

ORIGINAL ARTICLE

Evaluation of the efficacy and safety of a CS20[®] protective barrier gel containing OGT compared with topical aciclovir and placebo on functional and objective symptoms of labial herpes recurrences: a randomized clinical trial

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Abstract

Background Topical or systemic antiviral drugs reduce the duration of herpes simplex virus 1 (HSV-1) recurrences but may not alleviate functional symptoms.

Objectives To assess the efficacy and safety of CS20 (Acura 24[®]) protective barrier gel versus topical aciclovir and placebo in resolving functional symptoms in HSV-1 labial recurrences.

Methods A prospective, randomized, single-centre, assessor-blinded study of CS20 versus topical aciclovir or placebo. The primary endpoint was the total score of four herpes-related functional symptoms (pain, burning, itching, and tingling sensations), evaluated by visual analogue scale (VAS). Secondary endpoints encompassed objective skin changes (oedema, crusting and erythema), evaluated by specific clinical scores.

Results In a study of 106 patients, compared with placebo, a significant improvement in total functional symptom score was observed after 1 day of treatment in the CS20 group, but only after 7 days of treatment in the topical aciclovir group. Burning sensations were significantly reduced by CS20 compared with aciclovir (Days 1–2) or placebo (Days 1–7). Compared to placebo, CS20 significantly reduced pain intensity on Days 1–6. CS20 induced significant and early improvements in the clinical scores for oedema and crusting compared with placebo. Time to cure was similar for CS20 and aciclovir. The treatments were well tolerated and adverse events were comparable in the three treatment groups.

Limitations The single-centre and single-blind design of the study and the preselection of patients.

Conclusion CS20 showed superior effectiveness against functional symptoms (pain and burning) associated with HSV-1 labial recurrences and was similar to aciclovir for time to cure.

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Conflict of interest

A Khemis: no conflict of interest to disclose.

L Duteil: no conflict of interest to disclose.

AC Coudert: no conflict of interest to disclose. Laboratoires Carilène's employee as Pharmacist, Regulatory and Quality Assurance Director.

Y Tillet: Laboratoires Carilène's Consultant who contributed to the development of the study protocol and scientific publication.

O Dereure: He has been a consultant for Laboratoires Carilène and contributed to the scientific publication.

JP Ortonne: no conflict of interest to disclose.

Introduction

Labial or perioral outbreaks of vesicular herpetic lesions affect approximately 20–40% of the population.¹ These lesions

(commonly called cold sores) usually affect the lips. They present in most cases with a clinical sequence of events including primary infection (often unapparent) followed by a latency period and

single or, in a minority of cases, multiple recurrences, the frequency of which is influenced by internal or external triggers.² A small proportion of patients have outbreaks that are monthly or more frequent.¹

The vast majority of cases of herpes labialis are caused by herpes simplex virus type 1 (HSV-1).³ In a classic case of herpes labialis recurrence, six stages are defined: prodrome (localized burning, tingling or itching sensation), erythema, papule or oedema, ulcer, crusting and healed.¹ Lesions resolve spontaneously, usually within 7–14 days, but are characterized by an unsightly appearance and functional symptoms.⁴ Such functional symptoms occur very early and commonly include pain, burning, itching and tingling sensations, which can result in significant discomfort for patients.⁴ Functional symptoms are the main concern of most patients during the active period of the infectious flare, and yet, the most commonly used topical treatments for herpes labialis are antiviral agents, which have been shown to significantly reduce duration of herpes recurrences (by 10–15%), but not functional symptoms.^{5–7}

The development of an effective topical therapy for recurrent labial herpes in immunocompetent individuals has been difficult, because natural healing of lesions is rapid, making it more challenging to demonstrate clinical efficacy, and because it is difficult to identify a topical drug formulation that improves skin penetration without also causing undue irritation of the skin.¹ Another obstacle to development is the requirement for recruitment of large numbers of patients to clinical trials of such therapies, because of marked variations in lesion severity.¹

In all cases, topical antiviral therapies, such as aciclovir and penciclovir, are known to be limited by several factors, including small efficacy on signs and symptoms and formation of a scab during the healing process, because they do not afford benefits of lesion protection and repair.⁸ A novel protective barrier gel, CS20 (registered as Acura 24[®]) containing OGT (oxygenated glycerol triesters), has been developed for the treatment of HSV-1 labial recurrences, mainly to achieve more efficient and rapid relief from the functional discomfort induced by the flare and to maintain a moist environment for lesion repair and healing. The aim of the present randomized study was to assess the efficacy and safety of CS20 compared with topical aciclovir and placebo in the resolution of functional symptoms associated with HSV-1-related labial recurrences.

The use of an OGT-containing agent in this condition is based on the encouraging results obtained in several previous studies. Specifically, OGT induced anti-inflammatory effects and acceleration of healing in mouth mucous membranes, particularly gums with abrasions from completely removable dentures in totally edentulous patients,⁹ based on both objective (improvement of clinical signs such as pain, inflammation, etc.) and subjective signs (improved comfort when wearing dentures). It is also of interest to note the results of two RCTs assessing an OGT oral lubricant solution for the relief of symptoms of xerostomia compared with an aqueous saliva substitute containing electrolytes. In both psycho-

tropic drug-induced xerostomia and xerostomia in older patients, OGT solution was significantly superior to the comparator in improving mouth dryness, oral tissue condition and social life.^{10,11}

Materials and methods

Patients

Outpatients attending a hospital dermatology clinic for frequently recurring labial herpes were preselected for this study. Individuals who actually experienced a recurrence of labial herpes during the accrual period of 6 months after the initial visit were finally enrolled. Patients had to be immunocompetent, with no topical or systemic treatments (including antiviral agents, corticosteroids, immunomodulating drugs) that interfere with the immune system or with antiviral activity permitted during the 30 days before inclusion or during the trial period. The study was conducted in accordance with the International Conference of Harmonisation E6, Guideline for Good Clinical Practice (GCP) and applicable regulatory requirements. Prior to any inclusion, the study protocol had been approved by the ethics committee of Nice (France) (Trial N°08.045) in accordance with the Helsinki Declaration, and was registered in the AFSSAPS database under the number ID RCB 2008-A00824-51. All potentially eligible patients received appropriate written and verbal information regarding the design and purpose of the study, and a signed informed consent form was requested from each patient entering the study.

Study design and treatments

The trial was designed as a prospective, randomized, single-centre, assessor-blinded study, conducted in three parallel groups and organized in two successive phases: (i) a selection/eligibility phase; and (ii) a treatment phase. As the constituents of the products were different (CS20 gel vs. aciclovir cream), the study could not be designed as a double blind. To ensure blinding, the treatments were provided to the patients by a person not involved in the evaluations. The treatments were also 'anonymized' and provided in similar packaging, in such a way that the patient could not identify the treatment which was randomly assigned to him/her. The study was carried out at the Service de Dermatologie, Hôpital L'Archet 2 in Nice. The selection/eligibility phase lasted for a maximum of 6 months, during which recurrences of labial herpes occurring in preselected patients were recorded. Patients with a history of recurrent labial herpes with at least four infectious flares per year were preselected and eligible to participate in the screening visit. When the preselected patients experienced local functional symptoms consistent with a new herpes recurrence (pain, burning, tingling or numbness and itching), they were assessed by the investigator within 36 h, so that she/he could observe the recurrence and perform clinical assessments of the affected zone. The treatment phase lasted 2 weeks. During this phase, one of the three treatments being compared was randomly assigned to each of these patients: OGT-based CS20 protective barrier lip gel

(peroxidized corn oil 87.8%, micronized zinc oxide 1.0%, silicon dioxide 7.0%, orange-grapefruit flavouring 2.5%, mint flavouring 1.5%; $n = 35$) or topical aciclovir 5% cream ($n = 35$) or placebo gel (demineralized water QS, carbopol 0.3%, propyl paraben 0.2%, starch 5% and Kathon[®] CG 0.05%; $n = 36$). Each of these topical treatments was applied five times daily on visible lesions or on sites where symptoms were felt. Although the products were not identical in formulation (gel vs. cream), colour or odour, they were packaged and labelled in an 'anonymized' manner, and randomly assigned to the patients. Treatments were provided by a person not involved in the evaluations. Patients were evaluated on days 1, 2, 7 and 14 of treatment for primary and secondary endpoints, and were also asked to complete a daily symptom diary to record pain. Patients were finally asked to complete an acceptability and tolerability questionnaire on completion of the study.

Endpoints

Primary endpoint The primary endpoint of the study was the cumulative score of four functional symptoms (pain, burning, tingling and itching sensations), each of them being evaluated by the patient on a 100 mm visual analogue scale (VAS) (0 mm = no sensation, 100 mm = worst imaginable sensation according to the subject).

Secondary endpoints The secondary endpoints encompassed the following: individual elements of the cumulative score of functional symptoms: pain, burning, tingling and itching sensations; objective lesional scores (erythema, papules, vesicles) on a scale from 0 to 3 for each (0 = absence, 1 = mild, 2 = moderate, 3 = severe); time to cure (time of sloughing of the crust or of return to a normal skin appearance) as evaluated by the investigator; evaluation of local tolerability upon applications through a patient questionnaire; occurrence of adverse events (AEs).

Other Overall acceptability of the assigned treatment was assessed by a questionnaire. Questions related to acceptability of treatment regarding pain 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 the question concerning the safety of the test product:

'How well did you tolerate this treatment?' the following responses were available: very well, well, no opinion, not very well and badly.

Statistical analysis

The randomization list was independently prepared by the Centre de Pharmacologie Clinique Appliquée à la Dermatologie biostatistiques unit, using SYSTAT version 11.0 software (SPSS, USA) with

3 × 3 Latin square blocks. Unblinding of both physicians and patients was carried out at the end of the study. Intention-to-treat (ITT) and per protocol (PP) populations were analysed. Descriptive statistics (mean, standard deviation, sample size, normality test) were calculated for all variables, including demographical data. The Shapiro–Wilks test was used to check the normality of distribution of variables under scope and to define the most appropriate type of comparison test. The calculation of subset size indicated that a sample of 25 patients (35–10) by group allowed detection of a 20 mm between-groups difference on VAS scale with 91% power and an alpha risk of 5% using an estimated common standard deviation of 21 mm. According to the trial design, the number of patients lost to follow up was estimated to be 10 patients per treatment group. Therefore, the number of patients in each group of treatment was fixed at 35.

The Null working hypothesis was that CS20 is not different from the main comparator (H0: comparison vs. aciclovir). The alternative hypothesis was that CS20 is different from the main comparator (H1: comparison vs. aciclovir). For variables with a normal distribution, treatments were compared by pairs (with the main comparison being CS20 vs. topical aciclovir) using variance analysis procedure (General Linear Model) applied to repeated measures to assess the treatment effect. For variables with a non-normal distribution, the Kruskal–Wallis test (non-parametric test) was used to compare treatments' performance, the main comparison being CS20 vs. topical aciclovir. Distributions of responses to questionnaires were compared using the Pearson chi-square test or the Fisher's exact test.

No additional analyses, such as subgroup analyses and adjusted analyses, were planned *a priori* or performed *a posteriori*.

Results

Patients

A total of 185 patients were initially preselected to enter this trial according to a medical history of frequently recurring labial herpes, and 106 were finally enrolled (84 women and 22 men) with a mean age of 43 ± 13 years and a mean weight of 62 ± 11 kg. There were 35 patients in the CS20 group (five men), 35 in the aciclovir group (nine men) and 36 in the placebo group (eight men). Groups were comparable in terms of age, weight, height, systolic and diastolic blood pressure and pulse. Skin phototype was II, III and IV, respectively, in 5, 29 and 1 patients in the CS20 group, 9, 24 and 2 patients in the aciclovir group, 10, 23 and 3 patients in the placebo group, and 24, 76 and 6 patients in total.

All patients but two from the placebo group completed the study. In these two patients, the trial was interrupted because of a serious adverse event (SAE) (*Salmonella typhi* septicæmia) not directly related to the study treatment and because of personal reasons (holiday break). The presented data are based on ITT population.

Efficacy

Primary endpoint

Sum of subjective scores related to functional symptoms: The decrease in the sum of subjective scores (pain, burning, tingling and itching sensations), expressed as a percentage reduction compared with baseline, was statistically significant after Day 1 of treatment for CS20 vs. placebo ($P = 0.012$), and was still significant on Days 2 ($P < 0.001$) and 7 ($P < 0.0001$) (Fig. 1). Compared with baseline, the sum of subjective scores decreased by 35% on Day 1, 72% on Day 2 and 99.6% on Day 7, for patients receiving the gel containing OGT. The percentage reduction in the sum of subjective scores compared with baseline was not statistically different between topical aciclovir and placebo on Days 1 or 2, but was significantly higher in the topical aciclovir group vs. placebo on Day 7 (at the end of the herpes episode) ($P = 0.027$).

Secondary endpoints

Pain intensity score: The percentage reduction in pain intensity score (compared with baseline) was significantly higher with CS20 compared with placebo at Day 1 of treatment ($P = 0.047$) and the difference was still significant at Days 2 and 6 ($P = 0.018$) (Fig. 2). Topical aciclovir provided a significant reduction in pain intensity score vs. placebo only at Day 1 ($P = 0.017$). CS20 was significantly more effective than topical aciclovir in reducing the pain intensity score at Days 3 and 4 ($P = 0.016$).

Burning intensity score: The percentage reduction in burning intensity score (compared with baseline) was significantly higher with CS20 compared with placebo at Day 1 of treatment ($P = 0.004$) and CS20 was still significantly more effective than placebo at Days 2 ($P < 0.0001$) and 7 ($P = 0.038$) (Fig. 3). Topical aciclovir did not provide a significant reduction in burning intensity score compared with placebo at any time point. CS20 was significantly more effective than topical aciclovir in reducing the

burning intensity score at Days 1 and 2 ($P = 0.033$ and $P < 0.005$ respectively).

Tingling intensity score: The percentage reduction in tingling intensity score (compared with baseline) was significantly higher with CS20 compared with placebo at Day 1 of treatment ($P = 0.030$), and CS20 was still significantly more effective than placebo at Days 2 ($P < 0.001$) and 7 ($P < 0.001$) (Fig. 4). Topical aciclovir provided a significant reduction in tingling intensity score compared with placebo at Day 7 of treatment only ($P < 0.005$), at the end of the herpes episode. There were no significant differences between CS20 and topical aciclovir at any time point for this parameter.

Itching intensity score: The percentage reduction in itching intensity score (compared with baseline) was significantly higher with either CS20 or topical aciclovir compared with placebo at Day 7 of treatment only ($P < 0.01$ for both) (Fig. 5). There were no significant differences between CS20 and topical aciclovir at any time point for this parameter.

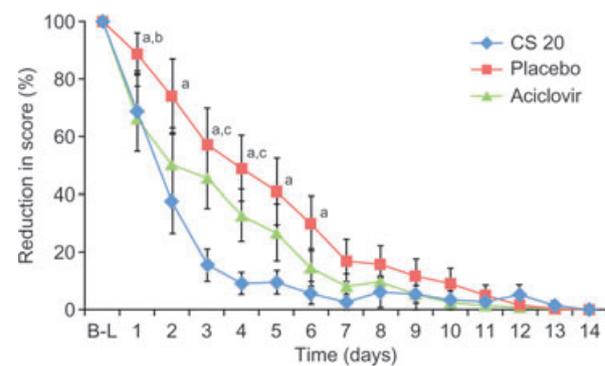


Figure 2 Percentage reduction in pain intensity score compared with baseline (mean \pm SEM). Significant differences were recorded as follows: (a) CS20 vs. placebo; (b) Aciclovir vs. placebo; (c) CS20 vs. aciclovir.

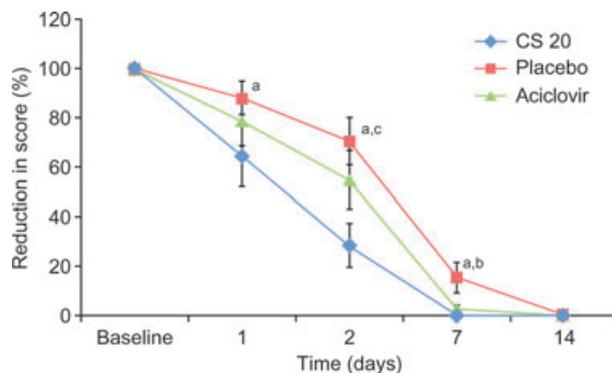


Figure 1 Percentage reduction in sum of subjective scores compared with baseline (mean \pm SEM). Significant differences were recorded as follows: (a) CS20 vs. placebo; (b) Aciclovir vs. placebo; (c) CS20 vs. aciclovir.

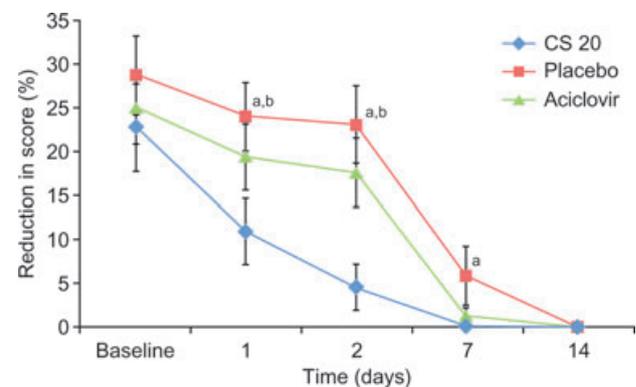


Figure 3 Percentage reduction in burning intensity score compared with baseline (mean \pm SEM). Significant differences were recorded as follows: (a) CS20 vs. placebo; (b) CS20 vs. aciclovir.

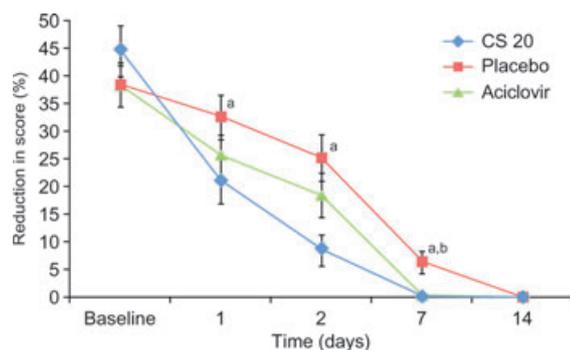


Figure 4 Percentage reduction in tingling intensity score compared with baseline (mean \pm SEM). Significant differences were recorded as follows: (a) CS20 vs. placebo; (b) Aciclovir vs. placebo.

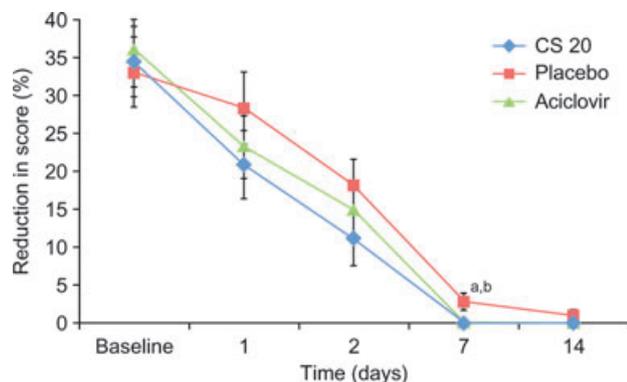


Figure 5 Percentage reduction in itching intensity score compared with baseline (mean \pm SEM). Significant differences were recorded as follows: (a) CS20 vs. placebo; (b) Aciclovir vs. placebo.

Lesion clinical scores: CS20 was significantly more effective in reducing local oedema than was placebo at Day 2 of treatment ($P = 0.001$) and this effect was maintained at Day 7 ($P = 0.023$). CS20 was significantly more efficient than placebo at Day 2 ($P = 0.009$) in decreasing crusting. Improvements in erythema ($P = 0.019$) and oedema ($P = 0.023$) were significantly more pronounced in the topical aciclovir group compared with placebo at Day 7 of treatment (at the end of the herpes episode). Conversely, active treatments did not improve the appearance of papules, vesicles or erosion/ulceration at any time point vs. placebo.

Time to cure: Time to cure (time of sloughing of the crust or of return to a normal skin appearance) was assessed at Day 7 and Day 14. There were no significant differences between CS20, aciclovir and placebo for this parameter (14/35 [40%] patients at Day 7 for either treatment, and 10/34 [29%] for placebo; 35/35 [100%], 33/35 [94%] and 30/34 [88%], respectively, at Day 14).

Safety and tolerability

All treatments were well tolerated. Overall, patients receiving either CS20 or topical aciclovir recorded a better local tolerability compared with placebo ($P = 0.019$ and $P = 0.043$ respectively) and CS20 and topical aciclovir had a comparable profile of local tolerability. Overall, 20 patients reported AEs, all of which were mild ($n = 7$) or moderate ($n = 15$). Of these 22 recorded AEs, nine were considered by the investigators to be related to the treatment, mainly burning and tingling sensations upon product application (CS20, $n = 1$; topical aciclovir, $n = 5$; placebo, $n = 3$) and an isolated case of perioral dry skin with CS20. The incidence of AEs was comparable between the three treatment groups. Only one SAE was reported during this study in a patient treated with placebo (*Salmonella typhi* septicaemia) and was considered to be unrelated to treatment.

Patient self-evaluation

In the CS20 group, 29/35 patients (83%) totally agreed that the treatment resulted in an improvement in pain relief compared with previous treatments, vs. 14/35 (40%) in the topical aciclovir group and 10/34 (29%) in the placebo group (no significant difference between topical aciclovir and placebo for this parameter). A significantly higher number of patients totally agreed that CS20 was more effective in accelerating healing than the placebo ($P = 0.014$).

Limitations

The single-centre design of the study and the preselection of patients according to their medical background with frequent herpes recurrences must be taken into account in the interpretation of results. However, these potential limitations are unlikely to significantly decrease the relevancy of data, as patients with the most refractory conditions were actually selected to enter this study. As the products being compared could be distinguished by the patients, it was not possible to use a double-blind design.

Discussion

The main objectives of treatment of labial herpes recurrences are faster relief from functional symptoms, and reductions in time to healing and in viral shedding duration. Oral aciclovir is well established in the treatment of mucocutaneous HSV infections.¹² However, in a review of five placebo-controlled and two comparative studies in the treatment of recurrent HSV-1, oral antiviral drugs only resulted in a modest decrease in lesion duration and associated pain.¹³ An evidence-based review performed in the US in 2008 described conflicting results.¹⁴ Although intermittent episodic therapy of recurrent labial herpes with topical aciclovir and penciclovir creams was shown in some trials to decrease lesion healing time and symptom severity,^{15–22} in various studies, aciclovir ointment and cream failed to show efficacy.^{23,24} 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 HSV-1 infections in humans.²⁵

CS20 is a labial protective gel that contains oxygenated glycerol triesters. These components build a protective film that adheres to and impregnates skin lesions in the presence of zinc oxide creating a moist environment favourable to lesion repair and healing. As a result of these physical properties, CS20 was evaluated for the symptomatic treatment of labial herpes.

In the present trial, topical treatment with CS20 resulted in a significant and early decrease in the sum of subjective scores for four functional symptoms (pain, burning, tingling and itching) associated with HSV-1 recurrent infection compared with placebo. This effect was observed as soon as Day 1 of treatment and persisted during the main part of herpes flare (7 days). However, a significant improvement in functional symptoms compared with placebo was only observed at the end of the herpes flare (Day 7 of treatment) when using topical aciclovir.

In comparison with placebo treatment, CS20 application provided a significant decrease in pain score from Day 1 through Day 6. The pain score was significantly lower in the CS20 group than the aciclovir group at two timepoints (Days 3 and 4). Burning sensation, a particular feature associated with labial HSV-1 recurrences, was more efficiently reduced by CS20 application compared with topical aciclovir (Days 1–2) or placebo (Days 1–7). Compared with placebo, topical aciclovir did not significantly improve burning symptoms. Tingling and itching scores were better improved in CS20 group. Tingling intensity was less in CS20 group than in placebo and aciclovir groups (D1–D7); however, the difference was significant compared with placebo, but did not reach significance compared with aciclovir. There was no significant difference between CS20, aciclovir and placebo in itching intensity.

A significant and early improvement in the clinical scores for oedema and crusting, both of them resulting in an unsightly appearance that is negatively perceived by the patient, was observed with CS20 gel. Topical aciclovir was associated with an improvement of the clinical scores for erythema and oedema, but only upon resolution of the infection. Comparison of clinical features at final healing did not reveal any significant difference between each of the three treatment groups. The use of CS20 gel resulted in a healing time comparable to topical aciclovir.

Self-administered patient questionnaires demonstrated a significant reduction in pain in the group treated with CS20 compared with topical aciclovir and placebo. In addition, a significantly higher percentage of the patients receiving CS20 reported a perception of improved healing when compared with placebo.

AEs included burning and/or dry skin sensations upon application of the three treatments, and were mild to moderate in nature. No SAEs could be related to any of the compared treatments. All three treatments were well tolerated.

Overall, this study strongly suggests that the use of OGT-based CS20 protective gel can offer an efficient and safe symptomatic

treatment to patients for functional discomfort, accompanied by a prompt improvement in the unsightly appearance associated with recurrent labial herpes.

Conclusion

CS20 is a protective barrier gel, which contains oxygenated glycerol triesters and forms a protective film that adheres to labial herpes recurrence-related lesions, penetrates in the lesions and creates a moist environment favourable to lesion repair and healing.

Applications of CS20 from the very beginning of a herpes recurrence result in a reduction in functional symptoms (pain, burning, tingling and itching), and a significant improvement in clinically visible lesions, compared with placebo. CS20 gel was significantly more effective than topical aciclovir in improving early functional symptoms, particularly sensations of burning and pain associated with HSV-1 labial recurrences. Time to cure was similar with CS20, aciclovir and placebo. CS20 gel endeavours to treat dermatology symptoms and does not relate to an antiviral activity. Accordingly, CS20 seems to meet the expectations of individuals suffering from labial herpes flares, with applications five times daily resulting in prompt relief from pain and burning sensation and improvement in physical appearance.

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