenced treatment with acyclovir or placebo within 72 hours of rash onset. Thereafter, timings of clinical assessments differed within each study. In study 1 [7], patients were seen daily during the first week, twice weekly for the first month, and monthly for a further 6 months. In study 2 [8], patients were evaluated daily during the first week, every other day during the second week, weekly for the next 2 weeks, and then monthly until month 6. In study 3 [10], patients were assessed at least twice during the first week, once during the second week, and then at months 1, 2, 3, and 6. In study 4 [9], patients were assessed daily during the first week, twice during the second week, weekly until month 1, and then at monthly intervals until month 6 only if pain was present. Concomitant therapy with systemic corticosteroids or tricyclic antidepressants was excluded in studies 1, 3, and 4 but was allowed in study 2. The numbers of patients prescribed such therapy were insufficient for assessing any effect on the statistical results. Analgesic therapy for zoster-associated pain was allowed but was not standardized either within or between individual studies. No formal analyses of these data were attempted.

For study 1, data on the time to complete cessation of pain, which had previously undergone independent validation, were supplied electronically to S-Cubed (Sheffield, UK). For studies 2, 3, and 4, demographic characteristics, times to event and/or no event for pain endpoints, treatment group, and details of covariates were extracted by one of the authors (R. K.) from data listings supplied by The Wellcome Foundation (Beckenham, UK). Any previously unaudited data were subjected to quality assurance checks, and appropriate corrections were made before further analysis. Data extraction was blind to treatment group to avoid bias.

Pain Endpoints

Pain was described as none, mild, moderate, or severe and was scored on a scale from 0 to 3. Pain scored as ≥ 2 was considered moderate/severe. In study 3, pain severity was assessed by means of a 100-mm visual analogue line; moderate/severe pain was defined as a score of ≥ 25 mm.

The time to event for the following pain endpoints was derived: complete cessation of pain, complete cessation of moderate/severe pain, complete cessation of postherpetic neuralgia (pain beyond day 30), and the first pain-free period. Data were available for ≥ 6 months for studies 1, 2, and 3. Follow-up was stopped in study 4 when patients first became pain-free for 1 month. Hence, times to complete cessation of pain were not available for this study.

Times to event were extracted differently in each trial to accommodate the ways in which data were recorded. Primarily, data extraction involved using midpoints of the interval between two dates or midpoints of periods over which pain scores were available. Complete cessation of pain was defined when all reports from any time point onward indicated no pain. Censoring was applied when pain was present at the last assessment. Complete cessation of moderate/severe pain was defined similarly. Complete cessation of postherpetic neuralgia was defined as subsequent absence of pain in patients who still had pain on day 30. A value of zero was assigned to loss of pain before day 30, and this score was retained in the analysis to preserve intent-to-treat principles. Definition of the time to the first pain-free period necessarily differed across studies to account for the different intervals used. In study 1, the intervals were days 1–7, days 8–10, days 11–22, day 23 to 1 month, and monthly thereafter. In study 2, the intervals were weekly during the first month and monthly thereafter. In study 3, the intervals were days 1–11, 12–20, 21–35, 36–79, 80–121, and 122–244. In study 4, the intervals were days 1–7, days 8–13, days 14–20, day 21 to 1 month, and monthly thereafter. The endpoint for this analysis was therefore defined as a pain-free period of 1 week during the first month or a pain-free period of 1 month thereafter. Thus, all studies were analyzed by the method utilized in the design of study 4.

Prognostic Factors Fitted as Covariates

Prognostic variables, which were subsequently incorporated into the regression analyses that determined treatment differences, were gender, age, duration of rash before treatment initiation, pain severity at presentation, and duration of prodromes. Gender (male vs. female), duration of rash before treatment initiation (<48 hours vs. ≥ 48 hours), pain severity at presentation (none/mild vs. moderate/severe), and duration of prodromes (<48 hours vs. ≥ 48 hours) were all fitted as binary variables. Age was included in the models as a continuous covariate. No data on the duration of prodromes were available for study 1.

Statistical Analysis

All analyses of individual trials and the meta-analyses were of the intent-to-treat population. All models were fitted by means of SAS software (version 6.08; SAS Institute, Cary, NC). The EXACT option within PROC PHREG in SAS was used to accommodate the heavily tied data that resulted from the designs of individual studies [19]. All statistical analyses were performed independent of the staff of The Wellcome Foundation.

The distribution of the time to event for each pain endpoint was estimated by means of the Kaplan-Meier product limit method [20]. Cox regression models were fitted with (adjusted) and without (unadjusted) covariates. Hazard ratios for acyclovir treatment vs. placebo were obtained with 95% confidence intervals and P values used in testing the significance of treatment differences. The Cox regression model was used to determine the influence of each covariate on the time to event for pain endpoints. Hazard ratios for treatment in each meta-analysis were derived by combining hazard ratios from individual studies in a weighted average. The weights used were the inverses of the corresponding SEs, thus reflecting the relative precision of the contributing individual studies. Median values for the duration of pain and the proportions of patients who were free of pain were derived from estimates made by the Kaplan-Meier method.

The proportions of all patients with pain, patients 50 years of age or older with pain, and all patients with moderate/severe pain at 3 or 6 months along with 95% confidence intervals were derived from estimates made by the Kaplan-Meier method and from SEs. The methodology used for the meta-analysis was based on established principles [21, 22].

Results

Studies 1, 2, and 3 (316 patients) provided data from which the times to complete cessation of pain, complete cessation of postherpetic neuralgia, and complete cessation of moderate/severe pain in all patients and in the subgroup of 186 patients who were 50 years of age or older could be derived. The time to the first pain-free period was derived from studies 1, 2, 3, and 4; these times were then combined for a separate meta-analysis (691 patients).

Demography and Baseline Characteristics

No major differences between treatment groups were evident within the studies or overall (data not shown). The mean age of the patients in studies 1, 2, and 3 was 52 years, but the mean age increased to 62 years when data for patients in study 4 were included. At least 60% of patients in each study began treatment within 48 hours of rash onset. More than one-half of the patients in each study reported moderate or severe pain at presentation, and most patients in studies 2, 3, and 4 also reported prodromes for at least 48 hours before the appearance of a rash.

In the subgroup of patients 50 years of age or older, the mean age was ~67 years; the age distribution did not differ markedly between acyclovir and placebo treatment groups. All other demographic and baseline characteristics were similar to those of the overall population.

Time to Complete Cessation of All Pain

The results of Cox regression for the time to complete cessation of pain in all patients and patients 50 years of age or older are shown in table 1 for the individual studies and for the meta-analysis. Hazard ratios for patients in the individual studies (range, 1.53–2.32) were comparable and were statistically significant in two of the three studies. The combined hazard ratio of 1.79 (95% CI: 1.34, 2.39; $P < .001$) indicates that complete cessation of pain occurs faster with acyclovir treatment than with placebo. Without adjustment for covariates, the combined hazard ratio was similar to the adjusted value of 1.70 (95% CI: 1.30, 2.22; $P < .001$).

In the analysis of the time to complete cessation of pain in patients 50 years of age or older, hazard ratios for the individual studies (range, 1.59–2.85) were comparable but were statistically significant only in study 2. The hazard ratio for the meta-analysis of this subgroup of patients was 2.13 (95% CI: 1.42, 3.19; $P < .001$), thereby indicating a greater benefit of acyclovir treatment for the older patient population. When unadjusted for covariates, the overall hazard ratio was 2.06 (95% CI: 1.44, 2.94; $P < .001$).

Time to Complete Cessation of Moderate/Severe Pain

The results of the adjusted analysis for the time to complete cessation of moderate/severe pain in all patients are shown in table 2. Hazard ratios for the individual studies favored acyclovir, although statistical significance was reached only in study 3. The hazard ratio for the meta-analysis was 1.46 (95% CI: 1.11, 1.93; $P = .007$), thus supporting the advantage of resolution of more severe pain with acyclovir treatment. Without adjustment for covariates, the hazard ratio for the meta-analysis remained similar at 1.52 (95% CI: 1.18, 1.97; $P = .0014$).

Time to Complete Cessation of Postherpetic Neuralgia

The results of the adjusted analysis for the time to complete cessation of postherpetic neuralgia in patients with pain beyond 30 days are provided in table 2. Hazard ratios for the individual studies ranged from 1.51 to 2.36 and were statistically significant in two studies. The overall hazard ratio was 1.81 (95% CI: 1.35, 2.43; $P < .001$), thereby demonstrating a treatment effect on more chronic pain. Similar results were obtained when

Table 1. Hazard ratios (acyclovir vs. placebo) for the time to complete cessation of zoster-associated pain in all patients and patients 50 years of age or older with or without adjustment for covariates.

	All patients		Patients 50 y of age or older	
Study	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Study 1				
Unadjusted	1.53 (1.08, 2.16)	.016	1.88 (1.15, 3.09)	.013
Adjusted	1.53 (1.08, 2.17)	.018	1.59 (0.93, 2.73)	.090
Study 2				
Unadjusted	1.73 (1.08, 2.78)	.024	2.25 (1.16, 4.35)	.016
Adjusted	1.92 (1.14, 3.22)	.013	2.85 (1.34, 6.04)	.007
Study 3				
Unadjusted	2.04 (1.04, 4.15)	.018	2.13 (1.00, 4.56)	.051
Adjusted	2.32 (1.00, 5.41)	.051	2.45 (0.99, 6.04)	.052
Meta-analysis				
Unadjusted	1.70 (1.30, 2.22)	<.001	2.06 (1.44, 2.94)	<.001
Adjusted	1.79 (1.34, 2.39)	<.001	2.13 (1.42, 3.19)	<.001

there was no adjustment for covariates (hazard ratio, 1.74; 95% CI: 1.33, 2.28; $P < .001$).

Time to First Pain-Free Period

The results of the adjusted analysis for the time to the first pain-free period are shown in table 2 for the four individual studies and the meta-analysis. Statistical significance was attained in only one individual study. When the data were combined, however, the hazard ratio for the meta-analysis was 1.31 (95% CI: 1.08, 1.60; $P = .007$), thus indicating a significant overall benefit of acyclovir treatment. Without adjustment for covariates, the hazard ratio was not substantially changed at 1.23 (95% CI: 1.02, 1.48; $P = .028$).

Proportions of Patients with Pain at 3 or 6 Months

The proportions of patients still experiencing any pain or moderate/severe pain 3 or 6 months after commencing treatment are summarized in table 3. This analysis includes patients 50 years of age or older. From the associated 95% confidence intervals, proportions were always significantly lower among the acyclovir-treated groups. More than one-third of the older patients in the placebo group still experienced pain at 6 months.

Prognostic Factors (Covariates) Influencing Time to Cessation of Pain

Increasing age and moderate/severe pain at presentation were generally associated with longer durations of pain (data not shown). Gender, the time from rash onset to initiation of treatment, and the duration of prodromes did not appear to influence pain outcome.

Summary of Major Endpoints

The results of the meta-analysis for the principal pain endpoints with adjustment for demographic covariates are summarized in figure 1 and table 4. Plots of the proportions of all patients with pain by different pain endpoints are shown in figure 2; these plots illustrating the consistent benefit of

Table 2. Hazard ratios (acyclovir vs. placebo) for the time to complete cessation of zoster-associated moderate/severe pain, the time to complete cessation of postherpetic neuralgia, and the time to the first pain-free period with adjustment for covariates.

	Moderate/severe pain		Postherpetic neuralgia		First pain-free period	
Study	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Study 1	1.25 (0.90, 1.72)	.18	1.51 (1.06, 2.16)	.023	1.37 (0.97, 1.94)	.07
Study 2	1.40 (0.82, 2.41)	.22	2.01 (1.19, 3.40)	.009	1.78 (1.07, 2.97)	.03
Study 3	2.28 (1.05, 4.97)	.038	2.36 (0.99, 5.60)	.053	2.25 (0.92, 5.50)	.07
Study 4	...	...	...	...	0.95 (0.75, 1.21)	.67
Meta-analysis	1.46 (1.11, 1.93)	.007	1.81 (1.35, 2.43)	<.001	1.31 (1.08, 1.60)	.007

Table 3. Proportions of patients with zoster-associated pain or with zoster-associated moderate/severe pain at 3 or 6 months.

	Percent of all patients with pain			Percent of patients 50 y of age or older with pain			Percent of all patients with moderate/severe pain		
Time	Acyclovir	Placebo	95% CI*	Acyclovir	Placebo	95% CI*	Acyclovir	Placebo	95% CI*
3 mo	21	43	11, 33	25	54	15, 43	6	13	0, 14
6 mo	12	25	4, 22	15	35	8, 34	2	9	1, 12

* For the differences between treatments.

acyclovir compared with placebo were derived by the Kaplan-Meier method. In every case, the hazard ratio and 95% confidence interval exceeded 1.0. As expected, the median times to complete cessation of moderate/severe pain and the first pain-free period were markedly shorter than the time to total cessation of all pain. The precision of the estimate of the hazard ratio, as indicated by 95% confidence intervals (figure 1), reflected the respective number of events for each comparison.

Discussion

This meta-analysis of four placebo-controlled, randomized, double-blind trials demonstrated the efficacy of oral acyclovir treatment of acute herpes zoster in accelerating the resolution of zoster-associated pain and all other parameters used to evaluate pain duration. Importantly, the prevalence of postherpetic neuralgia at 3 and 6 months was significantly reduced by at least 50% among treated patients. The results of each study, when analyzed individually by Cox regression, reflected those of earlier investigations [7–10, 13]. The benefit of acyclovir therapy was evident for all patients but was greatest for patients 50 years of age or older, in whom the pain of herpes zoster generally persists longer [17, 18].

While advancing age has long been recognized as predisposing to prolonged pain [17, 18], evidence linking or disassociating other presenting features with pain outcome has largely been circumstantial. Since patients 18 years of age or older were included in the analysis of the time to complete cessation of any and moderate/severe pain, the results of the meta-analysis indicated that irrespective of age patients with more severe pain at presentation are likely to suffer prolonged pain. This finding is consistent with the suggestions of other investigators [14–16]. Placebo-controlled trials of oral acyclovir for the treatment of herpes zoster have demonstrated the enhanced benefit of earlier treatment in hastening rash healing [9]. The meta-analysis suggested that the benefit of acyclovir on pain outcome is not limited to the first 48 hours of rash onset. This result is consistent with those of a randomized, controlled trial of valaciclovir vs. acyclovir [23]; this study revealed no effect of rash duration (up to 72 hours from onset) on pain outcome. Likewise, a large comparative study of acyclovir vs. netivudine [24] failed to show an effect of rash duration before treatment on pain duration. Therefore, treatment with acyclovir (or valaciclovir) may in general be appropriate for patients presenting up to 72 hours after rash onset. In contrast, the effect of famciclovir on pain appeared to depend on treatment initiation within 48 hours of rash onset [25].

In the three studies that defined both endpoints, the time to the first pain-free period in the placebo recipients was shorter than the time to complete cessation of pain; this finding indicates that measuring the time to initial cessation of pain can underestimate the total duration of zoster-associated pain, which reflects the recurrent nature of pain that can occur in a proportion of patients. Nevertheless, inclusion of the fourth

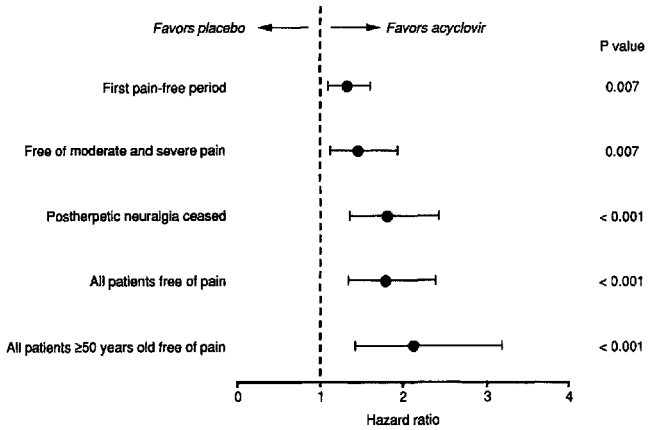

Figure 1. Estimates of hazard ratios and 95% confidence intervals for the meta-analysis of studies of acyclovir vs. placebo as treatment of herpes zoster by the various pain milestones.

Table 4. Median time to various milestones of zoster-associated pain with adjustment for demographic covariates.

	Median duration of pain (d)	
Milestone	Acyclovir	Placebo
First pain-free period	28	32
Free of moderate and severe pain	11	14
Postherpetic neuralgia ceased	. . .	. . .
All patients free of pain	28	67
All patients 50 y of age or older free of pain	41	101

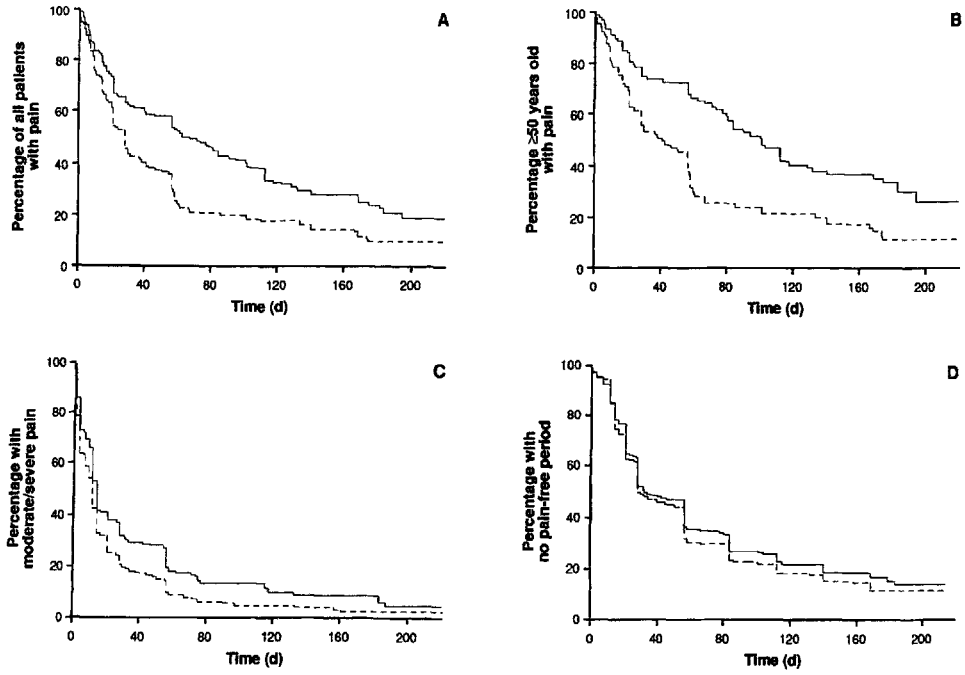

Figure 2. Plots of the proportions of patients with zoster-associated pain following treatment with acyclovir (---) or placebo (—) by pain endpoints. *A*, time to complete cessation of all pain (all patients); *B*, time to complete cessation of all pain in patients 50 years of age or older; *C*, time to complete cessation of moderate/severe pain (all patients); and *D*, time to the first pain-free period.

and largest study in the meta-analysis of the time to the first pain-free period showed that acyclovir treatment significantly reduces pain duration, even though the result for this individual study was inconclusive. Future studies should ensure that follow-up is sufficiently long for complete cessation of pain to be unequivocally established.

The analysis of the time to complete cessation of moderate/severe pain showed that resolution of this clinically important endpoint occurred more rapidly with acyclovir treatment than with placebo. Future studies evaluating drug therapy as treatment or prevention of the complications of herpes zoster would have greater value if pain severity was included in the analysis of pain, since the loss of moderate/severe pain is more likely to be associated with recovery of a patient's normal life-style and quality of life.

Although we placed greatest emphasis on the analysis of the time to complete cessation of pain, some clinicians are interested in the analysis of the time to cessation of postherpetic neuralgia. While we have included such an analysis for completeness, we would urge that great caution be used when placing singular emphasis on this measure for several reasons. First, it requires selection of an arbitrary definition, in our case pain beyond day 30. Even greater care would need to be taken if the definition of pain after healing had been used, since this definition would introduce the additional bias resulting from different effects of the treatments under study on healing itself. Second, the exclusion of patients without postherpetic neuralgia, by the selected definition, would contravene the intent-to-treat principles of analysis. We have avoided this problem by including all patients in our analysis and applying a value of zero to loss of pain beyond day 30. The resulting plot derived by the Kaplan-Meier method is essentially the same as that for the complete cessation of all pain starting at day 30, and the hazard ratios are virtually identical. Therefore, there is little value in adding this parameter to the others we have presented.

According to most definitions [4–6], pain persisting for at least 3 or 6 months may generally be considered established postherpetic neuralgia. The prevalence of postherpetic neuralgia, as denoted by proportions of patients with pain at 3 or 6 months, was substantially lower among acyclovir-treated patients than among those randomized to receive placebo. The prevalence of postherpetic neuralgia in placebo recipients (25%, all patients; 35%, patients 50 years of age or older) falls within the range of observations in classical epidemiologic surveys [17, 18].

This meta-analysis has demonstrated that acyclovir treatment of herpes zoster significantly speeds pain resolution by almost twofold. Milestones toward patients becoming completely pain-free—the initial relief of pain and the loss of moderate/severe pain—are also reached significantly more rapidly with acyclovir treatment than with placebo. As a result, significantly fewer patients receiving acyclovir therapy experienced postherpetic neuralgia at 3 and 6 months. These benefits are particularly evident in the higher risk group of older individuals, in whom pain resolution occurred on average more than twice as fast after acyclovir treatment.

Acknowledgments

The authors gratefully acknowledge the contribution of Claire Kirsopp of S-Cubed (Sheffield, UK) for assistance with the statistical analysis and the cooperation of Jane Crooks, Paul Fiddian,

Smita Shukla, and Anne Clemmer of The Wellcome Foundation (Beckenham, UK).

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