

A Randomized, Placebo-Controlled Comparison of Oral Valacyclovir and Acyclovir in Immunocompetent Patients With Recurrent Genital Herpes Infections

Stephen K. Tyring, MD, PhD; John M. Douglas, Jr, MD; Lawrence Corey, MD; Spotswood L. Spruance, MD; Jørgen Esmann, MD; for the Valaciclovir International Study Group

Objective: To compare valacyclovir hydrochloride with acyclovir in the treatment of recurrent genital herpes infection.

Design: A multicenter, double-blind, placebo-controlled, randomized, parallel-design study.

Setting: University clinics (dermatology, gynecology, and infectious diseases) and private practices.

Patients: One thousand two hundred patients with recurrent genital herpes simplex infections.

Interventions: Patients self-initiated oral therapy with 1000 mg of valacyclovir hydrochloride twice daily, 200 mg of acyclovir 5 times daily, or placebo for 5 days.

Main Outcome Measures: Resolution of all signs and symptoms of recurrent genital herpes infection.

Results: Both drugs were significantly more effective than placebo in speeding resolution of herpetic episodes (median duration, 4.8, 4.8, and 5.9 days, respectively); the hazards ratios for valacyclovir and acyclovir vs placebo were 1.66 (95% confidence interval [CI], 1.38-2.01) and 1.71 (95% CI, 1.41-2.06) (both $P < .001$). Similarly, vala-

cyclovir and acyclovir significantly hastened lesion healing (hazards ratios vs placebo were 1.88 [95% CI, 1.53-2.32] and 1.90 [95% CI, 1.55-2.34], respectively; $P < .001$). Pain duration was shorter in valacyclovir- and acyclovir-treated patients (median, 2 vs 3 days). Viral shedding stopped 2.55 times faster in patients treated with valacyclovir and 2.24 times faster in patients treated with acyclovir than in patients treated with placebo. Aborted episodes, in which lesions did not progress beyond the macule or papule stage, tended to occur in more patients treated with valacyclovir (25.9%) or acyclovir (24.8%) than in patients treated with placebo (19.8%). Valacyclovir and acyclovir did not differ significantly with regard to their respective effects on any of the above efficacy parameters. The nature, severity, and frequency of adverse events did not differ among the 3 treatment groups.

Conclusions: Twice-daily valacyclovir was as effective and well tolerated in the treatment of recurrent genital herpes simplex virus infection as 5-times-daily acyclovir. Therefore, valacyclovir could prove a useful alternative to acyclovir when convenience of dosing or compliance issues are the prime considerations in treatment.

Arch Dermatol. 1998;134:185-191

From the Department of Dermatology, University of Texas Medical Branch, Galveston (Dr Tyring); Denver Department of Public Health, Denver, Colo (Dr Douglas); Department of Laboratory Medicine, Virology Division, University of Washington, Seattle (Dr Corey); Department of Internal Medicine, University of Utah, Salt Lake City (Dr Spruance); and Department of Dermatology, Marselisborg Hospital, Aarhus, Denmark (Dr Esmann). Members of the Valaciclovir International Study Group are listed in the box on page 189.

THE INCIDENCE of genital herpes simplex virus (HSV) infections is rising worldwide.¹⁻⁵ Acyclovir (Zovirax, Glaxo Wellcome plc, Middlesex, England) has been widely used over the past decade as an effective and well-tolerated drug for the treatment of these infections.⁶⁻⁸ Studies have shown that acyclovir given at a dose of 200 mg 5 times daily for 5 days reduces the duration of viral shedding, time to healing, and time to cessation of new lesion formation,⁹⁻¹² and may completely prevent lesions from progressing beyond the macule or papule stage,⁹ if treatment is initiated within 24 hours of the first signs or symptoms of the recurrent HSV episode. The recommended regimen of acyclovir results in plasma acyclovir concentrations usually well above those needed to inhibit HSV type 1 and HSV type 2 replica-

tion,^{6,13} but proportionately higher concentrations cannot be achieved with increasing oral doses. Because of the low and limited oral bioavailability of acyclovir (approximately 20%¹⁴), and the possible compliance problems that can occur because of the 5-times-daily administration schedule, investigators have sought a prodrug of acyclovir that can produce high plasma acyclovir concentrations with fewer daily doses.

Valacyclovir (Valtrex, Glaxo Wellcome plc; formerly known as compound 256U87), the L-valine ester prodrug of acyclovir, is rapidly and almost completely converted to acyclovir after oral administration,¹⁵⁻¹⁷ increasing the oral bioavailability of acyclovir to 3 to 5 times that usually observed after administration of acyclovir.¹⁶ After multiple-dose administration of 1000 mg of valacyclovir 4 times daily to healthy adult volunteers, a peak mean (\pm SD) plasma

PATIENTS AND METHODS

PATIENTS

Eligible patients included otherwise healthy, immunocompetent males or females aged 13 years or older who had experienced 4 or more recurrences of genital herpes within the 12-month period prior to their entry into the study. Patients who had received long-term, suppressive acyclovir therapy within 12 months before the study were also eligible if they had had at least 1 recurrence within 3 months after treatment and within 3 months before the study. Patients were excluded from study participation if they had hepatic impairment (aspartate or alanine transaminase more than 3 times the upper limit of normal); renal impairment (estimated creatinine clearance <0.58 mL/s at North American sites or a serum creatinine level >120 $\mu\text{mol/L}$ at European sites); a history of hypersensitivity to acyclovir; a condition characterized by gastrointestinal malabsorption; were pregnant or were nursing mothers; received immunosuppressive, immunomodulatory, or other antiviral therapy; or were sexually active women of childbearing potential who were not using an effective contraceptive method.

STUDY DESIGN

This phase 3 multicenter, multinational clinical trial was double-blind, randomized, parallel-group, and 3-arm in design. It was conducted at 53 study centers, including 30 in Europe, 20 in the United States, and 3 in Canada. The study protocol was approved by the institutional review board at each study site, and written informed consent was obtained from all patients (or parents for patients younger than 18 years) after the nature of the procedures had been fully explained.

TREATMENT ALLOCATION AND PROCEDURES

At the screening visit, patients provided a medical history and underwent a physical examination, measurement of vital signs, clinical laboratory tests, and quantitative urinalysis of protein and blood. A pregnancy test was performed for women

of childbearing potential. A blood sample was obtained and assayed for HSV antibodies. Eligible patients were assigned to receive 1 of the following treatments for 5 days according to a 3:3:1 randomization schedule: oral valacyclovir, 1000 mg twice daily; oral acyclovir, 200 mg 5 times daily; or placebo 5 times daily. The study drug was supplied as capsules containing valacyclovir base as the hydrochloride salt plus excipient, or acyclovir (each with matching placebo capsules).

Patients were instructed to self-initiate treatment within 24 hours of the first signs or symptoms of a recurrence and to return to the clinic within 24 hours of starting treatment. Herpetic lesions were evaluated by clinicians on days 1, 2, 3, 5, and 7. In addition, patients kept a daily diary documenting the occurrence of any prodromal symptoms, compliance with medication schedules, and their assessments of pain, discomfort, and lesion healing. Evaluation continued at twice-weekly intervals after day 7 until all lesions had healed and clinical symptoms had resolved. At each clinic visit, existing herpetic lesions were classified by clinicians as macule/papule, vesicle/pustule/ulcer, crust, or healed lesion. Pain was classified by patients as none, mild, moderate, or severe. Lesions that did not progress beyond the macule/papule stage (including prodrome only) to the vesicular/ulcerative stage were considered aborted lesions. Clinicians' observations in the clinic and data in the patient diary were used to determine end points, unless the results conflicted, in which case the clinic observations took precedence. Viral swabs for HSV cultures were obtained from lesions at each visit for determination of viral shedding.

EFFICACY END POINTS

Primary efficacy end points included (1) length of episode, defined as the number of days between initiation of treatment and complete resolution of all symptoms and signs, including aborted episodes; and (2) time to lesion healing, defined as the number of days between initiation of treatment and complete reepithelialization of all lesions. With regard to the latter end point, residual erythema could still be present, but aborted episodes were excluded. Secondary efficacy end points included (1) viral shedding, in terms of the number of days between treatment initiation and the first negative lesion culture, with no subsequent positive virus

concentration of 4.96 ± 0.64 mg/mL (22 $\mu\text{mol/L}$) was reached, and an average area under the plasma acyclovir concentration vs time curve (AUC) of 15.70 ± 2.27 h- $\mu\text{g/mL}$ (69.7 $\mu\text{mol/L}$) was obtained.¹⁶

The objective of this phase 3 multicenter, double-blind, placebo-controlled trial was to compare the clinical efficacy and safety of a twice-daily valacyclovir regimen with that of a 5-times-daily acyclovir regimen in the acute treatment of recurrent genital HSV infection in immunocompetent patients.

RESULTS

PATIENT DEMOGRAPHICS AND ACCOUNTABILITY

A total of 1725 patients were enrolled at 53 study sites and randomized to treatment. Of these patients, 1200 experienced signs and symptoms of an HSV recurrence

and returned to the clinic having initiated treatment (intent-to-treat population); 525 patients had no recurrence and were excluded from analysis. There were no significant differences among the treatment groups with regard to demographic or baseline HSV characteristics (**Table 1**) or baseline hematology, blood chemistry, or urinalysis values (data not shown). Within the intent-to-treat group, 128 patients prematurely discontinued from the study primarily because of unavailability for follow-up (69 patients) or major protocol violations (26 patients) (Table 1). Overall, there were 230 patients in the intent-to-treat group with major deviations or violations from the protocol, including 114 (9.5%) who failed to initiate treatment within 24 hours, 57 (4.8%) who failed to take more than 80% of their study medication, 29 (2.4%) who failed to initiate treatment with a full dose of medication, 27 (2.3%) who took other antiviral or immunomodulatory drugs, and 3 (1.3%) with other protocol violations.

culture and proportions of patients never having a positive culture; (2) duration of pain, defined as the number of days between treatment initiation or the start of pain or discomfort and its complete resolution; (3) severity of pain and discomfort (categorized as none, mild, moderate, or severe); and (4) proportion of patients with aborted episodes.

QUANTITATION OF ACYCLOVIR IN PLASMA SAMPLES

Blood samples (5 mL) for determination of plasma acyclovir concentrations were taken on days 2 and 5 of the treatment period. Acyclovir concentrations were assayed by scintillation proximity radioimmunoassay.¹⁶ The area under the plasma acyclovir concentration vs time curve was calculated for patients receiving each active treatment to estimate comparative acyclovir exposure.

HSV ISOLATION

Swabs from genital lesions were passed in virus transport media, and an aliquot of this medium was used to inoculate monolayers of cultured cells at each participating study center. The cells were incubated at 37°C and examined daily for evidence of characteristic HSV cytopathic effects.

SERUM ANTIBODY ASSAY

Serum samples obtained at the time of the screening visit were frozen at -20°C and assayed for HSV type 2 antibodies as necessary, for patients for whom there was no documented history of a positive HSV culture and no positive culture during the treatment period. The assays were done by the Western blot procedure.¹⁸

SAFETY ANALYSIS

Safety evaluation included adverse event reporting at each visit and laboratory testing (hematology, blood chemistry, and urinalysis) at screening and on days 1 and 5. Investigators classified adverse events as to their seriousness, intensity, and possible causal relationship to study drug.

STATISTICAL ANALYSIS

A sample size of 450 patients in each active treatment group and 150 patients in the placebo group was chosen because it had sufficient power to detect differences between treatments in the length of episode (duration of all signs and symptoms) assuming proportional hazards functions. For comparison of valacyclovir and acyclovir treatment groups, the 450-patient sample size provided approximately 80% power to detect hazards ratios (HRs) of 0.83 or less and 1.2 or greater at the 5% significance level. For comparison of the valacyclovir or acyclovir group and the placebo group, the sample size provided more than 80% power to detect a 15% reduction in the proportion of patients with signs or symptoms at day 5, assuming that 60% of the placebo group had signs or symptoms at day 5.

The principal analysis was by intent-to-treat for all primary, secondary, and safety end points. The distributions of primary and secondary time-to-event end points were estimated using the Kaplan-Meier product limit survival method and were used to calculate median values. Differences between treatment groups were tested using Cox proportional hazards models that adjusted for any baseline imbalances and were expressed as the HR and the 95% confidence interval (CI) of the ratio. Hypothesis testing was performed on each primary end point for which the study was powered, with $P \leq .05$ considered significant. All tests were 2 tailed. Differences between treatment groups for secondary end points measuring proportions of patients were examined with the Cochran-Mantel-Haenszel test, controlling for sex and study center, and expressed as the relative risk and the 95% CI of the risk. Exploratory analyses of the intent-to-treat group examined the effect of age, time from prodrome or first sign to initiation of treatment, estimated amount of acyclovir absorbed, prior use of acyclovir for suppression, and the historical frequency of genital herpes recurrences. Age and time from prodrome or first signs to initiation of treatment were fitted as continuous variables to the Cox proportional hazards models; prior use of suppressive acyclovir (used vs not used) and number of recurrences in the previous year (≤ 8 vs ≥ 9) were also incorporated.

PRIMARY EFFICACY END POINTS

Length of Episode

Both valacyclovir and acyclovir treatments significantly decreased the length of HSV episode compared with placebo ($P < .001$). The median times to episode resolution were 4.8 and 4.8 days for valacyclovir and acyclovir, respectively, compared with 5.9 days for placebo (**Table 2** and the **Figure**). The episode had resolved in an estimated 75% of patients within 6 days with active drug treatment compared with 8 days with placebo. Hazards ratios (Table 2) indicated that episodes resolved 1.66 and 1.71 times faster in the valacyclovir and acyclovir groups, respectively, relative to placebo. No differences between valacyclovir and acyclovir were detected with regard to this efficacy parameter (HR, 0.98; 95% CI, 0.85-1.12).

Exploratory analysis of prognostic factors showed that patient sex did not markedly affect the length of epi-

sode (HR, 0.90; $P = .13$), although age did (HR, 0.99; $P < .001$). In younger patients, HSV episodes resolved faster than in older patients, eg, a patient 20 years younger than another could expect episodes to resolve about 23% faster. Analyses also suggested that earlier treatment was more beneficial in resolving episodes (HR, 0.99; $P = .01$), eg, patients initiating treatment within 6 hours after the prodrome achieved 11% faster episode resolution than those starting after 24 hours. In patients who experienced 8 or fewer recurrences within the previous year, episode resolution appeared to be 19% faster than in those experiencing 9 or more recurrences per year (HR, 0.81; $P = .003$).

Lesion Healing Time

Both valacyclovir and acyclovir significantly reduced time to lesion healing compared with placebo ($P < .001$). Median healing times were 4.8 and 4.8 days,

Table 1. Baseline Patient Characteristics and Disposition Status

Characteristics	Treatment Group		
	Valacyclovir Hydrochloride (n=512)	Acyclovir (n=506)	Placebo (n=182)
Mean age, y (range)	36 (17-77)	36 (19-79)	35 (20-74)
Sex, %			
Female	50.4	53.0	51.1
Male	49.6	47.0	48.9
Mean time since first genital HSV* episode, y (range)	6.8 (0-52)	6.9 (0-46)	6.5 (0-24)
Frequency of recurrent genital HSV in the preceding 12 mo, %			
≤8	70	66	68
≥9	30	33	32
History of positive HSV culture from a genital lesion, %	22	21	22
Prophylactic use of acyclovir in the preceding 12 mo, %	12	11	14
Herpes disease elsewhere, %	23	23	25
Facial	18	18	18
Ocular	0.2	0	1
Other	5	5	6
Premature study drug discontinuation, No. (%)	51 (10)	57 (11)	20 (11)
Serologic confirmation of HSV infection required, %	43.3	42.5	24.2

*HSV indicates herpes simplex virus.

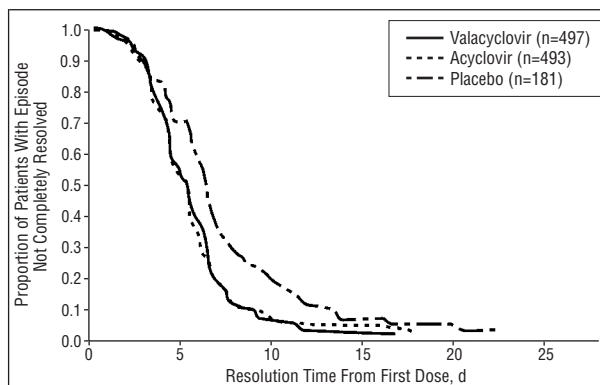
Table 2. Primary Efficacy End Points: Length of Episode and Lesion Healing Time*

Treatment	Median Event Duration, d	HR (95% CI) (Active Drug vs Placebo)
Length of Episode		
Valacyclovir hydrochloride	4.8	1.66 (1.38-2.01)
Acyclovir	4.8	1.71 (1.41-2.06)
Placebo	5.9	...
Lesion Healing Time		
Valacyclovir	4.8	1.88 (1.53-2.32)
Acyclovir	4.8	1.90 (1.55-2.34)
Placebo	6.0	...

*P<.001 for all comparisons with the corresponding placebo group. There were no statistically significant differences between the outcomes for the 2 active treatment arms. HR indicates hazards ratio; CI, confidence interval.

respectively, vs 6.0 days (Table 2 and Figure). Hazards ratios (Table 2) indicated that lesions healed 1.88 and 1.90 times faster in patients treated with valacyclovir and acyclovir, respectively, than in patients treated with placebo. No differences between valacyclovir and acyclovir were detected with regard to this efficacy parameter (HR, 0.99; 95% CI, 0.85-1.15).

Exploratory analysis of prognostic factors showed that healing time was 15% shorter in female patients than in male patients (HR, 0.85; P=.03). The lesion healing rate also showed a tendency to be faster in younger patients (HR, 0.99; P=.07), eg, patients 20 years younger than another could expect lesions to heal



Time to herpes simplex virus infection episode resolution for patients treated with valacyclovir hydrochloride, acyclovir, and placebo.

about 13% faster. In patients who experienced 8 or fewer recurrences within the previous year, the lesion healing rate appeared to be 18% faster than in patients experiencing 9 or more recurrences per year (HR, 0.82; P=.01). Time from onset of first signs or symptoms to treatment initiation did not significantly influence lesion healing.

SECONDARY EFFICACY END POINTS

Aborted Episodes

The proportion of patients with aborted episodes was higher in the valacyclovir and acyclovir groups (25.9% and 24.8%, respectively) than in the placebo group (19.8%), although the differences did not attain statistical significance. The frequency of aborted episodes in males and females in the valacyclovir group was similar (24.8% and 27.0%, respectively); however, in the acyclovir treatment group, more females than males had aborted episodes (28.4% vs 20.9%). More male patients who received valacyclovir had aborted episodes than males who received placebo (24.8% vs 13.5%).

Viral Shedding

At least 1 virus culture was obtained from approximately 90% of patients in each treatment group. Culture results were negative in 49% of the valacyclovir and acyclovir treatment groups, respectively, compared with 29% of the placebo group (Table 3). One or more positive HSV culture results were obtained from a greater proportion of placebo recipients compared with those receiving valacyclovir or acyclovir. For patients with at least 1 positive viral culture, both valacyclovir and acyclovir significantly reduced the duration of viral shedding compared with placebo (median duration, 2 days for both vs 4 days for placebo), with no differences between the 2 active agents (Table 4 and Figure). Hazards ratios indicated that the duration of viral shedding was 2.55 and 2.24 times longer in patients treated with placebo than in patients treated with valacyclovir and acyclovir, respectively (P<.001). Viral shedding tended to cease earlier in female patients than in male patients (HR=0.85, P=.12).

Table 3. Viral Shedding

	Treatment Group, No. (%) of Patients		
	Valacyclovir Hydrochloride	Acyclovir	Placebo
No lesion, no swab, or no results Swabbed	55 (10.7)	57 (11.3)	15 (8.2)
≥1 positive result	209 (40.8)	201 (39.8)	114 (62.6)
All cultures negative	248 (48.4)	247 (48.9)	53 (29.1)
Negative result recorded within 24 h of treatment initiation	185 (74.6)	197 (79.8)	37 (69.8)

Table 4. Secondary Efficacy End Points: Duration of Pain and of Virus Shedding*

Treatment	Median Event Duration, d	HR (95% CI) (Active Drug vs Placebo)	P
Duration of Pain			
Male			
Valacyclovir hydrochloride	2.0	1.39 (1.07-1.81)	.01
Acyclovir	2.6	1.32 (1.01-1.71)	.04
Placebo
Females			
Valacyclovir	3.0	1.33 (1.02-1.73)	.03
Acyclovir	3.0	1.39 (1.07-1.81)	.01
Placebo	4.0
Duration of Virus Shedding			
Valacyclovir	2.0	2.55 (1.91-3.40)	<.001
Acyclovir	2.0	2.24 (1.68-2.98)	<.001
Placebo	4.0

*HR indicates hazards ratio; CI, confidence interval.

Duration and Severity of Pain and Discomfort

Valacyclovir and acyclovir significantly decreased the duration of pain and discomfort compared with placebo ($P < .05$) in both males (median duration, 2, 2, and 3 days, respectively) and females (median duration, 3, 3, and 4 days, respectively) (Table 4). At day 3, there was strong evidence to suggest differences in proportions of patients with pain in each severity category among valacyclovir- and acyclovir-treated patients compared with placebo-treated patients ($P < .001$ and $P = .001$, respectively). Only 12% and 15% of patients in the valacyclovir and acyclovir groups, respectively, reported moderate or severe pain or discomfort compared with 25% of patients receiving placebo. By day 7, only 9% of patients in the valacyclovir and acyclovir groups reported pain or discomfort compared with 17% of patients in the placebo group ($P = .05$ and $P = .06$, respectively). No differences were detected between valacyclovir and acyclovir at day 3 or 7.

PLASMA ACYCLOVIR CONCENTRATIONS

For patients receiving 1000 mg of valacyclovir, the maximum average plasma acyclovir concentration was 4.29 $\mu\text{g/mL}$ (19.0 $\mu\text{mol/L}$) and the estimated average single-dose AUC was 20.6 h· $\mu\text{g/mL}$ (91.5 h· $\mu\text{mol/L}$).

The Valacyclovir International Study Group

F. Aoki, MD, University of Manitoba, Winnipeg; K. Beutner, MD, PhD, Solano Dermatology Associates, Vallejo, Calif; L. Bondesson, MD, Karolinska Hospital, Stockholm, Sweden; S. Borelli, MD, T. U. München, Munich, Germany; K. Bork, MD, Klinikum der Johannes-Gutenberg Universität, Mainz, Germany; B. Coble, University Hospital, Linköping, Sweden; L. Corey, MD, University of Washington, Seattle; E. Curless, MD, Bolton General Hospital, Bolton, England; B. M. Czametzki, MD, Universitätsklinikum Rudolf Virchow, Berlin, Germany; J. Douglas, MD, Denver Department of Public Health, Denver, Colo; L. Eron, MD, Infectious Disease Physicians Inc, Annandale, Va; J. Esmann, MD, Marselisborg Hospital, Aarhus, Denmark; K. Fife, MD, PhD, Indiana University Medical School, Indianapolis; C. Forszpaniak, MD, Diagnostic Services Inc, Naples, Fla; L. Goldberg, MD, Houston, Tex; A. Halsos, MD, Venerology Clinic, Health Council, Oslo, Norway; P. Hino, MD, Dermatology Center of Dallas, Dallas, Tex; H. J. Hulsebosch, MD, PhD, Academisch Medisch Centrum, Amsterdam, the Netherlands; R. H. Kaufman, MD, Baylor College of Medicine, Houston; H. Kessler, MD, Rush-Presbyterian-St Lukes Medical Center, Chicago, Ill; G. R. Kinghorn, MD, Royal Hallamshire Hospital, Sheffield, England; S. Kroon, MD, Odense Hospital, Odense, Denmark; T. Kurtz, DO, Des Moines, Iowa; W. Lang, MD, ViRx Inc, San Francisco, Calif; J. Lauharanata, MD, Helsinki University Central Hospital, Department of Dermatology/Venereology, Helsinki, Finland; L. Lefkowitz, MD, Vanderbilt School of Medicine, Nashville, Tenn; A. Martel, MD, University of Laval, St Foy, Quebec; C. McDonald, MD, Roger Williams Medical Center, Providence, RI; G. J. Mertz, MD, University of New Mexico, Albuquerque; P. Morel, MD, Hospital Saint Louis, Paris, France; R. Murphy, MD, Northwestern Memorial Hospital, Chicago; M. Negosanti, MD, Università degli Studi, Bologna, Italy; A. Nilsen, MD, Haukeland Hospital, Bergen, Norway; J. Paavonen, MD, Helsinki University Central Hospital, Helsinki; P. Piot, MD, Institute of Tropical Medicine, Antwerp, Belgium; K. Ramsey, MD, University of South Alabama, Mobile; T. Ruffli, MD, Kantonsspital, Basel, Switzerland; M. Ruhnek-Forsbeck, MD, Sophiahemmet, Stockholm; S. Sacks, MD, University of British Columbia, Vancouver, British Columbia; S. Safrin, MD, San Francisco General Hospital; J. Soltz-Szots, MD, Hospital Rudolfstiftung, Vienna, Austria; S. L. Spruance, MD, University of Utah, Salt Lake City; J. P. Stahl, MD, CHU de Grenoble, Grenoble, France; G. Stingi, MD, University Clinic of Dermatology, Vienna, Austria; A. Strand, MD, Akademiska Hospital, Uppsala, Sweden; P. Taylor, MD, Bristol Royal Infirmary, Bristol, England; R. N. Thin, MD, St Thomas' Hospital, London, England; S. Tyring, MD, PhD, University of Texas Medical Branch, Galveston; E. Van Hecke, MD, Universitair Ziekenhuis RU Gent, Ghent, Belgium; M. Van Heenen, MD, Hôpital Erasme, Brussels, Belgium; G. Vejlsgaard, MD, Rigshospitalet, Copenhagen, Denmark; J. Welch, MD, Kings College Hospital, London; A. M. Worm, MD, Bispebjerg Hospital, Copenhagen.

Corresponding estimates for the acyclovir recipients, after adjustment for unequal dose intervals, were 0.72 $\mu\text{g/mL}$ (3.2 $\mu\text{mol/L}$) for the maximum average concentration during the day and 2.27 h·mg/mL (10.1 h· $\mu\text{mol/L}$) for the single-dose AUC. For twice-daily valacyclovir dosing and

Table 5. Adverse Events Reported by 2% or More of Patients in Any Treatment Group

Adverse Event	Treatment Group, No. (%) of Patients		
	Valacyclovir Hydrochloride (n=510)	Acyclovir (n=508)	Placebo (n=181)
Headache	81 (16)	68 (13)	26 (14)
Nausea	30 (6)	37 (7)	21 (12)
Diarrhea	25 (5)	15 (3)	10 (6)
Abdominal pain	13 (3)	15 (3)	7 (4)
Dizziness	17 (3)	13 (3)	4 (2)
Asthenia	9 (2)	14 (3)	5 (3)
Dyspepsia	9 (2)	7 (1)	6 (3)
Rhinitis	4 (1)	14 (3)	2 (1)
Pain	4 (1)	9 (2)	4 (2)

5-times-daily acyclovir administration, the AUC values corresponded to average daily acyclovir AUCs of 41.2 h·µg/mL (183 h·µmol/L) and 11.35 h·µg/mL (50 h·µmol/L) for the valacyclovir and acyclovir regimens, respectively.

ADVERSE EVENTS AND LABORATORY FINDINGS

The most frequent adverse events were headache, nausea, diarrhea, and abdominal pain, and these were reported in a similar proportion of patients in each treatment group (**Table 5**). Of 6 serious adverse events reported, only 3, which occurred in 1 patient treated with acyclovir (poor concentration, feeling “spaced,” and feeling “tired”) were considered possibly attributable to study medication. Of the 9 treatment-limiting adverse events (events resulting in premature discontinuation of study drug) reported, 4 were noted in the valacyclovir group (headache [2 patients]; nausea and stomach cramps [2 patients]), 4 in the acyclovir group (nausea, diarrhea, vomiting, and gastritis, in 1 patient each), and 1 in the placebo group (pain at lesion site). No significant treatment-related change from baseline occurred in any clinical chemistry, hematology, or urinalysis parameter.

COMMENT

Our results indicate that the treatment of recurrent genital HSV infections with a twice-daily regimen of valacyclovir or a 5-times-daily regimen of acyclovir, administered for 5 days, is significantly more effective than placebo in decreasing the overall length of an episode, lesion healing time, duration of pain and discomfort, and the duration of viral shedding, with no significant differences between the 2 treatments. With a study population of 1200 patients, this is, to our knowledge, the largest clinical trial conducted to date to assess the efficacy and safety of antiviral agents as episodic treatment for patients with recurrent genital HSV infections.

The pattern of clinical improvement noted in the valacyclovir treatment group in this study was similar to that previously reported by Spruance et al¹⁹ in their large-scale, multicenter, placebo-controlled clinical trial, in which 987 otherwise healthy patients with recurrent genital herpes infections were treated with the same 1000- or a 500-mg

valacyclovir 5-day dosing regimen. As patients in both studies had very similar demographic and disease characteristics, and treatment was initiated at approximately the same time following onset of signs and symptoms (≤ 24 hours), major differences in study results would not have been expected. However, there were differences in the magnitude of changes in certain parameters. Spruance et al¹⁹ found that treatment with valacyclovir, 1000 or 500 mg twice daily, was associated with a more dramatic reduction in the length of the herpetic episode (median duration, 4.0 days vs 4.8 days in the present study) and lesion healing time (median, 4.1 days vs 4.8 days). As for secondary efficacy parameters, the findings of the present study were in close agreement with those of Spruance et al¹⁹ with respect to increase in the frequency of aborted episodes (25.9% vs 28.0%), decreasing the duration of pain in females (median, 3.0 days in both studies), and decreasing the duration of virus shedding (median, 2.0 days in both studies). However, we found that the valacyclovir 1000-mg regimen more markedly reduced the duration of pain in males (median, 2.0 days vs 2.6 days) (the median in the placebo group was 3.0 days in both studies).

The pattern of improvement in the acyclovir group was comparable to that reported in previous placebo-controlled clinical trials in which a 5-day regimen of acyclovir, 200 mg 5 times a day, was evaluated in immunocompetent patients with recurrent genital HSV infection.^{9-12,20} In contrast to the present study, these clinical trials involved smaller numbers of patients treated with acyclovir (31 to 106 patients vs 506 patients in the present study), examined fewer efficacy parameters, analyzed and reported treatment differences in efficacy parameters in terms of means instead of medians, and were inconsistent or unclear with regard to time of initiation of treatment (which varied from “at the earliest sign of a recurrence”⁹ to within 48 hours of signs and symptoms¹⁰). In only 3 of the 5 clinical trials was treatment initiated by patients, as it was in our study. Patient-initiated treatment has been shown to lead to a significantly faster healing time in recurrent genital HSV infections than clinic-initiated therapy.^{9,11} In all of the studies in which acyclovir treatment was patient initiated, the mean lesion healing time was reduced by approximately 1 to 2 days compared with placebo.^{9,11,20} In the present study, the median lesion healing time was likewise reduced by approximately 1 day (4.8 days vs 6.0 days with placebo) in the acyclovir treatment group. Reichman et al¹¹ found that the duration of virus shedding in patients treated with acyclovir was reduced by a mean of 1.7 days below the placebo value of 3.9 days, which is in agreement with the 2-day median reduction shown in the present study. The present study showed a significant reduction in the duration of pain with acyclovir treatment, in contrast to the smaller-scale study by Reichman et al,¹¹ who found that the change with treatment was not statistically significant.

There may be several reasons why no differences were detected between the valacyclovir and acyclovir treatments for the primary efficacy end points. The exact influence of peak or trough acyclovir plasma concentrations, frequency of high peak plasma acyclovir concentrations, or the overall daily AUC in terminating vi-

ral replication are not well understood. Although pharmacokinetic data in this study show that acyclovir plasma concentrations are substantially higher after administration of valacyclovir than acyclovir, such high concentrations may not be necessary because HSV types 1 and 2 are the most sensitive of all the human herpesviruses to acyclovir, the inhibitory concentration (IC₅₀) values averaging 0.02 µg/mL (0.1 µmol/L) and 0.22 µg/mL (1.0 µmol/L), respectively.^{6,13} Additional increments of antiviral efficacy may, therefore, be difficult to detect beyond what have already been achieved with acyclovir exposure from the standard oral regimen.

The exploratory investigation in this study also permitted an assessment of the effect of age, HSV recurrence frequency history, and patient sex on efficacy parameters. Age and HSV recurrence history (number of recurrences in the previous year) significantly influenced the overall length of episode and lesion healing time, with resolution times being longer in older patients and those experiencing more frequent recurrences. The time to treatment initiation after prodrome or first sign of a recurrence was only important in relation to length of episode, the parameter that included data from patients with aborted lesions. Previous studies have shown that early acyclovir treatment is preferable,²¹ which is supported by the exploratory results of the present trial. Both valacyclovir and acyclovir decreased the duration of pain and discomfort most markedly at study day 3, and the effect was more pronounced overall in male patients. The sex effect on pain and discomfort is consistent with that seen in previous studies.^{6,22} The greatest difference between valacyclovir and placebo with respect to the percentage of patients with aborted episodes (24.8% vs 13.5%) was also observed in male patients in this study.

One of the major goals of antiviral chemotherapy of recurrent HSV disease is to abort lesions. In this study, aborted episodes occurred in marginally more patients treated with valacyclovir and acyclovir than in those treated with placebo, but these differences did not attain statistical significance ($P=.10$). Previous investigations^{9,20} similarly found only trends for more aborted episodes of genital herpes in patients treated with the same acyclovir regimen that was evaluated in the present study. However, Spruance et al¹⁹ found that 5 days' treatment with either 1000 or 500 mg of valacyclovir twice daily significantly increased the overall frequency of aborted episodes by 40%, from 21% in the placebo arm to 28% to 31% with active treatment. The disparity among studies may be due to differences in baseline disease characteristics of the populations evaluated (eg, recurrence frequency or disease severity) or to design differences (eg, whether patient initiated early therapy was possible).

In this study, the daily acyclovir AUC estimates of 41.2 and 11.35 h·µg/mL (183 and 50 h·µmol/L) for the valacyclovir and acyclovir regimens, respectively, allowed the conclusion that the oral bioavailability of acyclovir from 1000 mg of valacyclovir is 2.62 times greater than that from 200 mg of oral acyclovir. Using the historical estimate of 20% for bioavailability from 200-mg oral acyclovir, this implies that the acyclovir bioavailability from 1000-mg valacyclovir dosing was approximately 52% in this study, which is similar to previous estimates.¹⁷ Interestingly, however, this higher systemic exposure of patients to acyclovir following

valacyclovir administration did not change the quality or quantity of adverse events, nor did it alter laboratory findings.

In conclusion, as twice-daily valacyclovir is as effective and well tolerated in the treatment of recurrent genital HSV infection as 5-times-daily acyclovir, it could prove a useful alternative to acyclovir when convenience of dosing or compliance issues are the prime considerations in treatment.

Accepted for publication September 16, 1997.

This study was funded by Glaxo Wellcome plc, Middlesex, England.

Presented in part at the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La, October 20, 1993.

Reprints: Stephen K. Tyring, MD, PhD, University of Texas Medical Branch, Department of Dermatology, Galveston, TX 77555-1019 (e-mail: Tyring@flash.net).

REFERENCES

- Johnson R, Lee F, Hadgu A, et al. US genital herpes trends during the first decade of AIDS prevalences increased in young whites and elevated in blacks. Presented at the International Society of Sexually Transmitted Disease Research; August 1993; Helsinki, Finland. Abstract 113.
- Johnson RE, Nahmias AJ, Magder LS, et al. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med*. 1989;321:7-12.
- Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*. 1983; 98:958-972.
- Webb DH, Fife KH. Genital herpes simplex virus infections. *Sex Transm Dis*. 1987; 1:97-122.
- Thin RL. Management of genital herpes simplex infections. *Am J Med*. 1988;85 (suppl 2A):3-6.
- O'Brien JJ, Campoli-Richards DM. Acyclovir: an updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*. 1989;37: 233-309.
- Whitley RJ, Gnann JW. Acyclovir: a decade later. *N Engl J Med*. 1992;327:782-789.
- Wagstaff AJ, Faulds D, Goa KL. Aciclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*. 1994;47:153-205.
- Goldberg LH. Oral acyclovir for episodic treatment of recurrent genital herpes: efficacy and safety. *J Am Acad Dermatol*. 1986;15:256-264.
- Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet*. 1982;1:571-573.
- Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. *JAMA*. 1984;251:2103-2107.
- Salo AP, Lassus A, Hovi T, Fiddian AP. Double-blind placebo controlled trial of oral acyclovir in recurrent genital herpes. *Eur J Sex Transm Dis*. 1983;1:95-98.
- Kucera LS, Furman PA, Elion GB. Inhibition by acyclovir of herpes simplex virus type 2 morphologically transformed cell growth in tissue culture and tumor-bearing animals. *J Med Virol*. 1983;12:119-127.
- de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother*. 1983;12(suppl B):29-37.
- Burnette TC, deMiranda P. Metabolic disposition of the acyclovir prodrug valacyclovir in the rat. *Drug Metab Dispos*. 1994;22:60-64.
- Weller S, Blum MR, Doucette M, et al. Pharmacokinetics of the acyclovir prodrug, valacyclovir after escalating single- and multiple-dose administration to normal volunteers. *Clin Pharmacol Ther*. 1993;54:595-605.
- Soul-Lawton J, Seaber E, On N, et al. Absolute bioavailability and metabolic disposition of valacyclovir, the L-valyl ester of acyclovir, following oral administration to humans. *Antimicrob Agents Chemother*. 1995;39:2759-2764.
- Ashley R, Cent A, Maggs V, Nahmias A, Corey L. Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus types 1 and 2. *Ann Intern Med*. 1991;115:520-526.
- Spruance SL, Tyring SK, Digregorio B, Miller C, Beutner K, the Valacyclovir HSV Study Group. A large-scale placebo-controlled trial of peroral valacyclovir for episodic treatment of recurrent herpes genitalis. *Arch Intern Med*. 1996;156:1729-1735.
- Ruhnek-Fosbeck M, Sandstrom E, Andersson B, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. *J Antimicrob Chemother*. 1985;16:621-628.
- Goldberg LH, Kaufman R, Conant MA, et al. Episodic twice-daily treatment for recurrent genital herpes. *Am J Med*. 1988;85(suppl 2a):10-13.
- Bryson YL, Dillon M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. *N Engl J Med*. 1983;308:916-921.