ORIGINAL ARTICLE

Factors influencing pain outcome in herpes zoster: an observational study with valaciclovir

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ABSTRACT

Aim of the study An observational study with valaciclovir was conducted to assess clinical outcome in herpes zoster, especially pain and associated neurological signs and symptoms in relation to a series of demographic and disease characteristics discernible at presentation. The safety and acceptability of valaciclovir for treatment of zoster was assessed in a wide variety of primary care and clinic referral settings.

Methods In total, 1897 immunocompetent adults with clinically diagnosed, localized acute herpes zoster were enrolled in this international, open-label study of valaciclovir. All subjects received treatment with oral valaciclovir (1000 mg three times daily) for 7 days from entry to the study and were asked to record the presence of zoster-associated pain and abnormal sensations throughout treatment and 6 months' follow-up. They were seen frequently in clinic to verify subjective assessments and for evaluation of rash healing. Safety and tolerability were assessed by adverse event monitoring.

Results Overall, 1191 subjects (63%) were aged ≥ 50 years, and 203 (11%) had ophthalmic zoster. Cessation of zoster-associated pain was significantly faster in the younger age group; median times to loss of zoster-associated pain were 23 days and 9 days in the ≥ 50 and < 50 years age groups, respectively. Similarly, abnormal sensations resolved significantly more rapidly in the younger subjects; the median duration of abnormal sensations was 31 days in the ≥ 50 year olds and 16 days in those aged < 50 years. In cases of ophthalmic zoster, the rate of pain resolution was not different from those with zoster in other dermatomes (median duration of pain 18 vs. 16 days). However, abnormal sensations persisted significantly longer in subjects with ophthalmic zoster than in those with zoster at other sites (47 vs. 22 days). In addition to advancing age, subjects suffering moderate to severe prodromal pain or acute pain during the rash phase were at significantly greater risk of zoster-associated pain and abnormal sensations persisting for longer. Subjects with concomitant neurological disorders were also more likely to develop prolonged abnormal sensations. Valaciclovir treatment was well tolerated, and adverse events were rare and generally mild.

Conclusion This study confirmed the prognostic importance of advancing age and the intensity of prodromal or acute pain as risk factors for prolonged zoster-associated pain and persisting abnormal sensations in the affected dermatome. Ophthalmic zoster and pre-existing neurological disorders are also identified as highly significant risk factors for prolonged abnormal sensations in herpes zoster.

Key words: herpes zoster, pain, valaciclovir, ophthalmic, age, prognostic factors

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Introduction

Herpes zoster is the most common infection of the peripheral nervous system and is often associated with considerable morbidity in the elderly.[1,2] Although the disease can occur at any time, in otherwise healthy individuals the risk of developing zoster increases markedly with age, with a significantly increased risk over the age of 50 years, thought to result from a decline in cellular immunity to varicella zoster virus (VZV).[3,4] For individuals who reach the age of 85 years, it is estimated that 50% will have suffered at least one attack of zoster.[5] An attack of zoster, especially in the elderly, often compounds one or more concomitant medical conditions, thus exacerbating a decline in the patient's overall quality of life.

The unilateral rash of herpes zoster is usually preceded and accompanied by pain,[6] which can persist for weeks, or months after the skin lesions have healed. Persisting zoster-associated pain, the most common complication of herpes zoster, is more likely in older subjects.[4,7–9] Clinical studies have found up to 30–45% of subjects over 60 years of age experience pain which persisted for more than 6 months to over one year.[6,9] The pain is often accompanied by abnormal sensations such as allodynia and paresthesia[1] which can be more distressing for patients than pain itself.

Thoracic dermatomes are most commonly involved (50–56% of patients) in herpes zoster, whilst cervical and cranial dermatomes are affected in 24–34% of patients.[10] Involvement of the ophthalmic dermatome accounts for 10–17% of cases of herpes zoster and is potentially the most serious because in addition to pain, there is the risk of visual impairment if VZV infects the eye.[11,12] Some studies suggest that acute and chronic pain in ophthalmic or cranial zoster is more persistent than that in thoracic or other dermatomes.[9,13,14]

Valaciclovir (Valtrex™) has been proven effective in controlled trials as treatment for herpes zoster, speeding resolution of zoster-associated pain and postherpetic neuralgia faster than aciclovir and being equally effective as aciclovir in stopping new lesion formation and speeding rash healing. These trials also identified some prognostic factors for the outcome of zoster-associated pain.[15,16]

Although the efficacy of antiviral therapy has been studied extensively, it is important to ensure that, even with antiviral therapy options, subjects at high risk of complications are identified as early as possible, so as to optimize management. Earlier studies with aciclovir suggested that factors such as age, duration and location of rash may play an important role in clinical outcome. This observational study with valaciclovir was conducted to assess clinical outcomes, especially pain and associated neurological signs and symptoms of herpes zoster, in relation to a series of demographic and disease characteristics discernible at initial presentation. The study also provided the opportunity to further assess the safety and acceptability of valaciclovir when prescribed in a wide variety of primary care and clinic referral settings in 26 different countries.

Materials and methods

Patients

Immunocompetent subjects 18 years of age or older with clinically diagnosed, localized acute herpes zoster were enrolled in this international, multicentre, open-label study of valaciclovir for the treatment of herpes zoster. The clinical diagnosis of herpes zoster was based on the presence of a unilateral dermatomal rash at presentation. Patients with herpes zoster ophthalmicus, defined as cutaneous lesions involving the ophthalmic branch of the trigeminal nerve, with or without ocular involvement, were included. It was not considered necessary to restrict participation to subjects presenting within 72 h of rash onset because the impact of valaciclovir treatment on pain outcome in herpes zoster may not be limited to 72 h.[17]

The study was outpatient-based, and included cases from dermatology, infectious diseases, teaching hospital and general practice clinics.

Pregnant, lactating and sexually active women of childbearing potential not employing adequate contraception were excluded, as were patients being treated with systemic immunosuppressive therapy, those who had received systemic or topical anti-VZV therapy in the week prior to entering the study, or those receiving any other investigational drug in the week prior to entering the study or while on study treatment. Also excluded were subjects with significant immune dysfunction, known infection with HIV or significantly impaired renal (estimated creatinine clearance < 35 mL/min) or liver (alanine transaminase levels greater than three times the upper limit of the normal range) function. Ethical approval was obtained from each study centre prior to enrolment in the study and written informed consent was obtained from each subject.

Study procedures

On initial presentation and entry into the study (day 1) a brief medical history was obtained, including details of any underlying medical condition, particularly those associated with chronic, underlying pain, and subjects were assessed to determine whether they had experienced prodromal pain, defined as pain before rash onset, its maximum intensity and duration. The dermatome(s) affected by the zoster rash was recorded.

All subjects received treatment with oral valaciclovir at 1000 mg (as two 500 mg tablets) three times per day from the day of presentation for 7 days. Compliance with study

medication was assessed on day 8 by a review of the contents of the tablet containers; all concomitant medications used up to day 15 were recorded.

Patients recorded daily on a diary card for the length of the study, the presence or absence of zoster-associated pain and abnormal sensations such as allodynia, numbness, tingling or paresthesia.

Clinical assessments

Presence or absence of pain was monitored and checked against the patient diary by the investigator on days 1, 8 and 29 then every 4 weeks up to 24 weeks, as was the presence or absence of abnormal sensations. Subjects were defined as achieving complete cessation of pain or abnormal sensations if they were free of pain or abnormal sensations for at least 28 days and had no subsequent recurrence during the 24-week observation period. Cutaneous assessments to determine lesion staging and rash healing were performed by the investigator on days 1 and 8. The percentage of total lesion area consisting of macules/papules, vesicles, crusts and healed lesions was determined in 10% increments. Safety and tolerability was assessed by adverse event monitoring.

Data analysis

Sample size estimation

It was estimated that 25% of the subjects aged ≥ 50 years would still be experiencing zoster-associated pain at 6 months from initiation of treatment. For patients < 50 years, this figure was estimated to be 15%. This age group comparison is equivalent to a hazard ratio of 1.37 for cessation of pain.[18] The expected standard errors for the proportion of subjects with pain at 6 months were 0.016 and 0.013 for the older and younger patient groups, respectively, resulting in 95% confidence intervals (CIs) of 0.22–0.28 and 0.12–0.18, respectively. Overall, 10% of subjects were estimated to have ophthalmic zoster with 30% still experiencing pain at 6 months. For subjects with non-ophthalmic zoster, this figure was estimated to be 20%. This non-ophthalmic vs. ophthalmic comparison is equivalent to a hazard ratio close to 1.34 for cessation of pain.[18]

All analyses were conducted using Statistical Analysis Systems software (SAS Institute, Inc, Carey, NC) and were based on estimation of important clinical outcome measures and their associated standard errors rather than on formal hypothesis testing. Four patient groups were of primary interest: subjects aged < 50 years, subjects aged ≥ 50 years and subjects with or without ophthalmic zoster. The primary endpoint, time to complete cessation of zoster-associated pain, was calculated relative to the first day of treatment with valaciclovir. Secondary endpoints were time to complete cessation of zoster-associated abnormal sensations and the proportion of subjects with 50% and complete (100%) rash healing at day 8. Other parameters assessed included duration of zoster-associated pain and zoster-associated abnormal sensations in relation to prodromal pain characteristics.

The distribution of times to cessation of pain and abnormal sensations were estimated by the Kaplan–Meier product limit survival method[19] and were derived separately for subjects aged ≥ 50 years vs. those < 50 years, and also for those with ophthalmic zoster and non-ophthalmic zoster. Median values and proportions with zoster-associated pain or abnormal sensations were derived from Kaplan–Meier estimates. Factors that may influence the duration of zoster-associated pain or abnormal sensations were fitted as covariates to Cox's proportional hazards models; in addition to age and zoster type, these included the presence or absence of prodromal pain or abnormal sensations prior to entry, their associated onset times relative to the start of treatment, severity of pain or abnormal sensations at entry and time from onset of rash to the start of treatment. Further exploratory analyses were conducted to assess pain outcome in subjects with neurological disorders. Proportions with pain or abnormal sensations, or 50% or 100% healed at day 8, were compared using Kaplan–Meier estimates and corresponding 95% CIs for the difference in proportions. Adverse events were categorized and detailed according to seriousness and attributability.

Results

Subjects

A total of 1897 subjects was enrolled at 172 study centres in 26 countries. Demographic characteristics for subjects 18–50 years and ≥ 50 years and for subjects with or without ophthalmic zoster are shown in Tables 1a and 1b, respectively. Overall, there were 1191 subjects (63%) aged ≥ 50 years and 203 (11%) had ophthalmic zoster. Fifty-eight per cent of females were aged ≥ 50 years and 11% of females presented with ophthalmic zoster. There were no major differences in gender in these key interest groups. A high proportion of subjects, more than 80%, experienced prodromal pain, which was of moderate or greater intensity in more than 50% . There was no difference in the percentage of subjects experiencing prodromal pain in relation to age or site of rash. Pain intensity at presentation was similar in subjects with ophthalmic and non-ophthalmic zoster, but a slightly greater percentage of patients over 50 years experienced prodromal pain of moderate or greater intensity compared with younger patients (63% vs. 54%). Overall, 58% of subjects presented and commenced treatment with valaciclovir within 72 h of the appearance of the herpes zoster rash.

Eighty-six per cent and 90% of subjects 18–50 years and ≥ 50 years, respectively, took ≥ 90% of the study medication.

Table 1 a) Demographic and disease characteristics by age; **b)** demographic and disease characteristics by rash location

a)	**18–50 years (*n* = 706)**	**≥ 50 years (*n* = 1191)**
Age (years)		
Median	35	66
Range	18–49	50–95
Female/male (%)	43/57	58/42
Ophthalmic zoster (%)	8	13
Prodromal pain		
Present/absent (%)	83/17	84/16
≥ Moderate intensity (%)	54	63
Median duration (hours)	38.5	44
Acute pain*		
Present/absent (%)	90/10	89/11
≥ Moderate intensity (%)	58	66
Rash onset prior to treatment		
≤ 72 h (%)	58	58
> 72 h (%)	42	42

b)	**Ophthalmic (*n* = 203)**	**Non-ophthalmic (*n* = 1694)**
Age (years)		
Median	62	56
Range	22–88	18–95
Female/male (%)	49/51	53/47
Prodromal pain		
Present/absent (%)	82/18	84/16
≥ Moderate intensity (%)	57	60
Median duration (hours)	32.5	42
Acute pain*		
Present/absent (%)	86/14	90/10
≥ Moderate intensity (%)	60	64
Rash onset prior to treatment		
≤ 72 h (%)	58	58
> 72 h (%)	42	42

* Acute pain defined as pain at or immediately before presentation

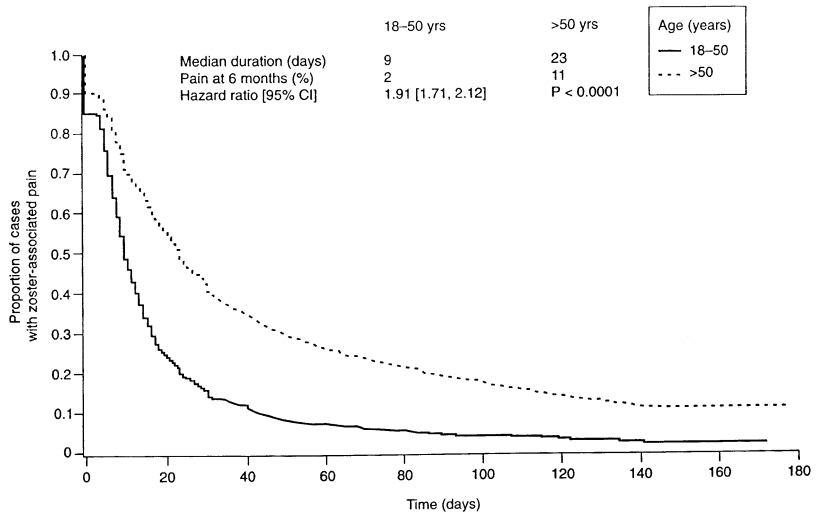
Data were analysed for all subjects enrolled in the study; 89% and 92% of subjects 18–50 years and ≥ 50 years, respectively, completed the 24-week study according to protocol. Nine per cent of subjects discontinued the study prematurely: adverse events 1.5%, lost to follow-up 4.3%, consent withdrawn 1.3%, death 0.4%, poor drug response 0.3%, and protocol violation 0.9%.

Primary analyses – duration of zoster-associated pain and abnormal sensations

The influence of age on the duration of zoster-associated pain is shown in fig. 1a. Resolution of zoster-associated pain was significantly faster in the younger age group. The hazard ratio (95% CI) for the relative rates of pain resolution in the 18–50 vs. ≥ 50-year-old age groups was 1.91 (1.71, 2.12), $P < 0.0001$, demonstrating that pain resolved almost twice as rapidly in the younger patient group. A more detailed breakdown of pain resolution by age in 10-year bands is illustrated in fig. 1b. The median time to cessation of pain was 9 days in the < 50 years age group compared with 23 days in subjects ≥ 50 years. Furthermore, more than five times as many subjects in the older age group (11%) still experienced pain at the end of the study (week 24) compared with the younger age group (2%).

Similar to zoster-associated pain, abnormal sensations in the dermatome affected by the zoster rash ceased significantly earlier in younger subjects (fig. 2). The hazard ratio (95% CI) for relative rates of resolution of abnormal sensations in the 18–50 vs. ≥ 50-year-old age groups was 1.68 (1.50, 1.88), $P < 0.0001$ and the median duration of abnormal sensations was almost twice as long for subjects ≥ 50 years (31 days) than for those < 50 years (16 days). Only 6% of those in the younger age group still experienced abnormal sensations at the end of the study compared with 21% in the ≥ 50 years age group.

The duration of zoster-associated pain and abnormal sensations in subjects with ophthalmic zoster and non-ophthalmic



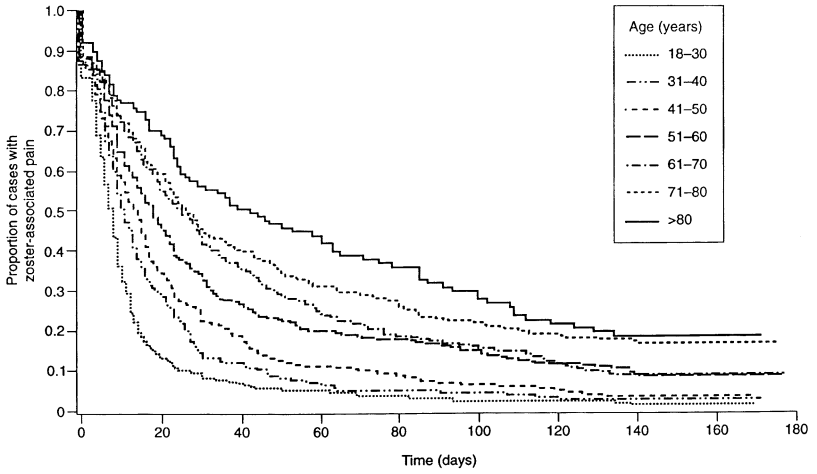


fig. 1a Time to cessation of zoster-associated pain in subjects aged 18–50 years or ≥ 50 years; **b** time to cessation of zoster-associated pain according to 10-year age bands

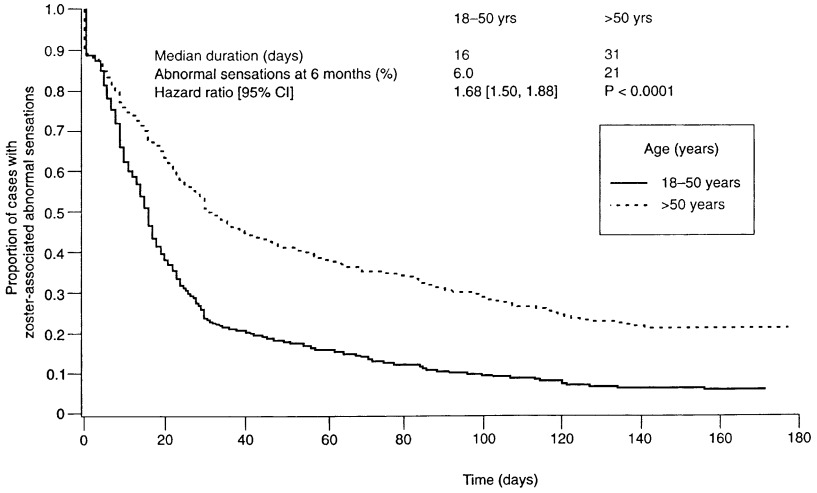


fig. 2 Time to cessation of abnormal sensations in subjects aged 18–50 years or ≥ 50 years

zoster is shown in fig. 3. There was no statistically significant difference in time to resolution of pain for subjects with non-ophthalmic vs. ophthalmic zoster (hazard ratio (HR) [95% CI] = 1.10 [0.93, 1.31], $P = 0.28$). Although there was little apparent difference overall in the median time to cessation of pain between the two groups (18 days vs. 16 days for ophthalmic and non-ophthalmic groups, respectively), from month 1 to month 6, zoster-associated pain was present consistently from day 20

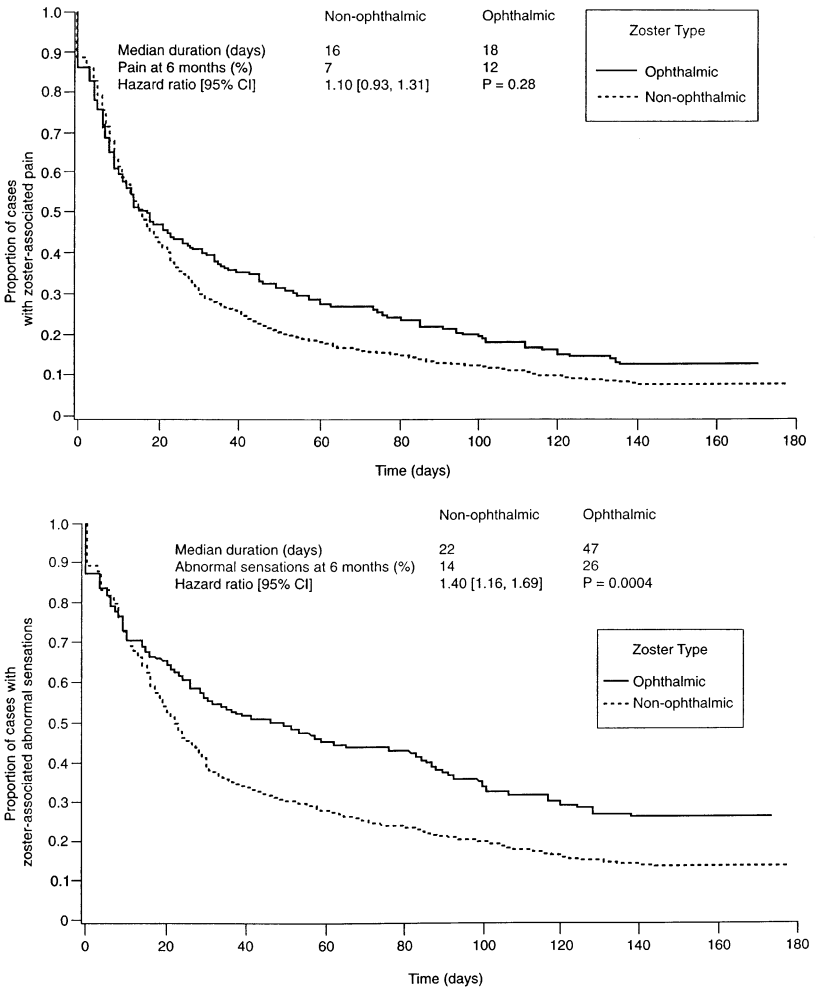


fig. 3a Time to cessation of zoster-associated pain in subjects with ophthalmic zoster and non-ophthalmic zoster; **b** time to cessation of abnormal sensations in subjects with ophthalmic zoster and non-ophthalmic zoster.

onwards in a higher proportion of subjects with ophthalmic zoster than those with non-ophthalmic zoster (12% vs. 7%, respectively, at 6 months). This finding was substantiated by the statistically significant difference seen for the duration of abnormal sensations for the non-ophthalmic vs. ophthalmic zoster groups (HR [95% CI] 1.40 [1.16, 1.69], $P = 0.0004$), indicating that abnormal sensations resolved approximately 40% more rapidly in subjects with non-ophthalmic zoster. The median duration of abnormal sensations was more than twice as long in subjects with ophthalmic zoster and abnormal sensations were still present at 6 months in 26% of subjects with ophthalmic zoster compared with 14% of those with non-ophthalmic zoster.

Exploratory analyses – prognostic markers for prolonged pain

The presence or absence of prodromal pain has independently been found to be a statistically significant factor in influencing pain duration;[20] this was also the case in the present study when the intensity of prodromal pain was included in a multivariate model (Table 2a, fig. 4). Subjects suffering moderate to severe prodromal pain (pain prior to rash onset) at or before presentation were at significantly greater risk of more prolonged zoster-associated pain. Similarly, subjects reporting moderate to severe acute pain (pain during the early rash phase) at or immediately before presentation were at greater risk for prolonged zoster-associated pain; median days for cessation of zoster-associated pain ranged from 9 to 10 for subjects presenting with no pain or noticeable/mild pain, to 15–25 days for those with moderate to severe pain. Prognostic markers which influenced the duration of abnormal sensations were comparable to those affecting zoster-associated pain (Table 2b).

The study included 141 (7%) subjects with concomitant neurological disorders, notably 28% with painful joint and orthopaedic conditions, 36% with cerebral vascular disorders and 21% with various other neuropathies and neuralgias, including Parkinson's disease and multiple sclerosis. It is of interest that these subjects were more likely to suffer from

Table 2 a) Prognostic markers for zoster-associated pain; **b)** prognostic markers for zoster-associated abnormal sensations

a)	Hazard ratio [95% CI]	*P*-value
Absence vs. presence of prodromal pain	1.12 [0.94, 1.35]	$P = 0.18$
Intensity of prodromal pain		
Non/noticeable/mild vs. moderate	1.30 [1.12, 1.52]	$P = 0.0008$
Non/noticeable/mild vs. severe/very severe	1.78 [1.53, 2.07]	$P < 0.0001$
Subjects without vs. with concomitant neurological disorders	1.10 [0.92, 1.33]	$P = 0.30$

b)	Hazard ratio [95% CI]	*P*-value
Absence vs. presence of prodromal pain	1.00 [0.83, 1.20]	$P = 0.97$
Intensity of prodromal pain		
Non/noticeable/mild vs. moderate	1.23 [1.04, 1.44]	$P = 0.01$
Non/noticeable/mild vs. severe/very severe	1.52 [1.30, 1.77]	$P < 0.0001$
Subjects without vs. with concomitant neurological disorders	1.55 [1.26, 1.91]	$P < 0.0001$

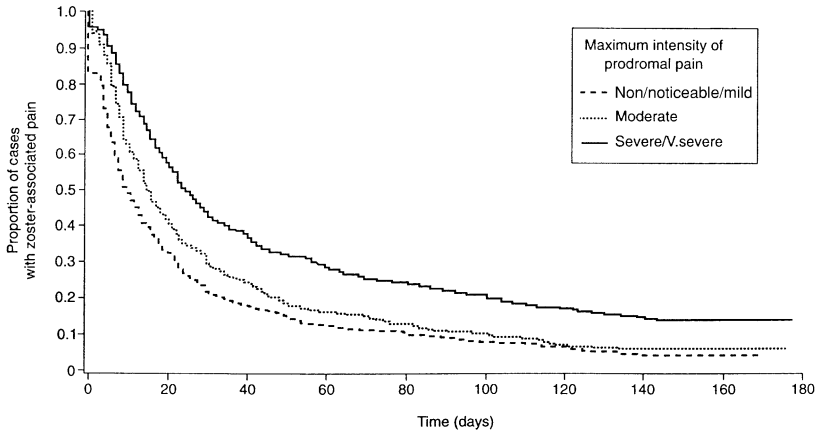


fig. 4 Time to cessation of zoster-associated pain in subjects with no/just noticable/mild, moderate, severe/very severe prodromal pain

prolonged zoster-associated abnormal sensations than subjects without such disorders, the hazard ratio (95% CI) for subjects without a neurological disorder vs. patients with such disorders was 1.55 (1.26, 1.91), $P < 0.0001$ (Table 2b). An association between concomitant neurological disorders and prolonged pain was not statistically significant, hazard ratio (95% CI) = 1.10 [0.92, 1.32], $P = 0.30$ (Table 2a).

Of importance, there was no loss of impact on pain or abnormal sensations when treatment was started later than 72 h from the onset of the rash. The median time to cessation of pain was 16 days in cases treated within 72 h from rash onset compared with 15 days for those treated after 72 h. Similarly, median times to cessation of abnormal sensations were 24 and 22 days, respectively, for cases treated ≤ 72 h or > 72 h from rash onset.

Cutaneous endpoints

There were no meaningful differences between the 18–50 and ≥ 50-year-old age groups in proportions with 50% rash healed by day 8 (71% and 68%, respectively) or with 100% rash healed by day 8 (29% and 21%, respectively). For those with or without ophthalmic zoster the proportions with 50% rash healed by day 8 (75% and 69%, respectively) or with 100% rash healed by day 8 (27% and 24%, respectively) were similar.

Safety

Valaciclovir was well tolerated, with adverse events being rare and similarly distributed across the two age groups. Table 3

Table 3 Adverse events reported by ≥ 2% of subjects during valaciclovir treatment

Adverse Event	18–50 years *n* = 706	≥ 50 years *n* = 1192*
Headache	3%	3%
Nausea	2%	4%
Constipation	1%	3%
Asthenia	1%	2%
Diarrhoea	1%	2%
Abdominal pain	2%	1%

* includes one subject given valaciclovir but who did not have zoster and was therefore excluded from efficacy analyses

summarizes the most common adverse events reported by ≥ 2% of subjects during valaciclovir treatment. Of the 1897 subjects who were enrolled into the study, four experienced adverse events during or immediately after treatment that were considered serious and possibly attributable to the study drug. There was one case each of temporary confusion, reversible skin rash and vomiting; one subject developed retinitis and dizziness. Of the 165 patients who withdrew from the study prematurely, 28 (1.5%) did so because of an adverse event; 17 of these withdrawals were due to an adverse event considered possibly related to valaciclovir therapy. Other adverse events resulting in study withdrawal were not considered treatment related and were generally associated with exacerbation of pre-existing medical conditions or diagnosis of a new one.

Discussion

This large observational study, involving almost 2000 subjects from a wide variety of clinical referral and primary care settings and cultural backgrounds, gives an increased insight into the demographic and disease features of herpes zoster discernible at initial consultation and how they might impact on clinical outcome. It allows us to identify risk factors which predispose subjects to complications, such as prolonged zoster-associated pain and zoster-associated abnormal sensations, and thus optimize disease management in such cases. In addition to advancing age, this study confirms the prognostic importance of severity of prodromal and acute pain (pain during the early rash phase) on prolonged zoster-associated pain and abnormal sensations. Trigeminal or ophthalmic zoster is also associated with more prolonged zoster-associated abnormal sensations and may be associated with persisting chronic pain.

Prolonged pain in herpes zoster is the most common complication of the disease and accompanying abnormal sensations and allodynia often exacerbate this. Advancing age is already recognized as a major factor influencing the epidemiology, clinical features and complications of zoster in otherwise healthy individuals.[10] This large database of 1897 subjects has confirmed, as predicted, that advancing age is a statistically significant risk factor for prolonged zoster-associated pain.[9,15,20,21] It is also a prognostic factor for persistent abnormal sensations, including numbness, tingling, paresthesia and allodynia, which are often more distressing to the patient than the pain itself.

The highest incidence of prolonged pain has been suggested to occur in subjects with ophthalmic zoster.[9,13] Prolonged pain has been reported in 30% of subjects with herpes zoster ophthalmicus aged ≥ 60, rising to 71% in those aged ≥ 80.[13] The duration of pain is also reported to be longer after trigeminal and/or ophthalmic zoster.[9,14] In the present study, 8% of subjects aged < 50 years presented with ophthalmic zoster, in contrast with 13% of subjects aged ≥ 50 years. Although pain was present in a higher proportion of subjects with ophthalmic zoster from months 1–6, statistical significance was not reached to confirm ophthalmic zoster overall as a risk factor for prolonged zoster-associated pain. The absence of any difference (between ophthalmic and non-ophthalmic zoster subjects) during the acute phase probably underestimated the magnitude of a difference during the chronic phase (months 1–6) in this overall analysis of zoster-associated pain, as the presence of ophthalmic zoster was a highly statistically significant prognostic factor for prolonged abnormal sensations. These findings are consistent with published therapeutic management guidelines which recommend that antiviral therapy should be given to all zoster patients over 50 years of age and to all patients with ophthalmic herpes zoster.[22,23]

Pain (including abnormal sensations) is the principal reason why most subjects seek consultation with a physician for zoster.[24] The pathophysiology of zoster pain is complex; replication of VZV within infected neurones early in acute zoster causes nerve damage and/or malfunction.[21,24] This in turn may trigger a series of additional mechanisms and lead to more persistent, chronic pain and postherpetic neuralgia.[14] More severe pain at presentation and during the acute rash phase has been suggested as predisposing to the development of prolonged pain,[15,25] perhaps as a consequence of initially greater nerve damage.

This study showed that, irrespective of age or the site of zoster, almost 90% of subjects had pain at presentation. This is supportive of the finding that pain is the primary reason for consultation with a physician. Although other studies have shown the presence of prodromal pain to be predictive of longer pain duration,[15,20] the association did not achieve statistical significance in this study. However, the intensity of prodromal pain was highly significant; the more severe the pain, the greater the risk of prolonged zoster-associated pain. This is consistent with the theory that the greater extent of initial VZV replication, with resultant sensory nerve damage, manifests as more severe prodromal pain and a greater likelihood of pain persisting. Results were similar for predicting longer duration of zoster-associated abnormal sensations. These data would support the use of antiviral therapy in subjects aged < 50 years presenting with at least moderate pain or abnormal sensations.[22]

The most important parameter affecting the speed of rash healing, and therefore rash severity, is generally thought to be the age of the subject – the older the subject, the longer the rash healing time.[6,26] The rash of ophthalmic zoster has been reported to heal more quickly than zoster at other sites.[26,27] Rash healing in the present study was not affected by age nor by the site of the rash.

This present study was outpatient-based, so subjects presented at different stages after rash onset. Most recent clinical trials of antiviral agents for herpes zoster have enrolled subjects within 72 h of the appearance of the rash,[15,28–31] because one study of aciclovir suggested that earlier therapy resulted in

faster rash healing.[29] However, it should not be assumed that antiviral therapy affects VZV replication in the sensory nervous system at the same rate as in the skin. The results from this present analysis show that no differences were detected on the duration of zoster-associated pain and abnormal sensations in subjects whose treatment was initiated after 72 h from rash onset compared with those who were treated earlier. This could be important as it indicates that valaciclovir therapy may be of benefit on zoster-associated pain/abnormal sensations, the more important clinical outcome, even when commenced outside what has come to be regarded as the normal 'treatment window' for zoster of up to 72 h from lesion onset. Future studies should consider prior duration or severity of pain rather than prior duration of rash to select and/or stratify cases.

Although gender has in the past been suggested as an important factor predisposing to prolonged pain, with females suffering more than males,[8] this may be a result of the greater longevity of women (that is advancing age rather than gender itself). Findings of this observational study are not indicative of a gender effect and are in agreement with more recent studies.[15,32]

Of note is the positive correlation between pre-existing chronic neurological disorders and prolonged abnormal sensations. The development of chronic zoster-associated pain, abnormal sensations and postherpetic neuralgia in some subjects is thought to involve central mechanisms triggered by the initial sensory nerve damage and malfunction.[33,34] When such central neuropathic pain mechanisms are already primed, for example, in chronic arthritis or diabetes, virus-mediated nerve damage in an acute zoster attack may more readily exacerbate their role.

This observational study provided a large database with which to monitor safety and compliance in a typical population with herpes zoster. With adverse events during treatment being infrequent and generally mild, tolerance to valaciclovir is considered excellent. The simple three-times-daily schedule was seen to be convenient, as evidenced by good compliance with the dosing regimen in both younger and older subjects.

These observations have illustrated the acceptability of valaciclovir for treatment of herpes zoster in a wide range of primary care and other referral settings, including dermatology clinics. In addition, the study confirmed the importance of a series of individual and disease characteristics which the physician may readily recognize at initial presentation, in terms of their influence on the outcome of zoster-associated pain and abnormal sensations. In addition to advancing age, greater prodromal and acute pain severity, the presence of ophthalmic zoster and pre-existing neurological conditions are additional risk factors prognostic for prolonged zoster-associated pain and associated neurological sequelae. The duration of the rash prior to treatment and the gender of the subject are not predictors of outcome on zoster-associated pain.

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References

1 Bhala BB, Ramamoorthy C, Bowsher D *et al.* Shingles and postherpetic neuralgia. *Clin J Pain* 1988; **4**: 169–74.

2 Weller TH. Varicella and herpes zoster: changing concepts of the natural history, control and importance of a not-so-benign virus. *N Engl J Med* 1983; **309**: 1434–40.

3 Miller AE. Selective decline in cellular immune response to varicella-zoster in the elderly. *Neurology* 1980; **30**: 582–7.

4 Raggozino MW, Melton LJ, Kurland LT *et al.* Population-based study of herpes zoster and its sequalae. *Medicine* 1982; **61**: 310–6.

5 Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. *Proc R Soc Med* 1965; **58**: 9–20.

6 Burgoon CF, Burgoon JS, Baldridge GD. The natural history of herpes zoster. *JAMA* 1957; **164**: 265–9.

7 Whitley RJ. In: Galasso GJ, Whitley RJ, Merigan TC. eds. *Antiviral Agents and Viral Diseases of Man*, 3rd edn. New York. Raven Press Ltd, 1990: 235–263.

8 Hope-Simpson RE. Postherpetic neuralgia. *J R Coll Gen Pract* 1975; **25**: 571–5.

9 De Moragas JM, Kierland RR. The outcome of patients with herpes zoster. *AMA Arch Dermatol* 1957; **75**: 193–6.

10 Wood MJ. Herpes zoster in immunocompetent patients. *Res Clin Forums* 1986; **8**: 61–70.

11 Harding SP. Management of ophthalmic zoster. *J Med Virol; Suppl*, 1993; **1**: 97–101.

12 Harding SP, Porter SM. Oral acyclovir in herpes zoster ophthalmicus. *Curr Eye Res* 1991; **10**: 177–82.

13 Harding SP, Lipton JR, Wells JCD. Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement. *Br J Ophthalmol* 1987; **71**: 353–8.

14 Wood MJ. Herpes zoster and pain. *Scand J Infect Suppl*, 1991; **78**: 53–61.

15 Beutner KR, Friedman DJ, Forszpaniak C *et al.* Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother* 1995; **39**: 1546–53.

16 Perry CM, Faulds D. Valaciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in herpesvirus infections. *Drugs* 1996; **52**: 754–72.

17 Wood MJ, Shukla S, Fiddian AP, Crooks RJ. Treatment of acute herpes zoster: effect of early (< 48 h) versus late (48–72 h) therapy with acyclovir and valaciclovir on prolonged pain. *J Infect Dis* 1998; **178** (Suppl. 1): S81–4.

18 Machin D, Campbell MJ. *Statistical Tables for the Design of Clinical Trials*. Oxford. Blackwell Scientific Publications, 1987.

19 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.

20 Whitley RJ, Shukla S, Crooks RJ. The identification of risk factors associated with persistent pain following herpes zoster. Accepted for publication in *J Infect Dis* 1998; **178** (Suppl. 1): S71–S75.

21 Portenoy RK, Duma C, Foley KM. Acute herpetic and postherpetic neuralgia: clinical review and current management. *Ann Neurol* 1986; **20**: 651–64.

22 Wood MJ, Kroon S, eds. *Management Strategies in Herpes: Reducing the Burden of Zoster-Associated Pain – Update*. Worthing. PPS Europe, 1997.

23 Special Report of the British Society for the Study of Infection. Guidelines on the management of shingles. *J Infect* 1995; **30**: 193–200.

24 Robinson PN, Fletcher N. Postherpetic neuralgia. *J R Coll Gen Pract* 1986; **36**: 24–8.

25 Wood MJ, Johnson RW, McKendrick MW *et al.* A randomised trial

of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med* 1994; **330**: 896–900.

26 Wildenhoff KE, Ipsen J, Esmann V *et al.* Treatment of herpes zoster with idoxuridine ointment, including a multivariate analysis of symptoms and signs. *Scan J Infect Dis* 1979; **11**: 1–9.

27 Wildenhoff KE, Esmann V, Ipsen J *et al.* Treatment of trigeminal and thoracic zoster with idoxuridine. *Scand J Infect Dis* 1981; **13**: 257–62.

28 Huff JC, Bean B, Balfour HH *et al.* Therapy of herpes zoster with oral acyclovir. *Am J Med* 1988; **85** (Suppl. 2a): 84–9.

29 Wood MJ, Ogan PH, McKendrick MW *et al.* Efficacy of oral acyclovir treatment of acute herpes zoster. *Am J Med* 1988; **85** (Suppl. 2a): 79–83.

30 Morton P, Thomson AN. Oral acyclovir in the treatment of herpes zoster in general practice. *NZ Med J* 1988; **102**: 93–5.

31 Tyring S, Barbarash RA, Nahlik JE *et al.* Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia. A randomised, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; **123**: 89–96.

32 Wood MJ, Kay R, Dworkin RH *et al.* Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster – a meta-analysis of placebo-controlled trials. *Clin Infect Dis* 1996; **22**: 341–7.

33 Bennett GJ. Evidence from animal models on the pathogenesis of painful peripheral neuropathy: relevance for pharmacotherapy. In: Basbaum AI, Besson J-M. eds. *Towards a New Pharmacotherapy of Pain*. Chichester. Wiley and Sons, 1991.

34 Gracely RH, Lynch SA, Bennet GJ. Painful neuropathy: altered central processing, maintained dynamically by peripheral input. *Pain* 1993; **51**: 75–194.