Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

How should zoster trials be conducted?

M. J. Wood and the Herpes Zoster Clinical Trial Consensus Group :

Hank Balfour, University of Minnesota, Minneapolis, USA; Karl Beutner, University of California, San Francisco, USA; Jean Bruxelle, Hopital Tarnier, Paris, France; Paul Fiddian, The Wellcome Foundation Ltd, Beckenham, Kent, UK; Robert Johnson, Bristol Royal Infirmary, Bristol, UK; Richard Kay, S. Cubed, Broomhill, Sheffield, UK; Joseph Portnoy, Jewish General Hospital, Montreal, Quebec, Canada; Bernard Rentier, University of Liege, Liege, Belgium; Seng-jaw Soong, University of Alabama, Birmingham, USA; Richard Whitley, University of Alabama, Birmingham, USA.

Department of Infection and Tropical Medicine, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5ST, UK

In 1994, an international group of interested clinicians and biostatisticians met to discuss the design of clinical trials in herpes zoster. They agreed that trials in herpes zoster should have prospectively agreed definitions of all outcome measures and plans for data analysis. In immunocompetent individuals, in whom pain is the major outcome measure, trials should only include patients over the age of 50 years, and for those recruited within 72 h of rash onset, should be designed to demonstrate superiority of any new therapy over existing antivirals. The primary endpoint should be time to cessation of pain for at least 4 weeks and, for the purposes of statistical analysis of its duration, the pain associated with herpes zoster ought to be considered as a continuum. All other variables, including the incidence of post-herpetic neuralgia and effects upon quality of life should be considered as secondary end-points. Evaluation of treatment effects on primary endpoints should be based upon an intent-to-treat (ITT) analysis and subgroup analysis should be used only to support the findings of the ITT analysis. These elements of good study design should be borne in mind in the evaluation of current and future trails of antiviral drugs in herpes zoster.

Introduction

Following the Second International Conference on the Varicella Zoster Virus, held in Paris in July 1994 (but independent of that Conference) a group of interested clinicians and biostatisticians met to discuss the conduct and analysis of clinical trials in herpes zoster. This paper summarizes their discussion, and presents their recommendations on trial design.

The development of guidelines for the conduct of drug trials in herpes zoster can be seen as serving several purposes. Firstly, it should minimize the expenditure of time and money required to establish new antiviral agents as safe and effective. Secondly, the widespread adoption of recommendations such as those outlined here should allow the findings of one study to be validated against those of others, and will facilitate meta-analysis. Thirdly, guidelines should allow clinicians to measure individual studies against an agreed yardstick of good research practice.

The aim of clinical studies of antiviral therapy in herpes zoster is to improve the outcome for patients. Given that primary objective, it may be possible to design trials that also contribute to our understanding of zoster and its pathophysiology. However, such considerations should be a secondary aspect of trial design.

The clinical picture

Herpes zoster is characterized by a unilateral dermatomal papulovesicular rash and by acute and, sometimes, chronic pain. In the immunocompetent patient the rash of herpes zoster is a relatively short-lived manifestation with, typically, new lesions forming for 3-5 days, scabbing occurring after 7-10 days and complete healing within 2-4 weeks. Complications other than pain are unusual except in the 10-15% of individuals with involvement of the ophthalmic division of the trigeminal nerve (Ragozzino *et al.,* 1982), 50% of whom are likely to develop intraocular complications (Harding, Lipton & Wells, 1987).

In the majority of immunocompetent patients, the most troublesome acute symptom of herpes zoster is pain and the most frequent complication is severe, potentially disabling, pain that may persist for months following the acute phase. There is general agreement that acute pain in herpes zoster is different from chronic pain

(conventionally termed post-herpetic neuralgia, or PHN) both in its quality and in its pathogenesis (Bhala *et al.,* 1988; Wood *et al.,* 1993). It would seem that peripheral mechanisms are responsible, at least in part, for acute pain, whereas the chronic pain of zoster is associated predominantly with more central events relating to damage and/or malfunction in the neurones of the spinal dorsal horn.

Neither patients nor clinicians are able reliably to determine the point at which acute pain becomes chronic, and different definitions of PHN have been used. Pain which persists beyond healing of the rash is one such definition (Watson *et al.,* 1988), whereas others have suggested that only patients whose pain continues beyond some arbitrary cut-off point (such as 30 days or 2 months from rash onset) have PHN (Sauer, 1955; Eaglstein, Katz & Brown, 1970). Given its uncertain definition, estimates of the incidence of PHN have varied. However, pain persisting for more than 1-2 months is thought to affect around 25% of zoster patients overall, and increases in incidence with age: it is experienced by only 5-10% of zoster patients who are less than 40 years of age but 70% of patients over 70 years develop PHN lasting for more than a month (Burgoon, Burgoon & Baldridge, 1957; de Moragas & Kierland, 1957). As well as the incidence, the duration of zoster pain is also significantly correlated with advancing age (Wood *et al.,* 1994b).

Immunocompromised patients with zoster may also suffer from PHN but there is no clear evidence that the pain is more severe or prolonged than in normal individuals. Viral replication is, however, more prolonged and this leads to more extensive and long-lasting cutaneous manifestations and to potentially life-threatening visceral dissemination of disease. In patients who are particularly heavily immunocompromised, such as those coinfected with human immunodeficiency virus (HIV), chronic relapsing skin rashes, sometimes associated with emergence of resistant strains of varicella-zoster virus (VZV), may occur.

Designing a study of therapy for herpes zoster

Choice of endpoints

The risk of Type I (false positive) error and the difficulty in interpreting study results increases with the number of primary endpoints used. Trials should therefore employ the minimum number of primary endpoints consistent with establishing efficacy, and the endpoint chosen should relate to the most important clinical problem of zoster in the population under study.

In immunocompetent individuals, prolonged pain that is resistant to conventional treatments is clinically the most frequent and severe complication of zoster and the primary outcome measure of zoster studies should therefore relate to pain. Several secondary endpoints can also be used in the evaluation of therapy. These include measures of antiviral activity, and measurement of the effect of treatment on quality-of-life parameters other than pain. Cutaneous efficacy endpoints, such as time to cessation of new lesion formation, though highly relevant to antiviral effect, should now be considered secondary, since rash healing in the immunocompetent individual normally progresses uneventfully and without complication. Direct measurement of antiviral efficacy (by viral culture rather than by surrogate markers related to the evolution of rash) is generally not required in immunocompetent individuals. Trials conducted specifically in patients with ophthalmic zoster will involve regular ophthalmological assessments of additional endpoints relating to ocular complications, distinguishing between corneal and intraocular VZV involvement both during the phase of viral replication and for several months afterwards.

Any significance testing relating to secondary endpoints requires cautious interpretation, and it can be argued that results from the analysis of secondary endpoints should be considered as exploratory findings.

In immunocompromised patients, such as those with lymphoproliferative or other malignancies, solid organ or bone marrow transplant recipients and those on large doses of immunosuppressive therapy, the primary efficacy endpoint should relate to the potentially life-threatening complication of viral dissemination. Speed of antiviral activity (by noting cessation of viral shedding, time to the end of new lesion formation, and parameters of rash development and healing) and pain may also be included but should be considered as secondary endpoints. In HIV-positive individuals the time to total crusting and healing and the frequency of zoster recurrences over a finite period should also be assessed. Certain centres may also choose to study VZV sensitivity to antivirals, thereby evaluating the potential for development of viral resistance.

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

Selection of patients

Patient selection is an important aspect of clinical trial design and patient numbers should be large enough to ensure that treatment groups are balanced with respect to variables that influence the likelihood and duration of the primary endpoint.

There are a number of factors that are now known to be correlated with the duration of prolonged pain in the immunocompetent patient with herpes zoster. As described above, age is a factor of major prognostic significance and pain is rarely a significant problem for patients under 50 years of age. Since the incidence and duration of chronic zoster-associated pain rises sharply with age, if recruitment of immunocompetent patients is confined to those over 50 years of age, then not only will this limit the study to patients most likely to achieve a clinically-meaningful benefit but also the power of a trial to detect treatment differences will be increased. Several studies have concluded that the severity of zoster pain at the onset of treatment is correlated with pain duration (Riopelle, Naraghi & Crush, 1984; Bruxelle, 1994; Wood *et al., 1994b).* Analysis of the large database gathered during the trials of acyclovir and valaciclovir suggests that the presence of prodromal pain also predicts outcome (Wood *et al.,* 19946). Since the duration of prodrome cannot easily be defined accurately and since the absence of prodromal symptoms does not necessarily indicate that there will be no subsequent chronic zoster-associated pain, trials should not exclude patients who do not have pain before or accompanying their rash.

In the immunocompromised, underlying disease and its management are important factors that may influence the potential for VZV dissemination and, in those coinfected with HIV, the stage of disease and possibly surrogate markers of disease progression such as CD4 cell count must be considered.

It may be appropriate to stratify patients according to these prognostic factors before randomisation to treatment arms. The influence of any imbalance in prognostic factors that may occur despite randomisation can then be taken into account by covariate analysis (see section below on statistical analysis).

Studies of antiviral efficacy in herpes zoster have generally enrolled patients and started treatment within 72 h of rash onset. This reflects the brief period of viral replication within the cutaneous lesions in the average case of zoster. It is accepted that viral replication occurs within the peripheral nerves for some time (usually several days) before the skin rash of zoster appears and logic would suggest that the earlier in the course of the illness that antiviral drugs are given, the better. Evidence for this is, however, conflicting. Some studies have suggested that patients treated within 48 h of rash onset have better responses to antivirals (Degreef *et al.,* 1994). An overview analysis of other studies, however, indicated that the effect of treatment was the same when it was begun 48-72 h after rash onset as when it was begun within 48 h (Wood *et al.,* 1994b). In a minority of immunocompetent patients, new lesions (and hence viral replication within the skin) continue to form for more than 72 h but the effect of antiviral treatment begun after 72 h on rash progression or pain has not been studied.

In the case of ophthalmic zoster, at least one study has suggested that the benefits upon ocular complications can be obtained if therapy is commenced up to one week after the appearance of the rash, and recruitment of such patients into trials is thus appropriate. If the time from rash onset to start of therapy is longer than 72 h for patients with ophthalmic zoster, then this group must be analysed separately.

Patients should be followed up for a period of at least six months (and, if resources allow, for 12 months or more) from the start of treatment.

Issues in the measurement of pain

Specific issues in the measurement of pain include:

Duration

Most patients with PHN will have pain during the acute phase of their illness and the pain is felt as a continuum (even though the qualitative aspects of pain while the rash is present are different from those of the pain felt several months later). Various attempts have been made to define a point at which acute zoster pain becomes PHN. Pain which persists beyond rash healing is one such definition. Other investigators have used an arbitrary cut-off point, considering, for example, that only those patients whose pain continues beyond 30 days from rash onset have PHN. There is no clear pathophysiological basis for these definitions, and their use risks the introduction of bias in the assessment of treatment effects upon duration of PHN.

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

Measuring the duration of PHN from any arbitrarily chosen time point (other than that of initial randomisation) involves the loss of patients from analysis, since it involves the deliberate exclusion of patients whose pain has resolved before that time. Furthermore, a number of patients will also have been lost to follow-up for some other reasons including adverse events or a poor response to treatment. Any loss of patients from analysis may upset the balance in treatment groups achieved initially by randomisation and risks the introduction of bias.

A more important source of bias, which may be systematic, arises when the time chosen to define the onset of PHN is influenced by treatment effect and so is likely to differ between groups. This is the case when rash healing is taken as the point from which to measure the duration of PHN, since treatment with antivirals certainly speeds the resolution of rash (Huff *et al.,* 1988; Wood *et al.,* 1988; Tyring *et al.,* 1993). The following hypothetical results provide an example (see Figure 1). Drug A heals rash at a median of 25 days, and leads to complete loss of pain at a median of 50 days from the start of treatment. Drug B heals rash later, at a median of 35 days, but is no different from drug A in its effect on pain, which again resolves at a median of 50 days. In this instance, defining PHN as starting at the resolution of rash has the entirely spurious effect of making drug B (15 days to loss of pain) seem superior to drug A (25 days to loss of pain) when the duration of PHN is measured.

The International Herpes Management Forum has therefore recently suggested that, if the duration of pain is to be measured, then pain should be considered as a continuum incorporating both acute and chronic pain, and that its duration should be measured from the start of treatment, as shown in Figure 2 (Wood *et al.,* 1993). The term zoster-associated pain (ZAP) is applied to this concept. The forum feels that this definition should be used in clinical trials evaluating drugs in herpes zoster.

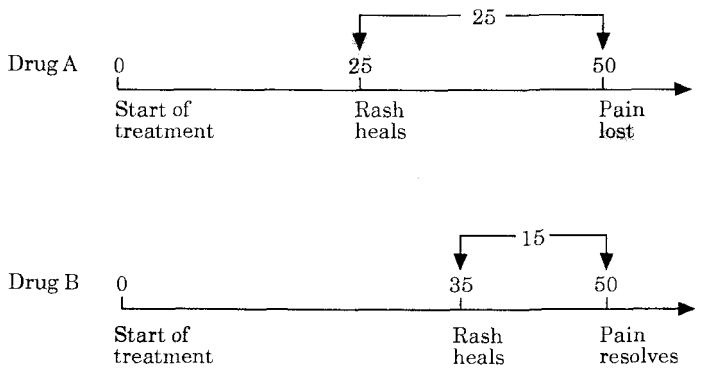

Figure 1. Taking the point of rash healing as the start of post-herpetic neuralgia makes drug B appear more effective in resolving pain than drug A. In fact the duration of pain in both cases is the same—50 days from the start of treatment.

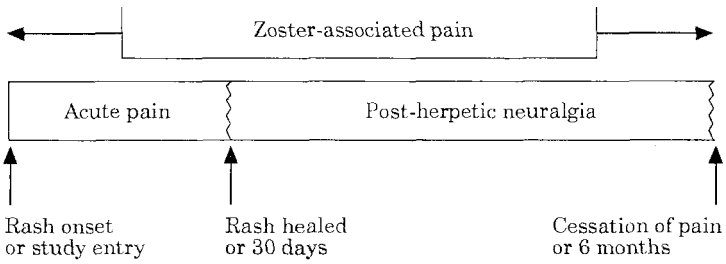

Figure 2. The concept of zoster-associated pain regards pain as a continuum rather than dividing the period of pain at some arbitrary point into acute and chronic phases.

Defining the end of pain is also problematic since some investigators have recorded pain-free intervals of varying duration followed by recurrence, perhaps with increased intensity (Huff *et al.,* 1993). Time to complete cessation of pain (within a defined time period) is therefore preferable as an endpoint to time of first cessation. Complete cessation needs to be defined carefully, requiring, for example, that the patient remains free of pain for a period of four or more weeks.

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

Prevalence/incidence

Measurement of the incidence of pain at various time points (it is not appropriate to refer to prevalence, since most questions ask whether the patient has experienced pain since their last assessment) can be undertaken without the need for argument about terminology (PHN or ZAP).

Severity

It has been suggested that pain intensity should be incorporated into any primary endpoint. It could be argued, for example, that reducing the incidence of severe pain is clinically the most important goal. However, confining interest to patients whose pain is initially severe has the disadvantage of reducing the number of cases available for analysis. There is a further problem since the assessment of pain is inevitably subjective and what might be significant to one patient may be insignificant to another. The use of visual analogue scales has been advocated but it is unlikely that agreement could be reached on any given level of pain as a measure of outcome. Systems used for categorising pain would differ between studies (in part as a function of linguistic factors) and would reduce their comparability. It is therefore most practical that for the primary endpoint patients are asked simply whether or not pain is present. Subgroup analysis (see below) might be undertaken for those with differing degrees of pain severity at recruitment.

Diary cards including the question "Is pain present? Answer Yes/No" represent a simple tool for investigating the effect of treatment on pain. From the data obtained, the incidence of pain at different timepoints, together with the duration of ZAP, can be established. Completed cards should be assessed daily over the first week to encourage patient motivation. Beyond that point, though cards may continue to be filled in daily, twice weekly assessment until healing is probably sufficient. Weekly collection of data by telephone or visit is then adequate. Monthly visits by an investigator should continue until 6 or possibly 12 months after the onset of treatment.

Analgesic use

The use of analgesics (if any), their type and dose are potentially confounding variables in a zoster trial. Their use should, therefore, be carefully monitored. Within a trial, an agreed protocol on pain management for use across treatment groups and centres is desirable, although it is recognised that this would be difficult to develop and agree for international multicentre studies.

Quality of life

There is a case for the inclusion of an overall quality-of-life measure, since recent evidence confirms that the impact of zoster on wellbeing is considerable (Lydick *et al.,* 1994). Given the difficulties of interpreting the severity of pain (see above), a patient questionnaire scoring the impact of pain on life is the most satisfactory way of assessing 'clinically significant pain'. Such information may be complemented by measures of resource utilisation (e.g. additional visits to the primary care physician or hospital specialist, and analgesic use). There are a number of validated methods that may be utilised to obtain these data but they are time consuming.

Other assessments

Certain study centres may have a special interest in, and the facilities needed to conduct, a detailed neurological examination and the testing of sensory thresholds (falling short of the induction of pain) in the skin area affected by zoster, comparing the results with those from the opposite (unaffected) dermatome. Other centres with particular expertise and resources, may undertake additional immunological or virological investigations. However, the ability to measure such variables should not be considered a requirement for participating centres in studies of zoster in which the principal objective is the evaluation of the efficacy of therapeutic interventions.

Safety and monitoring

Safety endpoints need to be carefully considered with novel antiviral drugs. The importance of the potential for adverse drug interactions, particularly in an elderly population, must also be taken into account. Independent monitoring of the quality of data being contributed by different centres during the course of the study is desirable but may not in all cases be achievable.

In studies involving immunocompromised patients, where the risk-benefit judgement is difficult to make, where there is the possibility of life-threatening disease, or when there is no commercially available alternative therapy,

an independent Data Monitoring and Safety Board is mandatory. This Board should perform interim analyses at previously agreed times or stages, for example, after the enrolment of a certain number of patients, so that the trial can be stopped early if there is clear evidence of a significant treatment effect or the emergence of toxicity. The methods of analysis and decision criteria used by the Board should be specified in advance.

Use of placebo

It has now been demonstrated that antiviral therapy is effective therapy for herpes zoster in both immunocompetent and immunocompromised patients. Studies in the immunocompromised showed, from an early date, that acyclovir was capable of preventing the life-threatening complication of visceral dissemination (Balfour *et al.,* 1983; Balfour, McMonigal & Bean, 1983), and there is no case for further placebo-controlled trials in such patients (whether dissemination has already occurred or not). In the immunocompetent host, the efficacy of acyclovir upon pain was more contentious with individual studies producing inconclusive results (Huff *et al.,* 1988, 1993; McKendrick, McGill & Wood, 1989; Morton & Thomson, 1989; Harding & Porter, 1991). A meta-analysis of three placebo-controlled studies of oral acyclovir (given at the standard dose of 800 mg five times daily for 7-10 days) in which the protocol required assessment of all patients (not just those who were still in pain) for a period of 6 months, has recently been reported (Wood *et al., 1994a).* The meta-analysis used time to complete cessation of ZAP as an endpoint and concluded that active treatment significantly shortened time to complete cessation of pain from a mean of 86 days in the placebo group to 49 days in patients given active treatment (Figure 3). Expressed as a hazard ratio, the probability of complete cessation of pain in patients treated with acyclovir was 1.79 (95% confidence intervals 1.35-2.34, $P < 0.001$), indicating that pain resolution occurred 1.79 times more rapidly in acyclovir- than in placebo-treated patients. A further analysis, including all the placebo-controlled studies and using time to loss of pain for a finite period (one month in the post-herpetic phase of follow-up), also demonstrated a statistically significant effect of acyclovir (Kay & Wood, 1995). A benefit over placebo for PHN (defined as pain persisting after rash healing) has been shown for patients treated with famciclovir at either 500 or 750 mg three times daily (Tyring *et a!.,* 1993; Cunningham, 1995), and further analysis showed benefits of these doses of famciclovir on pain measured as a continuum (Cunningham, 1995).

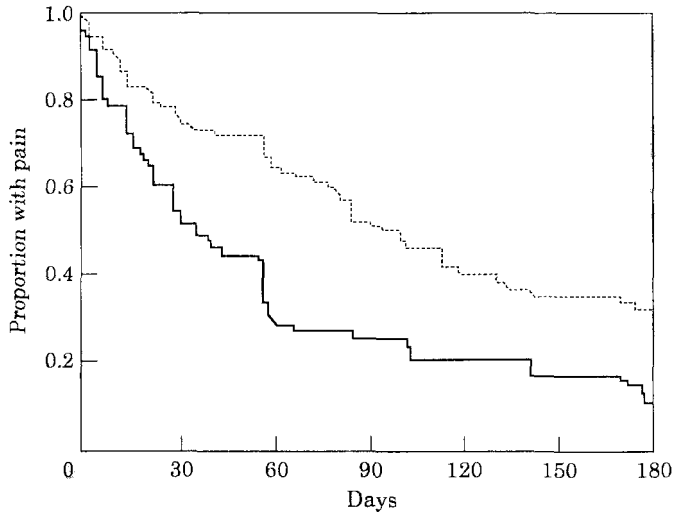

Figure 3. Duration of zoster-associated pain in patients aged > 50 years treated with acyclovir (——) or placebo (. . .) (acyclovir/placebo n = 186). Hazard ratio 2.13, P < 0.001. From Wood et al. (1994b).

Given the established benefit of antiviral therapy in patients enrolled within 72 h of rash onset, a placebo-controlled trial in this population is not ethically acceptable. To determine if treatment is effective if started later in the course of the rash, trials may be designed to include a patient group in whom treatment begins more than 72 h following rash onset and, in this instance, a placebo-controlled comparison is appropriate.

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

Statistical considerations

Hypotheses to be tested

Trials of new antiviral agents in herpes zoster should in general be designed to test the hypothesis that they are superior to an existing antiviral. Such an analysis, for example, has shown that valaciclovir is superior to cicyclovir in speeding the resolution of ZAP (Beutner *et ah,* 1995). Where a new treatment offers potential advantages of convenience (in dosing or in toxicity, for example), a trial designed to demonstrate equivalent efficacy may be appropriate. In this context, it should be noted that if a trial is not designed to demonstrate equivalence, i.e. it is designed to demonstrate superiority, then equivalence cannot be assumed by default. Substantially more patients are required to demonstrate equivalence than are required to demonstrate superiority.

Intent-to-treat analysis

Comparison of treatment efficacy should be based on an intent-to-treat analysis, i.e. all randomised patients should be included in the analysis of primary endpoints. The only exception is that any patients subsequently found to have entered the study on the basis of a misdiagnosis may be excluded. The primacy of intent-to-treat analyses has been recognised by the US Food and Drug Administration (Rockville 1988).

Equal intensity of follow-up

The completeness and intensity of follow-up should be the same in all patients. It should not be the case that patients whose lesions heal quickly, or who experience early resolution of pain, are less intensively investigated for the remainder of the study than those in whom the disease follows a longer course, since this alters the statistical power of the study with time.

Methods of analysis

Cessation of pain, the primary endpoint in zoster trials in immunocompetent patients, is a variable in which time-to-event is measured. Kaplan-Meier curves, as shown in Figure 3, represent the achievement of the clinical endpoint against time for each treatment group. Techniques used in the analysis of such 'survival' data, notably the Kaplan-Meier product limit method, are therefore appropriate.

From Kaplan-Meier curves it is possible to determine the proportion of each treatment population who have failed to achieve the endpoint (e.g. who are still experiencing pain) at any given time after the onset of treatment and to obtain median values for the time to the endpoint. Event rates over specified times (such as the proportion of patients ceasing to have pain between 3-6 months) can also be calculated.

Medians are frequently used as a convenient and apparently readily understandable means of reporting trial results. However, it should be remembered that medians refer only to one point (the 50% point) on the Kaplan-Meier plot and do not reflect the overall shape of the Kaplan-Meier curve. A more reliable and stable measure of overall treatment effect is achieved using the hazard ratio (also termed the relative risk or risk ratio) obtained by Cox regression analysis. This statistic represents the ratio of the hazard rates (the number of events or patients reaching the endpoint per unit time) evident in the two treatment groups. Thus, in a placebo-controlled trial, a hazard ratio of 1 would indicate that active treatment had no effect. A hazard ratio of 2 in the time to loss of pain, for example, would indicate that, compared with the placebo group, twice as many patients on active treatment experienced cessation of pain over the period of study. Providing that the hazard ratio between the two curves is constant, a significant difference between them is determined using the Wilcoxon log-rank test.

The importance of covariates

The use of covariates enables any difference in treatment effects to be more precisely determined. The inclusion of covariates in the analysis of zoster trials also has the effect of compensating for any imbalances in prognostic factors that may occur (despite randomisation) between treatment groups. Treatment comparisons should be reported both with and without adjustment for covariates. Only baseline demographic characteristics should be considered as covariates: any adjustment to the final results using prognostic factors defined after the start of treatment risks the introduction of substantial bias, since they will be confounded with treatment effects.

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

Subgroup analyses

It may be clinically useful to investigate possible interactions between baseline factors and the effects of treatment. However, there are several potential problems in conducting subgroup analyses. First, the number of patients involved in such analyses may be small compared to those included in the study as a whole. The statistical power of such comparisons is, therefore, reduced. Secondly, with reduced patient numbers, subgroups may no longer be comparable in terms of baseline characteristics of prognostic significance. If subgroups are defined in terms of variables observed after randomisation (such as compliance) or in terms of treatment effects, these problems are compounded. Thirdly, if a large number of comparisons is made between subgroups, the risk of false-positive error increases. Conventional significance values ($P < 0.05$) are no longer valid. If the primary analysis does not show differences between treatment groups, subsequent analyses demonstrating differences within subgroups should not be used to 'salvage' the trial. If used, the results of subgroup analyses should be consistent with those of the intent-to-treat analysis.

When subgroup analyses are performed, the results presented should include those from all groups defined within a subgroup variable, and not from selected groups only. For example, if the study protocol demanded treatment within 72 h of rash onset, and a subgroup analysis of patients treated within 24 h is conducted, the result should be presented alongside the analysis of the subgroup that started treatment 25-72 h from rash onset. In the case of age, similarly, analysis of subgroups both above and below the cut-off age should be presented. Reference should be made to supportive or contradictory findings from other studies, and any conclusions drawn should be expressed and interpreted with caution.

Summary of recommendations

(1) In immunocompetent patients, time to complete cessation of pain should be the primary outcome measure in trials of antiviral therapy in herpes zoster. Pain should be considered as a continuum measured from the onset of treatment. Any attempt to define chronic pain by reference to rash healing or by the use of an arbitrarily defined time point (such as thirty days from the start of therapy) risks the introduction of serious bias. Variables (such as time to the end of new lesion formation) that relate to antiviral efficacy, if required at all, should be considered secondary endpoints.

(2) In trials involving immunocompromised patients, the occurrence of disseminated disease should be considered a primary endpoint, along with pain. In these patients, cutaneous measures of antiviral efficacy are also appropriate.

(3) Placebo-controlled trials are no longer appropriate for immunocompromised patients or those treated within 72 h of rash onset.

(4) Trials in zoster should in general be designed to establish the superiority of new treatments over existing therapies. If a trial is not designed to prove equivalence, then equivalence cannot be assumed by default.

(5) Trials should have prospectively agreed definitions of all outcome measures and should also prospectively define plans for analysis.

(6) The analysis of primary endpoints should be based on intention-to-treat. For the purposes of comparing treatments, patients should be included in the treatment groups to which they were originally assigned.

(7) The statistical techniques that are most appropriate are the plotting of Kaplan-Meier survival curves for each treatment group (differences between curves being established by log-rank test), and the use of Cox regression analysis to establish hazard ratios (with confidence intervals) as a measure of treatment effects. Cox regression analysis also serves to adjust for covariates, which should again be prospectively defined.

(8) Subgroup analyses may be of use in identifying treatment effects (or lack of them) in particular groups of patients. Such groups should be defined according to baseline characteristics only. The results of such analysis should be interpreted with caution and evaluated formally in future studies.

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

References

Balfour, H. H., Bean, B,, Laskin, O. L., Ambinder, R. F., Meyers, J. D., Wade, J. C. *et al.* (1983). Acyclovir halts progression of herpes zoster in immuncompromised patients. *New England Journal of Medicine* 308, 1448-53.

Balfour, H. H., McMonigal, K. A. & Bean, B. (1983). Acyclovir therapy of varicella zoster virus injections in immunocompromised patients. *Journal of Antimicrobial Chemotherapy* 12, *Suppl. B,* 169-79.

Beutner, K. R., Friedman, D. J., Forszpaniak, C, Anderson, P. L. & Wood, M. J. (1995). Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrobial Agents and Chemotherapy* 39, 1546-53.

Bhala, B. B., Ramamoorthy, C, Bowsher, D. & Yelnoorker, K. N. (1988). Shingles and post herpetic neuralgia. *Clinical Journal of Pain* 4, 169-74.

Bruxelle, J. J. (1994). Prospective epidemiological study of painful and neurological sequelae induced by herpes zoster in patients treated early by oral acyclovir. In *Abstracts of the Second International Conference on the VZV, Paris, 1994.* Abstract.

Burgoon, C. F., Burgoon, J. S. & Baldridge, G. D. (1957). The natural history of herpes zoster. *Journal of the American Medical Association* 164, 265-9.

Cunningham, A. L. (1995). Clinical success in treating patients with famciclovir: optimism for the future. *Research and Clinical Forums* 17, 45-53.

Degreef, H. & the Famciclovir Herpes Zoster Clinical Study Group, (1994). Famciclovir, a new oral antiherpes drug: results of the first controlled clinical study demonstrating its efficacy and safety in the treatment of uncomplicated herpes zoster in immunocompetent patients. *International Journal of Antimicrobial Agents* 4, 241-6.

de Moragas, J. M. & Kierland, R. R. (1957). The outcome of patients with herpes zoster. *American Medical Association Archives of Dermatology* 75, 193-6.

Eaglstein, W. H., Katz, R. & Brown, J. A. (1970). The effects of early corticosteroid therapy on the skin eruption and pain of herpes zoster. *Journal of the American Medical Association* **211,** 1681-3.

Harding, S. P., Lipton, J. R. & Wells, J. C. (1987). Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement. *British Journal of Ophthalmology* 71, 353-8.

Harding, S. P. & Porter, S. M. (1991). Oral acyclovir in herpes zoster ophthalmicus. *Current Eye Research* 10, *Suppl.* 177-82.

Huff, J. C, Bean, B., Balfour, H. H., Laskin, O. L., Connor, J. D., Corey, L. *et al.* (1988). Therapy of herpes zoster with oral acyclovir. *American Journal of Medicine* 85, *Suppl. 2A,* 84-9.

Huff, J. C, Drucker, J. L., Clemmer, A., Laskin, O. L., Connor, J. D., Bryson, Y. J. *et al.* (1993). Effect of oral acyclovir on pain resolution in herpes zoster: a reanalysis. *Journal of Medical Virology, Suppl. 1,* 93-6.

Kay, R. & Wood, M. (1995). Meta analysis of placebo-controlled trials of oral acyclovir for the treatment of zoster and resolution of zoster-associated pain. In *Abstracts of Seventh European Congress of Clinical Microbiology and Infectious Diseases* 166. Abstract.

Lydick, E., Epstein, R. S., Himmelberger, D. & White, C. J. (1994). Herpes zoster and quality of life: a self-limited disease with severe impact. In *Abstracts of the Second International Conference on the VZV, Paris, 1994.*

McKendrick, M. W,, McGill, J. I. & Wood, M. J. (1989). Lack of effect of acyclovir on postherpetic neuralgia. *British Medical Journal* 298, 431. Morton, P. & Thomson, A. N. (1989). Oral acyclovir in the treatment of herpes zoster in general practice. *New Zealand Medical Journal* 102, 93-5.

Ragozzino, M. W., Melton, L. J., Kurland, L. T., Chu, C. P. & Perry, H. O. (1982). Population-based study of herpes zoster and its sequelae. *Medicine (Baltimore)* 61, 310-6.

Rockville, M. D. (1988). *Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.* US Dept of Health and Human Services: Food and Drug Administration, Center for Drug Evaluation and Research: July 1988.

Riopelle, J. M., Naraghi, M. & Grush, K. P. (1984). Chronic neuralgia incidence following local anesthetic therapy for herpes zoster. *Archives of Dermatology* 120, 747-50.

Sauer, G. C. (1955). Herpes zoster: treatment of postherpetic neuralgia with cortisone, corticotropin, and placebos. *American Medical Association Archives of Dermatology* 71, 488-91.

Tyring, S., Nahlik, J., Cunningham, A., Marley, J., Heng, M., Rea, T. & the Collaborative Famciclovir Herpes Zoster Study Group, (1993). Efficacy and safety of famciclovir in the treatment of patients with herpes zoster: results of the first placebo-controlled study. In *Program and Abstracts of the Thirty-Third Interscience Conference on Antimicrobial Agents and Chemotherapy*, *New Orleans, Louisiana, 1993.*

Published in: *Journal of Antimicrobial Chemotherapy (1995), vol. 36, iss. 6, pp. 1089-1101*
Status: *Postprint (Author's version)*

Abstract 1540, p. 400. American Society for Microbiology, Washington, DC.

Watson, C. P. N., Evans. R. J., Watt, V. R. & Birkett, N. (1988). Post-herpetic neuralgia: 208 cases. *Pain* 35, 289-97.

Wood, M. J. and the International Herpes Management Forum. (1993). *Management of Strategies in Herpes: how can the burden of zoster-associated pain be reduced?* PPS Europe Ltd, Worthing, UK.

Wood, M. J., Fiddian, A. P., Crooks, R. J. & Jones, D. A. (1994α). Effects of oral acyclovir on all zoster-associated pain including post-herpetic neuralgia. (Poster D3). In *Abstracts of the Second International Conference on the VZV, Paris, 1994.*

Wood, M. J., Ogan, P. H,, McKendrick, M. W., Care, C. D., McGill, J. I. & Webb, E. M. (1988). Efficacy of oral acyclovir treatment of acute herpes zoster. *American Journal of Medicine* 85, *Suppl. 2A,* 79-83.

Wood, M. J., Shukla, S., Gibb, A. & Fiddian, A. P. (19946). Important covariates for duration of zoster-associated pain. In *Program and Abstracts of the Thirty-Fourth Interscience Conference on Antimicrobial Agents and Chemotherapy*, Orlando, Florida, 1994. Abstract M24, p. 218. American Society for Microbiology, Washington, DC.