ORIGINAL ARTICLE

Evaluation of the activity and safety of CS 21 barrier genital gel® compared to topical aciclovir and placebo in symptoms of genital herpes recurrences: a randomized clinical trial

A. Khemis,[1] L. Duteil,[2] Y. Tillet,[3] O. Dereure,[4] J-P. Ortonne[1,*]

[1]Service de Dermatologie Hôpital L'Archet 2, Nice Cedex 3, France
[2]CPCAD, Hôpital L'Archet 2, Nice Cedex 3, France
[3]White-Tillet Consultants & Experts 35, Chelles, France
[4]Service de Dermatologie, Hôpital Saint-Eloi, Montpellier Cedex 5, France
*Correspondence: J.P. Ortonne. E-mail: ortonne@unice.fr

Abstract

Background Topical or systemic antiviral drugs reduce the duration of genital herpes recurrences but may not always alleviate functional symptoms.

Objectives To assess the efficacy and safety of oxygenated glycerol triesters-based CS21 barrier genital gel® vs. topical aciclovir and placebo (vehicle) in resolving functional symptoms and in healing of genital herpes recurrences.

Methods A prospective randomized controlled, investigator-blinded trial of CS21 barrier genital gel® vs. topical aciclovir (reference treatment) and placebo (vehicle) was designed. The primary endpoint was the cumulative score of four herpes-related functional symptoms (pain, burning, itching and tingling sensations). Secondary endpoints included objective skin changes (erythema, papules, vesicles, oedema, erosion/ulceration, crusts), time to heal, local tolerance and overall acceptability of the treatment as reported by a self-administered questionnaire.

Results Overall, 61 patients were included. CS 21 barrier genital gel® was significantly more efficient than topical aciclovir and vehicle for subjective symptoms and pain relief in genital herpes recurrences; additionally, time to heal was significantly shorter with CS 21 than with vehicle, whereas no significantly difference was observed between patients receiving topical aciclovir and vehicle. The treatments under investigation were well tolerated and the adverse events were comparable in the three treatment groups.

Conclusion Overall, these results support the interest of using of CS 21 barrier genital gel® in symptomatic genital herpes recurrences. Accordingly, this product offers a valuable alternative in topical management of recurrent genital herpes.

Received: 18 February 2013; Accepted: 5 July 2013

Conflicts of interest

Y. Tillet is a consultant for Laboratoires Carilène who contributed to the development of the study protocol and to scientific publication. O. Dereure has been a consultant for Laboratoires Carilène and contributed to the scientific publication. The remaining authors declare no conflicts of interest.

Funding sources

This study was supported by Laboratoires Carilene.

Introduction

Herpes virus simplex type 1 (HSV1) and type 2 (HSV2) are double-stranded DNA viruses mainly affecting mucous membranes. These ubiquitous viruses affect populations worldwide with lifelong infections marked by primary contact that may lead to highly symptomatic acute lesions followed by intermittent clinical and subclinical viral reactivation and shedding from mucosal surfaces. HSV infection is the main worldwide cause of genital ulcers related to sexually transmitted disease and both HSV1 and HSV2 may cause genital herpes. While HSV2 is still the main aetiological agent transmitted by sexual contact with identical risk factors compared to other sexually transmitted infections

(STI), western countries have seen an upsurge in primary genital HSV1 infection in the past decade probably owing to a delay in acquisition of oral HSV1 infection early in life.[1,2]

Genital HSV infection is both an individual and a public health issue since immunocompetent people may be affected by frequent, painful and psychologically distressing genital lesions with a significant impact on sexual life.[1,2] In addition, vertical infected mother–baby transmission during delivery may result in disseminated neonatal infection with potentially devastating, mainly neurological complications. Furthermore, mucosal disruption caused by genital herpes relapses favours sexually acquired HIV infection. In France, it is evaluated that 2 million people (3.3% of the general population) are affected by this highly common STI.

The frequency of clinical and subclinical viral reactivation varies widely depending on host and viral factors. Reactivations are symptomatic in a minority of cases and only 10 to 25% of patients with HSV2 immunity are aware that they have genital herpes.[2] Clinically relevant recurrent episodes usually begin with prodrome symptoms including tingling, burning sensations, itching, paresthesia and pain which usually persist or increase while local objective symptoms (vesicles, crusts, swelling) appear. Lesions usually heal spontaneously in 5 to 10 days. Short regimens of oral antiviral treatment reduce the duration of viral shedding and may prevent the development of objective lesions if the treatment is initiated within 24 h of the first signs or symptoms.[3,4] However, a significant number of patients only receive topical, sometimes over-the-counter treatment. These topical treatments include both non-antiviral and antiviral agents, and the latter ones have been shown to offer a modest reduction in duration of herpes recurrences (by 10 to 15%) but with no clear alleviation or shortening of functional symptoms which are nevertheless the main concern of most patients during the active period of the infectious flare.[3–12]

CS20® is a novel protective barrier gel, (registered as Acura 24®) containing OGT (oxygenated glycerol triesters) which maintains a moist environment, credited with both anti-inflammatory and healing-promoting properties on mucous, particularly oral membranes. Initially developed in gums abrasion related to completely removable dentures and in xerostomia with encouraging results both on subjective and objective symptoms,[13] this topical formulation has been more recently evaluated in labial herpes recurrences. In this latter indication, a randomized controlled trial comparing the performance and the safety of an OGT-containing CS20 protective barrier gel, topical aciclovir and a placebo (vehicle) cream concluded that CS20 resulted in significant and faster reduction in functional and clinical symptoms associated with HSV-1 labial recurrence compared with topical aciclovir and vehicle.[14]

Owing to these encouraging results, a further prospective randomized controlled trial was designed to assess the efficacy and safety of CS21 barrier genital gel®, a formulation adapted to the genital lesions, compared with topical aciclovir and placebo (vehicle) in the resolution of functional symptoms associated with recurrences of genital herpes.

Material and methods

Patients

Outpatients with a background of recurrent genital herpes and experiencing at least four episodes of recurrence per year were eligible to participate in the screening visit. Following the screening visit, patients should suffer at least a recurrence of genital herpes within a 4-month eligibility period. As soon as a patient experienced the first symptoms of recurrent genital herpes during the eligibility period, he/she was asked to consult the investigator within 36 h so that he/she could fulfil the time requirements; he or she was then required to start treatment within 12 h after the inclusion visit. Other main inclusion criteria included the following: patients of either sex, aged 18 years and above, covered by Social Security, not receiving an oral preventive treatment for recurrent herpes simplex genital infections (by aciclovir or valaciclovir), agreeing to comply with the study procedures until the end of the study and to take a blood test for HIV, Hepatitis B and C serology at the screening visit. To be included in the study, the patient had to be sero-negative for the aforementioned viral infections and to agree to comply with the study procedures until the end of the study. Women with childbearing potential were required to be using a reliable method of contraception (oral contraceptive pill, contraceptive injection or implant, IUCD or condoms) for at least one month before the start of the study, throughout the whole study period and for the month following the end of the study or had to provide a negative urine pregnancy test on the first day of the treatment. The final study protocol and related documents were reviewed and approved by the relevant Ethic Committee (CPP Sud Méditerranée V in Nice – 06-France) on November 2008. A comprehensive file encompassing the related study documents (including the protocol) was approved by the National French Competent Authority (Formerly Afssaps, currently ANSM). This study has been conducted in accordance with The Declaration of Helsinki as amended, the ICH E6-CPMP/ICH/135/95 guideline, the French Good Clinical Practices in vigor and the French Law in force. All selected subjects received oral and written information concerning the study. This information was approved by the above-mentioned Ethic Committee. Every enrolled patient in the study previously signed a written informed consent.

Study design and treatments

The study was designed as a prospective, multi-centre, randomized, controlled, investigator-blinded, three parallel groups study in order to compare efficacy and tolerance of CS21® barrier gen-

ital gel, a formulation containing oxygenated glycerol triesters (hereafter called OGT) to those of topical aciclovir and placebo cream (CS21® vehicle) in symptoms alleviation of genital herpes recurrences. Treatments were randomly assigned. The tested product was CS 21® of Laboratoires CARILENE (Montesson, France, batch n° 801026), with the following formula: peroxidized corn oil (OGT) (91.8%), micronized zinc oxide (1.0%), silicon dioxide (7.0%), Propyl paraben (0.2%). Reference product was Zovirax® (aciclovir) 5% cream of GlaxoSmithKline (Marly-le-Roi, France, batches n°C368961, n°C374963, n°C382078). Placebo formulation was CS21® gel vehicle without OGT (Laboratoires CARILENE, batch n°08L075). All three products were locally administered on lesions five times per day from the onset of the first symptoms (prickling, burning, itching), and the treatment should be started within 12 h after the inclusion visit as already mentioned. Treatment duration was up to 48 h after healing or for 15 days maximum. As the constituents and the external appearance of two of the products under scope were different (CS21® gel vs. aciclovir cream), the study could not be really designed as a double-blinded one. However, packaging and labelling of the products under investigation were anonymized by the promoter so that neither the patient nor the person in charge for dispensing the products to the patient could identify the dispensed treatment. The procedure was followed to ensure that no study investigator or clinician could have access to the nature of the tested product or to the randomization list. A person responsible for the dispensing of products under trial and independent of both study investigators and clinicians delivered the topical product to the subject according to the randomization list. In addition, both the person in charge for products delivery and the patients were required not to discuss the tested product or its modalities of application with the study investigators and clinicians. As a result, the study can probably be considered as practically double-blinded if not conceptually. Study centres were the following ones: Department of Dermatology, Hôpital L'Archet 2 (Nice, France; main investigator: Pr JP Ortonne), practices of Dr Mireille Ruer-Mulard (Martigues, France) and of Dr Bruno Halioua (Paris, France). Pr Jean-Paul Ortonne was the coordinator of the trial. Patients were evaluated at D1 (inclusion visit, before any application of topical product), D2 (24 h after first application), D3 (48 h after first application), D8 (7 days after first application) and D15 (14 days after first application) for primary and secondary endpoints.

Endpoints

Primary endpoint Primary endpoint was the sum of symptom intensity scores rating burning, itching and prickling sensation and pain, as assessed by the patient using a Visual Analogic Scale (VAS) of 100 mm (0 mm = no sensation, 100 mm = worst imaginable sensation). This criterion was then rated each day by the patient during the study duration (D1 to D15). To homogenize results and to facilitate the comparison between the three arms, the baseline value of the sum of intensity scores of subjective symptoms and pain was rated 100% for the three treatments before any product application; this sum was subsequently calculated for each visit and expressed as a percentage of the baseline score.

Secondary endpoints Secondary endpoints were clinical lesional scores evaluating erythema, papules, vesicles, oedema, erosion/ulceration, crusts through a semi-quantitative rating using a 0 to 3 scale for each item (0 = absence, 1 = mild, 2 = moderate, 3 = severe) and time to heal (day of sloughing off the crust or return to normal skin appearance), both of them assessed by the investigator; local tolerance (sensations during product application); number, grade and relationship with treatment of adverse events; overall acceptability of the treatment as reported by a self-administered questionnaire. For issues related to acceptability of treatment regarding symptoms reduction, acceleration of healing and likelihood that the participant would use the assigned product for subsequent herpes recurrences, patients recorded their responses based on the following options: totally disagree, tend to disagree, no opinion, tend to agree and totally agree. For safety self-assessment of the tested product, the patients were required to answer the question 'How well did you tolerate this treatment?' and the following responses were available: very well, well, no opinion, not very well, badly.

Statistical analysis

The randomization list was prepared in the CPCAD biostatistics unit using SYSTAT version 11.0 software (Systat Software, Inc., Chicago, IL, USA) by a qualified person not participating in the study. This list was composed of 3 × 3 Latin square blocks. Descriptive statistics (mean, standard deviation, sample size, normality test) were calculated for all variables, including demographic variables. Some variables were also represented graphically. The Shapiro–Wilks normality test was used to evaluate the distribution of each variable and thus select the most appropriate type of comparison test. The working hypotheses were given in the following: null hypothesis (H0): CS 21genital gel® is not different from the comparator (topical aciclovir or vehicle) and alternative hypothesis (H1): CS 21genital gel® is different from the comparator for the parameter under scope. The appropriate statistical test was applied to the difference between mean value for CS 21® and mean value for the comparator. The limit of significance of the test was set at $P = 0.05$. The following tests were used for intergroup comparisons: variables with a normal distribution: comparisons of treatments two by two by analysis of variance (General Linear Model) with repeated measures (Day) performed to assess the effect of treatment, centre and sex; variables with a non-normal distribution: the treatments were compared by the Kruskal–Wallis test (non-parametric test)

regarding the influence of treatment, centre and sex. The evolution of the number of healed lesions (cumulative proportion) as a function of time was analysed using survival curve analysis (Kaplan–Meier method). Survival curves obtained for both treatments were compared by the logrank test. Variables describing the local safety were analysed in a descriptive manner. Systemic safety analysis was based on adverse events records and results were presented in a descriptive manner. Answers to the self-administered questionnaires were analysed using the chi-squared test for comparison of several distributions. The detection of a difference in the sum of subjective scores (main criterion) of 20 mm or more on the VAS at 24 h from baseline with a limit of significance of 5% and a power of at least 90%, assuming a common standard deviation of 20 mm, requires the inclusion of 18 patients in each group. Based on an estimated overall level of drop-out events or of incomplete cases of 10%, 20 patients are necessary per parallel group.

Results

Patients

Sixty-one patients were randomized in this study (43 women and 18 men). The intention to treat (ITT) population was composed of the 61 subjects (43 women and 18 men) as the per-protocol (PP) population. No major protocol violations were observed during this study. Demographic data of the study population showed they were distributed in a homogeneous manner in the three treatment groups. Corresponding data are summarized in Table 1. One hundred and twenty-eight concomitant treatments were reported by 39 patients in this study. These treatments were used for various conditions such as arthritis ($n = 10$), headache or migraine ($n = 6$), hypercholesterolemia ($n = 5$), contraception ($n = 6$), venous insufficiency ($n = 4$), menopause ($n = 7$) and osteoporosis ($n = 8$).

Table 1 Demographic data

	Distribution by treatment group (mean ± SD)			Total
	CS 21®	Placebo	Aciclovir	
Number	21	20	20	61
Age (years) Min–Max	53 ± 14 30–74	49 ± 14 22–69	57 ± 14 27–76	53 ± 14 22–76
Weight (kg)	67 ± 11 48–96	63 ± 12 45–85	68 ± 15 50–110	66 ± 13 45–110
Height (cm)	168 ± 8 157–188	166 ± 10 153–192	169 ± 10 156–187	168 ± 9 153–192
Sex	F = 14; M = 7	F = 15; M = 5	F = 14; M = 6	F = 43; M = 18

Table 2 Sum of subjective scores (pain, itching, prickling, burning)

Parameter	Visit	CS 21®	Placebo	Aciclovir
Sum of subjective scores	D1	169.4 ± 85.4	147.2 ± 77.4	163.3 ± 78.6
	D2	80.0 ± 91.2	163.7 ± 81.3	139.3 ± 90.7
	D3	49.6 ± 82.0	103.2 ± 111.9	80.8 ± 61.4
	D8	9.5 ± 39.8	9.8 ± 24.0	9.5 ± 31.5
	D15	0.0 ± 0.2	0.2 ± 0.5	0.0 ± 0.0

Efficacy

Primary endpoint The evolution of the sum of subjective scores between D1 and D15 (mean ± SD) is presented in Table 2 with related results of statistical comparison between the three therapeutic arms in Table 3. More specifically, data showed that, at D2 and D3 (i.e. 24 and 48 h after first application), the sum of subjective scores was significantly lower in the group CS 21® compared to both vehicle and Aciclovir groups, while there was no significant difference between the three baseline scores. As expected, a similar result was also observed when considering the percentage of reduction of the sum of subjective scores compared to baseline (D1) for the three treatments, as showed in Fig. 1 illustrating the evolution of this parameter upon time. The pain score was significantly lower for the group CS 21® compared to Placebo group from D2 to D7 (with the exception of D3) and compared to Aciclovir group from D2 to D5 whereas no significant difference was identified between Aciclovir and vehicle group for this particular criterion at any time of the study (Fig. 2).

Furthermore, area under the curve (AUC) of the sum of the subjective scores from D1 to D15 was significantly lower with CS21 compared to vehicle ($P = 0.013$) and Aciclovir ($P = 0.014$), a data suggesting a better overall efficacy of the protective gel in reducing subjective symptoms related to herpes genital recurrence. Conversely, there was no statistically significant difference between Placebo and Aciclovir regarding AUC

Table 3 Results of statistical comparisons for the sum of the subjective scores

	Visit	CS 21® vs. Placebo	CS 21® vs. Aciclovir	Aciclovir vs. Placebo
Sum of subjective scores	D1	ns	ns	ns
	D2	CS 21® < placebo $P = 0.003$	CS 21® < aciclovir $P = 0.024$	ns
	D3	CS 21® < placebo $P = 0.026$	CS 21® < aciclovir $P = 0.024$	ns
	D8	ns	ns	ns
	D15	ns	ns	ns

ns, non-statistically significant.

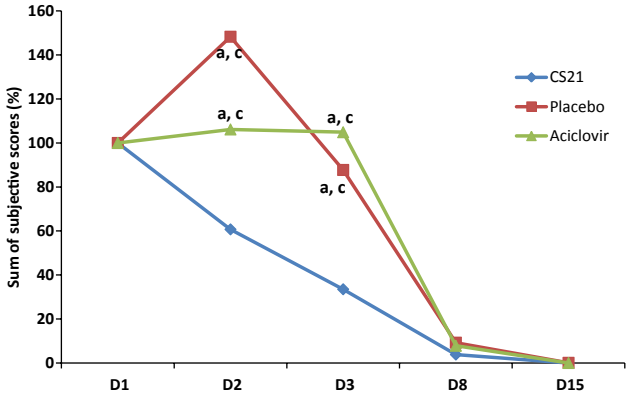

Fig. 1 Percentage of reduction of the sum subjective scores. Significant differences ($P < 0.05$) are indicated by the following: a = CS 21® < placebo; c = CS 21® < Aciclovir.

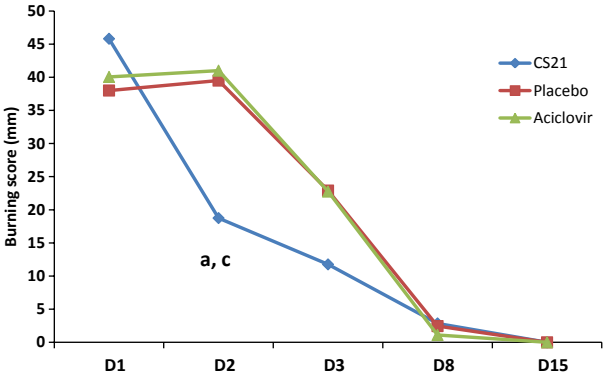

Fig. 3 Evolution of the burning score as a function of treatments. Significant differences ($P < 0.05$) are indicated by the following: a = CS 21® < placebo; c = CS 21®® < Aciclovir.

and specific performance at any evaluation visit. Specific results for pain intensity, burning and itching scores are showed in Figs 2, 3, and 4 respectively.

Secondary endpoint Clinical signs were significantly improved in the CS 21® group compared to vehicle and Aciclovir groups at D2 for oedema and papules and at D3 for erythema, oedema, papules and vesicles (Fig. 5). Conversely, there was no difference between Aciclovir and vehicle group as to lesional signs at any evaluation point. The mean healing time was 9.62 days, 11.5 days and 17.05 days in CS21, topical aciclovir and vehicle group respectively. The comparison of the three corresponding actuarial curves displayed significant inter-treatment differences for this parameter (logrank, $P = 0.01$). Specific analysis showed a significantly shorter healing time in the CS 21® group than in the Placebo group ($P = 0.04$), while there was a tendency in favour of CS 21® vs. Aciclovir ($P = 0.057$). The distribution of responses to the question 'According to your experience of herpes lesions would you say that the treatment reduced the painful sensations of the herpes?' is reported on Fig. 6 and CS21® was better rated than vehicle ($P = 0.002$) and Aciclovir ($P = 0.019$). Conversely, no difference was observed between Aciclovir and Placebo for painful sensation. There were no statistical differences between the three arms with respect to self-appreciated reduction in prickling, itching and burning sensations. As to local tolerance assessment, complains after product applications were recorded by patients at 16/244 tolerance assessment points (6.55%). They were equally distributed between the three treatments, and were most often described as sensations of burning and prickling occurring shortly after product application.

Adverse events (AEs) Twenty-two AEs were observed in this study in 12 patients. Among these 22 AEs, four were considered

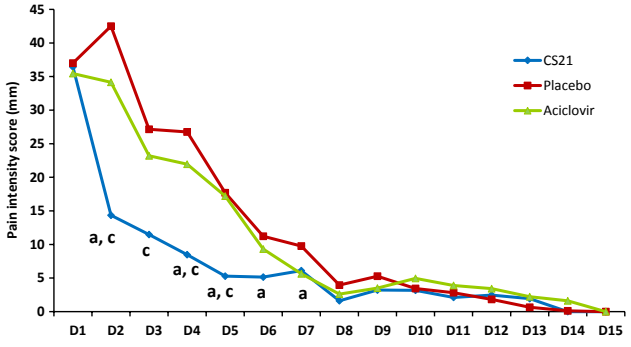

Fig. 2 Evolution of the pain intensity as a function of treatments. Significant differences ($P < 0.05$) are indicated by the following: a = CS 21® < placebo; c = CS 21® < Aciclovir.

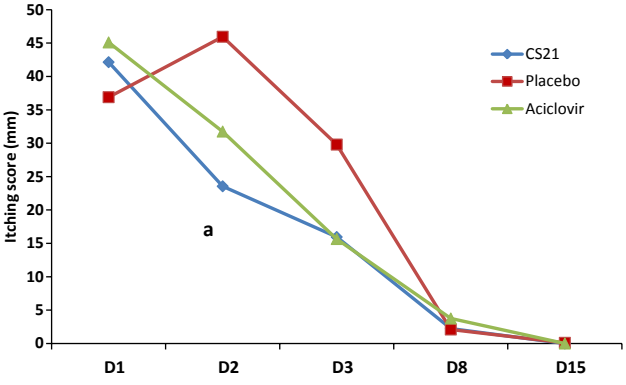

Fig. 4 Evolution of the itching score as a function of treatments. Significant differences ($P < 0.05$) are indicated by the following:a = CS 21® < placebo.

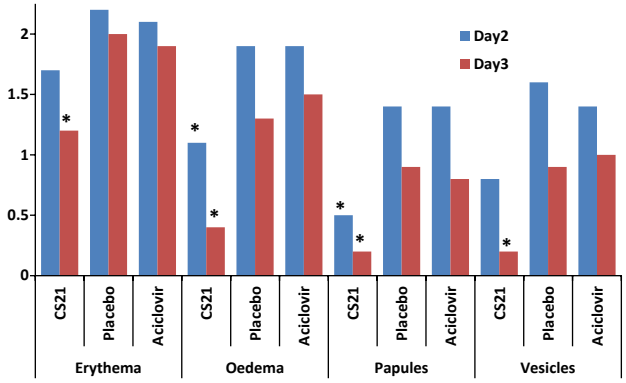

Fig. 5 Scores of clinical signs as a function of treatments. * = CS 21® < Placebo ($P \leq 0.016$) and CS 21® < Aciclovir ($P \leq 0.014$).

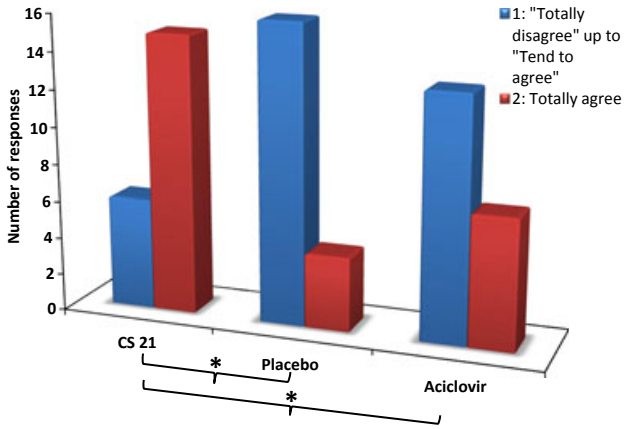

Fig. 6 Distribution of responses to the question 'According to your experience of herpes, would you say that the treatment reduced the painful sensations?'

somehow related to the products under scope with transient or more protracted burning, itching or prickling sensations occurring after CS 21® gel (one patient), placebo cream (two patients) or topical aciclovir (one patient) applications. These four related AEs were rated as weak (one patient) to moderate (three patients) in intensity.

Discussion

The objective of this prospective RCT was to evaluate the efficacy and safety of CS 21® genital protective barrier gel by comparison with topical aciclovir (Zovirax cream®) and vehicle in alleviating the subjective symptoms of recurrent genital herpes on three parallel groups of 20 patients. This study was designed after convincing results were previously obtained in a trial focusing on HSV-1-related labial herpes recurrences which showed a significantly faster reduction in functional and clinical symptoms associated with a similar OGT-based formulation (CS20®) compared with topical aciclovir and placebo.[14]

The main objectives of genital herpes recurrences treatment are faster relief of distressing functional symptoms and reduction of time to healing and of viral shedding duration. Oral antiviral drugs (aciclovir, valaciclovir and famciclovir) are well-established treatments of mucocutaneous HSV infections including genital recurrences but usually offer a modest reduction of lesion duration and associated pain in this latter indication. The performances of topical antiviral treatments (mainly aciclovir cream) are even more limited and only few RCT investigated their efficacy with conflicting results. Intermittent therapy of recurrent genital herpes with topical aciclovir cream resulted in some trials in shorter time to crusting and healing and in a decrease in symptom severity, but such a favourable outcome requires early patient initiation of therapy to provide significant clinical benefit.[6–8] Conversely, other studies failed to show efficacy on functional symptoms especially with respect to time to cessation of pain.[9–12]. Inadequate transcutaneous penetration of topical antiviral agents through the stratum corneum of the skin may be one of the limiting factors of topical therapy in recurrent infections in humans.[15] Accordingly, unmet needs persist regarding topical treatment of genital herpes recurrences especially for alleviation of functional symptoms.

CS21 is a genital protective gel that contains oxygenated glycerol triesters. These components build a protective film which adheres to and impregnates skin and mucosal lesions in the presence of zinc oxide. As a result of these physical properties, CS21 has been developed for the symptomatic treatment of genital herpes.

In the conditions of the trial, topical treatment with CS21® resulted in an overall significant and early (as soon as after only one day of treatment) improvement in cumulative and individual scores of four functional symptoms (pain, burning, prickling and itching) associated with recurrent genital herpes compared with vehicle and topical aciclovir, and this favourable effect was maintained during the main part of herpes flare for pain. Conversely, compared with placebo, topical aciclovir did not significantly improve this particular criterion at any evaluation time throughout the study. The self-questionnaire was in line with these data with a majority of patients totally agreeing with the proposition that CS 21® reduced the painful sensations of genital herpes, a data not shared by patients treated by Aciclovir or Placebo.

Furthermore, objective clinical signs were significantly and quickly improved in the CS 21® group compared to Placebo and Aciclovir groups, at D2 for oedema and papules and at D3 for erythema, oedema, papules and vesicles. Conversely, no difference was noted between topical Aciclovir and Placebo groups

with respect to lesional signs at any point of evaluation. Time to heal, as analysed by the actuarial curves method, was significantly shorter in the CS 21® group (9.6 days) than in the Placebo group (17 days), whereas no statistical difference was observed between aciclovir (11.5 days) and vehicle for this parameter.

Regarding local safety evaluation, all three tested products were well tolerated with infrequent and mild reactions, fairly equally distributed between the treatments and generally recorded as sensations of burning and prickling at the time of product application.

The preselection of patients according to their medical background with frequent herpes recurrences and the single-blinded design of the study related to the difference in external appearance of the products under scope must be taken into account in the overall interpretation of results. However, these potential limitations are unlikely to significantly decrease the relevancy of data since patients with the most refractory conditions were selected to enter this study.

Overall, this study strongly supports the hypothesis that the use of OGT-based genital protective gel, a topical formulation devoid of any specific antiviral activity, can offer patients a safe and quick symptomatic alleviation of functional discomfort, accompanied by a prompt improvement of physical changes associated with recurrent genital herpes. Accordingly, it offers a valuable alternative in topical management of recurrent genital herpes.

In conclusion, according to the data provided by this RCT, the OGT-based protective genital gel was significantly more efficient than topical aciclovir and vehicle for subjective symptoms control and pain relief in genital herpes recurrences; additionally, time to heal was significantly shorter with CS 21 than with vehicle whereas no significantly difference was observed between topical aciclovir and vehicle. Local tolerance of the gel was satisfying. Overall, these results support the use of CS21® barrier genital gel in symptomatic genital herpes recurrences.

Acknowledgements

The authors acknowledge the field work of Dr Bruno Halioua and Dr Mireille Ruer-Mulard in selecting and managing patients and in providing related data.

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