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Famciclovir Therapy (Famvir[®]) for Herpes Simplex and Herpes Zoster Infections

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ABSTRACT

Genital herpes simplex and herpes zoster infections are common afflictions that are associated with significant morbidity and a decreased quality of life. Famciclovir (Famvir[®], Novartis) is an orally administered prodrug of the antiviral agent penciclovir. Its unique pharmacokinetic profile makes it an efficacious, convenient and well-tolerated alternative to the traditionally prescribed acyclovir. Famciclovir is used for the acute treatment and suppressive therapy of recurrent genital herpes as well as for herpes zoster and its debilitating comorbidities. Famciclovir allows patients to manage or prevent symptoms, thereby significantly improving their quality of life. Its favorable safety profile makes it a good treatment choice for the elderly as well as for immunocompromised patients, including those infected with HIV.

KEY WORDS: famciclovir, herpes simplex, herpes zoster

Genital herpes simplex virus infection is considered by global health organizations to be a rapidly growing epidemic¹, with an estimated 107 million people infected worldwide.² Herpes simplex virus 2 (HSV-2), the primary associated strain, affects as many as one in five people. Herpes simplex virus 1 (HSV-1) also causes genital herpes (GH), but at a lower prevalence.^{3,4} Of those afflicted with GH, more than 75% who have a first outbreak will experience at least one recurrence, with most suffering approximately four attacks per year.² In the US, HSV-2 appears to play a major role in the heterosexual spread of HIV, making people more susceptible to HIV infection and making HIV-infected individuals more infectious.⁵

Herpes zoster (HZ), a condition resulting from reactivation of a latent varicella zoster virus (VZV) infection, is almost equally common, affecting up to 20% of the population. Although HZ can affect patients of any age, it is more often seen in patients over the age of 50. In immunocompetent patients, HZ is typically self-limiting, usually resolving within 4 weeks of rash onset. However, the infection is associated with significant morbidity, and particularly severe pain during the acute phase of infection. Some patients, especially the elderly and immunocompromised, can develop postherpetic neuralgia (PHN), a sharp pain that is a result of injury to peripheral nerves. It can last for an indefinite duration after the zoster rash has healed.⁶

Oral famciclovir has potent antiviral activity against HSV-1, HSV-2 and VZV, and is the only antiviral proven to reduce the duration of PHN.^{7,8} It is prescribed for the treatment or suppression of GH in

more than 50 countries and for treatment of HZ in more than 70 countries. Its indications include acute treatment of GH infections and suppression of recurrent GH, use in immunocompromised patients with HZ or herpes simplex infections, and treatment of HZ.

Mechanism of Action

In addition to very high and consistent bioavailability (77%), the active metabolite of famciclovir demonstrates extended longevity, with an intracellular half-life of 10–20 hours for HSV-1 and -2, respectively, and up to 11 hours for herpes zoster.⁹ In many clinical situations, this greater bioavailability allows famciclovir to be utilized at lower doses and/or at reduced dose frequencies than those used for acyclovir.

Upon ingestion, famciclovir undergoes rapid biotransformation to the active antiviral compound penciclovir. Using viral and cellular kinases, infected cells phosphorylate penciclovir, which then blocks replication of viral DNA via competition with deoxyguanosine triphosphate for viral DNA polymerase. In penciclovir-treated uninfected cells, concentrations of penciclovir triphosphate are barely detectable, indicating that herpes viral DNA synthesis and replication are selectively inhibited and the probability of toxicity to host cells is low.⁹

Drug Interactions

Because neither famciclovir nor penciclovir is metabolized through the P₄₅₀ enzyme system, there are no clinically significant interactions with many commonly prescribed drugs (e.g., cimetidine, allupurinol, theophylline, digoxin), making it a good treatment choice for patients

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who are taking multiple medications.¹⁰ Use of famciclovir has proven safe and effective in immunocompromised patients, including those with HIV, and it is the only treatment for GH or HZ approved by the US FDA for use in immunocompromised HIV-positive patients.¹¹ In all indicated patient populations, famciclovir is well tolerated, with a safety profile comparable to placebo.

Summary of Clinical Efficacy Trials

A Phase III study of 692 patients with recurrent GH compared self-initiated famciclovir treatment with placebo. The trial found that famciclovir, 125 mg, bid for five days, significantly reduced symptoms including pain, burning, itching and tenderness. As well, viral shedding, reduced by almost 50% (Table 1) the amount of time that the virus was actively reproducing and able to spread to uninfected cells. Episodic treatment with famciclovir provided convenient and effective therapy, and reduced periods of infectivity for those patients with recurrent GH whose frequency rates do not require continuous antiviral suppression.¹²

A clinical trial involving 455 patients with frequently recurring GH determined that suppressive therapy with famciclovir, 250 mg, bid for up to 1 year, significantly reduced the recurrence of outbreaks. Patients on famciclovir therapy experienced 1/5 the number of recurrences compared to those on placebo, and an 80% reduction in outbreaks over a 1-year period (Table 2). The median time to first recurrence was extended by 9 months with famciclovir treatment, and almost one-third of famciclovir-treated patients were recurrence-free after one year (compared with only 6% of placebo-treated patients). Suppressive therapy with famciclovir proved beneficial for patients experiencing at least six outbreaks per year and effectively helped patients manage GH symptoms by reducing the number of outbreaks and increasing the length of time before the next outbreak.¹³

Research has also demonstrated the safety and efficacy of famciclovir

treatment for recurrent GH in HIV-infected patients. A comparison of famciclovir (500 mg, bid for 7 days) with acyclovir (400 mg, 5 times per day for 8 days) in HIV-infected patients with recurrent HSV infection demonstrated comparable efficacy between the two treatments. However, because it does not interact with zidovudine¹⁴ and is taken only twice a day, famciclovir appears to be the better choice.¹⁵

Famciclovir has also been shown to be an effective, well tolerated treatment for herpes zoster in immunocompetent^{7,8,16-18} as well as immunocompromised¹⁹ patients, and is the only antiviral to reduce duration of PHN, the disease's most frequent debilitating complication. A trial involving 419 immunocompetent adults with uncomplicated HZ demonstrated that famciclovir, 500 mg, tid for 7 days, shortened the duration of PHN by 100 days in patients over the age of 50, and healed lesions 30% faster compared with placebo. Among the 44% of patients who developed PHN, the median duration was shorter in famciclovir-treated patients (63 days) when compared with placebo-treated patients (119 days).⁷

Side effects

The frequency, nature and severity of adverse events did not differ significantly from those experienced with placebo. The most commonly reported adverse events were headache, nausea and diarrhea.

Conclusion

Famciclovir is a safe, convenient treatment alternative for GH and HZ. It helps to alleviate symptoms of both afflictions, to ease the pain and burning of GH and shorten the duration of PHN. Episodic and suppressive treatment of recurrent GH with famciclovir reduces genital herpes infectivity within and among individuals, reducing the number of outbreaks and delivering more days free from active disease. Lack of significant clinical interactions with commonly prescribed medications makes famciclovir an excellent treatment

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Median time to event (d)	Famciclovir 125 mg, bid for 5 days	Placebo	P value
Complete healing	3.8	4.8	<.001
Loss of vesicles	1.8	2.9	<.02
Loss of ulcers	2.9	4.0	<.01
Loss of crusts	4.0	4.9	<.001
Loss of edema	1.9	2.6	<.01
Loss of all symptoms*	3.2	3.7	<.01

Table 1: Time-to-event analysis of treatment effects on recurrent GH symptoms and signs

*Loss of all symptoms, including tenderness, pain, itching, burning and tingling

Event	Famciclovir 250 mg, bid	Placebo	P value
Median time to first recurrence (d)	336	47	<.001
Median number of episodes, patient reported*	1.0	5.1	<.001
Median number of episodes, investigator reported**	0.0	4.4	<.001

Table 2: Treatment effects on time to first recurrence and lesional GH episodes per year

*Patient-reported lesional episode following self-assessment and not necessarily clinically confirmed by the investigator

**Lesional episode clinically confirmed lesional episode by investigator

Treatments for Chronic Palmoplantar Pustular Psoriasis

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ABSTRACT

Chronic palmoplantar pustular psoriasis (PPP) is a disabling condition characterized by recurrent crops of sterile pustules on a background of erythema, fissuring and scaling. Genetic and environmental factors have been implicated in its etiology. Topical treatments are frequently ineffective although corticosteroids under hydrocolloid occlusion have been demonstrated to be useful. There is evidence supporting the use of systemic retinoids, PUVA and a combination of both. Oral tetracycline antibiotics may be helpful, but rarely clear PPP. Cyclosporine has been shown to be of some benefit at low doses. The choice of systemic treatments for an individual patient is influenced as much by their potential side effects as by differences in efficacy.

Key Words: evidence, palmoplantar pustular psoriasis, review, therapy

Chronic palmoplantar pustular psoriasis, or pustulosis palmaris et plantaris (PPP), is an idiopathic condition characterized by recurrent sterile pustules on the palms and soles on a background of erythema, scaling and fissuring. Once established, it may last for decades. Significant morbidity can impair dexterity or mobility, and cause pain, pruritus and embarrassment. PPP may affect people of all ages and either sex, although it is more commonly seen in middle-aged women. It may be associated with other forms of psoriasis, although it appears to be a distinct entity in terms of epidemiology and pathophysiology. The onset of PPP has been closely linked with cigarette smoking in a number of studies from different parts of the world. Another environmental factor proposed to be of etiological importance is recurrent streptococcal tonsillitis.¹

The choice of treatment is heavily influenced by its side effect profile. Treatments are often disappointing and may cause side effects. This article summarizes the existing treatments and evidence available to support their use. It should be noted that most trials have been conducted over short time periods for what is essentially a chronic, relapsing-remitting disease that frequently requires long-term therapy. Outcome measures in these trials are poorly defined and few studies report on patients' subjective views.

Topical Treatments

Emollient Creams and Ointments

Topical treatments alone tend to be ineffective for PPP, although some patients may benefit from using emollient creams or ointments, particularly when the disease is mild. These can safely be used as frequently as the patient wishes.

Topical Corticosteroid Preparations

Superpotent topical corticosteroids may be effective in reducing the severity of PPP in the short term, and hydrocolloid gel occlusion has been shown to increase the numbers of patients who respond even when only a moderately potent steroid is used.^{2,3} Reapplication of cream under gel occlusion is applied every third day for a maximum of four weeks. In order to maintain remission, some physicians prescribe a weaker topical steroid for daily use, but evidence supporting this intervention is lacking. The potential side effects of topical steroids are well known to dermatologists: in particular, the skin around the medial longitudinal arch may be prone to atrophy.

Tar and Anthralins

Some dermatologists advocate the use of tar and anthralin preparations for PPP. There are no published randomized controlled trials

(RCTs) that demonstrate their efficacy. In addition, treatment can be messy and irritating.

Topical Retinoids

Although systemic retinoid therapy is effective, there is no published evidence to support the use of topical retinoids for PPP. Tazarotene gel, which was recently introduced to treat mild to moderate plaque psoriasis, has not yet been formally evaluated in PPP.

Systemic Treatments

Systemic Retinoids

Oral etretinate, at a dose of 0.6mg/kg/day, produces objective improvement in about 2/3 of PPP patients^{4,5} and remission has been maintained in those who responded to initial treatment.⁶ There is evidence to show that acitretin, which has now superseded etretinate, is as effective in the treatment of PPP at the same dose.⁷

Retinoids are highly teratogenic, and female patients must be warned of the risks. Acitretin, the hydrolysis product of etretinate, was developed because of the initial belief that it was eliminated from the body much more rapidly. However, subsequent analysis has shown that it may, under certain circumstances, be esterified *in vivo* into etretinate. Since terminal elimination of etretinate from body fat stores is very slow, contraceptive measures must be taken during treatment and for at least two years after discontinuing acitretin.

Side effects of acitretin include xerosis, photosensitivity, epistaxis and (reversible) alopecia. Fasting lipid and liver function tests should be checked prior to commencing and at intervals during treatment. There is a small risk of hyperostosis and extrasosseous calcification in patients on long-term therapy.

Liarozole is a novel drug that inhibits breakdown of all-trans retinoic acid, causing elevation of all-trans retinoic acid levels in the skin and plasma. Its effects and side effects are similar to synthetic retinoids but it is not believed to have a prolonged action following withdrawal. A small pilot study suggests that it may be effective in the treatment of PPP and may be worthy of further investigation.⁸

PUVA

Oral psoralen followed by irradiation with ultraviolet A (PUVA) has been shown to effect remission in PPP.^{5,9} Disadvantages include the need for the patient to attend a dedicated unit on a regular basis, a small incidence of nausea, and the inconvenience of having to protect skin and eyes from sunlight on treatment days.

Treatments for Induction of Remission	Relative Efficacy*	Evidence Quality**
Topical		
• Corticosteroids under hydrocolloid occlusion	++	+
• Topical PUVA	+/-	++
• Grenz Rays	+/-	+
• Emollients	NA	NA
• Tar and anthralin	NA	NA
• Topical retinoids	NA	NA
Systemic		
• Systemic retinoids	++	++
• PUVA	++	++
• Re-PUVA	+++	++
• Low dose cyclosporine	+	++
• Tetracyclines	+/-	++
• Methotrexate	NA	NA

Table 1: Treatments for Chronic Palmoplantar Pustular Psoriasis: Induction of remission

*Relative Efficacy: NA Data not available; +/- poor; + moderate; ++ good; +++ excellent

**Evidence Quality: NA not available; + randomized controlled trial (RCT); ++ two or more RCTs

Treatments for Maintenance of Remission	Relative Efficacy*	Evidence Quality**
• Low dose cyclosporine	+/-	+
• Short term PUVA after remission	+/-	+
• Systemic retinoids	+	+

Table 2: Treatments for Chronic Palmoplantar Pustular Psoriasis: Maintenance of remission

*Relative Efficacy: NA Data not available; +/- poor; + moderate; ++ good; +++ excellent

**Evidence Quality: NA not available; + randomized controlled trial (RCT); ++ two or more RCTs

Topical psoralen paint or gel avoids the systemic side effects of oral psoralens. It may, however, be irritating and poorly tolerated. Unlike systemic PUVA, studies have failed to demonstrate the superiority of topical PUVA over placebo,^{10,11} although a study comparing topical with systemic PUVA found no significant difference between them.¹²

PUVA was reported in different trials to be either better⁵ or worse¹² than systemic retinoids at effecting remission. Short-term PUVA, as a maintenance measure following remission brought about by potent topical steroid under occlusion, was not effective in a randomized control trial (RCT), which compared it with no treatment.³ A combination of retinoid and PUVA (re-PUVA) was demonstrated to be superior to PUVA alone in clearing PPP.¹³

Tetracycline Antibiotics

Patients who were treated with tetracycline antibiotics including clomocycline 170mg, three times daily,¹⁴ and tetracycline 250mg, twice daily demonstrated objective improvement over placebo.¹⁵ Adverse effects include nausea, phototoxicity and hepatitis. Few patients achieved clearance.

Cyclosporine

Erkko and colleagues demonstrated that cyclosporine was effective in improving chronic PPP at a dose of 2.5mg/kg daily in 2/3 of patients.¹⁶ They found that doses as low as 1mg/kg/day may be effective but suggest increasing the dose stepwise up to 4mg/kg/day if a satisfactory response is not obtained within 1-2 months.¹⁷ Patients must be monitored for hypertension and renal dysfunction. Some patients experience side effects, including gastrointestinal symptoms, hypertrichosis and headaches.

Other Treatments

Colchicine has been advocated for chronic PPP¹⁸ but evidence from RCTs suggests that its value is limited.^{19,20} Grenz ray therapy was shown to give some limited improvement and, where it is available, it may be valuable as an adjunct to other therapies.²¹ There is limited evidence suggesting that hydroxyurea is ineffective.²² There are no RCTs to date that support the use of methotrexate, and an uncontrolled trial did not show evidence of benefit.²³ The absence of even anecdotal reports of the use of topical vitamin D analogues such as calcipotriol and tacalcitol for PPP suggests that these are likely to be of limited benefit, though they have not as yet been formally evaluated.

Conclusion

A systematic review of published evidence supports the use of treatments for PPP that are listed here. None can reliably induce remission, nor maintain it once it is achieved. When side effects or inconvenience of available treatments are set against the often incomplete therapeutic responses achieved, it is clear that no treatment is yet ideal.

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choice for patient populations on multiple medications, such as the elderly and those infected with HIV.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antipsoriatic Agent</i>	Etanercept <i>Enbrel</i> [®] Immunex/Wyeth-Ayerst Laboratories	The US FDA gave priority review status to this tumor-necrosis-factor inhibitor in October 2001, for the treatment of psoriatic arthritis. No other product indicated for the treatment of the signs and symptoms of psoriatic arthritis has ever been reviewed by the US FDA.
<i>Antibacterial Agent</i>	Clindamycin 1%, Benzoyl Peroxide 5% <i>BenzaClin</i> [™] Dermik Laboratories	The US FDA approved a labeling change in September 2001, for this combination acne treatment. This product can be stored at room temperature for up to two months after being dispensed by a pharmacy.
<i>Oral Contraceptive</i>	Ethinylestradiol & Norethindrone Acetate <i>Estrostep</i> Pfizer	The US FDA approved an additional indication for this oral contraceptive in July 2001, to treat moderate acne in women over 15 years of age.
<i>Antihistamine</i>	Desloratadine <i>Aerius</i> [™] & <i>Neoclaritin</i> [™] Schering-Plough	The European Commission of the European Union granted marketing authorization in August 2001, for these 5mg tablets to be given once daily as a non-sedating treatment for the symptoms of chronic idiopathic urticaria in adults and children 12 years of age and older.
<i>Enzyme Replacement Therapy</i>	Agalsidase Alfa <i>Replagal</i> [™] Transkaryotic Therapies (TKT)	The Norwegian Medicines Agency granted marketing authorization in August 2001, to this enzyme replacement therapy for long-term treatment in patients with Fabry Disease. In October 2001, New Zealand and Iceland also granted marketing approval. It has now been approved in 18 countries worldwide.
<i>Antibacterial Agent</i>	Ciprofloxacin Geneva Pharmaceuticals	The US FDA tentatively approved an ANDA in August 2001, for this generic form of Bayer's Cipro [®] . It is indicated for treating urinary tract, skin, and other infections.
<i>Antifungal Agent</i>	Butenafine HCl <i>Mentax</i> [®] Bertek Pharmaceuticals	The US FDA approved a new indication in August 2001, for this antifungal agent. It is now indicated for the treatment of tinea (pityriasis) versicolor caused by <i>Malassezia furfur</i> (formerly <i>Pityrosporum orbiculare</i>).
Drug News		
<i>Public Health Advisory</i>	The US FDA is approving new labeling for the use of several antibiotics to treat anthrax. The use of this and additional information concerning dosing regimens of doxycycline and other antibiotics will be provided. Doxycycline is approved for the treatment of cutaneous and inhalation anthrax after exposure.	
<i>Anti-acne Agent</i>	Pilot Therapeutics signed an agreement with Bristol-Myers Squibb (BMS) giving Pilot exclusive, worldwide license to develop and market a class of oral retinoids patented by BMS. Pilot will initially develop the drugs as a treatment for severe acne and may also develop them as a cancer treatment. It will pursue development up to Phase IIa trials and will seek a partner for late-stage development, FDA approval and marketing.	
<i>Corticosteroids</i>	Connetics Corporation announced in October 2001, that it has made available 50gm cans of its topical corticosteroid foams: Luxiq [®] 0.12% (betamethasone valerate) and Olux [®] 0.05% (clobetasol propionate). These foams deliver treatment to affected areas through a novel foam vehicle and are indicated for the topical treatment of inflammatory and pruritic manifestations of corticosteroid responsive scalp dermatoses.	

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