Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus

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Background: Lichen sclerosus (LS) is a chronic inflammatory dermatosis that occurs mainly in the anogenital area and causes itching and soreness. Progressive destructive scarring may result in burying of the clitoris in females and phimosis in males. Affected people have an increased risk of genital cancers.

Objective: We sought to assess the effects of topical interventions for genital LS.

Methods: We undertook a systematic review and meta-analysis using the methodology of the Cochrane Collaboration.

Results: We included 7 randomized controlled trials with a total of 249 participants covering 6 treatments. Clobetasol propionate 0.05% was better than placebo in treating genital LS (participant-rated improvement/remission of symptoms: risk ratio 2.85 [95% confidence interval {CI} 1.45-5.61]; investigator-rated global degree of improvement: standardized mean difference [SMD] 5.74 [95% CI 4.26-7.23]) as was mometasone furoate 0.05% (change in clinical grade of phimosis: SMD −1.04 [95% CI −1.77 to −0.31]). We found no evidence supporting the efficacy of topical androgens and progesterone. There were no differences between pimecrolimus and clobetasol propionate in relieving symptoms through change in pruritus (SMD −0.33 [95% CI −0.99 to 0.33]) and burning/pain (SMD 0.03 [95% CI −0.62 to 0.69]). However, pimecrolimus was less effective than clobetasol propionate in improving gross appearance (investigator-rated global degree of improvement: SMD −1.64 [95% CI −2.40 to −0.87]).

Limitations: Most of the included studies were small.

Conclusions: The current limited evidence supports the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital LS. Further randomized controlled trials are needed. (J Am Acad Dermatol 2012;67:305-12.)

Key words: clobetasol propionate; corticosteroid; dihydrotestosterone; lichen sclerosus; meta-analysis; mometasone furoate; pimecrolimus; progesterone; systematic review; testosterone.

Lichen sclerosus (LS) is a chronic inflammatory dermatosis that occurs mainly in the anogenital area and causes itching and pain. In women and girls, postinflammatory scarring may cause fusion of the labia minora, narrowing of the vaginal introitus, and burying of the clitoris, resulting

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in dyspareunia, sexual dysfunction, and anal or genital bleeding. LS in men and boys usually occurs on the glans penis and/or foreskin, and may cause phimosis and painful erection. Meatal stenosis may lead to problems passing urine and urinary obstruction. The prevalence is estimated to be between 1:30 and 1:1000 in adults.[1,2]

The cause of LS is unknown, but there is a strong association with autoimmune diseases, eg, thyroid disease, alopecia areata, vitiligo, and pernicious anemia.[3] Up to 74% of affected people had circulating autoantibodies.[4] An increased incidence of autoantibodies to the extracellular matrix protein 1 was found in people with LS, which supports an autoimmune cause.[5] In addition, there is evidence of both autoantibody and T-cell reactivity to basement membrane proteins.[6,7] The high incidence of LS in postmenopausal women suggests a pathogenic role of reduced estrogen levels; however, a protective effect from estrogens, ie, women before menopause will not develop LS, has not been observed.[2,8] In men, a cause of chronic exposure of a susceptible epithelium to urine as a result of naviculomeatal dysfunction and urinary incontinence in the uncircumcised has been proposed.[9] Genetic factors are implicated, and cases of familial LS have been reported.[10] Immunogenetic studies have demonstrated a significant association with HLA class II antigen DQ7 and DRB1*12.[11,12]

LS has a tremendous impact on the quality of life by interfering with function (particularly sexual function) and self-image, and the resultant distress and anxiety are immediately apparent. Many affected people feel embarrassed; some have persistent itching and pain (despite successful control of the inflammation), and many are concerned about how the disorder may progress. The lifetime risk of the development of squamous cell carcinoma in women and men with genital LS is estimated to be 4% to 5%.[8,13,14] Also, vulval verrucous carcinoma has been associated with LS.[15]

There is no cure for LS; however, there are good outcomes as a result of treating the disease. These include the relief of symptoms and prevention of further anatomic changes (caused by sclerosis and fusion). Some clinical signs may be reversed, but any scarring that has occurred will remain.[16,17] It is possible that treatments may prevent malignant transformation, but this needs to be evaluated. However, reactivation of latent human papillomavirus infection has been found after topical corticosteroid therapy, which may increase the risk of vulval cancer and requires close follow-up.[18]

The objective of this study was to evaluate the level and quality of available evidence regarding the efficacy and reported adverse effects of topical interventions for genital LS, and to identify gaps in knowledge that require further research.

CAPSULE SUMMARY

- The current evidence supports the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital lichen sclerosus.
- There is no evidence supporting the use of topical androgens and progesterone in treating genital lichen sclerosus.
- Further randomized controlled trials are needed to determine the optimal potency and regimen of topical corticosteroids, examine other topical interventions, assess the duration of remission or prevention of flares, evaluate the reduction in the risk of genital cancers, and examine the efficacy in improving the quality of the sex lives of people with this condition.

METHODS

We undertook a systematic review and meta-analysis of randomized controlled trials (RCTs) on topical interventions for genital LS following a prespecified protocol according to the methodology of the Cochrane Collaboration.[19] A patient representative assisted us in improving the relevance and readability of this study.

Outcome measures

Primary outcomes included participant-rated improvement/remission of symptoms (in terms of quality of life, pain, itching, and dyspareunia), investigator-rated global degree of improvement (in terms of pallor, purpura, hyperkeratosis, ulceration, erosion, erythema, sclerosis, and scarring), and severe adverse drug reactions (ADRs) (that required withdrawal of treatment, including severe skin irritation or infection). Secondary outcomes included mild ADRs (being not severe enough to require cessation of treatment, eg, mild skin irritation, atrophy, or telangiectasia), duration of remission and/or prevention of subsequent flares, and development of genital squamous cell carcinoma or genital intraepithelial neoplasia. We expressed the results as risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes, and standardized mean difference (SMD) and 95% CI for ordinal outcomes.

Search strategy

We searched 16 databases and trial registers from inception to September 2011 (Table I). We scanned the bibliographies of the included studies, published