Intravenous Penciclovir for Treatment of Herpes Simplex Infections in Immunocompromised Patients: Results of a Multicenter, Acyclovir-Controlled Trial

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Received 29 September 1998/Returned for modification 7 December 1998/Accepted 22 February 1999

The efficacy and safety of penciclovir (PCV) for the treatment of herpes simplex virus (HSV) infections in immunocompromised (IC) patients were studied in a double-blind, acyclovir (ACV)-controlled, multicenter study. A total of 342 patients with mucocutaneous HSV infections received 5 mg of PCV per kg every 12 or 8 h (q12h or q8h) or 5 mg of ACV per kg q8h, beginning within 72 h of lesion onset and continuing for up to 7 days. The mean age of the patients was 49 years; 94% were white and 52% were female. The main reasons for their IC states were hematologic disorder (63%) and transplant plus hematologic disorder (16%). Clinical and virological assessments were performed daily during the 7-day treatment and then every other day until lesion healing. The primary efficacy parameter addressed new lesion formation. Secondary end points focused on viral shedding, healing, and pain. Approximately 20% of patients in each treatment group developed new lesions during therapy; thus, equivalence with ACV (defined prospectively) was demonstrated for both q12h and q8h PCV regimens. For all three treatment groups, the median time to the cessation of viral shedding was 4 days and the median time to complete healing was 8 days; there were no statistically significant differences in the rates of complete healing or the cessation of viral shedding when the results for PCV q12h and q8h were compared with those for ACV q8h. In addition, there was no statistically significant difference between PCV q12h or q8h, compared with ACV q8h, for the resolution of pain. PCV was well tolerated, with an adverse event profile comparable to that of ACV. In conclusion, PCV q12h is a well-tolerated and effective therapy for mucocutaneous HSV infection in IC patients and offers a reduced frequency of dosing compared with ACV q8h.

Herpes simplex virus (HSV) infections in immunocompetent patients are of relatively short duration and are generally self-limiting (15). HSV infections in an immunocompromised host, however, may be severe and prolonged and can spread without treatment, causing severe morbidity or mortality (9). The reactivation rate among seropositive transplant patients has been reported to be between 60 and 80% for patients with solid organ transplants and over 80% after allogenic bone marrow transplantation (6, 10, 12, 20). Intravenous treatment with acyclovir (5 mg/kg every 8 h [q8h] for 7 days), effective for the treatment of mucocutaneous HSV infection in immunocompetent patients, is the most commonly used therapy (7, 8, 20).

Penciclovir, a novel acyclic nucleoside analog, has demonstrated efficacy in cell culture against HSV types 1 and 2 as well as against varicella-zoster virus (2). The intracellular triphosphatase of penciclovir is considerably more stable than acyclovir triphosphate (in vitro half-life of 10 to 20 h in HSV-infected cells compared to 0.7 to 1 h for acyclovir), a potential pharmacological advantage for penciclovir (19). Also, penciclovir has been shown to be effective against a small percentage of acyclovir-resistant HSV strains in vitro (2). This activity may translate into a potential benefit in a subgroup of patients in whom the virus has become resistant to acyclovir, an important consideration for an immunocompromised patient population. A topical formulation of penciclovir currently is marketed for the treatment of recurrent herpes labialis in immunocompetent patients. Famciclovir, the orally bioavailable prodrug, is approved in the United States and other countries for the treatment of acute herpes-zoster virus infection and the treatment and suppression of genital herpes (14, 16, 17).

The results of an open, dose-escalation study of intravenously administered penciclovir in immunocompromised patients with mucocutaneous HSV infections indicated that intravenously administered penciclovir was effective for the treatment of mucocutaneous HSV infection in immunocompromised patients (18). The optimum intravenous dose of penciclovir for the treatment of HSV disease in such patients was 5 mg/kg q8h or every 12 h (q12h). The present report describes a randomized, double-blind, multicenter study comparing these two doses of intravenous penciclovir with acyclovir (5 mg/kg q8h for 7 days) for the treatment of mucocutaneous HSV infections in immunocompromised patients.

(Received 29 September 1998/Returned for modification 7 December 1998/Accepted 22 February 1999)

Received 29 September 1998/Returned for modification 7 December 1998/Accepted 22 February 1999

† Members of the Penciclovir Immunocompromised Study Group are listed in Appendix.

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**MATERIALS AND METHODS**

**Study medication.** Penciclovir and acyclovir were provided as vials of freeze-dried powder for reconstitution. Penciclovir vials contained 250 mg of active drug per vial with acyclovir contained either 250 or 500 mg, depending upon licensure in the participating countries.

**Treatment groups.** Patients who met the entry criteria were randomly assigned in a double-blind fashion to receive a 7-day course of treatment with 5 mg of penciclovir per kg q12h, 5 mg of penciclovir per kg q8h, or 5 mg of acyclovir per kg q12h.

A computer-generated randomization code with restricted access was used to allocate patients to the three treatment groups. An unblinded pharmacist at each center prepared the randomization envelopes in sequence. The pharmacist then assigned the study medication to each patient based on the randomization code for that protocol. The pharmacist was masked to the randomization envelopes in sequence. The pharmacist then assigned the study medication to each patient based on the randomization code for that protocol. In this study, herpes lesions comprised papules, vesicles or pustules, ulcers, and crusts on mucocutaneous membranes which were the result of HSV infection. Complete healing was defined as the first visit at which the patient reported no papules, vesicles or pustules, ulcers, or crusts and did not report any of these at any subsequent visit. The number of lesions was recorded as 0, 1, 2, 3 or 4.

**Anatomical diagrams.** Anatomical diagrams were provided as an aid for monitoring lesion progression and the appearance of new lesions. The cessation of viral shedding was defined as complete viral clearance and absence of new lesions.

**RESULTS**

**Characteristics of the study patients.** A total of 342 patients from 40 centers in nine countries were randomized and received at least one dose of study medication. Ten patients were withdrawn from the study during the treatment period, and a further 76 patients were withdrawn after the cessation of treatment. The most common reasons for withdrawal were concurrent disease or adverse experience, treatment failure, loss to follow-up, and protocol violation (Table 1). With the exception of protocol violation (higher for the acyclovir group), the numbers of patients withdrawn for each reason were similar across the three treatment groups.

The intent-to-treat population, which includes all 342 patients, is the basis for the analysis. Patients were allocated equally to the three treatment groups (115 received penciclovir q12h, 114 received penciclovir q8h, and 113 received acyclovir q12h). A comparison of patient demographics for the intent-to-treat population is shown in Table 2. In general, the demographic characteristics were similar across the three treatment groups. The majority of patients were Caucasian (94%), and the overall population was almost equally divided with respect to gender. The mean age ranged from 48 to 50 years.

Most patients (58 to 67%) were immunocompromised due to a hematologic disorder, which included leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome, and...
a reported history of having taken acyclovir at a time in the past for a medical condition. Of note, a large percentage of patients received strong nonsteroidal analgesics during the study (e.g., at least 20% of patients in each treatment group received morphine in various salt forms), which complicated the assessment of lesion pain as perceived by the patient.

Most patients were able to initiate therapy within 48 h of the onset of lesions. Lesion appearance at baseline was similar across treatment groups. Lesions were predominantly orolabial (>90% of patients), and most patients presented with ulcers (Table 4). Over half of the population had no prior history of orolabial mucocutaneous HSV infection. Approximately 80% of patients in each treatment group reported pain at baseline, with a slightly higher percentage of patients in the penciclovir groups reporting severe pain (19 to 21% for penciclovir versus 12% for acyclovir).

The percentage of patients shown to have a positive culture at baseline was 60% and 62% for the penciclovir q12h and q8h groups, respectively, compared with 54% of patients in the acyclovir q8h group. More than 90% of patients who had a positive culture were positive for HSV type 1, with the values comparable between treatment groups.

**Lesion end points.** During the course of the study, approximately 20% of patients developed new lesions during therapy (19% in the penciclovir q12h and acyclovir q8h groups and 21% in the penciclovir q8h group). Both penciclovir treatments were shown to be equivalent to acyclovir therapy for this primary end point; i.e., the upper limits of the 97.5% confidence intervals, 12% for penciclovir q12h and 14% for penciclovir q8h, were below the prespecified equivalence level of 20%. As assessments were made once daily, the time to healing is expressed as an integer. The median time to the healing of all lesions was 8 days across all three treatment groups, and comparisons of penciclovir to acyclovir were not statistically significant for the time to healing (Fig. 1 and Table 5).

**Viral shedding end points.** The median time to the cessation of viral shedding from all lesions was 4 days for all three treatment groups, and comparisons of penciclovir to acyclovir were not statistically significant (i.e., 97.5% confidence intervals for comparisons of penciclovir with acyclovir spanned 1). The percentage of patients who ceased shedding virus by day 7 was 85 to 87% in each treatment group. The confidence intervals for this proportion analysis spanned 0, indicating that there was no statistical evidence of any treatment difference between the penciclovir and acyclovir groups.

**Other clinical end points.** No patients were withdrawn because of the dissemination of HSV. Twenty patients (seven in each penciclovir group and six in the acyclovir group) were withdrawn for the other treatment failure reasons (i.e., clinical or virological failure requiring further anti-HSV therapy or continued lesion formation beyond day 7). The comparisons of penciclovir to acyclovir were not statistically significant. Most of the patients with treatment failures received acyclovir as an additional antiviral therapy even though acyclovir was one of the blinded treatment arms. As these patients were withdrawn from the study when further antiviral therapy was initiated, the impact of additional antiviral therapy on lesion healing is unknown.

As with the other efficacy parameters, no significant differ-
Viral resistance. Antiviral-resistant strains of HSV have become a concern for immunocompromised patients who receive multiple treatment courses or suppressive antiviral therapy for recurrent HSV episodes. In the present study, no penciclovir-resistant HSV isolates were identified. The testing of susceptibility to penciclovir was performed on 419 HSV samples, with 306 isolates from 125 patients treated with penciclovir and 113 isolates from 48 patients treated with acyclovir. A trend analysis on data for paired isolates (pretreatment and posttreatment HSV isolates) tested for penciclovir susceptibility indicates that there are no statistically significant differences in IC_{50} between these isolates from either penciclovir-treated or acyclovir-treated patient populations (P = 0.121 [analysis of covariance]). Moreover, for all isolates tested IC_{50} were below 0.7 μg of penciclovir per ml. The testing of all isolates for resistance to acyclovir is ongoing, and the complete results of resistance testing will be presented in a separate report.

Adverse events. The incidence of adverse events was generally comparable between the penciclovir and acyclovir groups. The most frequently reported adverse events were fever (reported by 11 to 15% of patients) and nausea (reported by 7 to 9% of patients in any treatment group). Fever and nausea were expected to be two frequently reported adverse events because of the degree of immunosuppression and the number of concomitant medications administered. The low incidence of these events (<4% in any group) and of serious adverse events which were considered to be either unrelated or probably unrelated to treatment, demonstrates that the overall safety profile reflects the immunocompromised state of patients may have had lesions in more than one location or at more than one stage at baseline.

The success of the penciclovir q12h regimen is particularly noteworthy because the reduced frequency of administration translates into possible patient convenience and the potential for reduced administration and nursing time compared with the q8h acyclovir regimen. In both groups 19% of patients experienced new lesion formation during therapy. Median values for the time to healing and the time to the cessation of viral shedding were also the same. The percentages of patients who had ceased viral shedding by day 7 were similar in the penciclovir and acyclovir groups (87 and 86%, respectively). In addition, the percentages of patients withdrawn for treatment failure were also similar between the penciclovir q12h and acyclovir q8h regimens (6 and 5%, respectively), and no statistically significant differences between groups were shown for the resolution of pain.

The majority of patients included in this study had underlying diseases which were severe enough to require hospitalization for at least the 7-day treatment period and, therefore, were treated with intravenous rather than oral therapy. Fever and nausea were expected to be two frequently reported adverse events because of the degree of immunosuppression and the number and types of concomitant medications administered. The low incidence of these events (<4% in any group) and of serious adverse events which were considered to be related or possibly related to treatment demonstrates that the overall safety profile reflects the immunocompromised state of patients.


discussion

HSV is a common opportunistic infection in immunocompromised patients. Due to the potential severity of HSV infection in these patients, effective therapies have been sought and the disease has been shown to be treatable (6–8, 18, 20). The results of this study demonstrate that penciclovir given either q8h or q12h is safe and as effective as acyclovir for the treatment of mucocutaneous HSV infection in immunocompromised patients.

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### TABLE 4. Baseline lesion assessment

| Location          | Penciclovir q12h (n = 115) | Penciclovir q8h (n = 114) | Acyclovir q8h (n = 113) |
|-------------------|-----------------------------|---------------------------|------------------------|
|                   | No. (%) of patients in treatment group | No. (%) of patients in treatment group | No. (%) of patients in treatment group |
| Papules           | 25 (22)                     | 31 (27)                   | 29 (26)                |
| Vesicles or pustules | 45 (39)                  | 51 (45)                   | 44 (39)                |
| Ulcers            | 77 (67)                     | 61 (54)                   | 69 (61)                |
| Crusts            | 14 (12)                     | 19 (17)                   | 15 (13)                |
| Overall           | 109 (95)                    | 108 (95)                  | 105 (93)               |

* Patients may have had lesions in more than one location or at more than one stage at baseline.

### TABLE 5. Lesion end points

| Treatment (no. of patients) | % of patients with new lesions during therapy (97.5% confidence interval)* | Time to healing (days) |
|-----------------------------|-----------------------------------------------------------------------------|------------------------|
| Penciclovir q12h (115)      | 19 (−11, 12)                                                               | 8                      |
| Penciclovir q8h (114)       | 21 (−9, 14)                                                                | 8                      |
| Acyclovir q8h (113)         | 19                                                                          | 8                      |

* Treatments are statistically equivalent because the upper limit of the 97.5% confidence interval is less than 20%.

There is no significant difference between treatments because the 97.5% confidence interval spans 1.
The lack of penciclovir resistance among the isolates tested appears to be unusual for an immunocompromised patient population, where resistance rates up to 9% have been noted (3, 5, 11, 13). The patient populations in studies which report high percentages of resistant viruses are typically bone marrow transplant recipients or patients in the late stages of AIDS who have serious or long-standing HSV infections. In the present study, only 0.9% of the patients had received acyclovir prior to participation in the study. Therefore, the absence of resistant virus in this population is not unexpected.

In conclusion, penciclovir administered either q6h or q12h is a safe and effective treatment for mucocutaneous HSV in these patients. In addition, penciclovir q12h offers a reduced frequency of dosing compared with current recommendations for acyclovir in this indication.

APPENDIX

The Penciclovir Immunocompromised Study Group comprises E. Anaissie, Houston, Tex.; C. Andre, Liège, Belgium; F. Andrien, Liège, Belgium; E. Archimbaud, Lyon, France; M. Baccarani, Udine, Italy; S. Balfour, Tampa, Fla.; C. Bernasconi, Pavia, Italy; W. Blau, Idar-Oberstein, Germany; J. Blumer, Cleveland, Ohio; D. Bodensteiner, Kansas City, Kan.; R. Boon, Harlow, United Kingdom; J. Bourhis, Villejuif, France; Y. Bousquet, Paris, France; P. Bramlett, Kansas City, Kan.; K. Briscoe, Fountain Valley, Calif.; J. Cahm, Besançon, France; C. Chabas, Besançon, France; P. Chervenik, Tampa, Fla.; D. Cedervans, Nantes, France; E. Deconcinck, Besançon, France; R. DeConti, Tampa, Fla.; J. Desens, Paris, France; W. Dinwoodie, Tampa, Fla.; G. Doolittle, Kansas City, Kan.; J. Dukter, Bronx, N.Y.; A. Einstein, Tampa, Fla.; A. Einzig, Bronx, N.Y.; G. Ellenbein, Tampa, Fla.; C. Fabian, Kansas City, Kan.; A. Fauser, Idar-Oberstein, Germany; K. Fields, Tampa, Fla.; T. File, Jr., Akron, Ohio; M. Gobbi, Genova, Italy; S. Goldstein, Tampa, Fla.; J. Greene, Tampa, Fla.; E. Greenwald, Bronx, N.Y.; S. Grehn, Berlin, Germany; J. Grote-Kiehn, Duisburg, Germany; R. Gucalp, Bronx, N.Y.; J. Harrousseau, Nantes, France; J. Hiemenz, Tampa, Fla.; S. Hiemenz, Tampa, Fla.; M. Hoffmann, Augsburg, Germany; J. Horton, Tampa, Fla.; A. Indorf, Akron, Ohio; P. Jessamine, Ottawa, Ontario, Canada; H. Jhangiani, Fountain Valley, Calif.; G. Justice, Fountain Valley, Calif.; W. Kaiser, Essen, Germany; J. Koenig, Akron, Ohio; J. Lacha, Prague, Czech Republic; A. Leaf, Bronx, N.Y.; A. Lin, Regina, Saskatchewan, Canada; H. Link, Hanover, Germany; P. Ljungman, Huddinge, Sweden; G. Lyman, Tampa, Fla.; S. Lynch, Harlow, United Kingdom; R. MacDonald, Harlow, United Kingdom; J. Magnette, Besançon, France; M. Magnette, Besançon, France; U. Malik, Bronx, N.Y.; R. McKittrick, Kansas City, Kan.; J. Mendelson, Montreal, Quebec, Canada; N. Milpied, Nantes, France; W. Moriconi, St. Louis, Mo.; R. Navari, Birmingham, Ala.; F. Nobile, Reggio Calabria, Italy; M. Nowroussian, Essen, Germany; F. Oberling, Strasbourg, France; C. Pailler, Villejuif, France; G. Perrine, Birmingham, Ala.; I. Pierri, Genova, Italy; C. Pipan, Udine, Italy; A. Prahst, Hannover, Germany; S. Rai, Harlow, United Kingdom; M. Reed, Cleveland, Ohio; S. Renger, Hannover, Germany; F. Rodgheti, Vicenza, Italy; C. Ross, Akron, Ohio; J. Ruckdeschel, Tampa, Fla.; H. Saba, Tampa, Fla.; R. Sackstein, Tampa, Fla.; R. Sadawani, Kansas City, Kan.; R. Saltzman, Collegeville, Pa.; D. Schapira, Tampa, Fla.; G. Schiller, Los Angeles, Calif.; G. Schlimok, Augsburg, Germany; S. Schwarz, Berlin, Germany; A. Serr, Idar-Oberstein, Germany; S. Shafman, Edmonton, Alberta, Canada; D. Signs, Akron, Ohio; J. Sparano, Bronx, N.Y.; T. Stein, Kansas City, Kan.; R. Stephens, Kansas City, Kan.; L. Sutton, Paris, France; J. Tan, Akron, Ohio; S. Taylor, Kansas City, Kan.; E. Thiel, Berlin, Germany; B. Toth, Houston, Tex.; M. Treny, Prague, Czech Republic; R. Trochelman, Akron, Ohio; B. Tucker, Birmingham, Ala.; A. Uden, Stockholm, Sweden; S. Vartivariant, Houston, Tex.; U. Venkatraj, Bronx, N.Y.; J. Vorlick, Brno, Czech Republic; S. Wadler, Bronx, N.Y.; M. Wegner, Augsburg, Germany; M. Westerhausen, Duisburg, Germany; P. Wijermans, The Hague, The Netherlands; C. Williams, Tampa, Fla.; S. Williamson, Kansas City, Kan.; P. Zorsky, Tampa, Fla.; and K. Zuckerman, Tampa, Fla.

ACKNOWLEDGMENTS

This study was funded, in part, by a grant from SmithKline Beecham Pharmaceuticals.

We thank Robert Sarisky and Jeffry Leary for providing virus resistance data.

REFERENCES

1. Boyd, M. R., T. H. Bacon, D. Sutton, and M. Cole. 1987. Antiherpetic virus activity of 9-(4-hydroxy-3-hydroxy-methylbut-1-yl)guanine (BRL 39123) in cell culture. Antimicrob. Agents Chemother. 31:1238–1242.

2. Boyd, M. R., S. Safrin, and E. R. Kern. 1993. Penciclovir: a review of the spectrum of activity, selectivity, and cross resistance pattern. Antivir. Chem. Chemother. 4(Suppl. 1):3–11.

3. Collins, P., and N. M. Ellis. 1993. Sensitivity monitoring of clinical isolates of herpes simplex virus to acyclovir. J. Med. Virol. 1993(Suppl. 1):58–66.

4. Cox, D. R. 1972. Regression models and life tables. J. R. Stat. Soc. B. 34:187–220.

5. Englund, J. A., M. E. Zimmerman, E. M. Swierkosz, J. L. Goodwin, D. R. Scholl, and H. H. Balfour. 1990. Herpes simplex virus resistant to acyclovir: a study in a tertiary care center. Ann. Intern. Med. 112:416–422.

6. Lazarus, H., R. Belanger, A. Candoni, M. Aoun, R. Jurewicz, S. Lynch, R. Boon, L. Marks, and the Penciclovir Immunocompromised Study Group. 1997. Efficacy and safety of penciclovir (PCV) for the treatment of HSV infections in immunocompromised (IC) patients. abst. I-H-2, p. 226. In Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.

7. Meyers, J. D., N. Flouryam, and E. D. Thomas. 1980. Infection with herpes simplex virus and cell-mediated immunity after marrow transplant. J. Infect. Dis. 142:338–346.

8. Meyers, J. D., J. C. Wade, C. D. Mitchell, R. Saral, P. S. Liemant, D. T. Durack, M. J. Levin, A. C. Segreti, and H. H. Balfour. 1982. Multicenter controlled trial of acyclovir for mucocutaneous herpes simplex infections in immunocompromised patients. Lancet 16389–1392.

9. Montogomerie, J. Z., D. M. Becroft, M. C. Croxson, P. B. Doak, and J. D. K. North. 1989. Herpes simplex virus infection after renal transplantation. Lancet 1:867–871.

10. Naraqi, S., G. G. Johnson, O. Jonasson, and H. M. Yamaschhuya. 1977. Prospective study of the prevalence, incidence and source of herpesvirus infections in patients with renal allografts. J. Infect. Dis. 136:531–540.

11. Nugent, F. J., N. Colin, M. Aymard, and M. Langlois. 1992. Occurrence and characterization of acyclovir-resistant herpes simplex virus isolates: report on a two-year sensitivity screening survey. J. Med. Virol. 36:1–12.

12. Pass, R. R., J. R. Whitley, J. D. Whelchel, A. G. Diehelm, D. W. Reynolds, and C. A. Alford. 1979. Identification of patients with increased risk of infection with herpes simplex virus after renal transplantation. J. Infect. Dis. 140:487–492.

13. Pottage, J. C., and A. Kessler II. 1995. Herpes simplex virus resistance to acyclovir: clinical relevance. Infect. Agents Dis. 4:115–124.

14. Sacks, S. L., F. Y. Ake, F. Diaz-Mitoma, J. Sellers, and S. Shafraan. 1996. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes: a randomized, double-blind multicenter trial. JAMA 276:64–49.

15. Spruance, S. L., J. C. Overall, E. R. Kern, G. G. Krueger, V. Plaim, and W. Miller. 1977. The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. N. Engl. J. Med. 297:69–75.

16. Spruance, S. L., T. L. Rea, C. Thoming, R. Tucker, R. Saltzman, and R. Boon. 1997. Penciclovir cream for the treatment of herpes simplex labialis. JAMA 277:1374–1379.

17. Tyrling, S., R. A. Barbashar, J. E. Nahlick, A. Cunningham, J. Marley, M. Heng, T. Jones, T. Rea, R. Boon, R. Saltzman, and the Collaborative Famciclovir Herpes Zoster Study Group. 1999. Famciclovir for the treatment of acute herpes zoster: effects on acute disease and post herpetic neuralgia. Ann. Intern. Med. 123:89–96.
18. Vartivarian, S., B. Toth, E. J. Anaissie, and L. Eron. 1995. Intravenous penciclovir for the treatment of mucocutaneous herpes simplex infection in immunocompromised patients, abstr. H109, p. 199. In Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.

19. Vere Hodge, R. A. 1993. Famiclovir and penciclovir: the mode of action of famiclovir including its conversion to penciclovir. Antivir. Chem. Chemother. 4:67–84.

20. Wade, J. C., B. Newton, C. McLaren, N. Flournoy, R. E. Keeney, and J. D. Meyers. 1982. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. Ann. Intern. Med. 96:265–269.