Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Oral Antivirals For The Treatment And Prevention Of Orolabial And Genital Herpes

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Context and policy issues:

Herpes simplex virus (HSV) exists as two types, 1 and 2 (HSV-1 and HSV-2).[1] These viruses lead to life-long infections that often remain latent in sensory nerve ganglia.[1,2] Primary HSV infections may be asymptomatic or may be associated with a range of symptoms, from mild to severe.[2,3] Recurrent infections are a result of viral reactivation, which can be triggered by numerous stimuli; these include physical or emotional stress, fatigue, immunosuppression, ultraviolet (UV) radiation, menses, and tissue damage.[2,3] Typically, HSV-1 has been associated with orolabial herpes, and HSV-2 with genital herpes; however, it is possible for HSV-1 to cause genital disease, and HSV-2 to cause orolabial disease.[1]

Orolabial herpes, also known as herpes labialis, is estimated to affect 20% to 40% of adults.[4] Most commonly, it causes pain and blistering of the lips and perioral area (cold sores, fever blisters) that resolve completely in seven to 10 days; fever and constitutional symptoms occur rarely.[4] Some people experience prodromal symptoms, such as localized pain, tingling, burning, and itching.[3,4] While the majority of episodes of orolabial herpes are mild and self-limiting, serious illness can result in immunocompromised individuals.[4] Recurrences are often shorter in duration and less severe than initial attacks.[4] Most patients with recurrent illness have fewer than three episodes; however, a small proportion of patients (i.e., 5% to 10%) experience six or more episodes annually.[3]

Genital herpes is one of the most common sexually transmitted infections.[5] Serologic data from the United States showed that 22% of adults had HSV-2 antibodies,[5] yet only 10% to 25% of such individuals are actually diagnosed as having genital herpes.[6] This discrepancy can be explained by the fact that up to 75% of primary infections, and many recurrent infections, go unrecognized.[6]

When primary infections are symptomatic, they often manifest with both local and systemic features. Typical local features include painful anogenital vesicles that burst, leading to superficial ulcerations.[5,7] Additional local symptoms include itching, vaginal or urethral discharge, and tender inguinal lymph nodes.[7] Systemic symptoms include fever, headache, and myalgia.[6,7] Symptoms associated with recurrent infections, which are more commonly associated with HSV-2 than HSV-1, tend to be milder and are generally confined to the genital area.[5,6] Importantly, viral shedding can occur from the genital tract of an infected individual at any time, meaning that even those who are asymptomatic can transmit HSV to sexual partners and newborns.[5,6] Notable sequelae of HSV infection include neonatal HSV disease, opportunistic infections in immunocompromised hosts, and psychosocial morbidity.[5] In addition, infection with HSV-2 has been associated with an increased risk of transmitting and acquiring HIV.[5]

The nucleoside analog antiviral agents, which include acyclovir, valacyclovir (the prodrug of acyclovir), and famciclovir, are active against HSV-1 and HSV-2. They work by interrupting viral DNA synthesis during active viral replication.[6] All three agents are approved for treatment of acute episodes (initial or recurrent) and prevention of recurrent episodes of genital herpes.[8] Valacyclovir is also approved for prevention of transmission of genital herpes and for treatment of orolabial herpes.[8] Famciclovir is also approved for treatment of recurrent episodes of orolabial herpes.[8] Some of these indications are specific to certain patient populations (e.g., immunocompetent patients, patients with HIV infection), which vary according to drug (see Table 1). The drugs also differ with respect to pharmacokinetics and recommended dosing regimens, and few direct comparisons amongst the agents exist.

Table 1: Approved indications for oral antiviral agents[8]

Indication	Drug		
	Acyclovir	Valacyclovir	Famciclovir
Orolabial herpes, treatment		X	X*
Genital herpes, treatment	X†	X‡	X§
Genital herpes, suppression	X‖	X¶	X‡
Genital herpes, reduction of transmission risk		X	

* For recurrent episodes in HIV-infected individuals
† For initial episodes
‡ In immunocompetent individuals
§ For recurrent episodes in immunocompetent individuals
‖ For unusually frequent recurrences (6 or more episodes per year)
¶ In immunocompetent or HIV-infected individuals

Research question:

What is the clinical efficacy of acyclovir, famciclovir, and valacyclovir, compared to one another or to placebo, for the treatment and prevention of orolabial and genital herpes?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, EMBASE, The Cochrane Library (Issue 1, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2002 and the present, and are limited to English language publications only.

Summary of findings:

OROLABIAL HERPES

One systematic review by Worrall,[4] published in 2006, and several randomized controlled trials (RCTs) were identified that evaluated the efficacy of oral antivirals for the treatment or prevention of orolabial herpes. The systematic review included RCTs that were at least single-blind; had a minimum of 20 participants, or at least 10 participants per treatment arm if there were multiple interventions; and had at least 80% follow-up. It also examined other systematic reviews.[4] Data from the review and from RCTs that were not included in the review are summarized below, according to type of treatment and intervention.

Treatment, first episode

Acyclovir versus placebo

The systematic review by Worrall summarized two small RCTs in children. The first RCT (n=20) evaluated children (mean age: 2 years) who had herpes simplex gingivostomatitis for fewer than four days. It found that acyclovir (200 mg 5 times daily) reduced the mean duration of pain compared with placebo (4.3 days vs. 5.0 days, respectively; p=0.05). The second RCT (n=72) assessed acyclovir (15 mg/kg 5 times daily for 7 days) in children aged one to six years who had herpes simplex gingivostomatitis for fewer than three days. Acyclovir significantly reduced the median time to healing compared with placebo (4 days vs. 10 days, respectively; median difference 6 days, 95% confidence interval [CI] 4 days to 8 days).[4]

Treatment, subsequent episodes

Acyclovir versus placebo

The systematic review by Worrall summarized two RCTs. The first RCT (n=174) studied the use of acyclovir (400 mg 5 times daily for 5 days), started early in a recurrent attack of orolabial herpes (when tingling was first experienced) in adults. It found that acyclovir significantly reduced the duration of symptoms compared with placebo (8.1 days vs. 12.5 days, respectively; p=0.02). The second RCT (n=149) evaluated acyclovir taken within 12 hours of onset of an attack, and found no significant difference in healing time or duration of pain between acyclovir and placebo (mean healing time: 7.78 days vs. 8.64 days, respectively; p-value not reported; mean duration of pain: 1.31 days vs. 1.35 days, respectively; p-value not reported).[4]

Valacyclovir versus placebo

The systematic review by Worrall summarized two RCTs that were presented in one paper. Both RCTs compared two valacyclovir regimens (2 g twice daily for 1 day and 2 g twice daily for 1 day followed by 1 g twice daily for 1 day) and placebo in people with recurrent orolabial herpes who were at least 12 years of age. The first RCT (n= 902) found that both valacyclovir regimens significantly reduced the median episode duration compared with placebo (4.0 days for 1-day regimen vs. 4.5 days for 2-day regimen vs. 5.0 days for placebo; p<0.001 for 1-day regimen vs. placebo; p=0.009 for 2-day regimen vs. placebo). Likewise, the second RCT (n=954) found that both valacyclovir regimens significantly reduced the median episode duration compared with placebo (5.0 days for

1-day and 2-day regimens vs. 5.5 days for placebo; p<0.001 for 1-day and 2-day regimens vs. placebo). No difference between the valacyclovir regimens was found in either trial (p-values not reported).[4]

Valacyclovir for 1 day versus 3 days

One double-blind RCT (n=308) by Laiskonis et al[9] by was identified. It assessed the use of two different valacyclovir regimens in patients with recurrent orolabial herpes. Participants were at least 12 years of age and had experienced four or more typical episodes annually. Treatment with valacyclovir (1000 mg twice daily for 1 day or 500 mg twice daily for 3 days) was self-initiated at the first symptom of an outbreak (before any visible signs developed). Each regimen employed placebo tablets that matched the valacyclovir tablets used in the comparative regimen to maintain blinding. The primary efficacy outcome was the proportion of patients with aborted lesions (lesion development blocked at or before the papule stage). In the intent-to-treat (ITT) population, which comprised 304 patients with evaluable data, lesions were aborted in 42.2% of patients in the 1-day regimen group and 46.7% of patients in the 3-day regimen group (treatment difference: -4.5%, 95% CI -16.3% to 7.4%; p=0.49), demonstrating no significant difference between the regimens. No significant differences in secondary endpoints (time to episode resolution, time to pain resolution, or time to lesion healing) were noted between the regimens either. The authors concluded that further studies are required to determine the optimal dose and duration of valacyclovir for the treatment of orolabial herpes. Of note, the methodology employed for randomization and allocation concealment were not described in the report.

Famciclovir versus placebo

One double-blind RCT (n=701) by Spruance et al[10] was identified. In this trial, two famciclovir regimens (1500 mg single dose and 750 mg twice daily for 1 day) and placebo were compared in immunocompetent adults with recurrent orolabial herpes (3 or more episodes of cold sores in the preceding 12 months). Prodromal symptoms had to have preceded at least 50% of previous recurrences and at least 50% of previous recurrences had to have progressed to the vesicular lesion stage. Participants were instructed to start therapy within one hour of the onset of prodromal symptoms and before any signs of lesions appeared. The primary efficacy outcome was the investigator-assessed time to healing of the primary vesicular lesions (complete loss of crust with re-epithelialization). This outcome was analyzed in the modified ITT population (n=477), which included all patients who developed vesicular orolabial herpes lesions during treatment. Both famciclovir regimens significantly reduced the time to healing for primary lesions compared with placebo. For the single-dose regimen, the median time to healing (95% CI) in days was 4.4 (3.9 to 5.0); the corresponding values for the single-day regimen and placebo were 4.0 (3.8 to 4.8) and 6.2 (5.7 to 7.0), respectively. Time to healing did not differ significantly between the two famciclovir regimens. The single-dose famciclovir regimen, but not the single-day regimen, also significantly (p<0.001) reduced the median time to resolution of pain and tenderness (a secondary outcome) compared with placebo (1.7 days vs. 2.9 days, respectively). Of note, the authors did not report sufficiently on the use of placebo tablets to ensure that blinding of patients and care providers was maintained.

Prevention

Acyclovir versus placebo

The systematic review by Worrall summarized three RCTs. The first RCT (n=147) included skiers with a history of orolabial herpes brought on by UV light. It found that acyclovir (400 mg twice daily, beginning 12 hours before UV exposure) significantly reduced the frequency of attacks and duration of symptoms compared with placebo ($p<0.05$). The second RCT (n=239), which examined skiers with a history of recurrent orolabial herpes, found no significant difference in lesion occurrence between those who took acyclovir (800 mg twice daily, starting the day prior to UV exposure and continuing for 3 to 7 days) and those who took placebo (21 of 93 [23%] vs. 21 of 102 [21%], respectively; $p=0.92$). The third RCT (n=20) found that acyclovir (400 mg twice daily for 4 months) was associated with 53% fewer clinical recurrences than placebo ($p=0.05$).[4]

In summary, prophylactic use of acyclovir appears to reduce the frequency of attacks of orolabial herpes compared with placebo; however, data from RCTs are conflicting.

Valacyclovir versus placebo

The systematic review by Worrall summarized a pooled analysis of two RCTs (n=98) that assessed the use of valacyclovir (500 mg daily for 4 months) in patients with a history of at least four episodes of orolabial herpes in the previous year. Valacyclovir significantly decreased the chance of recurrence and significantly increased the time to recurrence compared with placebo (no recurrence within 4 months: 62% vs. 40%, respectively; $p=0.041$; mean time to recurrence: 13.1 weeks vs. 9.6 weeks, respectively; $p=0.016$).[4]

An additional double-blind RCT (n=150) by Miller et al[11] was identified. It studied the use of valacyclovir in people aged 12 years or older with a history of recurrent orolabial herpes (at least 1 recurrence per year) who were scheduled to receive routine dental care. Participants were randomized, using a computer-generated randomization code, to receive valacyclovir (2 g within 1-hour prior to the dental procedure, 2 g on the evening of the procedure, then 1 g twice daily the following day) or matching placebo. Several efficacy outcomes were assessed, including the percentage of patients who experienced a recurrence after the dental procedure, although no primary outcome was specified. In the 125 patients with evaluable efficacy data, the authors reported that valacyclovir reduced the recurrence rate compared with placebo (7 of 62 [11.3%] vs. 13 of 63 [20.6%], respectively); however, no p-value was reported, and there was no other indication that the finding was statistically significant. Valacyclovir was associated with a statistically shorter time to cessation of lesion-related pain than placebo (3.2 days vs. 6.2 days respectively; $p=0.006$), but lesion severity scores were similar between groups. All other statistically significant findings were for combined endpoints that were not specified as outcomes of interest a priori.

In summary, data from RCTs have consistently demonstrated that prophylactic use of valacyclovir reduces recurrences of orolabial herpes compared with placebo.

Famciclovir versus placebo

The systematic review by Worrall summarized one RCT (n=248) that evaluated three dosages of famciclovir (125 mg, 250 mg, and 500 mg), each given three times daily for

five days, in adults with a history of recurrent orolabial herpes induced by sun exposure. Treatment began 48 hours after artificial UV light exposure. While no significant difference amongst the groups was seen in number of lesions (p-value not reported), there was a significant reduction in the size and duration of lesions with the 500 mg dose compared with placebo (mean size of lesions: p=0.04; mean time to healing: reduced by 2 days; p=0.01).[4]

GENITAL HERPES

Two systematic reviews[5,12] and several RCTs were identified that evaluated the efficacy of oral antivirals for the treatment or prevention of genital herpes. The more recent of the two systematic reviews by Jungmann[5] was published in 2006; it summarized systematic reviews, including the second one[12] identified by our search, and also RCTs that were at least single-blind; had a minimum of 20 participants; and had at least 80% follow-up. Data from the review by Jungmann and from RCTs that were not included in it are summarized below, according to type of treatment and intervention.

Treatment, first episode

Acyclovir versus placebo

The systematic review by Jungmann summarized three RCTs. The first RCT (n=119 with first-episode genital herpes; total n=180) assessed acyclovir at a dose of 200 mg five times daily for 10 days and found that this regimen significantly decreased time to complete lesion healing compared with placebo (12 days vs. 14 days, respectively; p=0.005), and also reduced the formation of new lesions (proportion of people with new lesions after 48 hours of therapy: 18% vs. 62%, respectively; p=0.001), duration of pain (median: 5 days vs. 7 days, respectively; p=0.05), and duration of viral shedding (median: 2 days vs. 9 days, respectively; p<0.001) in patients with first-episode genital herpes. The second RCT (n=31) evaluated acyclovir at a dose of 200 mg five times daily for five days. It found that acyclovir significantly reduced the duration of viral shedding compared with placebo (median: 1 day vs. 13 days, respectively; p<0.01), as well as the duration of pain (median: 4 days vs. 8 days, respectively; p<0.05). The third RCT (n=48; 31 women and 17 men) studied acyclovir 200 mg five times daily for 10 days versus placebo. In this trial, acyclovir significantly reduced the duration of viral shedding compared with placebo (mean in women: 4.9 days vs. 17.7 days, respectively; p=0.001; mean in men: 6 days vs. 15 days, respectively; p=0.02) and also time to crusting (mean in women: 8.8 days vs. 15.0 days, respectively; p=0.01; mean in men: 5 days vs. 15 days, respectively; p=0.01).[5]

Acyclovir versus valacyclovir

The systematic review by Jungmann summarized one RCT (n=643) that compared acyclovir (200 mg 5 times daily for 10 days) with valacyclovir (100 mg twice daily for 10 days). It found no significant difference between the agents in terms of duration of viral shedding (hazard ratio [HR] 1.00, 95% CI 0.84 to 1.18), healing time (HR 1.08, 95% CI 0.92 to 1.27), or duration of symptoms (HR 1.02, 95% CI 0.85 to 1.22).[5]

Treatment, subsequent episodes

Acyclovir versus placebo

The systematic review by Jungmann summarized one non-systematic review and one RCT. Of note, the author of the systematic review did not explain why results of a non-systematic review, which didn't meet predetermined inclusion criteria, were included in the report. In the non-systematic review (number of RCTs not reported, n=650), acyclovir (200 mg 5 times daily or 800 mg twice daily, each for 5 days) or placebo was started at the first sign of a recurrence of genital herpes. It found that acyclovir reduced the duration of viral shedding compared with placebo (1 day vs. 2 days, respectively), as well as the duration of lesions (5 days vs. 6 days, respectively; significance not assessed). In the RCT (n=131), acyclovir (800 mg 3 times daily for 2 days) was compared to placebo in people with at least three recurrences of genital herpes in the previous 12 months. It found that acyclovir significantly reduced the duration of lesions compared with placebo (median: 4 days vs. 6 days, respectively; p=0.001), as well as the duration of episodes (median: 4 days vs. 6 days, respectively; p<0.001) and viral shedding (median: 25.0 hours vs. 58.5 hours, respectively; p=0.04).[5]

In summary, data from RCTs have consistently demonstrated that treatment with acyclovir reduces the duration of lesions and viral shedding associated with genital herpes compared with placebo.

Valacyclovir versus placebo

The systematic review by Jungmann summarized one other systematic review (1 RCT, n=987) that reported on the effects of two valacyclovir regimens (500 mg or 1000 mg, each twice daily for 5 days) versus placebo. Self-initiated valacyclovir significantly decreased episode duration compared with placebo (median: 4 days vs. 6 days, respectively; HR 1.9, 95% CI 1.6 to 2.3), as well as viral shedding (median: 2 days vs. 4 days, respectively; HR 2.9, 95% CI 2.1 to 3.9). Valacyclovir also increased the rate of aborted recurrences compared with placebo (31% vs. 21%, respectively; RR 1.5, 95% CI 1.1 to 1.9).[5] It was not reported whether there were any statistically significant differences between the two dosage regimens.

Valacyclovir for 3 days versus 5 days

The systematic review by Jungmann summarized two RCTs. In the first RCT (n=531), three-day and five-day regimens of valacyclovir 500 mg twice daily were compared in people with a minimum of six recurrences of genital herpes a year. It found no difference between the three-day and five-day regimens in episode duration (median: 4.7 days vs. 4.6 days, respectively; significance not reported) or aborted recurrences (27% vs. 21%, respectively; RR 1.23, 95% CI 0.92 to 1.65). Overall, people who initiated treatment within six hours of the first signs or symptoms of recurrence were significantly more likely to have an aborted episode than those starting treatment after six hours (odds ratio [OR] 1.93, 95% CI 1.28 to 2.9). The second RCT (n=800) assessed three-day and five-day regimens of valacyclovir 500 mg twice daily in people with at least four recurrences of genital herpes yearly. It found no significant difference between the three-day and five-day regimens in lesion healing time (median: 4.4 days vs. 4.7 days, respectively; HR 0.95, 95% CI 0.81 to 1.13) or rate of aborted lesions (25% vs. 27%, respectively; RR 1.04, 95% CI 0.83 to 1.32).[5]

In summary, data from RCTs have consistently demonstrated that there is no significant difference between the effects of three-day and five-day regimens of valacyclovir on rates of aborted lesions in patients with genital herpes.

Acyclovir versus valacyclovir

The systematic review by Jungmann summarized one other systematic review and one RCT. In the systematic review (1 RCT, n=739), acyclovir (200 mg 5 times daily for 5 days) was compared with valacyclovir (500 mg twice daily for 5 days). It found no significant difference between treatments in healing time (HR 0.96, 95% CI 0.80 to 1.14) or viral shedding (HR 0.98, 95% CI 0.75 to 1.27). The RCT (n=467) compared acyclovir (200 mg 5 times daily for 5 days) with valacyclovir (1000 mg twice daily for 5 days) in patients with HIV infection. It found no significant difference between the agents for time to lesion healing (HR 0.98, 95% CI 0.79 to 1.22) or episode duration (HR 0.93, 95% CI 0.75 to 1.14).[5]

Famciclovir versus placebo

The systematic review by Jungmann summarized one other systematic review and two RCTs. The systematic review (1 RCT, n=467) found that five days' therapy with famciclovir (125-500 mg twice daily) significantly reduced the duration of lesions compared with placebo (median: 4 days vs. 5 days, respectively; p-value not reported) and also the duration of viral shedding (2 days vs. 3 days, respectively; p-value not reported). It was not reported whether there were any statistically significant differences between the different famciclovir dosages studied.[5]

The first RCT (n=308) compared famciclovir (125 mg, 250 mg, or 500 mg, each twice daily for 5 days) and placebo in people presenting within 6.5 hours of symptom recurrence. It found that all dosages of famciclovir significantly reduced the time to cessation of viral shedding compared with placebo (125 mg: HR 3.29, 95% CI 2.19 to 4.95; 250 mg: HR 3.26, 95% CI 2.16 to 4.92; 500 mg: HR 3.56, 95% CI 2.29 to 5.53) and also the time to complete lesion healing (125 mg: HR 1.48, 95% CI 1.06 to 2.08; 250 mg: HR 1.74, 95% CI 1.23 to 2.46; 500 mg: HR 1.79, 95% CI 1.26 to 2.53). There was no difference in efficacy among the different famciclovir doses studied.[13] The second RCT (n=329) evaluated famciclovir (1000 mg twice daily for 1 day) in people with a minimum of four recurrences of HSV-2-associated genital herpes in the previous 12 months. It found that self-initiated famciclovir significantly decreased the time to healing of aborted and non-aborted lesions (combined) compared with placebo (3.5 days vs. 5.0 days, respectively; $p<0.001$).[5]

In summary, data from RCTs have consistently demonstrated that treatment with famciclovir reduces the duration of lesions and viral shedding associated with genital herpes compared with placebo.

Acyclovir versus famciclovir

The systematic review by Jungmann summarized two RCTs. The first RCT (n=204) found no significant difference between acyclovir and famciclovir in time to lesion healing (5.4 days vs. 5.1 days, respectively; mean difference +0.3 days, 95% CI -0.3 to +0.8). The second RCT (n=193) compared acyclovir (400 mg 5 times daily for 1 week) and famciclovir (500 mg twice daily for 1 week) in people with HIV infection who were on stable antiretroviral treatment. It found no significant differences between acyclovir and

famciclovir in the following endpoints: time to healing (median: 7 days vs. 7 days, respectively; HR 1.01, 95% CI 0.79 to 1.29), duration of viral shedding (median: 2 days vs. 2 days, respectively; HR 0.93, 95% CI 0.68 to1.27), time to loss of symptoms (median: 4 days vs. 4 days, respectively; HR 0.99, 95% CI 0.75 to 1.30), or risk of developing new lesions during treatment (13% vs. 17%, respectively; absolute risk increase +3.4%, 95% CI -4.8% to +11.5%).[5]

Prevention

Acyclovir versus placebo

The systematic review by Jungmann summarized one other systematic review, one non-systematic review, and two subsequent RCTs that addressed clinical outcomes. The systematic review (n=799) included five RCTs that assessed the use of acyclovir (800 mg or 1200 mg per day) initiated at 36 weeks' gestation. It found that acyclovir significantly reduced HSV recurrence at delivery compared with placebo (OR 0.25, 95% CI 0.15 to 0.40). No cases of neonatal HSV were reported in either acyclovir or placebo groups.[5]

The non-systematic review included two RCTs. In the first RCT (n=32), acyclovir 800 mg per day significantly reduced recurrence rates at two years compared with placebo (freedom from recurrence: 5 of 18 [28%] vs. 0 of 14 [0%], respectively; absolute risk reduction [ARR] 28%, 95% CI 1% to 51%). In the second RCT (n=75), acyclovir 400 mg twice daily significantly reduced recurrence rates at one year compared with placebo (freedom from recurrence: 21 of 48 [44%] vs. 0 of 28 [0%], respectively; ARR 44%, 95% CI 26% to 56%).[5] Of note, the author of the systematic review did not explain why results of a non-systematic review, which didn't meet predetermined inclusion criteria, were included in the report.

In the first subsequent RCT (n=1479), acyclovir 400 mg twice daily significantly reduced recurrence rates at one year compared with placebo (freedom from recurrence: 49% vs. 5%, respectively; HR 0.21, 95% CI 0.16 to 0.27). The second subsequent RCT (n=1146) also found that acyclovir 400 mg twice daily significantly reduced recurrence rates at one year compared with placebo (2% vs. 13%, respectively; p<0.0001). Long-term follow-up of 210 adults in this trial who completed five years of continuous treatment with acyclovir showed that 53% to 70% of participants were free of recurrences each year.[5]

In summary, data from RCTs have consistently demonstrated that prophylactic use of acyclovir reduces recurrences of genital herpes compared with placebo.

Valacyclovir versus placebo

The systematic review by Jungmann summarized one other systematic review (2 RCTs, n=1861) and two additional RCTs that addressed clinical outcomes. In the first RCT (n=382) included in the review, valacyclovir (500 mg once daily for 16 weeks) significantly increased time to recurrence compared with placebo (HR 0.10, 95% CI 0.11 to 0.21). The second RCT (n=1479) included in the review compared four different valacyclovir regimens (1000 mg 4 times daily, 500 mg 4 times daily, 250 mg 4 times daily, and 250 mg twice daily, all for 1 year) with placebo. It found that valacyclovir increased freedom from recurrence compared with placebo in a dose-dependent manner (48-50% with valacyclovir 1000 mg 4 times daily vs. 40% with valacyclovir 500 mg 4 times daily vs. 22% with valacyclovir 250 mg 4 times daily vs. 5% with placebo;

significance not reported). It was stated that the 250 mg twice daily regimen also improved freedom from recurrence by 40% compared with placebo;[5] however, this value appears to be a relative reduction as opposed to an absolute reduction.

The first additional RCT (n=239) evaluated valacyclovir (500 mg twice daily for up to 6 months)[14] in people with HIV infection and a history of recurrent HSV. It found that valacyclovir significantly reduced recurrence rates at six months compared with placebo (freedom from recurrence: 65% vs. 26%, respectively; relative risk [RR] 2.5, 95% CI 1.8 to 3.5) and increased time to first recurrence (median: >180 days vs. 59 days, respectively; HR 16.7, 95% CI 7.3 to 33.3). The second additional RCT (n=112) assessed valacyclovir (500 mg twice daily), started around 36 weeks' gestation, in pregnant women with a history of recurrent genital herpes caused by HSV-2.[15] It found that valacyclovir significantly reduced HSV recurrence in late pregnancy compared with placebo (6 of 57 [11%] vs. 15 of 55 [27%], respectively; RR 0.4, 95% CI 0.2 to 0.9), but did not significantly decrease the proportion of women with active lesions at delivery (3 of 57 [5%] vs. 8 of 55 [15%], respectively; RR 0.4, 95% CI 0.1 to 1.3) or reduce viral shedding within seven days of delivery (5 of 48 [10%] vs. 6 of 50 [12%], respectively; RR 0.9, 95% CI 0.3 to 2.7).[5]

Another double-blind RCT (n=338) by Sheffield et al[16] was identified. It studied valacyclovir use in pregnant women with a history of genital HSV. Participants were randomized at 36 weeks' gestation, using a computer-generated random number table, to receive valacyclovir (500 mg twice daily) or identical-appearing placebo until delivery. Efficacy outcomes of interest were not specifically stated, but the purpose of the study was to estimate the efficacy of valacyclovir in reducing clinical and virologic evidence of HSV infection at the time of delivery. Results demonstrated that valacyclovir significantly reduced the proportion of women with clinical genital HSV at delivery compared with placebo (7 of 170 [4%] vs. 21 of 168 [13 %], respectively; p=0.009; OR 0.30, 95% CI 0.12 to 0.73). In the 164 women with PCR data available, the authors reported that valacyclovir significantly decreased the likelihood of a positive PCR result at delivery compared with placebo (7 of 85 [8%] vs. 19 of 79 [24%], respectively; p=0.01; OR 0.28, 95% CI 0.11 to 0.72; number need to treat [NNT] 7). Valacyclovir also decreased the number of cesarian deliveries performed due to HSV compared with placebo (7 of 170 [4%] vs. 21 of 168 [13%], respectively; p=0.009; OR 0.3, 95% CI 0.12 to 0.73; NNT 11). No infant in either group had a positive HSV culture at birth.

In summary, data from RCTs have consistently demonstrated that prophylactic use of valacyclovir reduces overall recurrences of genital herpes compared with placebo; however, data are conflicting regarding the effects of prophylactic valacylovir on the reduction of active genital lesions at the time of delivery in pregnant patients.

Acyclovir versus valacyclovir

The systematic review by Jungmann summarized one RCT (n=1062) that evaluated 48 weeks of therapy with acyclovir (400 mg twice daily) or valacyclovir (500 mg twice daily or 1000 mg once daily) in people with HIV infection. It found no significant difference between either dose of valacyclovir and acyclovir in time to recurrence (HR for valacyclovir 500 mg twice daily vs. acyclovir: 0.73, 95% CI 0.50 to 1.06; HR for valacyclovir 1000 mg once daily vs. acyclovir: 1.31, 95% CI 0.94 to 1.82). The rate of recurrence was significantly higher with the valacyclovir 1000 mg daily regimen than with the 500 mg twice daily regimen (people remaining recurrence-free at 48 weeks: 71% vs. 82%, respectively; HR 1.80, 95% CI 1.26 to 2.57; p<0.05).[5]

Famciclovir versus placebo

The systematic review by Jungmann summarized one other systematic review (2 RCTs, n=830). In the first RCT (n=455) included in the review, three famciclovir regimens (250 mg twice daily, 125 mg 3 times daily, or 250 mg 3 times daily, each for 1 year) were compared with placebo. It found that famciclovir significantly increased time to first recurrence compared with placebo (median: 11 months with famciclovir 250 mg twice daily vs. 8 months with famciclovir 125 mg 3 times daily vs. 10 months with famciclovir 250 mg 3 times daily vs. 1.5 months with placebo; p-value not reported). The second RCT (n=375 women) included in the review found that famciclovir (125 mg twice or 4 times daily, 250 mg twice or 4 times daily, or 500 mg 4 times daily, each for 4 months) significantly increased the proportion of people without recurrences compared with placebo (78% with 250 mg twice daily vs. 42% with placebo; p-value not reported; no other data reported). It also found that 250 mg twice daily was the most effective dosage for reducing recurrences.[5]

Three additional double-blind RCTs were identified. The first RCT (n=177) by Sacks[17] assessed the use of famciclovir in adult women with a history of frequent (at least every 2 months for 6 months in those not receiving treatment or monthly for 1 month after cessation of suppressive treatment) and recurrent genital HSV-2 infection. Participants were randomized to receive one of two different famciclovir regimens (125 mg or 250 mg, each 3 times daily) or placebo for 16 weeks. The authors pointed out that the study commenced prior to the dose-ranging studies that identified the approved suppressive dose of 250 mg twice daily. Famciclovir significantly reduced the proportion of days of asymptomatic viral shedding from any genital site (the primary efficacy outcome) compared with placebo, both with the 125 mg regimen (0.52% vs. 3.1%, respectively; OR 6.1, 95% CI 3.5 to 10.8; p<0.0001) and the 250 mg regimen (0.35% vs. 3.1%, respectively; OR 7.7, 95% CI 4.0 to 14.4; p<0.0001). Both doses of famciclovir also resulted in a significant reduction in the proportion of days of symptomatic HSV-positive shedding from any genital site (a secondary outcome) compared with placebo (0.72% with the 125 mg regimen vs. 5.53% with placebo; OR 8.0, 95% CI 4.9 to 13.2; p<0.0001; 0.19% with the 250 mg regimen vs. 5.53% with placebo; OR 31.3, 95% CI 12.1 to 80.8; p<0.0001). For this secondary outcome, the higher dose of famciclovir was significantly more effective than the lower dose (p<0.0001). Of note, the methodology employed for randomization and allocation concealment were not described in the report.

The second and third additional RCTs (total n= 469) were of identical design and were summarized in one paper by Tyring et al.[18] These trials included otherwise healthy adults with a history of recurrent genital HSV infection. Recurrent disease was defined as at least six recurrences in the previous 12 months for those not receiving treatment or at least six recurrences during any 12-month period in the two years prior to study entry for those receiving suppressive acyclovir. A computer-generated randomization code was used to assign participants to either famciclovir 250 mg twice daily or identical-appearing placebo tablets for 52 weeks. During the treatment period, the investigators permitted any patient who experienced two virologically-confirmed or three clinically-confirmed recurrences to receive open-label famciclovir (250 mg 3 times daily) for the remainder of the study. The primary efficacy parameters included the proportion of patients who remained HSV recurrence-free (confirmed by viral culture) for at least six months after the start of the study and the time to first clinically-confirmed lesional episode. There was a higher withdrawal rate in the placebo group compared with the famciclovir group (176 of 233 [76%] vs. 91 of 236 [39%], respectively; significance not

reported), primarily related to lack of efficacy (121 of 176 [69%] vs. 31 of 91 [34%]; significance not reported); this could have compromised blinding in the study. In evaluable patients (number not reported), famciclovir significantly increased the proportion of people who were free from virologically-confirmed lesions for at least six months compared with placebo (RR 2.290; p<0.001). Famciclovir also increased the time to first clinically-confirmed lesional episode compared with placebo (HR 3.1, 95% CI 2.4 to 4.0; p<0.0001).

In summary, data from RCTs have consistently demonstrated that prophylactic use of famciclovir reduces recurrences of genital herpes and increases time to first recurrence compared with placebo.

Famciclovir versus valacyclovir

One paper was identified that reported on two double-blind RCTs comparing famciclovir (250 mg twice daily) with valacyclovir (500 mg daily) in patients with recurrent genital herpes.[19] In the first RCT (n=320), the treatment period was 16 weeks and the primary efficacy outcome was the proportion of patients with a clinically-confirmed recurrence during the study. Two participants in the famciclovir group and three participants in the placebo group were excluded from the efficacy analyses after developing a recurrence of genital herpes within five days of study entry. In the remaining participants, there was no significant difference between treatments in the proportion of people who developed clinically-confirmed recurrences (34% with famciclovir vs. 28% with valacyclovir; RR 1.10, 95% CI 0.94 to 1.28; p=0.22). In the second RCT (n=70), the treatment period was 10 weeks and the primary efficacy outcome was the proportion of days with PCR-detected HSV from swabs of the genital area. The results showed that famciclovir was associated with a higher proportion of HSV shedding days than valacyclovir (3.2% vs. 1.3%, respectively; RR 2.33, 95% CI 1.18 to 4.89; p=0.014). The authors concluded that valacyclovir appears to be somewhat superior to famciclovir for suppression of genital herpes and associated viral shedding. Of note, the methodology employed for randomization and allocation concealment were not described in the report.

Conclusions and implications for decision or policy making:

In patients with a first episode of orolabial herpes, the use of acyclovir appears to reduce the duration of pain and time to healing compared with placebo, but data are insufficient to make any firm conclusions.[4] In patients with recurrent episodes of orolabial herpes, acute treatment with acyclovir, valacyclovir, or famciclovir may marginally reduce the duration of pain and healing time (by approximately 1 day) compared with placebo.[3,4] Prophylactic use of the oral antivirals may reduce the frequency and severity of recurrent attacks of orolabial herpes; however, the optimal timing and duration of treatment are unknown.[4] No studies have directly compared the efficacy of different oral antiviral agents in patients with orolabial herpes.

In patients with a first episode of genital herpes, acyclovir and valacyclovir have been shown to effectively decrease symptoms, though it is unclear based on available evidence whether one drug is more effective than the other.[5] In patients with recurrent episodes of genital herpes, acyclovir, valacyclovir, and famciclovir all appear to be equally beneficial as acute treatment to reduce the duration of symptoms, lesion healing time, and viral shedding.[5,7] The agents all effectively reduce the frequency of episode recurrences when taken as daily as maintenance treatment.[5] In people with HIV infection, oral antivirals are generally believed to be beneficial for treatment of first and

recurrent episodes of genital herpes, and also for prevention of recurrent episodes; however, data from placebo-controlled trials are sparse.[5]

In long-term studies of patients using daily oral antivirals for prophylaxis against recurrence of genital herpes, acyclovir, valacyclovir, and famciclovir were all well-tolerated.[5] Some patients using acyclovir were followed for up to seven years, while those using valacyclovir or famciclovir were followed for up to one year.[5] Nausea and headache were infrequently reported, and treatment discontinuation due to adverse effects was rare.[5] Adverse effects with short-term use in patients with genital herpes were similar, with nausea and headache reported with similar frequencies amongst the agents.[5]

Current evidence with the oral antivirals is limited by the absence of head-to-head comparisons in patients with orolabial herpes and the relatively restricted data from active-comparator trials in patients with genital herpes. Nonetheless, available evidence suggests that the oral antiviral agents are all similarly effective for treatment of recurrent episodes of orolabial herpes, and also for the treatment and prevention of genital herpes.

Officially approved dosage regimens for the oral antivirals are generally supported by the systematic reviews and RCTs summarized above. Therefore, choice of therapy is likely to depend on the cost of an agent and convenience of dosing.

Prepared by:

Brent Ruddock, BScPhm
Melissa Severn, MISt
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439

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