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CONCISE COMMUNICATION

Valaciclovir as a single dose during prodrome of herpes facialis: a pilot randomized double-blind clinical trial

O.CHOSIDOW, Y.DROUAULT,* R.GARRAFFO† AND P.VEYSSIER,‡ FOR THE VALACICLOVIR HERPES FACIALIS STUDY GROUP

Department of Internal Medicine, Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier Pitié-Salpêtrière, Université Paris VI, 47-83 boulevard de l'Hôpital, 75 651 Paris cedex 13, France
**Department of Dermatology, Hôpital Tarnier-Cochin, Paris, France*
†Department of Pharmacology, Hôpital Pasteur, Nice, France
‡Department of Internal Medicine, Centre Hospitalier, Compiègne, France

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Summary

Background Randomized clinical trials of valaciclovir in recurrent herpes labialis are lacking.
Objectives To determine whether a single course of valaciclovir, i.e. 500, 1000 or 2000 mg, administered during the prodrome of herpes facialis, could be beneficial.
Methods Three hundred and forty-five out-patients with herpes labialis were screened and randomized for a multicentre, double-blind clinical trial. Ninety-six patients had no recurrence after 6 months of follow-up; 249 patients were finally included in the intent-to-treat (ITT) population. The main outcome measure was the rate of aborted episodes at day 3. The three treatment groups were similar at baseline.
Results There was no statistically significant difference between the groups in rates of aborted lesions at day 3 in the ITT population, in particular between the 500 mg and 2000 mg treatment groups.
Conclusions Although a placebo group was not included in this pilot study, a single dose of valaciclovir was not considered beneficial in patients with recurrent herpes facialis.

Key words: herpes facialis, randomized clinical trial, valaciclovir

Although recurrent herpes facialis is considered a benign disease, frequent episodes may be disfiguring.[1] The different treatment regimens are still disappointing and an effective treatment would be warranted in some patients. Authors of a recent review of antiviral therapy for herpes labialis pointed out the absence of available data concerning the use of valaciclovir (VACV),[2] the prodrug of aciclovir (ACV) but with a better oral bioavailability.[3] The concept of high doses initiated during prodrome has been particularly emphasized.[2] We report the results of a pilot clinical trial of a single dose of VACV, i.e. 500, 1000 or 2000 mg, administered during the prodrome of recurrent herpes facialis.

Correspondence: O.Chosidow.
E-mail: olivier.chosidow@psl.ap-hop-paris.fr

Patients and methods

Study design

This pilot clinical trial was a multicentre, randomized, dose-ranging, parallel-group study intended to assess the efficacy and tolerability of a single dose of VACV in recurrent herpes facialis. The study was approved by an institutional Ethics Committee (CCPPRB Ile de France-Pitié-Salpêtrière) and was performed in accordance with Good Clinical Practice guidelines (European Community Directive 91/507/EEC).

Patients

Eligible patients were randomly assigned to receive a single dose of VACV at 500, 1000 or 2000 mg, administered during the prodrome of herpes facialis.

The randomization was centralized and balanced by centre. The study medications were supplied by GlaxoSmithKline Pharmaceuticals. Eligible patients were immunocompetent men or women aged 18 years or older who had experienced three or more recurrences of herpes facialis within the 12-month period prior to entry into the study. Recurrences had to be systematically associated with a prodrome already well-known to the patients, as there is a good predictive value (85%) of a prodrome resulting in an outbreak of herpes simplex virus (HSV) vesicles in recurrent herpes simplex labialis.[1] Subjects were out-patients recruited from private medical practices of dermatologists or general practitioners. Patients had to be able to self-initiate the treatment in the 2-h period following the onset of the prodrome of their next recurrence. They were not allowed to use any local treatment or cosmetics during the prodromal or lesional phase of herpes facialis. Patients were excluded from study participation if they used to have more than 50% of recurrences that aborted spontaneously; had facial skin lesions that could interfere with the outcome of herpes facialis, e.g. eczema or psoriasis; were human immunodeficiency virus-positive; were suspected to have poor compliance; had renal impairment or a history of hypersensitivity to ACV or VACV; were pregnant or nursing mothers; had received antiviral therapy, corticosteroids or immunosuppressive drugs within the 15-day period prior to the study; or were sexually active women of child-bearing potential who were not using effective contraception.

Potentially eligible adult out-patients were actively recruited by each of the participating centres. Written informed consent was obtained from each patient prior to enrolment. At the screening visit (visit 1), patients provided a medical history and underwent a physical examination. Eligible patients were then randomized in a 1 : 1 : 1 ratio to one of the treatment arms: VACV 500 mg, 1000 mg or 2000 mg as a single dose. Because of the differences in dosage, we used a double-placebo procedure to preserve blinding: patients randomized to VACV 500 mg also received three placebo (dummy) VACV tablets and those randomized to VACV 1000 mg also received two placebo VACV tablets. The tablets were issued in a convenient 'pocket' blister pack. Patients were instructed to self-initiate treatment within 2 h of the prodromal phase of their next recurrence. Patients without herpes recurrence after 6 months follow-up returned the blister pack and were not included in the intent-to-treat (ITT) population (see below).

End-points

The patients attended the clinic for evaluation (absence of lesion, macule, papule, vesicle, crust) within 72 h (day 3) after initiating treatment (visit 2). Clinical evaluation was also performed on day 5 (visit 3) and 24–48 h after loss of crust (visit 4). Compliance was assessed by pill count of returned blister packs.

All randomized patients who received at least one dose of the study medication were included in the ITT and safety populations. Patients without any major protocol violation were included in the per protocol (PP) population.

The primary efficacy end-point was the rate of aborted episodes at day 3. Aborted episodes were defined as episodes that did not progress beyond the papule stage.[4] Non-aborted episodes were those that progressed to the vesicle stage before healing. The secondary end-point, evaluated in patients experiencing non-aborted episodes, was the time to healing calculated from the time of initiation of therapy until the time of the loss of crust. Safety was determined by adverse experience reports in each treatment group.

Statistical analysis

The objective of this study was to compare the rates of aborted episodes of herpes facialis among the three groups of VACV dosage. In a previous study, it was found that the percentages of aborted 'lesions' in patients treated topically, before vesicles developed, were 15% in the placebo group and 35% in the ACV group (not statistically significantly different).[4] We thus hypothesized that the rate of aborted episodes in the lowest VACV dosage group, i.e. 500 mg, would be 25%. It was assumed that 50% aborted episodes in either the 1000 mg group or 2000 mg group would be clinically relevant. Therefore, a minimum sample size of 60 patients per arm with alpha = 0·05 and beta = 0·20 would provide sufficient power to detect a difference between the 500 mg and 2000 mg groups. Because of the design of herpes trials,[5] such that once randomized, the patients had to start treatment only after the next recurrence of prodrome, a population of 90 patients per arm was planned to be certain of obtaining the required number of patients. The statistical report and statistical analysis were performed using SAS version 6.1.2 software (SAS Institute Inc., Cary, NC, U.S.A.).

The principal analysis was by ITT for all end-points. A PP analysis was also performed. The aborted episode

criterion was analysed as a dichotomous variable and its 95% confidence interval calculated. The statistical analysis was performed as follows: rates of aborted lesions were compared using a χ^2 test between dose levels 500 mg and 2000 mg at a two-sided 5% level. If the difference was significant, then the comparison was performed between dose levels 500 mg and 1000 mg. We aimed to determine the lowest dose giving a rate of blocked lesions either significantly higher than that given by a dose level of 500 mg or giving a rate higher than 50%. The distribution of the secondary time-to-healing end-point was estimated using Kaplan–Meier estimates and log-rank tests.

Results

The controlled trial took place from 10 October 1998 (first patient recruited) to 24 June 1999 (last follow-up visit). Three hundred and forty-five patients were screened at 52 French study sites and were randomized to treatment. Of these patients, 96 had no recurrence after 6 months of follow-up. Finally, 249 patients were included in the ITT population as shown in Fig. 1. Among this population, 92% presented with herpes labialis. A summary of baseline characteristics is provided in Table 1. The three treatment groups were similar with regard to sex, age and number of recurrences in the previous 12 months.

There was no statistically significant difference between the groups in rates of aborted lesions at day 3 in the ITT population, in particular between the 500 mg and 2000 mg treatment groups (Fig. 2). The results were similar in the PP population: 38% ($n = 69$) in the 500 mg group vs. 44% ($n = 71$) in the 2000 mg group ($P = 0{\cdot}43$). The Kaplan–Meier time-to-healing plot of patients with non-aborted lesions did not show any difference between the three groups (Fig. 3). The frequency, nature and severity of adverse events did not differ among the three treatment groups (data not shown).

Discussion

Recurrent herpes facialis, including herpes labialis, is a common disease estimated to occur in up to 40% of the U.S. population.[6] Although benign in most cases, recurrent herpes facialis may be associated with transient but real consequences such as pain, crusting, superinfection, aesthetic and social disturbances. Moreover, herpes facialis may lead to significant morbidity in susceptible patients, e.g. HSV-seronegative individuals, especially babies and infants, patients with underlying atopic dermatitis or immunocompromised individuals. Therefore, an effective treatment, either topical or systemic, would be helpful. However, the conclusions of a recent editorial review as well as the recent French consensus conference pointed out the absence of well-demonstrated and/or clinically relevant treatments for recurrent herpes facialis.[2,7] For example, topical therapy with penciclovir as well as docosanol 10%, a recent over-the-counter U.S. Food and Drug Administration-approved topical treatment, was shown to be statistically effective compared with placebo but with only a 0·7-day reduction in median

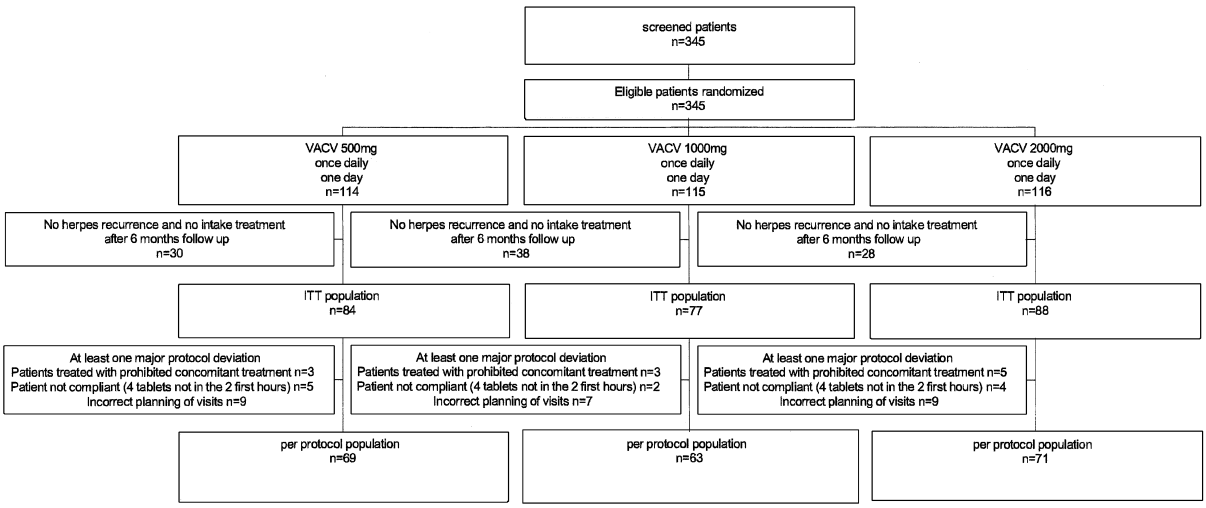

Figure 1. Flowchart of recruitment, randomization, intent-to-treat (ITT) population and per protocol population. VACV, valaciclovir.

Table 1. Summary of baseline characteristics (intent-to-treat)

	Valciclovir			
	500 mg (n = 84)	1000 mg (n = 77)	2000 mg (n = 88)	Total (n = 249)
Sex F/M	65/19	55/22	63/25	183/66
Age, mean ± SD (years)	40 ± 14	40 ± 14	43 ± 15	41 ± 14
Number of recurrences in the previous 12 months, median (range)	4·5 (3–12)	5·0 (3–20)	4·0 (3–12)	5·0 (3–20)
In the previous 12 months, number of patients having				
3–5 recurrences	57 (68%)	48 (62%)	61 (69%)	166 (67%)
≥ 6 recurrences	27 (32%)	29 (38%)	27 (31%)	83 (33%)

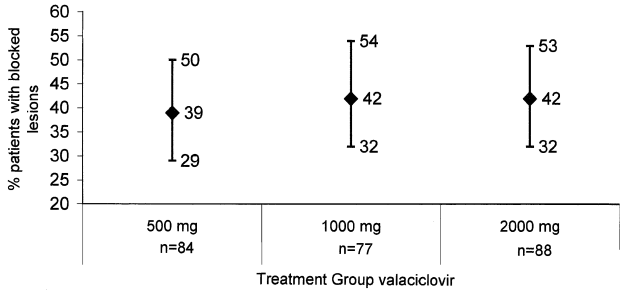

Figure 2. Rates of blocked lesions at visit 2 (day 3). Mean and 95% confidence interval; intent-to-treat population.

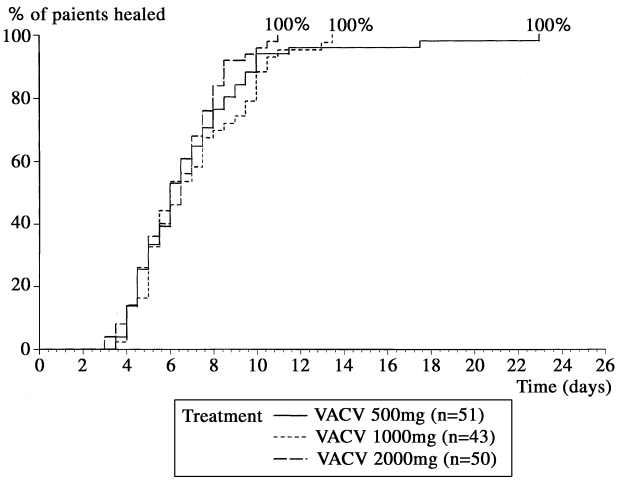

Figure 3. Kaplan–Meier plots for time to healing of vesicles for patients for whom lesions had not been blocked. VACV, valaciclovir.

healing time.[8,9] However, the vehicle was not strictly a placebo and could have had a local therapeutic effect, e.g. improving or altering healing in a non specific manner, and therefore biasing the differences between the groups. Oral ACV did not alter either time of complete healing or duration of pain.[10]

We considered that increasing the ratio of aborted episodes would probably be able to improve the condition of patients with herpes facialis. An optimum treatment has to be taken as soon as possible in the prodromal period and to be easy to use. A clinical trial was therefore planned using VACV, the prodrug of ACV, which has 3–5 times greater bioavailability.[3] High doses of VACV were chosen under the hypothesis that ACV tissue concentration would exceed the 50% inhibitory concentration against HSV, with a longer lasting effect, during the prodromal phase where viral replication and epidermal involvement could be limited. Our study showed that a single dose of VACV 2000 mg or 1000 mg did not show any difference from the 500 mg group in terms of rates of aborted episodes at day 3. We are aware of the absence of a placebo arm in the study. However, in a randomized controlled trial of recurrent herpes simplex labialis, ACV did not show any differences from the placebo; VACV being the prodrug of ACV, it can be hypothesized that the absence of difference in our trial could be considered as an absence of a relevant therapeutic effect of VACV.[11]

The rate of aborted episodes in the lowest VACV dosage group was higher (39%) than originally estimated (25%), leading to an underpowering of the study. Before excluding the usefulness of such higher dosages, it would be interesting to investigate the effect of a VACV regimen of 1 or 2 days or longer, compared with placebo, with regard to aborted episodes, lesion episodes, duration, pain/discomfort and quality of life. In that way, it has recently been shown in recurrent genital herpes that a 2-day course of ACV (800 mg three times daily) was a convenient alternative and

that a 3-day course of VACV (500 mg twice daily) was equivalent to a 5-day course.[12,13]

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Author's note

Since the submission of the study, one full paper has been published in the field of valacyclovir treatment of facial herpes. Laiskonis A, Thune T, Neldam S, Hiltunen-Back E. Valacyclovir in the treatment of facial herpes simplex virus infection. *J Infect Dis* 2002; 186 (Suppl 1): S66–70.

References

1 Spruance SL, Overall JC Jr, Kern ER *et al.* The natural history of recurrent herpes simplex labialis. *N Engl J Med* 1977; **297**: 69–75.
2 Vander Straten M, Carrasco D, Lee P, Tyring SK. A review of antiviral therapy for herpes labialis. *Arch Dermatol* 2001; **137**: 1232–5.
3 Balfour HH. Antiviral drugs. *N Engl J Med* 1999; **340**: 1255–68.
4 Fiddian PA, Yeo JM, Stubbings R, Dean D. Successful treatment of herpes labialis with topical acyclovir. *Br Med J* 1983; **286**: 1699–701.
5 Chosidow O, Drouault Y, Leconte-Veyriac F *et al.* Famciclovir vs. aciclovir in immunocompetent patients with recurrent genital herpes infections: a parallel-groups, randomized, double-blind clinical trial. *Br J Dermatol* 2001; **144**: 818–24.
6 Higgins CR, Schofield JK, Tatnall FM, Leigh IM. Natural history, management and complications of herpes labialis. *J Med Virol Suppl* 1993; **1**: 22–6.
7 ANAES. Prise en charge de l'herpès cutanéo-muqueux chez l'immunocompétent. URL: http://www.anaes.fr
8 Spruance SL, Rea TL, Thoming C *et al.* Penciclovir cream for the treatment of herpes simplex labialis: a randomized multicenter, double-blind, placebo-controlled trial. *JAMA* 1997; **277**: 1374–9.
9 Sacks S, Thisted RA, Jones TM *et al.* Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: a multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2001; **45**: 222–30.
10 Raborn GW, McGaw WT, Grace M *et al.* Oral acyclovir and herpes labialis: a randomized, double-blind, placebo-controlled study. *J Am Dent Assoc* 1987; **115**: 38–42.
11 Spruance SL, Stewart JCB, Rowe NH *et al.* Treatment of recurrent herpes simplex labialis with oral acyclovir. *J Infect Dis* 1990; **161**: 185–90.
12 Wald A, Carrell D, Remington M *et al.* Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis* 2002; **34**: 944–8.
13 Leone P, Trottier S, Miller JM. Valacyclovir for episodic treatment of genital herpes: a shorter 3-day treatment course compared with 5-day treatment. *Clin Infect Dis* 2002; **34**: 958–62.