A double-blind, randomized study assessing the equivalence of valacyclovir 1000 mg once daily versus 500 mg twice daily in the episodic treatment of recurrent genital herpes

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Valaciclovir is a prodrug of acyclovir with more favourable bioavailability. Twice daily oral administration of valaciclovir is recommended in patients with genital herpes. A double-blind, randomized, controlled, multicriteria equivalence trial was conducted to determine whether od treatment with valaciclovir 1000 mg is as effective as bd treatment with 500 mg in patients with recurrent genital herpes. A total of 922 immunocompetent outpatients were treated with either regimen for 5 days; treatment was self-initiated at the first symptoms of the next recurrence.

The principal outcome measures were the percentage of lesions healed at day 6, time to healing, time to cessation of pain, discomfort or itching, the percentage of abortive episodes and safety. Equivalence was assessed by comparison of 80% confidence limits for each measure; the two regimens were regarded as equivalent if the lower confidence limit was higher than a pre-determined equivalence limit calculated to show a maximum 10% inferiority of valaciclovir 1000 mg od against valaciclovir 500 mg bd. Intention-to-treat analysis showed that the two treatments were equivalent for each outcome measure. Hence, it is concluded that valaciclovir 1000 mg od is as effective as 500 mg bd as self-initiated therapy in patients with recurrent genital herpes.

Introduction

Genital herpes is a common disease with an increasing incidence.\textsuperscript{1} While primary genital infection may be caused by herpes simplex virus (HSV)-1 or -2, most cases of recurrent genital herpes are caused by HSV-2.\textsuperscript{2} This condition is a major health problem because it strongly enhances the risk of acquiring other sexually transmitted diseases, including HIV.\textsuperscript{3}

Despite its limited oral bioavailability, oral acyclovir, administered either episodically at the first signs of a recurrence or continuously for suppression in the most severely affected patients, became the standard drug for the treatment of recurrent genital herpes.\textsuperscript{4,5} Oral valaciclovir, the L-valyl ester of acyclovir, is well absorbed and rapidly converted to acyclovir in the liver, resulting in a three- to five-fold increase in acyclovir bioavailability compared with oral acyclovir.\textsuperscript{6,7} Clinical trials comparing these two drugs in genital herpetic have demonstrated that valaciclovir has similar activity to that of acyclovir.\textsuperscript{6-10} The length of the episode, time to lesion healing, duration of viral shedding and duration of pain/discomfort were improved in both acyclovir and valacyclovir groups compared with the placebo group, but no significant differences between the acyclovir and valacyclovir groups were demonstrated. The recommended dosage of valaciclovir is 500 mg bd for 5 days in the treatment of recurrent genital herpes.

These results may challenge the concept of pharmacokinetic studies being of crucial importance in selecting appropriate doses of antiviral drugs.\textsuperscript{11} Regimens of such drugs are often designed to achieve drug concentrations in blood or other body fluids similar to those shown to be effective in cell cultures infected by the virus to be treated.\textsuperscript{12} Since pharmacokinetic parameters originate mainly from extracellular measurements, they may be poor predictors of efficacy in viral infections, which are intracellular diseases.

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Unfortunately, it is impossible to monitor the concentration of the active compound, acyclovir-triphosphate, within the HSV-infected epithelial cells in vivo.

To address this question further and to improve patient compliance by providing simpler dosing, we have evaluated valacyclovir 1000 mg od and 500 mg bd in the early treatment of a recurrence of genital herpes in immunocompetent patients. As we questioned the equivalence of these two regimens rather than evaluating a difference of one versus another, we designed a large-scale, multicentre, randomized, double-blind, parallel groups, multicriteria equivalence trial.

Materials and methods

Protocol

Male and female outpatients, aged 18 years and above, with recurrent genital herpes were enrolled if they had experienced at least four recurrences in the previous 12 months or at least one recurrence within 3 months following discontinuation of suppressive acyclovir therapy. Pregnant, nursing and sexually active women of childbearing potential not protected against pregnancy were excluded, as were patients treated with antiviral or immunomodulating agents, patients with immunodeficiency, or patients with impaired renal, gastrointestinal or hepatic function. Previous inclusion in the same study was not allowed. Local ethics committee approval was obtained, and all patients gave written informed consent. Investigators were dermatologists (58%), gynaecologists (31%) or trained general practitioners (11%) in private practice, working in association with 25 French university departments which served as regional coordinating centres.

Eligible patients were randomized to receive either valacyclovir 1000 mg od or valacyclovir 500 mg bd for 5 days. Study medication was dispensed at inclusion. Patients self-initiated therapy at the first signs or symptoms (including prodromal phase) of their next recurrence and returned to their physician for assessment at days 2 and 6 after starting treatment. Existing ano-genital lesions were classified as macule/papule, vesicle/pustule/ulcer, crust or healed lesions, and all adverse experiences were recorded. Patients kept a diary to record twice daily their compliance with the treatment and their assessments of pain, discomfort and itching. Pain was evaluated with a visual analogue scale (VAS) and a verbal scale of four items: none, mild, moderate or severe; discomfort was evaluated by VAS, and itching by a four-item verbal scale. Patients also recorded the presence or absence of any visible lesions and the date of healing of all lesions.

Multiple efficacy and safety endpoints were used, as the trial was designed to demonstrate equivalence of both regimens. Some endpoints were assessed by the investigator: percentage of patients with completely healed lesions at day 6, percentage of patients with abortive episodes (prodromal phase not followed by the occurrence of any skin or mucous membrane lesions), and adverse experiences. Others were assessed by the patients themselves: time to healing, which was defined as the number of days between initiation of therapy and complete healing of lesions (patients with aborted lesions were excluded), and cessation of pain, itching or discomfort.

Statistics

The sample size was calculated for each endpoint to allow equivalence, defined by a maximum difference of 10% between both groups, to be determined with a type I risk of 10% and a power of 95%. The larger sample size was retained as the sample size of the study. This calculation gave a sample size of 360 patients per group, based on the percentage of patients with completely healed lesions at day 6 evaluated by investigators, assuming a 70% healing rate at day 6 in both groups. In previous studies of patient-initiated treatment of genital herpes recurrences, approximately 30% of selected patients did not experience recurrence during the study and so 950 patients were planned to be included in the study.

The intention-to-treat analysis group included all randomized patients who returned to their investigator for the day 2 visit before the fourth month after the closure date for inclusions. For endpoints, which were percentages without any adjustment for prognostic factors (percentage of patients with completely healed lesions at day 6 and percentage of patients who experienced any adverse experience), the difference between treatments was assessed by the difference in percentage in the two groups. Since previous studies have identified gender as an important factor, the percentage of patients with abortive episodes was adjusted for gender and the relative risk used to assess the difference between groups. For adjusted endpoints (time to complete lesion healing, time to cessation of pain, time to cessation of itching, time to cessation of discomfort), the relative risk was used to assess the difference between groups. For each endpoint, the 80% CI of the difference between the two groups was calculated; equivalence was regarded as demonstrated with a 10% type I risk if the lower confidence limit was higher than a pre-defined equivalence limit (calculated to show a maximum 10% inferiority of valacyclovir 1000 mg od against valacyclovir 500 mg bd). The two regimens were regarded as equivalent if equivalence was demonstrated for each of the six efficacy criteria and safety criteria. Statistical analyses used SAS 6.08 software (SAS Institute Inc, Cary, NC, USA).

Assignment and blinding

Patients were randomly assigned by means of a computer-generated random list, in blocks of four, to receive od or bd treatment. Placebo tablets, similar in appearance and taste to valacyclovir tablets, were provided to maintain the study
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Blinding in both groups of patients. Numbered blister packs containing tablets of valacyclovir and placebo were prepared for each patient included, before the beginning of the trial. Successful blinding was maintained among participants, investigators and data analysts until the end of data analysis.

Results

Patient disposition and follow-up

A total of 1199 patients were randomized (Figure 1), of whom 922 initiated valacyclovir before the closing date of the trial (444 in the 1000 mg od group and 478 in the 500 mg bd group; \( P = 0.04 \)). As a double dummy was used in the study, this difference between the two groups in terms of enrolment appeared to be due to hazard. Seventy-four treated patients did not complete the study as planned, mostly because of poor compliance with therapy, late start of therapy or co-prescription of a forbidden drug.

Analysis

Patients' characteristics at screening were similar in each group (Table I). The diagnosis of herpes recurrence was clinically confirmed (presence of papules, vesicles or...
crusts) at the day 2 visit in 95.5 and 94.2% of the patients without an abortive episode in the 1000 mg od and 500 mg bd groups, respectively. No patient discontinued valacyclovir because of intolerance. The nature, incidence and severity of reported adverse events were similar in both groups (Table II), and there was no evidence that any particular adverse event was related to valacyclovir.

Table III displays the efficacy results. Equivalence between both regimens was found for all criteria. Abortive episodes were experienced by 9.5 and 9.6% of treated patients in the 1000 mg od and 500 mg bd groups, respectively. This gave a relative risk of 1.002 (80% CI 0.975–1.030). The lower confidence limit was higher than the equivalence limit of 0.9, indicating equivalence for this criterion. Complete healing of the lesions was recorded by the investigator at the day 6 visit in 81 and 78% of the patients with a non-abortive episode. Moreover, at that date, 82 and 77% of the patients evaluated their lesions as healed in the 1000 mg od and 500 mg bd groups, respectively; thus, the results of self-evaluation were comparable to the investigators’ assessments. The median times to lesion healing were 3.4 and 3.6 days in the 1000 mg od and 500 mg bd groups, respectively. The median times to cessation of pain, discomfort or itching (Figure 2) were 2.5, 2.9 and 2.5 days, and 2.5, 2.6 and 2.1 days, respectively. Both methods for assessing pain, the VAS and the simple verbal scale, yielded similar results (data not shown). Exploratory analyses failed to reveal any effect of gender on these endpoints.

Discussion
This study shows that valacyclovir 1000 mg od for 5 days is equivalent in efficacy and safety to the recommended dosage of 500 mg bd for 5 days in patient-initiated episodic treatment of recurrent genital herpes.
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In recent years, equivalence trials have been used increasingly. However, the question of what constitutes equivalence between two treatments and how this can be demonstrated remains open. Indeed, a non-significant difference between treatments does not necessarily indicate equivalence. Studies measuring a single criterion design are useful, but they can only establish equivalence with respect to that criterion alone. This study used a multicriteria design. Thus, we are able to clearly demonstrate equivalence with respect to all criteria of importance. Moreover, the equivalence for each criterion was defined by a maximum difference of 10% between groups, which is often difficult to achieve for all criteria.

Most of our patients have been followed by private practitioners. Thus, our results reflect the usual use of valacyclovir in recurrent genital herpes, as compared with the artificial conditions in hospital-based phase III studies, in which viral cultures are performed daily. However, this approach precluded the harvesting of viral cultures from the genital lesions; thus, it was not possible to assess any difference in the reduction of HSV shedding. Because the diagnosis of genital herpes is often clinically easy and because herpes viral cultures from the lesions lack sensitivity, we believe that our decision not to perform viral cultures was justified.

The trial was a double-blind, randomized study, following good clinical practice guidelines. Several other lines of evidence support the validity of our findings. First, similar results have been obtained in two different ways.

Table III. Efficacy and safety of od and bd valacyclovir (VACV) as episodic therapy for recurrent genital herpes (intent-to-treat analysis)

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>VACV 1000 mg/day od</th>
<th>VACV 500 mg/day bd</th>
<th>Estimated difference between VACV 1000 mg od – VACV 500 mg bd groups</th>
<th>80% CI of difference&lt;br&gt;</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with aborted episodes</td>
<td>9.5</td>
<td>9.6</td>
<td>1.002</td>
<td>(0.975; 1.030)</td>
<td></td>
</tr>
<tr>
<td>Percentage of patients with complete healing</td>
<td>81</td>
<td>78</td>
<td>2.6</td>
<td>(0.2; 5.0)</td>
<td></td>
</tr>
<tr>
<td>at the sixth day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to complete healing</td>
<td>3.4 days</td>
<td>3.6 days</td>
<td>1.225</td>
<td>(1.095; 1.371)</td>
<td></td>
</tr>
<tr>
<td>Time to cessation of pain</td>
<td>2.5 days</td>
<td>2.1 days</td>
<td>0.920</td>
<td>(0.821; 1.030)</td>
<td></td>
</tr>
<tr>
<td>Time to cessation of discomfort</td>
<td>2.9 days</td>
<td>2.6 days</td>
<td>0.958</td>
<td>(0.860; 1.068)</td>
<td></td>
</tr>
<tr>
<td>Time to cessation of itching</td>
<td>2.5 days</td>
<td>2.1 days</td>
<td>0.944</td>
<td>(0.847; 1.051)</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage of patients with an adverse event</td>
<td>16</td>
<td>17</td>
<td>1.1</td>
<td>(–2.0; 4.3)</td>
<td></td>
</tr>
</tbody>
</table>

*aThe one-sided 90% CI is the interval of values superior to the lower limit of the two-sided 80% CI.
*bEquivalence is assessed when the lower limit of CI is superior to 0.90.
*cEquivalence is assessed when the lower limit of CI is superior to 0.10.
*dKaplan–Meier estimates of median times, hazard ratio from Cox’s model. Equivalence is assessed when the lower limit of CI is superior to 0.76.

Fig. 2. Kaplan–Meier estimates of patient-assessed time to cessation of itching in both regimens of valacyclovir. Treatment: –––– VACV 500 mg bd groups, - - - - - - VACV 1000 mg od groups.

Fig. 3. Kaplan–Meier estimates of patient-assessed time to healing, cessation of pain, and discomfort yielded similar patterns. Treatment: ——— VACV 500 mg bd groups, ……… VACV 1000 mg od groups.
Furthermore, our criteria were similar to those used in previous studies with valacyclovir or acyclovir in the episodic treatment of recurrent genital herpes.\textsuperscript{4,8–10} Our figures for the percentage of patients with completely healed lesions at day 6, median time to complete healing or to cessation of pain are similar to those reported previously, with a trend to shorter duration in our study which might account for less severe recurrences in our outpatient population.

Our results may be considered slightly provocative because valacyclovir 1000 mg od produces plasma concentrations of acyclovir above the 50% inhibitory concentration (IC\textsubscript{50}) for most acyclovir-sensitive HSV-2 isolates for only 10 h/day.\textsuperscript{6} Numerous arguments, however, favour the hypothesis that this regimen of valacyclovir is effective in recurrent genital herpes. First, the areas under the concentration–time curve (AUCs) for 24 h, which reflect the body's exposure to acyclovir, are higher during therapy with oral valacyclovir 1000 mg od, compared with those obtained with the usual dosage of 200 mg acyclovir five times daily.\textsuperscript{6} Furthermore, acyclovir plasma concentrations during the first 10–12 h after administration of 1000 mg valacyclovir od are far higher than those during treatment with acyclovir 200 mg five times daily.\textsuperscript{6} In HSV disease, the 'site of infection' is the sensory nerve/ganglia, with the epithelium being the site to which the virus travels when it reactivates, thus causing tissue damage and pain. Concentrations of acyclovir within the epithelium have been shown to be higher than in dermis or hypodermis after oral administration of the drug.\textsuperscript{15} The apparent elimination half-life of acyclovir in this compartment also seems to be longer than in plasma.\textsuperscript{16} Thus, high concentrations of acyclovir may be obtained for a prolonged time in the epithelium after oral valacyclovir administration. The fate of acyclovir within the infected cells should also be considered. A cyclovir is preferentially taken up and selectively converted to the active triphosphate form (A CV-TP) in HSV-infected cells, leading to concentrations of A CV-TP within those cells far higher than in the extracellular compartment.\textsuperscript{17,18} In-vitro experiments have shown that when acyclovir is removed from the culture medium of HSV-infected cells pre-treated with acyclovir, the intracellular concentration of A CV-TP declines.\textsuperscript{18} However, this decline is slower when low concentrations of acyclovir remained in the medium and a plateau was reached at 6 h in the presence of 1 \( \mu \text{M} \) extracellular acyclovir.\textsuperscript{12} We speculate that these conditions are similar to those observed within the infected cells of the epidermis after valacyclovir 1000 mg od. High levels of the active A CV-TP might thus be maintained in vivo during a prolonged period within the target cells. Finally, A CV-TP is an irreversible inhibitor of the viral DNA polymerase,\textsuperscript{15} and thus a prolonged duration of action might be anticipated.\textsuperscript{17}

In conclusion, valacyclovir 1000 mg od for 5 days has equivalent efficacy and safety to the approved regimen of valacyclovir 500 mg bd in the patient-initiated treatment of recurrent genital herpes. Since od regimens enhance patient compliance, we believe that our results provide a clinically useful alternative regimen, which may be preferred by some patients. Once daily regimens for acute therapy should not, however, be extended without further investigation in clinical situations where the viral load of HSV is higher, such as HSV primary infection, or where viral replication is high and less easily terminated by acyclovir, such as in immunocompromised patients.\textsuperscript{19} We have also shown that a multicriteria equivalence trial can be performed on an outpatient basis, provided that well organized coordinating and monitoring structures are established. Finally, in addition to the pharmacokinetic profile, intracellular potency should also be considered as an important factor in establishing antitherpetic drug dosing schedules.

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\section*{References}


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