Antivirals, Herpes Simplex Virus (HSV)
Therapeutic Class Review (TCR)

October 26, 2018

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
acyclovir (Zovirax®)[1]	generic, Mylan	▪ Treatment of herpes zoster (shingles) ▪ Treatment of varicella (chickenpox) in patients > 2 years old ▪ Treatment of genital herpes simplex (initial and recurrent episodes)
buccal acyclovir (Sitavig®)[2]	Farmea	▪ Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults
famciclovir[3,4]	generic	▪ Treatment of herpes zoster (shingles) ▪ Treatment and suppression of recurrent genital herpes in immunocompetent adults ▪ Treatment of recurrent episodes of orolabial or genital herpes infections in HIV-infected patients ▪ Treatment of recurrent herpes simplex labialis (cold sores) in immunocompetent adults
valacyclovir (Valtrex®)[5]	generic, GlaxoSmithKline	▪ Treatment of herpes zoster (shingles) ▪ Treatment of genital herpes – Immunocompetent patients with initial or recurrent episode – Suppression in immunocompetent or HIV-infected patients – Reducing heterosexual transmission to susceptible partners ▪ Treatment of herpes labialis (cold sores) in patients ≥ 12 years old) ▪ Treatment of varicella (chickenpox) in immunocompetent patients 2 to 18 years old

Brand Famvir® (famciclovir) was discontinued as of January 31, 2017 for reasons unrelated to safety and efficacy; generics remain available.

OVERVIEW

The 2017 Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) surveillance estimated that there are 19 million new STD infections every year in the United States (US).[6] HSV is most often transmitted by people unaware they have infection and/or who are asymptomatic. HSV shedding can occur when the patient is asymptomatic. There are 2 types of herpes simplex virus, HSV-1 and HSV-2. HSV-1 usually establishes latency in the trigeminal ganglion lesions on the lower lip or face. HSV-2 resides in the sacral ganglion at the base of the spine and produces lesions and/or viral shedding in the genital area. However, it is possible to have either virus affecting either region, as well as other areas. Herpes simplex virus type-2 (HSV-2) infections are the most common cause of genital ulceration in the U.S. HSV-2 seroprevalence is more common in women and non-Hispanic African Americans. HSV-2, by causing genital ulcerations, has been found to increase the risk of acquiring human immunodeficiency virus (HIV).[7]

HSV infections are chronic, life-long infections. Management of genital herpes includes counseling and methods to reduce transmission, such as use of condoms, avoidance of sexual activity during infection recurrences, and suppressive antiviral therapy. Antivirals do not eradicate HSV.[8] They are used to treat and partially control the signs and symptoms of infection during initial and recurrent herpes episodes. These agents are also given as daily suppressive therapy to reduce the frequency of episodes.

The 2015 CDC STD recommendations for genital herpes do not indicate a preference for any of the 3 oral agents (acyclovir, famciclovir, valacyclovir) either for initial or recurrent episodes.[9] Chronic suppressive therapy for patients with frequent recurrences may include any 1 of the 3 oral agents

according to the CDC STD guidelines. Oral antiviral therapy is preferred over topical antiviral therapy. Topical treatment with antivirals offers minimal clinical benefit, and its use is discouraged.

Varicella-zoster virus (VZV) causes an acute, localized infection commonly known as chickenpox. After this acute infection, VZV lies dormant in the dorsal root ganglia for many years before potentially re-emerging to cause herpes zoster, commonly known as shingles.[10] Approximately 1 in 3 persons will develop herpes zoster during their lifetime, resulting in an estimated 1 million episodes in the US annually, with about half of all cases occurring in patients ≥ 60 years of age. About 10 to 13% of these patients will develop postherpetic neuralgia (PHN); likelihood of occurrence and its severity increases at ≥ 60 years.

Reactivation of VZV may be due to aging, stress, or immunosuppression.[11] The virus spreads along nerve tracts, causing pain or a burning sensation followed by a painful, blistering rash. The infection may spontaneously disappear after 2 to 4 weeks and rarely recurs. Relief of pain may be all that is required. In severe cases of shingles, nerve palsy, continued neuralgia, or blindness as a result of eye lesions caused by VZV, may persist after the acute infection disappears. The goal of treatment of herpes zoster is to reduce pain in immunocompetent patients and stop viral replication in immunocompromised patients and those with ophthalmic herpes zoster.[12] Antivirals reduce the duration of viral shedding and development of new lesions, and promote healing of the rash. The effect of antivirals on the development of postherpetic neuralgia are less clear; however, several meta-analyses and clinical trials have demonstrated that antivirals significantly reduce the duration or incidence of prolonged pain.[13,14,15,16] Risk factors for postherpetic neuralgia include older age, female gender, presence of prodromal symptoms, greater rash severity, and greater acute pain severity.[17] Guidelines for the management of herpes zoster support the use of any of the 3 agents for first line therapy.[18] Clinical guidance was released in 2018 by the CDC Advisory Committee on Immunization Practices (ACIP) regarding the use of shingles vaccines. The 2-dose recombinant zoster vaccine Shingrix, was listed as preferred over the live attenuated zoster vaccine (Zostavax®) and recommended in adults ≥ 50 years of age.[19] The new guidelines suggest that Zostavax use be limited to cases where an informed discussion has occurred between the patient and a healthcare provider when the patient has a personal preference for Zostavax, is allergic to Shingrix, or has a desire for an immediate vaccination when Shingrix is unavailable. Additionally, patients that have received Zostavax in the past are recommended to subsequently receive Shingrix after consideration is given to age of the patient and the amount of time that has elapsed since the Zostavax dose.

PHARMACOLOGY[20,21,22,23]

Drug	Mechanism of Action
acyclovir (Zovirax, Sitavig)	▪ Acyclovir is an acyclic analogue of the natural nucleoside, guanosine; it is activated via monophosphorylation by HSV-induced thymidine kinase; selective affinity results in the activation and concentration of acyclovir in virus-infected cells over normal cells; 2 additional phosphorylations result in acyclovir triphosphate, a substrate for and preferential inhibitor of viral, rather than cellular, DNA polymerase; it binds to HSV DNA polymerase, is incorporated into viral DNA, and thereby inhibits viral DNA replication ▪ Acyclovir has *in vitro* inhibitory activity against HSV-1, HSV-2, VZV, Epstein-Barr virus (EBV), and cytomegalovirus (CMV)
famciclovir	▪ Famciclovir is a pro-drug; it is the diacetyl 6-deoxy analog of the active antiviral compound, penciclovir; penciclovir is phosphorylated into a monophosphate form that is converted into penciclovir triphosphate; viral DNA synthesis and replication are inhibited by penciclovir ▪ Famciclovir has inhibitory activity against HSV-1, HSV-2, VZV, and EBV
valacyclovir (Valtrex)	▪ Valacyclovir is the L-valyl ester prodrug of acyclovir and is rapidly converted to acyclovir, which has affinity for the viral enzyme thymidine kinase encoded by HSV and VZV; therefore, valacyclovir has similar viral inhibitory activity as acyclovir

PHARMACOKINETICS[24,25,26]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion (%)
acyclovir (Zovirax)	10-20	2.5-3.3	At least 1 metabolite	Renal: 62-91 Fecal: minimal
famciclovir	77	2.3 for penciclovir	One active – penciclovir; 3 inactive	Renal: 73 Fecal: 27
valacyclovir (Valtrex)	55	2.5-3.3	Rapidly converted to acyclovir	Renal: 46 Fecal: 47

In pharmacokinetic studies, buccal acyclovir (Sitavig) was undetectable at 5 hours (had a delayed appearance) and did not reach concentration levels needed for systemic antiviral activity.[27]

CONTRAINDICATIONS/WARNINGS[28,29,30,31,32]

Acyclovir (Zovirax, Sitavig) and valacyclovir (Valtrex) are contraindicated in patients with hypersensitivity to acyclovir. Famciclovir is contraindicated in patients with known hypersensitivity to the product, its components, or penciclovir cream (Denavir®).

Renal failure, in some cases resulting in death, has been observed with acyclovir and valacyclovir therapy. Thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), which has resulted in death, has occurred in immunocompromised patients receiving acyclovir or valacyclovir, including patients with advanced HIV disease, patients having undergone allogenic bone marrow transplant, and renal transplant. Cases of acute renal failure have been reported in patients with underlying renal disease who have received inappropriately high doses of famciclovir for their level of renal function. Dosage reduction is recommended when administering famciclovir to patients with renal impairment.

Central nervous system (CNS) adverse effects, such as agitation, hallucinations, confusion, and encephalopathy, may occur in elderly patients (with or without reduced renal function) and in patients

with underlying renal disease who receive higher than recommended doses of valacyclovir for their level of renal function. Use with caution in elderly patients and reduce dosage in patients with renal impairment. Valacyclovir should be discontinued if CNS adverse effects occur.

CNS adverse effects, such as dizziness, confusion, and hallucinations, as well as thrombocytopenia, palpitations, and abnormal liver function tests, have been observed in post-marketing studies with famciclovir. Dermatological and tissue disorders such as urticaria, Stevens-Johnson syndrome, and angioedema were also associated with famciclovir usage in post-marketing analysis.

Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible CNS symptoms, such as those that have been reported in patients treated with intravenous acyclovir. Adequate hydration should be maintained.

DRUG INTERACTIONS[33,34,35,36]

Co-administration of probenecid with intravenous acyclovir (Zovirax) has been shown to increase the mean acyclovir half-life and the area under the concentration-time curve (AUC). Urinary excretion and renal clearance were correspondingly reduced. No drug interactions are expected with buccal acyclovir (Sitavig) due to its low dose and minimal systemic absorption.

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir, the active metabolite of famciclovir.

No clinically significant drug interactions have been observed with valacyclovir (Valtrex).

ADVERSE EFFECTS[37,38,39,40]

Drug	Headache	Nausea	Dizziness	Abdominal Pain	⇧ AST	Diarrhea
acyclovir (Zovirax) 400 mg twice daily n=586 continuous treatment (n=589 intermittent treatment of occurrences)	reported (2.2)	4.8 (2.4)	reported	nr	reported	2.4 (2.7)
buccal acyclovir (Sitavig) 50 mg buccal tablet given as a single dose	3 (3)	nr	1 (1)	nr	nr	nr
famciclovir 125 mg daily to 1 gm twice daily	13.5-22.7 (5.4-17.8)	2.5-12.5 (3.6-11.6)	nr	0-1.1 (1.2-3.4)	2.3 (1.2)	4.9-7.7 (1.2-4.8)
valacyclovir (Valtrex) 500 mg twice daily to 1 gm 3 times daily	11-38 (8-14)	4-15 (5-8)	2-4 (1-2)	3-11 (2-6)	1-4.1 (0-3)	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported. AST = aspartate aminotransferase

In clinical studies for the treatment of herpes labialis in adolescents with valacyclovir, the adverse effects most commonly reported were headache (17%) and nausea (8%). In pediatric patients (ages

one month to 12 years of age), adverse effects reported in pharmacokinetic and safety studies of valacyclovir included diarrhea (5%), pyrexia (4%), dehydration (2%), herpes simplex (2%), and rhinorrhea (2%). In clinical trials for buccal acyclovir (Sitavig), administration site irritation and pain were both reported in about 1% of the population.

SPECIAL POPULATIONS[41,42,43,44]

Pediatrics

Herpes Infections

Intravenous acyclovir (Zovirax) has been shown to be safe in pediatric patients, but safety and effectiveness of oral formulations of acyclovir in children < 2 years of age have not been established.[45] Safety and effectiveness of buccal acyclovir (Sitavig) have not been established in pediatric patients. The ability of pediatric patients to follow the application instructions has not been evaluated. Due to the potential for choking, use of buccal acyclovir in younger children is not recommended.

Safety and efficacy in children < 18 years of age have not been established for famciclovir.

Valacyclovir (Valtrex) is approved for the treatment of herpes labialis episodes in children 12 years of age and older.

Varicella Infections

Acyclovir is approved for treatment of varicella in children 2 years of age and older. The use of acyclovir for the treatment of varicella in children has decreased since the arrival of the varicella vaccine for the prevention of varicella infections in children.

Valacyclovir is approved for the treatment of chickenpox in children ages 2 to 18 years of age. Valacyclovir oral suspension (25 mg/mL or 50 mg/mL) can be prepared from the 500 mg caplets; acyclovir is available as an oral suspension.

Geriatric

Elderly patients are more likely to have reduced renal function and require dose reduction. Elderly patients are also more likely to have increased renal or CNS adverse events with valacyclovir and acyclovir. In clinical studies assessing the efficacy of famciclovir in treating herpes zoster, there were no differences in overall adverse effects between younger and older patients. Thus, there are no suggested dosage adjustments in geriatric patients treated with famciclovir. Yet, caution should be taken when administering all HSV agents to elderly patients due to decreased renal function associated with age.

Pregnancy

Acyclovir, famciclovir, and valacyclovir are Pregnancy Category B.

Prevention of neonatal exposure to herpes requires the avoidance of contracting genital HSV during the third trimester and avoidance of exposure of the infant to active herpetic lesions during delivery.[46] Safety data for agents in this category are not robust; the majority of data are with acyclovir.

HIV-positive Patients

Patients with HIV may have severe and prolonged episodes of HSV lesions.[47] In general, HSV shedding is more common in patients with HIV. The CDC recommends any 1 of the 3 agents for daily suppressive therapy in patients infected with HIV. Resistance of HSV to all of these drugs is higher in immunocompromised patients (6% to 7%) than in immunocompetent patients (< 0.5%).[48, 49, 50]

Renal Impairment

All systemic products in this category require dose and/or interval adjustments for renal impairment.

DOSAGES[51,52,53,54]

FDA-Approved Dosages

Drug/ Dosage Forms	Initial genital herpes	Recurrent genital herpes	Chronic suppressive genital herpes	Herpes zoster	Herpes labialis (cold sores)	Varicella
acyclovir (Zovirax) 200 mg capsule; 400 mg, 800 mg tablets; 200 mg/5 mL suspension;	200 mg 5 times per day for 10 days	200 mg 5 times per day for 5 days	400 mg twice daily for up to 12 months	800 mg 5 times per day for 7 to 10 days	--	**2 years and older:** Less than 40 kg: 20 mg/kg per dose orally 4 times daily for 5 days 40 kg and up: 800 mg 4 times a day for 5 days
acyclovir (Sitavig) 50 mg buccal tablet	--	--	--	--	50 mg buccal tablet applied to upper gum, and allowed to adhere and dissolve throughout day (within 1 hour of symptom onset and before the appearance of any signs of herpes labialis lesions)	--
famciclovir 125 mg, 250 mg, 500 mg tablets	--	1 gm twice daily for 1 day For HIV+ patients, 500 mg twice daily for 7 days for genital herpes	250 mg twice daily for up to 12 months	500 mg 3 times daily for 7 days	1,500 mg as a single dose For HIV+ patients, 500 mg twice daily for 7 days for orolabial herpes	--
valacyclovir (Valtrex) 500 mg, 1,000 mg tablets	1 gm twice daily for 10 days	500 mg twice daily for 3 days	500 mg to 1 gm daily For HIV+ patients, 500 mg twice daily For reduction of heterosexual transmission: 500 mg daily	1 gm 3 times daily for 7 days	**≥ 12 years:** 2 gm every 12 hours for 1 day	**Ages 2 to <18 years:** 20 mg/kg 3 times daily for 5 days; not to exceed 1 gm 3 times daily

2015 CDC Recommended Dosages for Genital HSV Infections[55]

Drug	Initial genital herpes	Recurrent genital herpes	Chronic suppressive genital herpes
acyclovir (Zovirax)	200 mg 5 times per day for 7 to 10 days OR 400 mg 3 times daily for 7 to 10 days	400 mg 3 times daily for 5 days OR 800 mg twice daily for 5 days OR 800 mg 3 times daily for 2 days	400 mg twice daily
		For HIV+ patients, 400 mg 3 times daily for 5 to 10 days	For HIV+ patients, 400 mg to 800 mg twice to 3 times daily
famciclovir	250 mg 3 times daily for 7 to 10 days	125 mg twice daily for 5 days OR 1 gm twice daily for 1 day OR 500 mg for 1 dose, then 250 mg twice daily for 2 days	250 mg twice daily
		For HIV+ patients, 500 mg twice daily for 5 to 10 days	For HIV+ patients, 500 mg twice daily
valacyclovir (Valtrex)	1 gm twice daily for 7 to 10 days	500 mg twice daily for 3 days OR 1 gm once daily for 5 days	500 mg* to 1 gm daily
		For HIV+ patients, 1 gm twice daily for 5 to 10 days	For HIV+ patients, 500 mg twice daily

* Valacyclovir 500 mg daily for suppressive therapy may be less effective than other regimens in patients with high frequency recurrences (>10 episodes per year).

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials performed in the United States comparing oral agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Herpes Zoster - Uncomplicated

acyclovir (Zovirax)

Acyclovir has been shown to be effective in the treatment of chickenpox in at least 2 double-blind placebo-controlled studies in normal children ages 2 to 16 years that were conducted in the early 1990s prior to the availability of the varicella vaccine for children.[56,57] Treatment in both studies began within 24 hours of rash onset and was given as acyclovir 20 mg/kg 4 times daily for 5 to 7 days. Children ages 12 to 16 years received 10 mg/kg 4 times daily orally for 5 to 7 days. Beneficial effects of acyclovir included earlier defervescence, fewer varicella lesions, and absence of new lesions after 3 days of acyclovir, and accelerated crusting and healed stages. No differences in disease complications were noted in either study. Acyclovir was well tolerated in the children with no serious adverse effects reported.

acyclovir (Zovirax) versus famciclovir

In a double-blind, parallel-group study, 55 immunocompetent adults with acute uncomplicated herpes zoster were randomized to treatment with famciclovir 250 mg 3 times daily or acyclovir 800 mg 5 times daily.[58] Treatment was initiated within 72 hours of onset of the zoster rash and was continued for 7 days. Famciclovir was as effective as acyclovir for healing the cutaneous lesion, as indicated by the time to full crusting (11 days with famciclovir, 10 days with acyclovir; p=0.761) and loss of acute phase pain (famciclovir 20 days, acyclovir 27 days; p=0.683). Both groups experienced loss of vesicles on day 6. Loss of ulcers occurred in 1 day in both groups. Loss of crusts were similar between the 2 groups (acyclovir 27 days; famciclovir 20 days; p=0.558). Famciclovir was well tolerated and had a more favorable adverse event profile compared to acyclovir. Constipation, hematuria, and glycosuria were the most commonly reported adverse events. The dose of famciclovir used in this study is 50% lower than the approved dosage for this indication.

Another double-blind study compared the clinical efficacy of acyclovir 800 mg 5 times daily and famciclovir 750 mg once daily, 500 mg twice daily, or 250 mg 3 times daily in the treatment of acute uncomplicated herpes zoster in immunocompetent adults.[59] Patients (n=559) presented within 72 hours after rash onset and were randomized to famciclovir 750 mg daily, 500 mg twice daily, or 250 mg 3 times daily or acyclovir 800 mg 5 times daily. All patients were given treatment for 7 days. Complete healing was assessed at 4 weeks or whenever completed healing occurred. Healing was defined as time to full crusting of lesions, loss of vesicles, cessation of new lesion formation, and a 50% reduction in affected skin. Healing and loss of acute pain were similar among the 4 groups. The development of postherpetic neuralgia was not assessed in this study. Headache was the most commonly reported adverse effect. Five discontinuations were reported with both famciclovir and acyclovir. The doses of famciclovir used in this study are one-third to one-half lower than the dose recommended for this indication.

acyclovir (Zovirax) versus valacyclovir (Valtrex)

A randomized, double-blind, multicenter trial evaluated the safety and efficacy of acyclovir and valacyclovir in the treatment of herpes zoster in 1,141 immunocompetent adults.[60] Patients presented within 72 hours of onset of rash. Patients were randomized to 1 of 3 groups: valacyclovir 1 gm 3 times daily for 7 or 14 days or acyclovir 800 mg 5 times daily for 7 days. The primary outcome parameters were the succession of pain, time to cessation of new lesion formation and/or increase in lesion area,

and time to greater than 50% crusting or healed rash. Valacyclovir treatment for 7 or 14 days significantly accelerated the resolution of pain (p=0.001 and p=0.03, respectively) compared with acyclovir treatment. Median cessation of pain was 38 and 44 days, respectively, with valacyclovir 7- or 14-day treatments compared to 51 days with acyclovir. No significant differences in time to cessation of new lesions and or increase in lesion area were reported among the groups: valacyclovir 7-day versus acyclovir (hazard ratio [HR], 1.03 [95% CI, 0.89 to 1.2]); valacyclovir 14-day versus acyclovir (HR, 0.99 [95% CI, 0.85 to 1.14]); valacyclovir 7- versus 14-day (HR, 1.05 [95% CI, 0.91 to 1.21]). No significant differences in the time to greater than 50% crusting or healing lesions were reported among the groups: valacyclovir 7-day versus acyclovir (HR, 1 [95% CI, 0.87 to 1.16]); valacyclovir 14-day versus acyclovir (HR, 1.02 [95% CI, 0.88 to 1.18]); valacyclovir 7- versus 14-day (HR, 0.98 [95% CI, 0.85 to 1.14]). Valacyclovir 14-day group had a shorter duration of abnormal sensations compared to acyclovir (HR, 1.27 [95% CI, 1.07 to 1.52]). All other groups were similar. No significant differences in pain intensity, quality of life, or unpleasantness were reported among the groups. Valacyclovir 7- and 14-day groups had a similar percentage of patients reporting pain after 6 months (19.9% and 18.6%, respectively) that was significantly lower than the percentage reporting the same in the acyclovir group (25.7%; valacyclovir versus acyclovir, p=0.02). No differences in adverse drug events were observed among the groups.

famciclovir versus valacyclovir (Valtrex)

A study compared the clinical efficacy of valacyclovir 1 gm 3 times per day to famciclovir 500 mg 3 times a day for 7 days in the treatment of acute uncomplicated herpes zoster. [61] A total of 597 outpatients, aged 50 years and older, who had herpes zoster were enrolled in a double-blind, randomized trial. The primary outcome was complete cessation of zoster-related pain. The occurrence of postherpetic neuralgia was also assessed. Secondary endpoints included time to cessation of zoster-associated abnormal sensations, pain intensity, rash healing, and lesion dissemination. No difference in resolution of zoster related pain were seen in this comparison of valacyclovir (42 days) and famciclovir (49 days; HR, 1.02 [95% CI, 0.84 to 1.23]). Postherpetic neuralgia was similar in both groups (HR, 1.01 [95% CI, 0.84 to 1.23]). No differences were reported with any of the secondary endpoints including time to cessation of zoster-associated abnormal sensations, pain intensity, rash healing (p=0.26), and lesion dissemination. Headache and nausea were the most common events reported for each agent.

Herpes zoster – Immunocompromised Patients

acyclovir (Zovirax) versus famciclovir

In a randomized, double-blind, multicenter study, 148 patients (ages 12 years and older) with clinical evidence of localized herpes zoster received either oral famciclovir 500 mg 3 times daily or acyclovir 800 mg 5 times daily for 10 days.[62] The efficacy and safety of famciclovir were evaluated for the treatment of herpes zoster in patients who were immunocompromised following bone marrow transplant (BMT) or solid organ transplantation or oncology treatment. An equivalent percentage of patients in the famciclovir and acyclovir groups, 77% and 73%, respectively, reported new lesion formation while on therapy. The median time to cessation of new lesions was 3 days with acyclovir and 4 days with famciclovir. The median time to full crusting was 8 days for famciclovir and 9 days for acyclovir (HR, 1.26 [95% CI, 0.88 to 1.82]). The median time to complete healing was 20 days with famciclovir and 21 days with acyclovir (HR, 0.98 [95% CI, 0.67 to 1.42]). The median time to loss of acute pain was 14 and 17 days for famciclovir and acyclovir, respectively (HR, 0.71 [95% CI, 0.71 to

1.75]). In summary, there were no significant differences between the groups in the median time to cessation of new lesion formation, full crusting, complete healing of lesions, or loss of acute phase pain. Treatment with famciclovir was well tolerated with a safety profile comparable to that of acyclovir.

Herpes Zoster - Ophthalmic

acyclovir (Zovirax) versus famciclovir

Famciclovir and acyclovir were compared in a randomized, double-blind trial with 454 patients with ophthalmic herpes zoster involving the trigeminal nerve.[63] Therapy was famciclovir 500 mg 3 times daily or acyclovir 800 mg 5 times daily for 7 days. Ocular manifestations of ophthalmic zoster were similar in the 2 groups (famciclovir, 58% versus acyclovir, 58.2%). There was no difference in visual acuity loss either. Both therapies were well tolerated.

acyclovir (Zovirax) versus valacyclovir (Valtrex)

A multicenter, double-blind study enrolled 110 immunocompetent patients with ophthalmic herpes zoster diagnosed within 72 hours of skin eruption.[64] Patients were randomized to treatment with valacyclovir 1 gm 3 times daily or acyclovir 800 mg 5 times daily, each with matching placebo control. Ocular complications of ophthalmic herpes zoster were similar in the valacyclovir and acyclovir treatment groups with the main complications being conjunctivitis (54% and 52%), superficial keratitis, stromal keratitis (both 13%), and uveitis (13% and 17%). Pain duration and severity and outcome of skin lesions were similar between groups. Pain was reported after 1 month in 25% of the valacyclovir group and 31% in the acyclovir group. Three percent of each group reported pain at week 24. Both valacyclovir and acyclovir produced similar outcome for skin lesions. Total healing (100%) was reported in 83% and 87% of the valacyclovir and acyclovir groups, respectively, at day 14. The most frequent adverse events were vomiting and edema of the eyelids or face, which occurred in 3% to 5% of patients.

Genital Herpes Simplex – Initial Episode

acyclovir (Zovirax) versus valacyclovir (Valtrex)

A multicenter, randomized, double-blind clinical trial compared 10-day regimens of valacyclovir 1 gm twice daily and acyclovir 200 mg 5 times daily in the treatment of 643 healthy adults with first-episode genital herpes.[65] Patients were enrolled if symptoms had presented in less than 72 hours prior to enrollment. Patients received the randomized therapy plus a matching placebo. Patients (n=24) who had antibodies to HSV-1 and HSV-2 were excluded from the analysis since this represented a recurrent infection. Time to healing of all lesions and the duration of viral shedding were the primary outcome parameters. Valacyclovir and acyclovir did not differ significantly in efficacy with respect to duration of viral shedding (three days in both groups), portion of patients forming new lesions, duration of pain, maximum number of lesions, and time to loss of all symptoms. Adverse experiences were generally infrequent and mild and were comparable in the two treatment groups.

Genital Herpes Simplex - Recurrent

acyclovir (Zovirax) versus famciclovir

Two hundred and four patients with recurrent genital herpes were randomized in a double-blind, double-placebo, parallel-design study to famciclovir 125 mg twice daily or acyclovir 200 mg 5 times daily.[66] The mean time to complete healing of lesions was 5.1 days for famciclovir and 5.4 days for acyclovir (p=not significant [NS]). There were no differences detected in the proportion of patients having complete healing at the different days of evaluation, as well as in the duration until the complete resolution of all the symptoms. The frequency, nature, and severity of adverse events did not differ between the two treatment groups.

acyclovir (Zovirax) versus valacyclovir (Valtrex)

In a double-blind study, 739 patients with a history of recurrent genital HSV infection were randomized to receive either oral valacyclovir 500 mg twice daily or acyclovir 200 mg 5 times daily for 5 days for treatment of their next recurrent episode.[67] Patients self-initiated therapy at the first signs and/or symptoms of the HSV recurrence, then were assessed in clinic on 5 occasions over 7 days, then twice weekly thereafter until lesions had healed. The time to healing of all lesions and the duration of all signs and symptoms were the primary endpoints. Duration of episode which was the time from treatment initiation to complete resolution of all signs and symptoms was similar between valacyclovir (4.7 days) and acyclovir (4.6 days [HR, 0.93; 95% CI, 0.79 to 1.08; p=0.34]). Lesion healing time was similar between valacyclovir (4.4 days) and acyclovir (4.5 days [HR, 0.96; 95% CI, 0.8 to 1.14]). Percentages of patients in whom all HSV cultures were negative were similar in the valacyclovir and acyclovir groups at 59% and 54%, respectively. There was no difference in the ability of each drug to prevent the development of vesicular/ulcerative lesions (HR, 1.08; 95% CI, 0.82 to 1.42). Duration and severity of pain were similar between the 2 groups (HR, 0.93; 95% CI, 0.78 to 1.06). The safety profiles of valacyclovir and acyclovir were comparable with adverse experiences being infrequent and generally mild. In patient-initiated therapy, acyclovir 200 mg 5 times daily and valacyclovir 500 mg twice daily provide similar time to healing all lesions and reduce the development of new lesions in recurrent genital HSV infections.

In a multicenter, double-blind study, 1,200 people with recurrent genital HSV infections were randomized to self-initiated oral therapy with valacyclovir 1 gm twice daily, acyclovir 200 mg 5 times daily, or placebo for 5 days.[68] The primary endpoints included the length of the episode and time to lesion healing. Secondary endpoints included duration and severity pain and discomfort, viral shedding, and proportion of aborted episodes. Valacyclovir (median duration until herpetic resolution 4.8 days; HR, 1.66 [95% CI, 1.33 to 2.01]) and acyclovir (4.8 days; HR, 1.71 [95% CI, 1.41 to 2.06]) significantly reduced the length of time of episode compared to placebo (5.9 days). Median healing times were significantly earlier with valacyclovir (4.8 days; HR, 1.88 [95% CI, 1.53 to 2.32]) and acyclovir (4.8 days; HR, 1.9 [95% CI, 1.55 to 2.34]) compared to placebo (6 days). Pain duration was shorter in both active treatment groups (both $p<0.05$), and viral shedding stopped earlier in patients on active treatment (both $p<0.001$). Both active treatments reduced the severity of pain and discomfort compared to placebo on day three (valacyclovir, $p<0.001$; acyclovir, p=0.001). Aborted episodes occurred more frequently with valacyclovir (25.9%) and acyclovir (24.8%) than placebo (19.8%), although this did not achieve statistical significance. The safety profiles of valacyclovir and acyclovir were comparable. Valacyclovir and acyclovir reduce the length of a genital HSV episode and reduced the time to healing

compared to placebo. The dose of valacyclovir studied in this trial is twice the dosage recommended by the CDC for this patient population.[69]

Over a 52-week period, a study examined the dose-response relationship of once-daily valacyclovir for the suppression of genital HSV infections in 1,479 immunocompetent patients with frequently recurring infections.[70] Twice-daily acyclovir and valacyclovir were also evaluated. In the randomized, double-blind study, patients were randomized to valacyclovir 250, 500, or 1,000 mg once daily or 250 mg twice daily, acyclovir 400 mg twice daily, or placebo for 1 year. All patients had a history of at least 6 recurrences of genital herpes per year. Suppressive therapy was discontinued for at least three months prior to enrollment. Episodic therapy with valacyclovir was given for 5 days for recurrences. The primary endpoint was the time to first recurrence of genital HSV infection which was defined as number of days since randomization until first onset of lesions. No significant difference between active treatments for suppression HSV recurrences was demonstrated (all tested comparisons, p=NS); all were significantly more effective than placebo at suppressing HSV recurrences (all comparisons versus placebo; p<0.01). All valacyclovir treatment groups had longer time to first recurrence compared to placebo. Acyclovir was not tested versus placebo but numerically looked to favor acyclovir. The percentage of patients without recurrences were reported as follows: 48% of valacyclovir 1 gm daily group, 40% of valacyclovir 500 mg daily group, 50% of valacyclovir 250 mg twice daily group, 22% of valacyclovir 250 mg daily group, 49% acyclovir group, and 5% of the placebo group. Patients with more than 10 recurrences had a lower rate of response to suppression overall. These patients are best treated with valacyclovir 1 gm daily, valacyclovir 250 mg twice daily, or acyclovir 400 mg twice daily. Patients with less than 10 recurrences per year had a similar response rate with valacyclovir 500 mg or 1 gm once daily or 250 mg twice daily or acyclovir 400 mg twice daily. Adverse events were generally mild, infrequent, and similar in nature to placebo. The most common adverse event reported in all groups was headache.

In a double-blind, three-period crossover trial, the efficacy in suppression of shedding of genital HSV in 69 immunocompetent patients was compared.[71] Patients received valacyclovir 500 mg twice daily, acyclovir 400 mg twice daily, or placebo for 7-week time periods in random order. Daily genital mucosal swabs were collected from the patients. HSV was detected at least once in 90% of patients by culture and 98% by DNA polymerase chain reaction (PCR). Genital HSV shedding detected by culture was detected in 86% while on placebo, 12% while on valacyclovir and 24% while on acyclovir (both p<0.01). By PCR detection, HSV shedding was detected in 93%, 65%, and 76% while on placebo, valacyclovir, and acyclovir, respectively (valacyclovir versus placebo, p<0.001; acyclovir versus placebo, p=0.01). Antiviral therapy significantly reduced the HSV shedding compared to placebo by both culture and PCR detection methods with no significant differences in frequency or quantity of HSV shedding between the 2 antivirals. The geometric mean number of HSV DNA detected PCR copies/mL decreased from $10^{5.2}$ for placebo to $10^{3.9}$ and $10^{3.6}$ with valacyclovir and acyclovir, respectively (both p<0.001 versus placebo). The levels of valacyclovir and acyclovir suppression of HSV DNA were similar. Valacyclovir was associated with a significant decrease in the frequency of total HSV shedding by both viral culture (relative risk [RR], 0.03 [95% CI, 0.01 to 0.07]; p<0.001) and PCR (RR, 0.18 [95% CI, 0.12 to 0.26]; p<0.001) compared to placebo. A similar decrease in the frequency of total HSV shedding was observed with acyclovir compared with placebo (RR, 0.05 [95% CI, 0.03 to 0.1] for culture and RR, 0.2 [95% CI, 0.15 to 0.28] for PCR; p<0.001 for both). Days with genital lesions were reported in 2.8% for valacyclovir (p<0.001), 3.1% with acyclovir (p<0.001), and 22.1% with placebo.

famciclovir versus valacyclovir (Valtrex)

In a multicenter, multinational, double-blind, parallel-group study, 1,179 adults with a history of recurrent genital herpes were randomized to receive either single-day famciclovir 1 gm (administered twice daily) versus 3-day valacyclovir 500 mg (administered twice daily).[72] Patients initiated treatment within 6 hours after a recurrence. Single-day famciclovir therapy was non-inferior to 3-day valacyclovir therapy in reducing time to healing of all genital herpes lesions (median time to healing, 4.25 days versus 4.08 days, respectively). There was no significant difference in time to resolution of symptoms associated with recurrence. The overall incidence of adverse events was similar (23.2% for the famciclovir group versus 22.3% for the valacyclovir group). Additionally, the median time to next recurrence from treatment initiation was 33.5 days for famciclovir and 38 days for valacyclovir.[73] No drug resistance to penciclovir, the active metabolite of famciclovir, was observed at baseline nor did any develop by the time of the next recurrence. The study had no placebo arm, typing of viral isolates was not performed, and viral resistance testing was restricted to penciclovir only.

Two randomized, double-blind, placebo-controlled studies comparing daily famciclovir 250 mg bid with valacyclovir 500 mg daily were performed. Study 1 randomized 320 participants and compared the clinical effect of the drugs given for 16 weeks, and study 2 enrolled 70 HSV-2 seropositive subjects and compared the virologic effect of the drugs given for 10 weeks.[74] In study 1, the time to first recurrence was similar in famciclovir and valacyclovir recipients (HR, 1.17; 95% CI, 0.78 to 1.76), but time to first virologically confirmed recurrence was shorter among famciclovir recipients (HR, 2.15; 95% CI, 1 to 4.6). In study 2, HSV was detected on 3.2% of days among famciclovir recipients and 1.3% of days among valacyclovir recipients (RR, 2.33; 95% CI, 1.18 to 4.89). Valacyclovir appear to be somewhat better than famciclovir for suppression of genital herpes and associated shedding.

Genital Herpes Simplex – Reduced Transmission

valacyclovir (Valtrex) versus placebo

A randomized, double-blind study evaluated the effectiveness of valacyclovir in reducing the risk of transmission of genital herpes in heterosexual, monogamous discordant couples (n=1,484 couples).[75] The patients with HSV-2 were randomized to valacyclovir 500 mg once daily or placebo for 8 months. Of the participating couples, 78.1% completed the study. Over 70% of the source partners reported taking at least 95% of the prescribed doses. Immunocompetent, heterosexual, monogamous couples with 1 clinically infected with HSV-2 and the other susceptible to HSV-2 were eligible for participation. The patient with recurrent genital herpes must have had fewer than 10 episodes per year, over 18 years of age, and use of daily antiviral therapy outside the study protocol was not permitted. The inclusion criteria for the susceptible partner were an age of 18 years or older and HSV-2 seronegativity. Both partners were required to be immunocompetent and in good health, and the couple was required to use effective contraception. Acquisition of HSV-2 infection was defined as the isolation of HSV-2 in culture, the detection of HSV-2 DNA, or HSV-2 seroconversion in the susceptible partner during the course of the trial. Clinically symptomatic genital herpes infection in the susceptible partner was a primary outcome of the study. A total of 41 new HSV-2 and four HSV-1 infections were acquired during the course of the study in the susceptible partners. Of these 45 new infections, 14 were from sexual partners receiving valacyclovir and 31 were from partners receiving placebo. Of the 20 symptomatic acquisitions of HSV-2, 16 occurred among the 741 partners of placebo recipients (2.2%), as compared with four among the 743 partners of valacyclovir recipients (0.5%) (RR, 0.25; 95% CI, 0.08 to 0.74;

p=0.01). HSV-2 had been acquired by 27 of the susceptible partners of placebo recipients (3.6%) as compared with 14 of the susceptible partners of valacyclovir recipients (1.9%) (HR, 0.52; 95% CI, 0.27 to 0.99; p=0.04). HSV-2 shedding occurred on 3.3% and 0.9% of the days among the valacyclovir-treated women and men, respectively, as compared with 11.4% and 9.2% of the days among placebo-treated women and men. Adverse effects were similar between the valacyclovir- and placebo-treated patients. Valacyclovir 500 mg daily reduces the transmission of genital herpes in immunocompetent, heterosexual, monogamous couples with one clinically infected with HSV-2 and the other susceptible to HSV-2.

Herpes Labialis

There are no direct comparative trials with the oral antivirals for the treatment or prevention of herpes labialis. All agents in this category have shown to prevent and treat oral HSV lesions in placebo-controlled studies.

A number of double-blind trials with acyclovir for oral herpes have been completed.[76,77] The early trials with acyclovir from the 1980s were generally small populations and open-label.[78,79] Buccal acyclovir (Sitavig), in a double-blinded placebo controlled trial, was shown to reduce the median duration of oral herpetic episodes by one-half day as compared to placebo.[80] Famciclovir has also been shown to be effective and safe in the prevention and treatment of oral HSV infections and in the HIV-positive population.[81, 82, 83, 84] Valacyclovir has been studied in a variety of dosage regimens for the treatment of recurring oral HSV infections including a simple 2 dose regimen.[85, 86]

META-ANALYSIS

Acyclovir has been shown to reduce fever earlier in acute varicella infection in otherwise healthy children and adolescents according to a systematic review that included data through June 2005.[87] Studies were randomized controlled studies in children through age 18 years. Three studies were included. Acyclovir reduced the number of days with fever (-1.1 days; 95% CI, -1.3 to -0.9) and reduced the maximum number of lesions (-76 lesions; 95% CI, -145 to -8). Complications with chickenpox and adverse effects were clinically important differences between acyclovir and placebo.

A meta-analysis compared the clinical efficacies of the different oral antiviral drugs prescribed prophylactically to suppress recurrent genital herpes.[88] A total of 14 randomized clinical trials were selected, including a total of 6,158 patients. The global relative risk of developing at least 1 recurrence during the study was reduced by 47% (95% CI, 45 to 49) in antiviral drug groups compared with the placebo. The best evaluated regimens, with comparable efficacies, were acyclovir 400 mg twice daily, valacyclovir 250 mg twice daily, famciclovir 250 mg twice daily, and valacyclovir 500 mg once daily. The analysis confirmed high clinical efficacy of all agents for the prevention of recurrent genital herpes.

SUMMARY

The oral agents which are approved for herpes infections include acyclovir (Zovirax), buccal acyclovir tablets (Sitavig), famciclovir, and valacyclovir (Valtrex). Based on available data, all of the agents have similar efficacy and adverse effects.

The 2015 Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) treatment guidelines for genital herpes do not recommend any 1 of these 3 agents over another for the treatment of initial or recurrent episodes of genital HSV infections. Chronic suppressive therapy for

patients with frequent recurrences may include any 1 of the 3 agents; however, famciclovir may be slightly less effective for suppression of viral shedding in genital herpes.

Acyclovir (Zovirax), famciclovir, and valacyclovir agents have similar efficacy for the treatment of herpes zoster, and recent guidelines support the use of any of the 3 agents for first-line therapy.

All oral agents in this class have demonstrated safety and effectiveness in the treatment of herpes labialis. Acyclovir (Sitavig) offers a buccal tablet formulation, with minimal systemic absorption, to treat oral herpetic lesions. It has not been compared to other oral formulations.

Both acyclovir (Zovirax) and valacyclovir are approved for the treatment of varicella (chickenpox).

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