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A phase 2, multicenter, placebo-controlled study of single-dose squaric acid dibutyl ester to reduce frequency of outbreaks in patients with recurrent herpes labialis

To the Editor: Herpes labialis is a common condition with painful blisters or sores around the lips, and there are limited choices to prevent or reduce the severity of outbreaks.[1] It is caused by herpes simplex virus type 1 (HSV-1) and, less commonly, type 2 (HSV-2). Squaric acid dibutyl ester (SADBE) is a topical immunosensitizer to treat verruca vulgaris and alopecia areata.[2,3] Previously, a single topical dose of 2% SADBE dissolved in dimethyl sulfoxide (DMSO) applied to the arm skin significantly extended the time to the next outbreak.[4] In a separate study, a single topical dose of 2% SADBE in DMSO on the arm in patients with frequent outbreaks significantly improved immune response to HSV-1 in vitro 8 weeks later, with a significant increase in interferon gamma expression.[5] In this study, we explored whether a regimen with a second dose of topical 0.5% SADBE to the upper arm skin might be superior to a single dose of 2% SADBE to reduce the frequency or severity of herpes labialis.

After institutional review board approval and written informed consent, this study was conducted at 5 centers with patients with 4 or more herpes labialis episodes in the previous 12 months. Participants were randomly assigned to receive either (1) 1 dose of 2% SADBE on day 1, (2) 2% SADBE on day 1 and a second lower-dose (0.5%) booster on day 22, or (3) DMSO vehicle only on days 1 and 22. All participants were followed for 1 year.

Eligible individuals (N = 140) enrolled with a median number of outbreaks of 6 (mean, 7.8) in the prior 12 months. The 1-dose group had superior results versus the placebo group in time to next outbreak from day 43 to 121 ($P = .024$) (Fig 1), mean number of outbreaks in days 43 through 121 (0.231 ± 0.125 standard error in the 1-dose group vs 0.610 ± 0.068 in the placebo group; $P = .011$), and proportion of participants with an outbreak in days 43 through 121 (9/39 [23%] in the 1-dose group vs 19/41 [46%] in the placebo group; $P = .036$). The average number of moderate or severe outbreaks over days 43 through 121 was also reduced in patients receiving 1 dose of SADBE (0.128 ± 0.339) versus placebo (0.390 ± 0.703) ($P = .04$), as well as over days 1 through 365 in the 1-dose (0.641 ± 0.931) versus placebo group (1.341 ± 1.76) ($P = .04$).

Notably, the 2-dose group had superior results compared with the placebo group on these same measures, but not significantly so. Why the 1-dose may be superior to the 2-dose regimen remains to be investigated, but we hypothesize that the second dose at lower concentration may tolerize or downregulate the immune changes from the 2% SADBE in the first dose.

The largest improvements observed in the SADBE-treated groups occurred within days 43 through 121 of the study. One possible reason may be that SADBE takes about 6 weeks to exert maximal effect on the

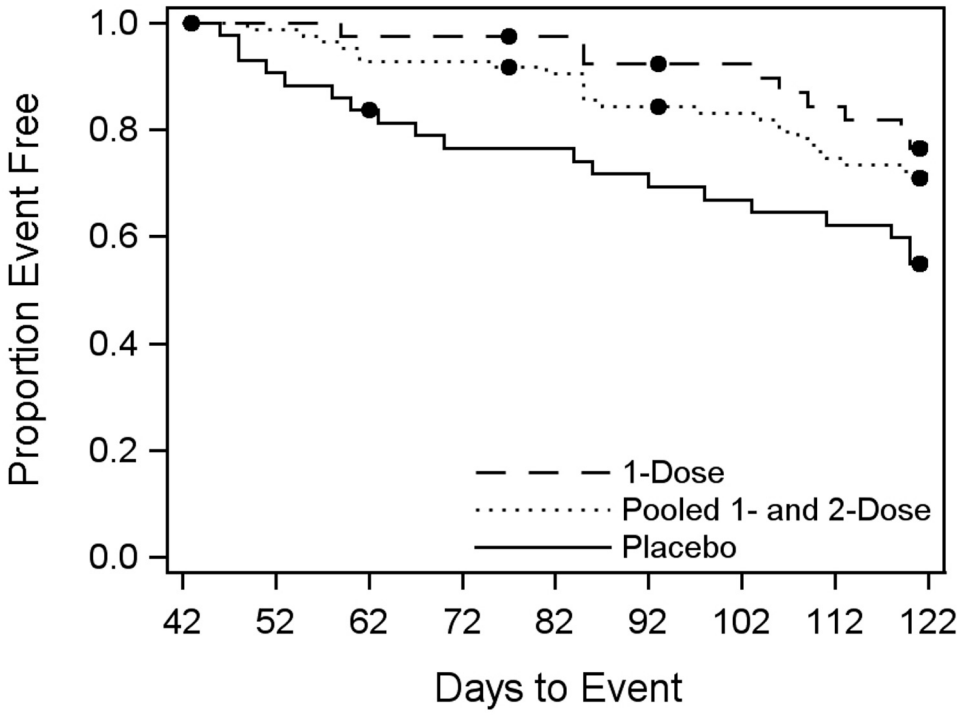

Fig 1. Outbreak-free proportion by Kaplan-Meier method from day 43 to day 121 in the 1-dose group (n = 41, 32 censored), pooled 1- and 2-dose groups (n = 85, 61 censored), and placebo group (n = 43, 24 censored). One-dose group versus placebo group: $P = .024$; hazard ratio with 95% confidence interval, 2.419 (1.094-5.351). Pooled 1- and 2-dose treatment groups versus placebo group: $P = .049$; hazard ratio with 95% confidence interval, 1.814 (0.993-3.312).

Table I. Adverse events scored by investigators as definitely, probably, or possibly study-medication related

Adverse event*	Placebo, n (47 participants)	SADBE: 1 or 2 doses, n (92 participants)
Administration site conditions		
Erythema	4	15
Itching or irritation	1	8
Tingling or stinging	4	0
Purpura	0	1
Boil	0	1
Subtotal	9	25
Tingling (not at administration site)	3	2
Flushing and burning sensation on face	0	3
Herpes lesion on genitals, anus, or spine	1	2
Dermatitis from bandage adhesive	2	0
Irritation or itching (not at administration site)	0	2
Rash (not at administration site)	0	1
Retention hyperkeratosis	0	1
Lightheadedness	1	0
Pimple	0	1
Papule on lip	0	1
Anemia	1	0
Total	17	38

SADBE, Squaric acid dibutyl ester.

*All adverse events were grade 1 (n = 49) or grade 2 (n = 6), with no grade 3 or higher adverse events.

immune system, and the effects begin to taper off at approximately 3 to 4 months after the first dose.

The most common adverse event type was administration site reactions, which all were mild or moderate, and all resolved within 3 months (Table I), suggesting a favorable risk-benefit profile for topical 2% SADBE in high-frequency herpes labialis.

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Patients with a familial predisposition to hidradenitis suppurativa have a distinct clinical phenotype

To the Editor: The etiology of hidradenitis suppurativa (HS) involves genetic and environmental factors.[1] Approximately 38% of patients with HS report a family history of HS, and 27% report at least 1 first degree relative with the disease.[2,3]

We explored the potential differences between patients with and without HS in a first degree relative in a prospective cohort of 447 consecutive newly referred patients with HS attending a tertiary dermatologic university center (Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark). Information on family history, disease characteristics including demographic and risk factors, severity of HS, specific localization of HS lesions, lipid levels and inflammatory markers in blood, and comorbidities were collected by interview and clinical examination.

In total, 159 (35.6%) patients with and 288 (64.4%) without HS in a first degree relative were identified (Table I). We found significant differences between these 2 groups: patients who reported HS in a first degree relative had an earlier age at onset of HS compared to patients without HS in a first degree relative ($P < .001$), were more often female ($P < .014$), and had more severe disease measured by Hurley score ($P = .006$). Furthermore, anatomic localization of HS lesions varied significantly so that patients with familial HS more often had involvement of the axilla ($P = .012$) and the groin ($P = .012$). Finally, a higher number of anatomic regions affected by HS were seen in patients with familial history ($P = .003$). After multiple adjustment, we found statistically significant differences between patients with and without HS in a first degree relative for age at onset of HS ($P < .001$) and involvement of the axilla ($P = .048$). Treatment patterns did not differ between patients with and without familial history of HS.

Our results indicate that familial cases of HS tend to be more classic in their clinical presentation, whereas the nonfamilial (sporadic) cases are more atypical.

The female preponderance, tendency to obesity, postpubertal onset, frequent premenstrual flares, and the improvement often observed during pregnancy and postmenopause[4] suggest a hormonal influence. However, no specific hormones have been implicated. We found that patients with familial HS were more often women, but no differences were observed between patients with familial and