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# Is Famciclovir Superior to Valacyclovir as a Treatment for Recurrent Gential Herpes in Reducing Outbreak Duration and Frequency?

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# Is famciclovir superior to valacyclovir as a treatment for recurrent genital herpes in reducing outbreak duration and frequency?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine "Is famciclovir superior to valacyclovir as a treatment for recurrent genital herpes in reducing outbreak duration and frequency?"

**STUDY DESIGN:** This review is based on three double-blind, randomized controlled trials (RCTs) published in 2006, 2008, and 2009. The studies compared the efficacy and safety of famciclovir (FCV) vs. valacyclovir (VCV) in the treatment of genital herpes.

**DATA SOURCES:** All articles used were published in English, in peer-reviewed journals, and found using PubMed.

**OUTCOMES MEASURED:** The effectiveness of famciclovir and valacyclovir was evaluated based on the proportion of patients with aborted lesions, the time to resolutions of lesions of active infection and all associated symptoms, the time to next reoccurrence, and the proportion of patients with a recurrence.

**RESULTS:** All three studies found that there were no significant differences in efficacy or safety in terms of clinical disease manifestations between FCV and VCV. Median time to healing of herpes lesions was similar in both groups (4.25 days vs. 4.08 days), and about one-third of patients in both groups experienced aborted lesions. A follow-up study showed similar times to next recurrence (33.5 days vs. 38 days). Values for evaluating frequency of recurrences proved to be similar as well, with 34% of the FCV group and 28% of the VCV group experiencing an outbreak within a 16-week post-treatment period, and the mean number of recurrences being 0.11 and 0.10, respectively.

**CONCLUSIONS:** The results of the three RCTs demonstrate that famciclovir is equally effective compared to valacyclovir, but does not appear to be superior in treating genital herpes. However, the shorter dosing schedule of famciclovir for herpes recurrence may provide a more convenient treatment option for some patients, and further comparative studies are warranted to investigate whether improvements in virologic disease manifestations from previous *in vivo* murine studies translate into clinically meaningful results.



**KEY WORDS:** Valacyclovir, famciclovir, recurrent, genital herpes.

INTRODUCTION

Genital herpes is a highly contagious sexually transmitted disease most commonly caused by herpes simplex virus type 2 (HSV-2), although the rate of herpes simplex virus type 1 (HSV-1) genital infection has been rising due to the increase in oral-genital transmission. After an initial HSV-2 infection, over 90% of patients experience a reactivation of latent virus residing in the cell bodies of neurons at some point in their lives, and about one-third have frequent outbreaks (>6 per year).[1] Although non-lethal and often asymptomatic, recurrent outbreaks as well as the infections potential to the patient's sexual partners results in significant psychological stress to the patient. Social stigma and shame also add to the negative impact on the patient's quality of life.[3] While the disease remains incurable, treatment is possible. This paper evaluates three randomized trials (RCTs) comparing the efficacy and safety of famciclovir vs. valacyclovir in the episodic treatment of genital herpes.

In the U.S., approximately 17% of adults are seropositive for HSV-2, making it one of the most common sexually transmitted diseases. Worldwide, the condition has become epidemic and the prevalence is 30%.[1] The cost of incident infections was $1.8 billion in 2000, and projected to increase to $2.7 billion by 2025 as the incidence and prevalence continues to rise. Projected cost over the next 25 years is estimated at $61 billion.[5] Approximately 499,655 healthcare visits related to HSV occurred in 2000, with 2,056,1180 pharmacy claims. While these values clearly represent the severity of genital herpes as a public health problem, only 9%-50% of infected individuals are aware of their infection, which results in less healthcare visits than would be expected.[4]

It is unknown as to why some patients never have a subsequent outbreak while others have severe, continuous outbreaks. Still others may have asymptomatic recurrent reactivation of

virus. This variability in disease presentation further complicates its management and causes its transmission to be unpredictable.[11] It is known that transmission can occur during active outbreaks and possibly during latent viral shedding, but there are no methods available to patients for them to definitively know when they are experiencing viral shedding, and no clear connection has been made between viral titer level and chance of transmission to a partner, with only the latter being clinically relevant.[9] Additionally, genital vs. oral and other forms of herpes infections cannot be differentiated based on seropositivity alone, making detection and screening a challenge.[1] Finally, medical practitioners should be aware of the psychosocial concerns associated with genital herpes. Decreased self-esteem, anger, depression, social isolation, and guilt often accompany a new diagnosis. Many patients experience significant distress due to their perceived lack of control of the disease, sexual and/or social rejection, and the lifelong course of infectivity.[10]

Currently, three oral antivirals are approved for the treatment of genital herpes: Acyclovir (ACV), valacyclovir (VCV), and famciclovir (FCV). ACV was the first to be approved in the early 1980s, but its low bioavailability of 10-20% presented a possibility for drug improvement. FCV, a prodrug of penciclovir (which is structurally similar to ACV), and VCV, the l-valine ester and prodrug of ACV, were discovered later on to have improved systemic absorption and longer duration of action.[7] Other treatments include over-the-counter pain relievers, such as ibuprofen and acetaminophen, and a wide range of alternative therapies, including but not limited to Echinacea, propolis, Prunella vulgaris, Rozites caperata, warm water soaks, lysine, baking soda, cornstarch, tea bags, ice, and aloe vera.[11]

Only the antiviral medications have been proven to be clinically effective in treating genital herpes. Most other methods are home-remedies for symptomatic relief and there is

limited, if any, scientific literature. Treatment with antivirals centers around three approaches: First occurrence, recurrence, and suppression. Early treatment soon after the first outbreak has been shown in mice to significantly reduce the possibility of future outbreaks by reducing the viral load that remains in the neural ganglia. Recurrent outbreaks are best treated within the first 24 hours of prodromal symptoms due to the rapid burst of viral replication during this time. Various regimens of episodic therapy differing in drug quantity, dosing frequency, and length of treatment are available, ranging from 1-5 days. [1] Suppressive therapy on a daily basis reduces the frequency of recurrence and viral shedding.[6] While various trials have already demonstrated the safety and improved efficacy of these antivirals compared to placebo within the three treatment modalities, few direct comparison RCTs of the antivirals have been performed. [7]

OBJECTIVE

The objective of this systematic review is to determine "Is famciclovir superior to valacyclovir as a treatment for recurrent genital herpes in reducing outbreak duration and frequency?"

METHODS

Specific selection criteria of three RCTs were used for this selective EBM review. The population chosen consisted of patients, at least 18 years of age, immunocompetent, with a history of frequent recurrent genital herpes (>4-6 recurrences per year). The intervention used in each RCT was FCV as daily and episodic therapy compared to VCV. All of the studies utilized included several outcomes but for the purpose of this review, the outcomes measured reflected the efficacy of FCV and VCV in reducing recurrent outbreak duration, frequency, and severity. Outcomes involving the virologic effects of the drugs were omitted from this review in order to focus on patient oriented evidence that matters (POEMs).

Some keywords utilized in the search for RCTs included valacyclovir, famciclovir, recurrent, and genital herpes. All articles were published in peer-reviewed journals and in the English language. The author researched the studies through PubMed and selected the articles based on their relevance to the clinical question and if they included POEMS. Inclusion criteria included RCTs published after 1996, with patients who had a clinical diagnosis with lab evidence of HSV, and at least 4 recurrences in the preceding 12 months prior to therapy. Exclusion criteria included patients under the age of 18, immunocompromised, renal disease, hepatic impairment, GI malabsorption, and pregnancy. The statistics reported or used in these studies were RRR, ARR, NNT, RRI, ARI, NNH, p-values, hazard ratios, and CIs. Table 1 shows the demographics and characteristics of the included studies.

OUTCOMES MEASURED

The outcomes measured were the proportion of patients with aborted lesions, the time to resolutions of lesions of active infection and all associated symptoms, the time to next reoccurrence, and the proportion of patients with a recurrence. These outcomes were measured by using patient self-reports and regular evaluations by clinical assessors throughout the study period to confirm or deny the presence of outbreak sign/symptoms and monitor lesion healing.[1,2,6] Self-reports consisted of diary entries detailing the exact time of onset, symptoms, and the lesion stage. Full healing was defined as loss of crust with re-epithelialization of the skin. Those collecting the patient self-reports and the assessors themselves were blinded to the patients' group assignment.

Table 1: Demographics & Characteristics of included studies

| Study | Type | # Pts. | Age (yrs) | Inclusion Criteria | Exclusion Criteria | W/D | Interventions |
|---|---|---|---|---|---|---|---|
| Abudalu[1] (2008) | Double blind RCT | 1179 | 18-85 years | Patients 18 years or older with a clinical diagnosis of HSV 1 or 2, lab evidence of HSV, hx of at least 4 recurrences of genital lesions in the preceding 12 mo. or prior to suppressive therapy | Hx of renal dz, hepatic impairment, GI malabsorption, immunosuppre-ssion, pregnancy, use of concomitant cimetidine and/or probenecid therapy | 57 | 1 tab 1 g famciclovir BID x 1 day vs. 1 tab 500 mg valacyclovir po BID 3 day. Therapy initiated w/in 6 hrs after the onset of prodromal symptoms and/or genital herpes |
| Bodsworth [2] (2009) | Double blind RCT | 666 | >18 years old | Patients who successfully completed the *Abudalu* study and experienced a reoccurrence of genital herpes during the acute phase of the study | Same as *Abudalu* | 0 | Same as *Abudalu* |
| Wald[6] (2006) | Double blind RCT | 320 | >18 years old | Patients 18 years or older with a hx of at least 6 recurrences in the past year, or prior to suppressive therapy | Kidney impairment, liver dz, HIV, pregnancy, receipt of other investigational drugs, hx of resistant HSV infection, sensitivity to nucleoside analogues | 32 | 1 tab 250 mg famciclovir po BID vs. 1 tab valacyclovir 500 mg po qd |

RESULTS

This selective EBM review was performed on three RCTs, all of which performed a head-to-head comparison of famciclovir vs. valacyclovir in an adult, immunocompetent population

***Time to healing and resolution of symptoms***. In the 2008 study by Abudalu et al, single day FCV (1000 mg bid) was compared to 3-day VCV (500 mg bid) in the episodic treatment of genital herpes. Both treatment groups exhibited similar time to healing of non-aborted lesions, 4.25 days for patients receiving FCV and 4.08 days for patients receiving VCV, with a median treatment difference of 0.16 days (p= 0.48; 95% CI= -0.15 to 0.60) and hazard ratio of 1.08 (95% CI; 0.88-1.32). Time to resolution of all symptoms associated with infection, which included pain, itching, burning, tingling, and tenderness, were similar as well, with a median of 72.9 hours for FCV, 72.0 hours for VCV (p=0.75), and hazard ratio of 1.03 (95% CI=0.86-1.24) (Table 2).[1]

**Table 2**: Famciclovir vs. valacyclovir on the time to healing of lesions and all related symptoms (Abudalu et al., 2008)[1]

| Efficacy Parameter | No. of patients | Median days to healing of lesions | Median days of difference in time to healing between treatments | No. of patients whose symptom(s) resolved | Median hours to resolution. |
|---|---|---|---|---|---|
| Famciclovir | 249 | 4.25 | 0.16 | 236 | 72.9 |
| Valacyclovir | 253 | 4.08 | | 238 | 72.0 |

***Proportion of aborted lesions.*** Similar proportions of patients with aborted lesions following initiation of treatment were found between the two groups (32.7% of the FCV group and 33.6% of the VCV group).[1]

Table 3 displays the treatment effects on the proportion of patients with aborted lesions. The ARR shows an small increase in non-aborted lesions of the FCV group compared to having

| **Table 3**: Famciclovir vs. valacyclovir on the proportion of patients experiencing non-aborted lesions (Abudalu et al., 2008)[1] | | | | |
|---|---|---|---|---|
| Proportion of VCV patients with non-aborted lesions | Proportion of FCV patients with non-aborted lesions | Relative Risk Reduction (RRR) | Absolute Risk Reduction (ARR) | Number needed to treat (NNT) |
| | | $\frac{\text{EER - CER}}{\text{CER}}$ | EER - CER | 1/ARR |
| 0.664 | 0.673 | 0.014 | 0.009 | 112 |

non-aborted lesions with FCV treatment compared to VCV. NNT is calculated to determine the number of patients that need to receive FCV to prevent a bad outcome (non-aborted lesions). With a positive NNT, this is interpreted as single-day FCV treatment of 112 patients results in one more person developing non-aborted lesions compared to the VCV control group.

***Time to next recurrence.*** Bodsworth et al. in 2009 was a follow-up study of Abudalu et al. to assess the long-term effect of episodic treatment on disease progression. 87.6% (324/370) of the FCV recipients and 89.8% (342/381) of the valacyclovir recipients agreed to participate in this subsequent study, and they were prohibited from initiating suppressive therapy within the 6-months following the healing of lesions. Of these patients, 61.1% of the FCV group and 60.6% of the VCV group experienced another recurrent outbreak during the follow-up period, with a mean time to next recurrence from treatment initiation of 33.5 days for FCV and 38.0 days for VCV (Table 4). [2]

**Table 4:** Time to next recurrence within 6-month follow-up period (Bodsworth et al., 2009)[2]

| | No. of patients who continued to the follow-up period | No. of patients with next recurrence during follow-up period | Median days to next recurrence from treatment initiation | Median of differences (days) | 95% CI |
|---|---|---|---|---|---|
| Famciclovir | 324 | 226 | 33.5 | -3.00 | (-8.00, 2.00) |
| Valacyclovir | 342 | 231 | 38.0 | | |

***Proportion with a recurrence.*** Suppressive therapy was analyzed in the study by Wald et al. by comparing 250 mg bid FCV with 500 mg q am VCV for 16 weeks, with primary endpoint being the proportion of patients that experienced a clinically confirmed recurrence during that period. The end results were similar between the two groups, with approximately 34% of the famciclovir group and 28% of the valacyclovir group having a recurrence at some point (Relative risk/hazard ratio = 1.10; 95% CI = 0.94-1.28). [6]

**Table 5**: Famciclovir vs. valacyclovir on suppression of genital herpes recurrences during 16 weeks of administration (Wald et al., 2006)[6]

| | Proportion with a clinically confirmed recurrence | Relative Risk/Hazard Ratio for Famciclovir | 95% CI | *P* Value |
|---|---|---|---|---|
| Famciclovir | 34% | 1.10 | (0.94-1.28) | *P* = 0.22 |
| Valacyclovir | 28% | | | |
| Treatment effects on patients with a recurrence | | | | |
| Proportion of VCV patients having a recurrence | Proportion of FCV patients having a recurrence | Relative Risk Reduction (RRR) | Absolute Risk Reduction (ARR) | Number needed to treat (NNT) |
| | | $\frac{\text{EER - CER}}{\text{CER}}$ | EER - CER | 1/ARR |
| 0.28 | 0.34 | 0.21 | 0.06 | 17 |

Table 5 summarizes the results and treatment effects of Wald et al. The ARR shows a small increase in rate of recurrence with the FCV group compared to the VCV group, and RRR represents the effectiveness of FCV and the relative probability of experiencing a recurrence with FCV treatment compared to VCV. NNT is calculated to determine the number of patients that need to receive FCV to prevent a recurrence, interpreted as daily FCV treatment of 17 patients over 16 weeks results in one more person developing a recurrence compared to the VCV control group.

***Exclusions and compliance.*** All studies utilized consisted of similar inclusion/exclusion criteria, with a few exceptions. Abudalu et al. prohibited the use of concurrent cimetidine and/or probenecid therapy due to drug interactions and the possibility of increasing FCV and VCV drug levels, and only Wald et al. specifically stated that those with a history of HSV resistant to acyclovir or penciclovir were to be excluded. Both studies also commented on a high rate of compliance with study medications. For Wald et al., median adherence was 100% and 98% for the VCV and FCV arm, respectively, while Abudalu et al. reported that 97% of the FCV patients received the proper 2 doses on day 1 and 92.2% of the VCV patients received all 6 doses over 3 days. [1,6]

***Safety and Tolerability.*** Adverse events in all trials were mostly mild to moderate in intensity, with headaches and nausea being the most common. Rates of AEs were similar between the two drugs (23.2% for FCV and 22.3% for VCV, NNH = 112, Abudalu et al.) and consistent with previously established safety profiles. In Abudalu et al., 2 patients in the FCV arm reported serious AEs of myocardial ischemia and suicide attempt, and 1 patient of the VCV arm reported polysubstance abuse. Hiatal hernia and chest pain were the only serious AEs reported by 2 subjects in the VCV treatment group of Wald et al., and both were deemed unrelated to the study medication. [1,6]

**Table 6**: Adverse Effects (Abudalu et al., 2008)

| Control Event Rate (CER) | Experimental Event Rate (EER) | Relative risk increase (RRI) | Absolute risk increase (ARI) | Number needed to harm (NNH) |
|---|---|---|---|---|
| | | $\frac{\text{EER - CER}}{\text{CER}}$ | EER - CER | 1/ARR |
| .223 | .232 | 0.0404 | 0.009 | 112 |

Table 6 outlines the treatment effects on AEs. A small RRI, ARI, and large NNH relative to the study indicate that AEs for both drugs were comparable.

DISCUSSION

While the trials by Wald et al. showed no major difference in time to first clinically confirmed recurrence, it did find a significant difference in time to first virologically confirmed recurrence and percentage of days with viral shedding, with VCV performing better than FCV. [6] However, a clinical connection failed to be made with this data and thus was not be included in this SR. This limitation exists across many studies due to the fact that viral load has been shown to exhibit a complex relationship with disease pathogenesis and transmission. With transmission being a big concern for many patients, this relationship needs to be further explored. [10] Likelihood of transmission is not based on viral titer alone, still occurs despite daily suppressive therapy, and may be affected by other factors such as site/size of area of exposure, viral strain, inoculum size, physiochemical barriers, innate immunity, and genetics. [9] The three trials analyzed in this review all showed similar efficacy between VCV and FCV based on clinically measurable factors, but Wald et al. and others have shown advantages to certain antivirals based on viral factors. [6,7] With FCV exhibiting a longer intracellular half-life, whereas VCV irreversibly terminates viral DNA replication, these subtle differences should encourage continued exploration on possible clinical benefits.[7] Additionally, the release of the results from Wald et al. were delayed for 7 years by the pharmaceutical companies, possibly in an attempt to suppress unfavorable data against FCV. [6,7]

The other limitation that remains in this SR is that Bodsworth et al. failed to include a placebo arm. Thus, assessments of short-course therapy on natural history of HSV could not be made. [2]

Acyclovir as an intervention was not considered in this review for a number of reasons. First of all, numerous RCTs have performed pair-wise comparisons of ACV with FCV and VCV,

already establishing comparable efficacy of the latter two with the former. Second, ACV's low bioavailability is seen as a disadvantage compared to the other antivirals, especially with VCV being converted to ACV once systemically absorbed with higher serum concentrations. Finally, fewer head-to-head comparisons of FCV with VCV have been published, which was the desired focus of this review. [7]

While both FCV and VCV have already been established as relatively safe drugs, it should be made aware that one known case of VCV-induced psychosis and mania was reported in 2009 in an adolescent female with no previous psych history. Previously, similar findings have only been limited to the elderly and immunocompromised with ACV and penciclovir. This represents an incredibly rare but serious adverse effect. [8]

## CONCLUSION

Based on this review, famciclovir is not superior to valacyclovir as a treatment for genital herpes in reducing outbreak frequency and duration. However, it appears to at least be equally effective, and the shorter single-day dosing schedule of FCV for herpes recurrence may provide a more convenient treatment option for some patients. Further comparative studies are warranted to investigate whether improvements in virologic disease manifestations from previous *in vivo* murine studies translate into clinically meaningful results. [7] In addition, variations in dosing regimens should be considered. These explorations could potentially have huge implications in regards to herpes patients' improvements in quality of life.

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