Acta Derm Venereol 2015; 95: 847–849

SHORT COMMUNICATION

Safety and Efficacy of Human Fibroblast Lysate Cream for Vulvar Lichen Sclerosus: A Randomized Placebo-controlled Trial

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Accepted Jan 20, 2015; Epub ahead of print Jan 29, 2015

Lichen sclerosus (LS) is a chronic inflammatory disorder that predominantly affects the anogenital skin. It has been estimated that it affects one in 60 women (1). Typical vulvar LS lesions are white plaques with areas of focal purpura, excoriation, and erosions (2). Frequently accompanying these lesions are architectural changes of the vulva, including scaring of the clitoral prepuce (phimosis), resorption of the labia minora, and narrowing of the introitus. Moreover, 4–6% of women with vulvar LS develop squamous cell carcinoma (SCC) (3). Histopathological changes of LS include hyperkeratosis of the epidermis, epidermal atrophy with loss of rete ridges, homogenization of collagen in the upper dermis, and a lichenoid (band-like) inflammatory infiltrate in the dermis (2). Vulvar LS has also been associated with circulating auto-antibodies to endothelial cell adhesion molecules (ECAM-1) and to bullous pemphigoid antigens BP180 and BP230 (4, 5).

Currently, the gold standard for treatment for vulvar LS is application of ultra-potent topical corticosteroid such as clobetasol propionate. Corticosteroids have repeatedly been shown to be safe and effective in the treatment of LS leading to a significant resolution of hyperkeratosis, purpura, fissures, and erosions (6, 7, 8). Furthermore, preliminary data indicate that the risk of malignant transformation may also decline with corticosteroid use (3, 9, 10). However, long-term use of corticosteroids may be associated with serious systemic and local side effects, including dermal thickening, skin atrophy, superimposed infections, rebound dermatitis, and adrenal insufficiency (11–13). Hence, it would be beneficial if there were an effective alternative to corticosteroids for the treatment of vulvar LS.

Human fibroblast lysate cream (HFLC), also known as cutaneous lysate (Neogyn cream™, Neogyn, Inc Jersey City, New Jersey, USA), which is obtained from cultured human fetal fibroblasts, has been shown to contain anti-inflammatory cytokines including interleukin (IL) 1 receptor antagonist (IL-1ra), IL-10, and IL-13, as well as wound-healing growth factors EGF, FGFs and VEGF which could potentially participate in anti-inflammatory activity. HFLC does not promote the proliferation of SCC nor does it interfere with the normal apoptotic processes *in vitro* (14). Recently, a placebo-controlled crossover study indicated that the HFLC reduces symptoms of provoked vestibulodynia, another inflammatory condition of the vulva (15). Therefore, this pilot study was designed to further evaluate the safety and efficacy of HFLC in patients with vulvar LS.

METHODS

This double-blind placebo-controlled study included 30 female subjects over the age of 18 with biopsy-proven vulvar LS. Investigational Review Board approval for the study was obtained from the Anne Arundel Medical Center IRB. All patients signed informed consent prior to participating in this trial. The mean age of the participants was 58 years. All subject were recruited from a medical center that specializes in the treatment of vulvovaginal disorders. The trial consisted of a two-week screening period and a subsequent 12-week treatment period. A total of 3 visits over 14 weeks were conducted with each subject using a uniform evaluation schedule for screening, baseline and final visits. During the screening period a 5-mm punch skin biopsy was collected from each patient to confirm active vulvar LS and to exclude diagnoses of lichen planus, psoriasis, candidiasis, and vulvar intraepithelial neoplasia. Additionally, a vulvoscopy was performed at the screening visit and after the 12-week treatment period to screen for vulvar carcinoma. Subjects of childbearing potential were required to use two forms of birth control to be eligible to participate. All eligible participants were randomized to receive the HFLC (a proprietary blend of the lysate and emollient cream) or placebo. Both the HFLC and placebo contained the same emollient base which contains water, octyldodecanol, decyl oleate, glyceryl stearate, propanediol, glycerin, stearic acid, wheat germ oil, Ceteareth-20, cetyl alcohol, borage seed oil, dimethicone, glycosphingolipids, Myreth-3 myristate, Ceteareth-12, tocopheryl acetate, cetearyl alcohol, cetyl palmitate carbomer, triethanolamine, BHT, disodium EDTA, phenoxyethanol, and caprylyl glycol. Subjects were instructed to apply one gram of their respective creams to the affected areas of the vulva twice daily for 12 weeks. A second punch biopsy was obtained after the 12-week treatment period.

The primary outcome variable was the change in histopathologic inflammation as determined by two blinded dermatopathologists between the pre and post treatment biopsies. Secondary efficacy variables included a deviation from baseline in vulvar pruritus and burning as assessed by patients using two separate 0–10 point visual analog scale (VAS) questionnaires: the VAS-PR and VAS-BP. These questionnaires were completed in the center at screening, baseline and week-12 visits and were submitted weekly by mail during the treatment period. Additional secondary efficacy variables included an Investigator's Global Assessment (IGA), performed by a physician (AG) who specializes in the treatment of vulvar dermatoses who rated the severity of the disease (lichenification, ulceration, and induration) with a 0–3 scale at the screening, baseline and 12 week

 doi: 10.2340/00015555-2052
 ISSN 0001-5555

visits. To evaluate changes in quality of their sexual function, the participants used a validated instrument, the Female Sexual Function Index (FSFI), during the screening and 12-week visits. Digital photographs were taken at baseline and at the 12 weeks visits. In addition, all adverse events were recorded and physical examinations were performed at each visit.

Statistical analyses included descriptive statistics for demographic variables and baseline characteristics. Median symptom scores and histologic grading were tabulated. Non-parametric tests, Wilcoxon signed-rank test and Mann-Whitney *U* test, were used for the IGA and inflammation variables and *t*-tests (paired and independent) were employed for the VAS scales. The paired *t*-test was also used to analyze the FSFI results.

RESULTS

All 30 subjects completed the study and both the HFLC cream and placebo creams were well tolerated. There were no significant adverse events during the trial.

There was no significant change in histopathologic inflammation, as measured by two blinded dermatopathologists, between the biopsies obtained at the screening and 12 weeks visits for both the HFLC cream ($p=0.783$) and placebo ($p=0.670$).

There was significant improvement of the IGA at 12 weeks with both the HFLC cream and the placebo cream as compared with baseline ($p=0.006$ and $p=0.038$, respectively) (Fig. S1[1]); 60% of the HFLC participants showed a decrease of at least one point on the IGA scale, whereas only 33% of the placebo group had improvement. The mean decrease in IGA points was 0.9 (2.6–1.7) for the HFLC group and 0.5 (2.3–1.8) for the placebo group. However, due to the small sample size in this study, this difference was not statistically significant ($p>0.2$).

The subjects' improvement in vulvar pruritis as measured by the VAS-PR, showed that subjects assigned to the active agent experienced a 43% decrease in pruritus ($p=0.005$) as compared with a 51% decrease for those on the placebo ($p=0.001$). However, the difference in change in pruritus symptoms between the two groups was not significant ($p=0.226$). There was a 51% reduction in vulvar burning and pain as measured by the VAS-BP in participants who used the active HFLC cream ($p=0.002$) and a 43% reduction in subjects using the placebo cream ($p=0.005$). The differences between the two groups were not statistically significant ($p=0.86$). Lastly, there were no significant difference in sexual function as measured by the FSFI between baseline and the 12 week visit in either the active agent ($p=0.98$) or the placebo group ($p=0.89$).

DISCUSSION

The subjective measures of the study, the IGA, VAS-BP, VAS-BR suggest that twice-daily HFLC use over 12-weeks is well tolerated and may result in a decrease in vulvar discomfort from baseline from both the physician and patient perspectives. While the results do not show a statistically significant difference between the HFLC and placebo, the trend toward symptom reduction may represent a meaningful decrease in vulvar LS symptoms that is clinically valuable.

The main limitation of this study was its small sample size, which most likely contributed to the lack of statistically significant results. In addition, the study was limited by a lack of long-term follow-up of patient response to treatment. Further investigation with a larger sample size and a longer duration is warranted to further delineate the benefits of HFLC versus placebo for vulvar LS symptom reduction. A post-hoc power analysis was performed to determine the probability of detecting a significant effect, if one is present. In order to have power of 0.80 the sample size would have to be at least 64 subjects per group.

While symptoms reduction is important in treating vulvar LS, it is critical that the disease-related inflammation is controlled as it increases the risk of vulvar SCC (6). Because both the active agent and placebo did not show a statistically significant decreases in inflammation, as determined by histological examination, HFLC can not be recommended as a solitary treatment for vulvar LS. Instead, the potential for HFLC treatment lies in its potential to act as an adjuvant vulvar care therapy in combination with the high potency corticosteroid.

Conflict of interest: Andrew T. Goldstein received research funding for this study from Neocutis, Inc. Frank Dreher is an employee of Neocutis, Inc.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2052

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