Famciclovir in Treatment of Acute Herpes Zoster: Results of Two Post-marketing Surveillance Studies in Germany

Sir,

Post-marketing surveillance (PMS) supplies important information on the profit–risk evaluation of a drug after its approval. Its importance derives from the fact that it is carried out in routine clinical everyday life and without the patient and investigator selection biases that result from controlled clinical studies. Herpes zoster is a common disease that affects up to 20% of the population (1). Most patients suffer from cutaneous lesions and acute-phase pain. In immunocompetent patients symptoms are usually self-limiting, resolving within 4 weeks after the onset of rash (2). However, up to 70% of herpes zoster patients develop post-herpetic neuralgia (PHN) (3), a debilitating pain that persists for a long time after the initial infection. Most notably up to 70% of elderly patients develop this complication, which is more severe and lasts considerably longer than in younger patients. Antiviral therapy, anti-inflammatory steroids, blockers of the sympathetic nerve system and analgesics are the main measures for prevention and treatment of PHN. In addition, tricyclic antidepressants are also used. However, the therapy of choice is antiviral agents applied early in the acute phase of zoster (4). An antiherpes agent which effectively reduces zoster-associated pain is famciclovir, the well-absorbed oral prodrug form (bioavailability 77%) of penciclovir (5), with activity against varicella-zoster virus, herpes simplex virus types 1 and 2, Epstein–Barr virus and hepatitis B virus. Clinical trials have shown that famciclovir alleviates the symptoms of acute and chronic herpes zoster and reduces time to resolution of shingles-associated pain (6–9).

A prospective observational cohort study, including 5,949 evaluable patients, was conducted to assess famciclovir therapy in routine use in patients with acute herpes zoster. Further objectives were to collect epidemiological data and to reveal pre-therapy risk factors influencing the clinical outcome in famciclovir-treated patients, especially in terms of persisting pain.

MATERIAL AND METHODS

The two PMS studies were carried out between January 1995 and June 1995 (1995 PMS) and between September 1995 and September 1996 (1996 PMS) in German medical practices. Physicians completed a 4-page questionnaire for each patient. The aim of the 1995 PMS was to examine the efficacy and safety of famciclovir and to provide characteristics of herpes zoster patients. The emphasis of the 1996 PMS was to obtain more information on persisting zoster-associated pain. All patients were assessed before and after treatment for clinical symptoms of herpes zoster. Patients in the 1996 PMS were also followed up for persisting pain, defined as any pain $\geq$4 weeks after start of therapy. Patients were included and excluded according to the German physician circular, i.e. immunocompromised patients and patients $<$18 years old were excluded. The recommended dosage of famciclovir was 250 mg t.i.d. for 7 days. Adverse events were documented separately. The data were analysed using descriptive statistical methods.

RESULTS

In 1995 and 1996 a total of 6,126 patients were observed (3,917 in 1995 and 2,209 in 1996), 5,949 (97.1%) of whom were evaluable. For the safety analysis all documented patients were included. Of the 5,949 patients evaluated, 2,645 patients (45%) were male and 3,291 (55%) female (13 patients not specified). The mean age of patients was 57 years (range: 18–101). No relevant differences in terms of demographic and clinical parameters were observed when comparing the populations of the two PMS studies.

Almost all patients (99.6%) received the recommended dosage of famciclovir 250 mg t.i.d. for the recommended duration of 7–8 days (80.6%). Only 246 patients (4.1%) were treated for $>$12 days. Ninety-four patients (1.6%) discontinued the therapy, the most frequent reasons for discontinuation being "recovery" (n= 35) and "adverse events" (n= 37).

The location of the afflicted dermatomes were thoracic in 3,208 patients (53.9%), lumbar in 962 patients (16.2%), cranial in 776 patients (13.0%), cervical in 475 patients (8.0%) and sacral in 224 patients (3.8%). In 302 patients (5.1%) $>$one area was affected. For 20 patients (0.3%) a dissemination was reported.

Before the start of therapy 264 patients (4.4%) had no zoster-associated pain, 2,219 patients (37.3%) had pain tolerable without analgesics, 3,077 (51.7%) had pain tolerable with analgesics and 386 (6.5%) suffered from intolerable pain that was not ameliorated by analgesics. Occurrence of severe zoster pain (both tolerable and intolerable with analgesics) was markedly reduced from 58.2% before therapy to 15.8% after therapy.

Table I. *Combined key data of PMS 1995 and PMS 1996*

Patients	
Documented	6,126
Evaluable (%)	5,949 (97.1)
Mean age (y) (range)	57 (18–101)
Underlying disease reported (%)	1,912 (32)
Zoster-associated pain (% pre-/post-therapy)	
No pain	4/41
Pain tolerable without analgesics	37/43
Pain tolerable with analgesics	52/15
Intolerable pain	7/1
Persisting pain (PMS 1996 only)	
Any pain $>$4 weeks (%)	201 (10.4)
Adverse events, n (% of all patients)	
Nausea	37 (0.60)
Headache	29 (0.47)
Abdominal complaints	16 (0.26)
Dizziness	16 (0.26)
Vomiting	6 (0.10)
Diarrhea	5 (0.08)
Others	43 (0.70)

In the 1996 PMS only 201 of 1,934 evaluable patients (10.4%) reported persisting pain after >4 weeks. The logistic regression method identified the following statistically significant parameters that increased the probability of persisting pain: elevated age; female gender; severity of zoster-associated pain before therapy; large number of afflicted dermatomes; and long period between onset of lesions and start of therapy.

Of 6,126 documented patients 259 (4.2%) reported a total of 403 adverse events. Only 151 adverse events were assessed as possibly, probably or definitely related to famciclovir treatment. The most frequently reported adverse events were nausea, headache, abdominal complaints, dizziness, vomiting and diarrhea. Nine (2.2%) of the adverse events were serious. Six were unrelated to the famciclovir therapy, 2 were probably related (“abdominal disorder” and “abdominal cramps”) and 1 was not specified.

DISCUSSION

The results of these two PMS studies demonstrate that famciclovir therapy is safe and efficient for the treatment of herpes zoster. The second observational study (PMS 1996) supports the findings of previously published placebo-controlled studies showing that famciclovir facilitates the resolution of pain (6–9). Furthermore, in the PMS 1996 study only 10.4% of patients developed persisting pain after >4 weeks. This indicates that the incidence of zoster-associated pain still persisting after 4 weeks in famciclovir-treated patients is low compared to that reported in previous studies (8,10), with special regard to investigations in patients not treated with antivirals, which revealed a PHN rate of >20% (10). However, PHN rates reported in previously published studies, and especially data from aciclovir-treated patients, cannot be compared with our results as patients with pain before therapy are used as a baseline in some studies (11,12) or else definitions of PHN are different (13).

In this PMS study, risk factors for developing PHN revealed in famciclovir-treated patients were similar to those for patients not treated with famciclovir (10,14), i.e. the benefit of famciclovir is independent of the patient’s individual risk profile.

Therapy with famciclovir for herpes zoster was well tolerated. The safety profile of famciclovir in these observational studies was similar to those found in controlled clinical studies with respect to the most commonly reported adverse events, although the frequency of adverse events reported here was lower than that in controlled clinical trials (15).

In summary, these observational data obtained under field conditions support the recommendation to treat patients with zoster with famciclovir, thereby reducing the risk of persisting pain.

REFERENCES

1. Ragozzino MW, Melton KJ, Kurland LT, Chu CP, Perry NO. Population-based study of herpes zoster and its sequelae. Medicine 1982; 61: 310–316.
2. Whitley RJ. Varicella-zoster virus infections. In: Galasso GJ, Whitley RJ, Merigan TC, eds. Antiviral agents and virus diseases of man, 3rd edn. 1990: 235–263.
3. Kost RG, Straus SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention [review]. N Engl J Med 1994; 335: 33–42.
4. Johnson RW. Herpes zoster and postherpetic neuralgia. Optimal treatment. Drugs & Aging 1997; 10: 80–94.
5. Pue M, Benet LZ. Pharmacokinetics of famciclovir in man. Antiviral Chem Chemother 1993; 4: 47–55.
6. Degreef H. 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. Int J Antimicrob Agents 1994; 4: 241–246.
7. Tyring S, Barbarash RA, Nahlik JE, the Collaborative Famciclovir Herpes Zoster Study Group. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and postherpetic neuralgia: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995; 123: 89–96.
8. McKendrick M, Wood M, Degreef H, Delescluse J, Decroix J, De Maubeuge JR. Eduction of zoster-associated pain (ZAP) by famciclovir. 6th International Congress for Infectious Diseases, Prague, Czech Republic, 1994: Abstract 588.
9. Carrington D. Reducing the duration of zoster-associated pain with famciclovir. 1st European Congress of Chemotherapy, Glasgow, UK, 1996: Abstract W 114.
10. Meister W, Neiß A, Gross G, Doerr HW, Höbel W, Malin J-P, et al. Prognostic score for postherpetic neuralgia in ambulatory patients. Infection 2000; 26: 359–363.
11. Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother 1995; 39: 1546–1553.
12. Wood MJ, Shuka S, Fiddian AP. Effect of early versus late therapy of acute herpes zoster on prolonged pain. 8th European Congress of Clinical Microbiology and Infectious Diseases Conference, Lausanne, Switzerland, 1997: 1433.
13. Wood MJ, Ogan PH, McKendrick MW, Core CD, McGill JL, Webb EM. Efficacy of oral acyclovir in acute treatment of herpes zoster. Am J Med 1988; 85: 79–83.
14. Wutzler P, Doerr HW, von Essen J, Gross G, Höbel W, Malin J-P, et al. Epidemiology of herpes zoster. Biotest Bull 1997; 5: 301–306.
15. Saltzmann R, Jurewicz R, Boon R. Safety of famciclovir in patients with herpes zoster and genital herpes. Antimicrob Agents Chemother 1994; 38: 2454–2457.

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