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Mini review

Famciclovir: review of clinical efficacy and safety

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Abstract

Famciclovir is the well-absorbed oral form of penciclovir, an antiviral agent with potent activity against varicella-zoster virus (VZV) and herpes simplex virus types 1 (HSV-1) and 2 (HSV-2). After oral administration, famciclovir is rapidly converted to penciclovir with a bioavailability of 77%. Penciclovir is efficiently phosphorylated to the active metabolite, penciclovir-triphosphate, and has a prolonged intracellular half-life of approximately 9–10 h in VZV-infected cells, and 10 and 20 h in cells infected with HSV-1 and HSV-2, respectively. Two multicenter clinical trials have shown that famciclovir given during the acute zoster phase accelerated healing of cutaneous lesions. More importantly, in a placebo-controlled study, famciclovir reduced the duration of postherpetic neuralgia (PHN), particularly in elderly patients. Famciclovir has also been proven effective in treating recurrent genital herpes, as demonstrated by a reduction in times to cessation of viral shedding, complete healing, and loss of all symptoms. One study showed that suppressive therapy with famciclovir was effective in reducing genital herpes episodes in patients with frequent recurrences. A promising new area of investigation for famciclovir is controlling virus replication in patients with chronic hepatitis B virus (HBV) or HBV reinfections after liver transplant. Results from a double-blind, placebo-controlled, pilot study and several case reports have shown that famciclovir, alone or in combination with other agents, decreased HBV-DNA levels and was well tolerated with long-term treatment. Available clinical data indicate that famciclovir is an effective agent for treating herpes zoster and genital herpes and holds significant promise for the treatment of chronic HBV infection and HBV reinfection after liver transplantation.

Keywords: Famciclovir; Clinical effiacy, famciclovir; Safety testing, famciclovir; Herpes simplex, clinical studies; Varicella-zoster, clinical studies

1. Introduction

Famciclovir is the oral prodrug of penciclovir, an antiviral agent with activity against varicella-

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Abbreviations: VZV varicella-zoster virus; HSV herpes simplex virus; HBV hepatitis B virus; PHN postherpetic neuralgia.

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zoster virus (VZV), and herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) (Boyd et al., 1987, 1988, 1993; Bacon and Schinazi, 1993). Famciclovir is rapidly and extensively absorbed following oral administration. Famciclovir is effectively metabolized, in the intestinal wall and liver, by removal of the two acetyl groups to give 6-deoxy-penciclovir, which is then oxidized at the 6-position of the purine ring to form penciclovir (Vere Hodge et al., 1989; Vere Hodge, 1993; Vere Hodge et al., 1993a,b). Within herpesvirus-infected cells, the viral enzyme thymidine kinase efficiently converts penciclovir to penciclovir monophosphate, which is converted by other cellular enzymes to the active metabolite, penciclovir triphosphate (Vere Hodge and Perkins, 1989; Vere Hodge and Cheng, 1993). Penciclovir triphosphate inhibits viral replication through competitive inhibition of viral DNA polymerase (Earnshaw et al., 1992; Vere Hodge and Cheng, 1993).

Until the introduction of famciclovir for the treatment of uncomplicated herpes zoster, acyclovir was the only available antiviral agent for the treatment of this infection. The mechanism of action of acyclovir, which is an acyclic guanosine analog like famciclovir, is also through phosphorylation of the monophosphate catalyzed by viral thymidine kinase. Phosphorylation to the triphosphate ester is completed by other cellular enzymes and results in subsequent inhibition of viral replication. However, famciclovir shows a much improved pharmacokinetic and bioavailabilty profile when compared with acyclovir (Pue et al., 1994). Unlike acyclovir, which is poorly absorbed after oral administration and has a 10–20% bioavailability (Weller et al., 1993), famciclovir is rapidly and extensively absorbed following oral administration as shown in a study of twelve healthy male volunteers, where the absolute bioavailability of famciclovir was 77% (Pue et al., 1994). The pharmacokinetic profile of penciclovir is linear over the therapeutic dose range of famciclovir (125–750 mg), which is in contrast to a decrease in the systemic availability of acyclovir as the dose is increased (Pue et al., 1994; de Miranda and Good, 1992). Penciclovir triphosphate has a prolonged intracellular half-life in VZV-infected cells (9–14 h) and in cells infected with HSV-1 (10 h) and HSV-2 (20 h) (Earnshaw et al., 1992; Standring-Cox et al., 1994; Vere Hodge and Perkins, 1989; Bebault et al., 1995), which may contribute to the persistent antiviral effect seen in vivo.

This review will examine recent clinical efficacy and safety data for famciclovir in the treatment of herpes zoster and genital herpes. Early reports on the successful use of famciclovir in treating patients with chronic hepatitis B virus (HBV) infections will also be discussed, since there is currently no satisfactory treatment for chronic HBV infections (Mutchnick et al., 1994).

2. Efficacy against herpes zoster

The onset of herpes zoster is characterized by a vesicular rash and moderate to severe pain, with pain often preceding the rash (Whitley, 1994; Straus, 1993). The incidence of herpes zoster increases with age and was reported to be more than 40% in patients aged 50–70 years old (Hope-Simpson, 1965). The skin infection usually resolves within 4–6 weeks, but a percentage of patients continue to suffer pain after the rash has healed (Whitley, 1994; Loeser, 1986). Persistent pain after healing of all zoster lesions is termed postherpetic neuralgia (PHN) (Portenoy et al., 1986; Watson and Evans, 1986). The etiology of PHN is not known, but there is general agreement that it results from virus-induced damage to nerve tissue. It is the most common complication of herpes zoster, is associated with significant morbidity, and is generally refractory to many forms of treatment. As with acute herpes zoster, the risk of PHN increases with advancing age. The incidence of PHN was reported to be 40% in patients 50 years old with an increase in incidence to 70% in patients 70 years of age or older (de de Moragas and Kierland, 1957).

Although acyclovir therapy has proven effective in decreasing the symptoms of acute zoster infection, acyclovir has not shown a consistent benefit in managing PHN (Wood et al., 1987, 1988, 1994; Huff et al., 1988; McKendrick et al., 1986; Sasadeusz and Sacks, 1993). Famciclovir has been studied in two large clinical trials where its effects

Table 1
Time to loss of postherpetic neuralgia [a]

	Overall patients			Patients ⩾50 years old		
	Famciclovir (500 mg)	Famciclovir (750 mg)	Placebo	Famciclovir (500 mg)	Famciclovir (750 mg)	Placebo
n	61	68	56	41	47	31
Median (days)	63	61	119	63	63	163
Hazard ratio	1.7	1.9	–	2.6	2.6	–
P-value	0.02	0.005	–	0.004	0.003	–

[a] Reproduced with permission from Tyring et al. (1995)

on both rash healing of acute herpes zoster and control of acute pain were evaluated. In addition, the effects of famciclovir on the duration of PHN, which was prospectively defined, was analyzed in the placebo-controlled trial. In both trials, time-to-event data were analyzed using the Cox proportional hazard regression model, with hazard ratios greater than 1 indicating that the event occurred sooner for the famciclovir groups than for the acyclovir or placebo groups.

The placebo-controlled study was a prospective, randomized, double-blind trial in which famciclovir was evaluated in 419 intent-to-treat immunocompetent adult patients who presented within 72 h of the appearance of the herpes zoster rash (Tyring et al., 1995). Patients received either 500 mg or 750 mg of famciclovir or placebo three times daily for 7 days. The mean patient age was 50 years and about half of the patients were women. Over half of the patients had > 50 lesions at the start of treatment, and most had moderate or severe zoster pain.

Accelerated healing of skin lesions, as demonstrated by reduced times to full crusting and loss of vesicles, ulcers and crusts, was noted in patients treated with famciclovir compared with those who received placebo. The median duration of viral shedding was reduced from 2 days in the placebo group to 1 day in famciclovir-treated patients. The reduction in the duration of viral shedding was statistically significant for famciclovir versus placebo ($P = 0.0005$). Median times to loss of acute pain were 20, 21 and 22 days for the famciclovir 500 mg, 750 mg and placebo groups, respectively, with hazard ratios of 1.2 and 1.1 for the 500-mg and 750-mg groups, respectively. Although there was no significant difference in the hazard ratios for acute pain for patients overall, the 500-mg famciclovir recipients with severe rash (> 50 lesions) at enrollment lost pain approximately two times faster compared with those on placebo ($P = 0.003$).

Patients were assessed for PHN every month for 5 months following healing, where PHN was prospectively defined as the pain persisting after the herpes zoster lesions had healed. Of the 419 patients, 185 (44%) developed PHN. The duration of PHN was significantly reduced ($P = 0.02$; $P = 0.005$, respectively) in patients treated with 500 mg and 750 mg of famciclovir compared with those who received placebo. Patients receiving either dose of famciclovir lost PHN two times faster than those receiving placebo, with a reduction in the median duration of PHN of approximately 2 months.

In the subgroup of patients who were $\geqslant 50$ years of age and most prone to develop PHN, the median time for resolution of PHN was 2.6 times faster in patients who received famciclovir than in those who received placebo (hazard ratio = 2.6) (Table 1). The median number of days to loss of PHN in these older patients was reduced from 163 days in the placebo group to 63 days in both of the famciclovir groups ($P = 0.004$ and $P = 0.003$ for the 500-mg and 750-mg famciclovir groups, respectively). This represented a reduction in the median duration of PHN of more than 3 months (Fig. 1).

The second study was a double-blind, double-dummy, randomized study that compared the

efficacy and safety of famciclovir with acyclovir in 545 immunocompetent patients with acute herpes zoster (Degreef et al., 1994). Patients were treated with either famciclovir (250 mg, 500 mg, or 750 mg) three times a day or acyclovir (800 mg) five times a day for 7 days. As in the placebo-controlled study, treatment was started within 72 h of the onset of zoster rash. The patient population was similar to that of the placebo-controlled trial. All dose levels of famciclovir were equally effective as acyclovir for healing cutaneous lesions. Median times to full crusting, cessation of new lesion formation, loss of vesicles and loss of crusts were comparable in famciclovir- and acyclovir-treated groups. Median time to loss of acute pain was also similar for the famciclovir groups (21, 14 and 21 days for 250 mg, 500 mg and 750 mg, respectively) and the acyclovir group (21 days). Thus, this study showed that famciclovir, administered less often and at a lower dose, was comparable to acyclovir in the treatment of acute uncomplicated herpes zoster.

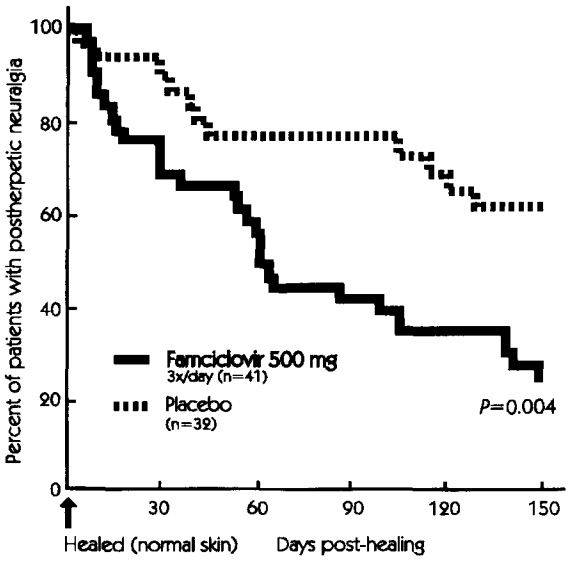

Fig. 1. Time to loss of postherpetic neuralgia in patients ⩾ 50 years old receiving 500 mg of famciclovir. Adapted with permission from Tyring et al. (1995)

3. Efficacy against genital herpes

Herpes simplex virus type I is commonly associated with oral-labial infections (cold sores) while HSV-2 is primarily associated with genital herpes infections. The incidence of genital herpes infection may range from 1% to 80% in the adult population depending on several factors including age, socioeconomic group, number of sexual partners, and sexual preference (Corey, 1994). Despite the increased public awareness of sexually-transmitted diseases, the incidence of genital HSV diseases continues to rise worldwide. In contrast to first episode genital herpes infections, which are characterized by systemic symptoms (fever, headache and malaise) and localized genital lesions, recurrent genital infections are generally limited to localized genital lesions.

Penciclovir has been shown to have antiviral activity against HSV-1 and HSV-2 in vitro and in vivo (Boyd et al., 1987; Bacon and Schinazi, 1993; Vere Hodge and Cheng, 1993; Field et al., 1995). In an in vivo murine immunosuppression model for HSV-1, famciclovir was effective in controlling infection and no recurrence of infectious virus was seen on cessation of therapy (Field et al., 1995). This was in contrast to the effect seen with valaciclovir, the oral prodrug of acyclovir, where recurrence of viral replication was seen in the animals 2 days after valaciclovir therapy was stopped. The clinical role of famciclovir in the treatment of recurrent genital herpes has been demonstrated in two clinical trials, and its potential role in the suppression of genital herpes has also been investigated.

Two double-blind, randomized, placebo-controlled, multicenter Canadian studies were conducted to evaluate the efficacy and safety of oral famciclovir in the treatment of recurrent genital herpes (Data on file, SmithKline Beecham[1]; Sacks et al., 1994a,b). Treatment was patient-initiated in one and clinic-initiated in the other. In both studies, patients received either 125 mg, 250 mg or 500 mg of famciclovir or placebo twice daily for 5 days, initiating therapy 6 h or less after prodrome

[1] Data on file: SmithKline Beecham Pharmaceuticals, Philadelphia, PA.

Table 2
Effects of famciclovir treatment [a] in patients with recurrent genital herpes

	Famciclovir(125 mg)		Famciclovir(250 mg)		Famciclovir(500 mg)		Placebo	
	PI	CI	PI	CI	PI	CI	PI	CI
Time to cessation of viral shedding								
n	59	58	58	61	66	47	63	63
Median (days)	1.6	1.5	1.5	1.7	1.3	1.4	3.3	3.4
Hazard ratio	2.6	3.3	3.3	3.3	4.2	3.6		
P-value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001		
Time to complete healing								
n	108	78	100	78	103	73	88	79
Median (days)	3.8	4.4	3.7	4.0	4.1	3.9	4.8	5.0
Hazard ratio	1.7	1.8	1.7	2.2	1.7	2.2		
P-value	0.0004	0.0009	0.0005	0.0001	0.0011	0.0001		

PI, Patient-initiated; CI, Clinic-initiated.
[a] Patients received famiciclovir or placebo twice daily for 5 days.
References: Sacks et al. (1994a,b). See also data on file, SmithKline Beecham Pharmaceuticals, Philadelphia, USA.

or lesion onset. Treatment was initiated in 467 (217 men; 250 women) patients in the patient-initiated study and 308 (162 men; 146 women) patients in the clinic-initiated study. Symptoms and lesions were assessed twice daily and lesions were swabbed for viral culture twice daily for the first 5 days and then daily until complete healing. In the patient-initiated study, pretreatment viral cultures were positive in 51%, 45%, 55% and 63% of famciclovir 125-mg-, 250-mg-, 500-mg- and placebo-treated patients, respectively. In the clinic-initiated study, pretreatment viral cultures were positive in 74%, 79%, 67% and 84% of the 125-mg, 250-mg, 500-mg famciclovir-treated and placebo-treated patients, respectively. In both studies, all famciclovir doses significantly reduced times to cessation of viral shedding and complete healing (Table 2). In addition, time to loss of all symptoms was significantly reduced for all treatment groups when compared with placebo for both studies ($P < 0.05$).

A multicenter, placebo-controlled trial was conducted to evaluate the efficacy of famciclovir in suppressing genital herpes recurrences in women with frequent episodes (≥ 6 per year) (Mertz et al., 1994). A total of 375 women received oral famciclovir, at doses of 125 mg and 250 mg administered once or twice daily, 500 mg once daily, or placebo for 4 months. The median time to the first clinical recurrence was 3.8 months in the famciclovir 125-mg once daily group and greater than 4 months in all the other famciclovir treatment groups. This was in contrast to a median time to first clinical recurrence of 2.7 months for the placebo group. The time to first clinical recurrence was significantly prolonged in patients who received famciclovir 125 mg twice daily ($P = 0.031$) or 250 mg twice daily ($P = 0.0001$). The results for time to first virologically-confirmed recurrence were similar to those noted for clinically confirmed recurrence, with statistical significance ($P < 0.05$) also achieved for the famciclovir 250-mg once daily group. Patients who were treated with famciclovir 250 mg twice daily had the most clinically significant prolongation in time to first recurrence. Oral famciclovir given twice daily for 4 months was well tolerated and appeared to effectively suppress recurrent genital herpes in this study population. The results from this trial highlight the potential future use of famciclovir for suppression of genital herpes.

4. Efficacy against hepatitis B

Hepatitis B virus (HBV) infection may be associated with a variety of liver diseases including acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. A proportion of patients who develop chronic liver disease as a result of HBV will eventually require a liver transplant due to severe disease progression. While the liver transplant can be lifesaving, endogenous reinfection with HBV is a frequent complication, causing significant morbidity and mortality. Currently, there is no satisfactory treatment for chronic HBV infections and therefore a need exists to identify more effective alternate forms of therapy, especially to treat immunocompromised patients who do not respond to interferon therapy (Mutchnick et al., 1994).

Penciclovir has been shown to inhibit viral replication in vitro in duck hepatocytes infected with duck HBV (Shaw et al., 1994). Famciclovir, the oral prodrug of penciclovir, has been shown to inhibit HBV replication in vivo in hepatic and nonhepatic tissues of ducklings that had been infected in ovo with duck HBV (Tsiquaye et al., 1994). Penciclovir has also exhibited potent inhibitory activity ($EC_{50} = 0.2\ \mu M$) against human HBV replication in the transfected human hepatoma cell line HepG 2.2.15 (Korba and Boyd, 1996).

Mok and coworkers have recently reported that similar levels of penciclovir-triphosphate were detected in both uninfected and HBV-transfected liver cells (Mok et al., 1995), suggesting that the inhibition of HBV by penciclovir involves a mechanism other than the selective phosphorylative process seen in inhibition of the herpesviruses. HBV replicates its DNA by a multi-step process. Genomic RNA in HBV infected cells is transcribed from viral DNA by host RNA polymerase. HBV DNA polymerase mediates both reverse transcription and DNA-directed viral DNA synthesis. Using an in vitro translation system, the duck HBV polymerase has been shown to act as a primer for DNA synthesis and exhibit reverse transcriptase activity (Zoulim and Seeger, 1994). These investigators have further shown that penciclovir inhibits priming of HBV reverse transcription by inhibiting the synthesis of the short DNA primer, suggesting that penciclovir may inhibit HBV by acting at the early stage of reverse transcription (Zoulim et al., 1995). Using viral polymerase in core particles from human HBV-transfected cells, penciclovir-triphosphate was shown to inhibit the viral polymerase at a low concentration ($K_i = 0.04\ \mu M$) (Mok et al., 1995). In comparison, much higher concentrations of penciclovir triphosphate are required to inhibit host DNA polymerase, the reported K_i values for DNA polymerase α being 175 μM (Earnshaw et al., 1992) and 200 μM (Ilsley et al., 1995). Therefore, the selective activity of famciclovir against HBV is due to its greater than 4000-fold higher affinity for the viral polymerase than the host polymerase.

The promising results from in vitro and animal studies have led to the use of famciclovir to suppress viral replication in patients with chronic HBV infections and HBV reinfections after liver transplants. The efficacy of famciclovir in the treatment of 17 patients with chronic HBV infection was evaluated in a double-blind, placebo-controlled, pilot study (Main et al., 1994). Twelve patients received either 250 mg or 500 mg three times daily and five patients received placebo for 10 days. Six of the eleven evaluable patients showed a 90% decrease in levels of HBV-DNA. This reduction in HBV-DNA levels was maintained in four patients (three of whom received 250 mg t.i.d.) throughout the 10-day treatment period. No reduction in HBV-DNA levels was noted in the evaluable placebo recipients. Famciclovir was well tolerated in all patients with no evidence of hepatotoxicity.

Famciclovir was successfully used to treat a patient who received a liver transplant for liver failure from chronic HBV infection (Angus et al., 1994). The patient subsequently developed recurrent hepatitis and showed high levels of HBV-DNA at 5 months after transplantation. Famciclovir was used as maintenance therapy following treatment with a combination of ganciclovir and foscarnet. After 2 months of maintenance treatment with famciclovir, levels of HBV-DNA and HBsAg had decreased thirty-fold and liver biochemistry was normal. At the time of

the report, the patient had been well for 32 months after transplantation.

More recently, the same group of investigators reported the results of treatment with famciclovir in 38 HBV-positive orthotopic liver transplant patients (Angus et al., 1995). The median time to occurrence of HBV reinfection was 6 months after transplantation. All 38 patients were positive for serum HBV-DNA prior to famciclovir treatment. The patients were treated with 500 mg of famciclovir three times a day (if renal function was poor, dose frequency was reduced) for up to 21 months (median: 6 months) in an open compassionate use protocol. Detailed HBV-DNA data that were available for 27 of these patients showed an 80% decrease in HBV-DNA levels in 15 of the 27 patients. HBV-DNA was undetectable in the serum of 9 of the 27 patients by conventional hybridization assay, and three of the nine patients were HBV negative as determined by polymerase chain reaction (PCR). The decrease in HBV-DNA levels was usually seen at 4 weeks and continued declining during treatment, and was usually associated with a concomitant decrease in transaminase levels. At the time of the report, seven of the patients had been successfully treated for more than 1 year and showed good tolerance of famciclovir over this period of time.

In another case report, Boker and coworkers reported use of famciclovir in combination with a short course of prostaglandin E in a patient who developed severe hepatitis B 6 months after liver transplantation (Boker et al., 1994). Intravenous prostaglandin E, to suppress liver inflammation, was given at 5 mg/kg/h for 17 days and oral famciclovir, at a dosage of 750 mg three times a day, was begun on day 14. The famciclovir dosage was reduced to 500 and 250 mg three times a day after 10 days and 20 weeks, respectively. Initial prostaglandin E therapy reduced the inflammatory activity as evidenced by the decrease in transaminase levels, but had no effect on HBV replication. Consecutive long-term treatment with famciclovir showed a profound decrease in HBV-DNA levels and a continued decrease in levels of transaminase. HBeAg and HBV-DNA, as detected by PCR, were negative after 28 weeks of famciclovir treatment, but HBsAg was still present after 31 weeks of treatment. Liver histology showed a marked reduction in cellular infiltration. The combination therapy of a short prostaglandin E course to reduce inflammation and famciclovir to suppress viral replication was successful and enabled the patient to return to work.

5. Safety of famciclovir

Results of an integrated safety analysis of 13 completed clinical studies showed that famciclovir is well tolerated by patients with either herpes zoster or genital herpes (Saltzman et al., 1994). The analysis included 1607 patients from 11 completed, randomized, double-blind clinical trials of famciclovir and two open studies. The famciclovir recipients in these studies included 816 patients with herpes zoster (4 trials), 409 patients with acute genital herpes (7 trials) and 382 patients from two genital herpes suppression studies. The mean duration of exposure to famciclovir was 28.8 days (range, 1–173 days); however, this included 32 patients who were treated for approximately 4 months in two genital herpes suppression studies. When patients from these two long-term studies were excluded, the mean duration of exposure to famciclovir was 5.8 days. Two-thirds of the patients (814 patients in the herpes zoster trials; 253 patients in the genital herpes trials) received 750 mg or more of famciclovir daily (dose range was from 125 mg to 2.25 g). Headache (9.3%), nausea (4.5%) and diarrhea (2.4%) were the most common adverse events reported as related (includes the categories of related, probably related, possibly related and causalities which were unassessible or not indicated) to famciclovir. The incidence and severity of these events were comparable to those occurring in the placebo groups (7.9%, 4.2%, and 2.3%, respectively). None of the reports of headache, nausea or diarrhea were serious and no serious adverse experience among famciclovir-treated patients was considered to be related or probably related to the medication.

No clinically significant differences between the famciclovir and placebo groups were observed

when laboratory parameters related to hematology, hepatic function, renal function, serum electrolytes, muscle and bone metabolism and glucose levels were measured. Administration of famciclovir also showed no clinically relevant changes in urinalysis parameters. Although 1.4% and 2.5% of famciclovir recipients showed increases in the levels of alanine transaminase and serum phosphatase, respectively, similar number of patients on placebo (1.2% and 1.5%) also showed respective increases in these two enzymes.

The effect of famciclovir on testicular function was studied in men with a history of recurrent genital herpes (Sacks, 1993). None of the 34 men who received 250 mg of famciclovir twice daily for 18 weeks showed any clinically adverse effect on the sperm parameters measured during the treatment period and 8 weeks posttreatment. Famciclovir was well tolerated by all the study participants.

Currently, over 300 patients with chronic HBV infection are enrolled in an ongoing multicenter, double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of famciclovir 125 mg, 250 mg and 500 mg three times daily, compared to placebo (see footnote 1). Patients have completed 4 months of treatment and an 8-month follow-up phase is ongoing. Safety evaluations consist of monitoring adverse events and laboratory tests, including liver function, lipase, amylase, and lactate. Reports of patients receiving famciclovir for more than a year as treatment for HBV infections post liver transplant, indicate that famciclovir is well tolerated (Angus et al., 1995). In addition a pharmacokinetic analysis, evaluating a single 500-mg dose of famciclovir administered to 14 patients with chronic hepatic disease showed that systemic availability is comparable between the hepatic patients and healthy subjects (Boike et al., 1994).

6. Resistance of VZV and HSV to famciclovir

Repeated or prolonged antiviral treatment of patients who experience recurrent infections with VZV or HSV may lead to drug resistance. The majority of acyclovir-resistant VZV and HSV strains are cross-resistant to penciclovir, but cross-resistance is not universal and there are documented acyclovir-resistant strains that are susceptible to penciclovir (Boyd et al., 1993). Acyclovir and penciclovir are both inactive against strains of viruses that lack thymidine kinase. However, some mutant strains, where the viral thymidine kinase has an altered ability to phosphorylate thymidine analogues, are resistant to acyclovir but susceptible to penciclovir (Boyd et al., 1993). A study of seven clinical isolates of acyclovir-resistant VZV strains with altered thymidine kinase phenotype identified one isolate that was susceptible to penciclovir (Tallerico et al., 1993). Safrin and Phan reported cross-resistance in 23 clinical isolates of HSV; however, foscarnet-resistant strains were susceptible to penciclovir (Safrin and Phan, 1993). Lack of total cross-resistance between acyclovir and penciclovir was also observed in five well-characterized HSV mutant strains where the DNA polymerase showed altered phenotype (Chiou et al., 1995). These HSV mutants varied in their susceptibilities to penciclovir: one exhibited 2-fold hypersensitivity, one showed marginal (1.3-fold) resistance, and three showed only 3-fold resistance; however, none of these strains were highly resistant to penciclovir. Although these findings of low-grade resistance to famciclovir suggest that cross-resistance may not be clinically relevant in famciclovir therapy, the effect of repeated and prolonged treatment on potential cross-resistance remains inconclusive.

7. Conclusion

Famciclovir is an effective and well-tolerated oral antiviral agent for the treatment of acute uncomplicated herpes zoster and recurrent genital herpes. Results of one clinical trial showed that famciclovir is as effective as acyclovir in accelerating the healing of acute zoster lesions and in relief of acute pain. In a placebo-controlled trial, famciclovir was superior to placebo in shortening the duration of viral shedding and accelerating lesion resolution. More importantly, famciclovir was proven effective in shortening the duration of

PHN, particularly among elderly patients who are at greatest risk of developing this common complication of herpes zoster. Other studies showed that famciclovir is proven effective in managing recurrent genital herpes either with patient-initiated or clinic-initiated treatment within 6 h of lesion onset and that it is effective in suppressing genital herpes recurrence in patients who experience frequent episodes. Lastly, the use of famciclovir to suppress viral replication in patients with chronic hepatitis B and in those experiencing HBV reinfection after liver transplantation is a promising area of clinical investigation in which there are currently very few options. Experience in over 1,600 herpes zoster and genital herpes patients treated in clinical trials has shown that famciclovir is well tolerated. Thus, available clinical data indicate that famciclovir is a proven effective agent in the treatment of herpes zoster and recurrent genital herpes, and holds significant promise in the treatment of chronic HBV and hepatitis B reinfection after liver transplantation.

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