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Short communication

# Oral brivudin in comparison with acyclovir for herpes zoster: a survey study on postherpetic neuralgia

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**Abstract**

This concerns a double-blind survey study on 608 herpes zoster patients treated with 1× 125 mg oral brivudin ($n = 309$) or 5× 800 mg acyclovir ($n = 299$), both for 7 days, during two prospective, randomised clinical herpes zoster trials. The survey aimed at evaluating the outcome of the two treatment regimens on postherpetic neuralgia (PHN). During a follow-up ranging from 8 to 17 months after start of treatment, former study participants aged ≥50 years were interviewed for the occurrence of PHN. Neither the investigators nor the patients were aware of which treatment the patients received during acute herpes zoster. The incidence of PHN, defined as zoster-associated pain occurring or persisting after rash healing was significantly lower in brivudin recipients (32.7%) than in acyclovir recipients (43.5%, $P = 0.006$). Mean duration of PHN was similar with brivudin (173 days) and acyclovir (164 days, $P = 0.270$). Despite some methodological disadvantages common to this type of study, the present survey provides for the first evidence that brivudin treatment during acute herpes zoster favourably affects the incidence of PHN in immunocompetent elderly herpes zoster patients.


*Keywords:* Brivudin; Herpes zoster; Postherpetic neuralgia (PHN)

Herpes zoster is regularly accompanied by acute zoster-associated pain (ZAP). Particularly elderly patients suffer from chronic pain prevailing after resolution of acute signs and symptoms of herpes zoster, the so-called postherpetic neuralgia (PHN). PHN is the most feared complication of herpes zoster in immunocompetent patients and is often refractory to treatment. The incidence of PHN is difficult to assess because different definitions of PHN have been used in the past, e.g. pain after rash healing, pain at month 1, month 3, or month 6 after start of treatment. For pain regardless of severity, prospective data from placebo-groups of clinical studies suggest an incidence of approximately 60% at month 1 after enrolment (McKendrick et al., 1989; Dworkin et al., 1998), which decreases with time. Studies conducted with the antiviral agents famciclovir and valaciclovir (Beutner et al., 1995; Dworkin et al., 1998; Tyring et al., 1995, 2000) as well as meta-analyses on studies conducted with acyclovir (Crooks et al., 1991; Jackson et al., 1997; Wood et al., 1996) indicate that antiviral therapy, if initiated early during acute herpes zoster, can favourably affect not only acute pain but also the incidence and/or the duration of PHN.

Brivudin [(*E*)-5-(2-bromovinyl)-2′-deoxyuridine] is a nucleoside analogue with a high and selective activity against varicella-zoster virus and herpes simplex virus type 1 (De Clercq, 1984, 1993; Andrei et al., 1995). Two randomised, double-blind clinical studies demonstrated the therapeutic efficacy of oral brivudin 125 mg once daily in comparison to oral acyclovir 800 mg five times daily, both for 7 days, in alleviating acute signs and symptoms of herpes zoster (a dose-ranging study in 642 herpes zoster patients (unpublished data) and a Phase III study in 1227 patients; Wassilew and Wutzler, 2003). These two clinical multicentered studies were conducted in succession between 14 October 1996 and 14 August 1997 and shared a common study protocol: Eligible patients were immunocompetent Caucasian adults with clinically diagnosed herpes zoster presenting within 48 h after first vesicular eruption.

The development of PHN in study participants (≥50 years) was analysed in the double-blind survey study

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reported here. The survey comprised patients who had received a 7-day treatment course with either brivudin 125 mg once daily or acyclovir 800 mg five times daily. PHN was defined as pain of any intensity after rash healing. Only patients aged 50 years or older were included since the risk of developing PHN is known to increase with age (Whitley et al., 1998). Screening of patients according to the selection criteria (main criterion: age ≥50 years) was performed under double-blind conditions. When the survey was planned and data were collected, investigators, patients, and data management personnel were unaware of which treatment the patients had received during acute herpes zoster.

Former study participants ≥50 years were contacted by telephone once at a point in time between 8 and 17 months after the start of treatment and were interviewed for the occurrence of PHN after rash healing. If PHN had occurred or persisted, patients were summoned to a clinic visit, and duration, intensity, and type of PHN were assessed by the investigator.

Clinical endpoints were the overall prevalence of PHN after rash healing, the duration of PHN measured by the time from start of treatment to end of PHN, the intensity of PHN using a 6-point scale ranging from 0: "none" to 5: "unbearable", the pattern of PHN ("regular" or "irregular"), and the type of PHN comprising the categories "steady throbbing", "steady burning", "intermittent sharp or shooting", and "allodynia". Treatment of PHN with analgesics, antidepressants, or other drugs was also recorded.

Prevalence and duration of PHN were analysed using a logistic regression model and a Cox proportional hazard model, respectively, which were adjusted for the covariates "age", "pain intensity at baseline" and "study" (dose-ranging study or Phase III study). A 5% significance level (two-sided) was used to indicate differences between the treatment groups.

A total of 662 patients were selected for the survey, 126 (19%) being from the dose-ranging study and 536 (81%) from the Phase III study (see Fig. 1). Of these 662 patients, 608 (brivudin: $n = 309$, acyclovir: $n = 299$) could be contacted and were ready to participate (survey patients). Of these patients, 545 had terminated the original study according to protocol (analysis patients). Main results were as follows:

With respect to baseline characteristics, no significant differences were observed between the treatment groups (see Table 1). Among all surveyed patients, PHN had developed in 32.7% of the patients formerly treated with brivudin and in 43.5% of the acyclovir recipients. The incidence of PHN was significantly lower after brivudin treatment than after acyclovir treatment ($P = 0.006$, see Table 1 and Fig. 2).

The mean duration of PHN in affected patients ($n = 205$, analysis population) was 173 days with brivudin and 164 days with acyclovir, the difference between the treatment groups not reaching statistical significance ($P = 0.270$).

No significant differences as to the type and pattern of PHN were observed between the treatment groups. The majority of patients in both treatment groups reported having irregular pain episodes (brivudin: 80.6%, acyclovir: 80.4%) and pain was characterised by most patients as being intermitted sharp or shooting (brivudin: 51.6%, acyclovir: 41.1%), or as allodynia (brivudin: 29.5%, acyclovir: 26.9%).

The survey study presented here provides for the first time evidence of the effects of oral brivudin on the outcome of PHN. Regardless of the controversially discussed question whether or not acyclovir therapy positively influences PHN (Wood et al., 1996; McKendrick et al., 1989; Crooks et al., 1991; Jackson et al., 1997), the fact that the incidence of PHN was approximately 25% lower under brivudin than under acyclovir clearly indicates that brivudin treatment during acute herpes zoster favourably affects the outcome of PHN. As with all surveys of this nature, it carried certain disadvantages: patients were asked for PHN assessment at different points in time, i.e. between 8 and 17 months after the start of treatment for acute herpes zoster. Accordingly, the capacity

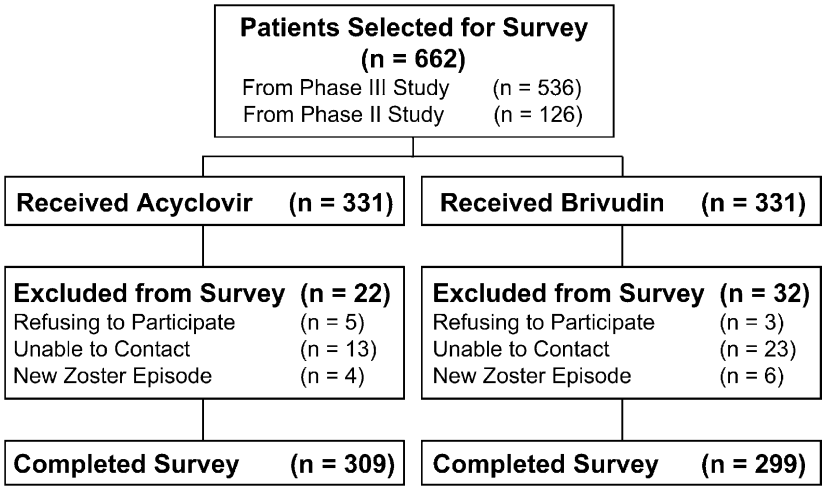


Fig. 1. Study participants' flow. Only patients aged 50 years or older ($n = 662$) were followed up for the occurrence of PHN in the survey study.

Table 1
Poststudy survey on postherpetic neuralgia (PHN) demographic data and results from logistic regression[a]

| | Survey patients | | Analysis patients | |
|---|---|---|---|---|
| | Brivudin ($n = 309$) | Acyclovir ($n = 299$) | Brivudin ($n = 283$) | Acyclovir ($n = 262$) |
| Demographics | | | | |
| Female:male (%) | 63.8:36.2 | 57.5:42.5 | 64.3:35.7 | 57.6:42.4 |
| Mean age ± S.D. (years) | 64.6 ± 9.4 | 64.4 ± 9.3 | 64.5 ± 9.5 | 64.3 ± 9.3 |
| Incidence of PHN | | | | |
| Patients with PHN (%) | 101 (32.7%) | 130 (43.5%) | 93 (32.9%) | 112 (42.7%) |
| Odds ratio ($CI_{95\%}$) | 1.61 (1.15–2.25) | | 1.54 (1.08–2.20) | |
| $P$ value$_{(1)}$ | 0.006 | | 0.018 | |

$P$ value$_{(1)}$: test for difference.
[a] Covariates are age (log), pain at baseline, gender, study.

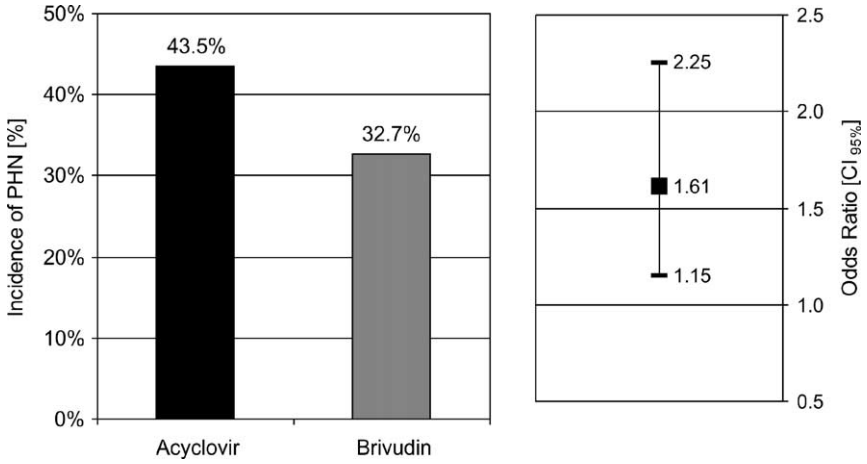


Fig. 2. Left panel: comparison of the overall incidence of PHN after zoster treatment with brivudin 125 mg once daily or acyclovir 800 mg five times daily, both for 7 days (survey population, $n = 608$). Right panel: graphical display of the 95% confidence interval with lower and upper limit (▬) and the point estimate (■).

to recall the exact course of pain may have differed among the patients. However, this should merely have influenced the assessment of the duration, but not that of the incidence of PHN. On the other hand, the survey had the advantage of being conducted in a double-blind manner as neither the patients nor the investigators were informed about the former treatment, and it was conducted in a large study population. Moreover, the investigator had to review and verify patients' reports on pain during a patient visit to the study centre.

Since PHN is the most troublesome complication of herpes zoster in the immunocompetent elderly patient and, once established, is often extremely difficult to treat and has a major impact on the quality of life, the data presented here are of particular clinical relevance and provide valuable new information on antiviral treatment of herpes zoster.

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