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Systematic Review

Treatment Modalities for Genital Lichen Sclerosus: A Systematic Review

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Abstract: Background: Lichen sclerosus (LS) is a chronic, inflammatory dermatosis that affects both genital and extragenital sites. It is often difficult to treat and may lead to a variety of complications if not adequately treated. The mainstay of therapy involves topical corticosteroids, topical calcineurin inhibitors, and systemic immunomodulators. Although a variety of topical, oral, and procedural therapies are available, a review comparing relative efficacy is lacking. To this end, this systematic review aimed to summarize the literature regarding treatment modalities and their respective response rates in patients with genital LS. Methods: A literature search was conducted in accordance with PRISMA guidelines. Results: This review qualitatively summarizes information from 31 randomized controlled trials, encapsulating a total of 1507 patients with LS, the majority of which were female (n = 1374, 91%). Topical corticosteroids, the mainstay of therapy for LS, were discussed throughout the literature, and proved to be more efficient than topical calcineurin inhibitors, topical hormonal therapy, topical vitamin E oil and cold cream. However, other treatment modalities proved to be more efficient than topical corticosteroids, including CO_2 and Nd:YAG laser therapies, and the addition of polydeoxyribonucleotide intradermal injections, to steroid therapy. Finally, other modalities that proved to be efficient in the treatment of LS included silk undergarments, human fibroblast lysate cream, platelet-rich plasma, acitretin, and surgical intervention. The risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials. Limitations included the inclusion of only randomized controlled trials, moderate or high risk of bias, and heterogeneity in treatment regimens, among others. Conclusion: Although high-potency topical corticosteroids have validated efficacy in the management of LS, other treatment modalities, including steroid-sparing agents and/or procedural adjuncts, have been demonstrated to have a beneficial role in the treatment of LS.

Keywords: lichen sclerosus; treatment; management; response; steroids; surgery

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1. Introduction

Lichen sclerosus (LS) is a chronic inflammatory dermatosis commonly affecting anogenital skin and is often difficult to treat, leading to a multitude of complications [1,2]. Most notably, LS has the capacity for malignant transformation, including anogenital squamous cell carcinoma and verrucous carcinoma [3,4]. Its exact prevalence is unknown, with the literature ranging from 1 in 1000 to 1 in 300 patients living with the disease [5]. Such variations are hypothesized to be secondary to frequent misdiagnosis and asymptomatic patients [5]. While both sexes can be affected, the prevalence is thought to be a lot higher in females with upwards of a 10:1 female to male ratio [5]. Moreover, all ages can be affected, with women typically presenting with a bimodal age distribution with one peak between the ages of 8 and 13, and the second being during the fifth and sixth decades [5]. It commonly presents with pruritus, pain/discomfort, atrophy and scarring, and has a significant impact on patients' quality of life [6,7]. LS affects patients' quality of life not only symptomatically, but also due to its associated loss of normal vaginal or penile architecture resulting in psychological distress [8]. Treatment is difficult, and, in cases where LS is not recognized early and treated aggressively, it can progress and cause debilitating symptoms and significant morbidity [9]. As with many inflammatory dermatoses, the gold standard treatment is high-potency topical corticosteroids, and in patients with penile involvement, circumcision is indicated if patients are refractory to corticosteroids [10]. However, recent studies have begun to explore a multitude of other treatment modalities for LS, including topical calcineurin inhibitors, topical and systemic retinoids, and phototherapy [11]. It is important to note that while a plethora of treatment modalities have been explored in the literature and may have been proven to be efficacious in managing the symptoms and architectural changes associated with LS, only corticosteroids have the capacity to reduce the risk for malignant potential [12]. Moreover, in addition to being useful in avoiding progression to differentiated vulvar intraepithelial neoplasia (dVIN), topical corticosteroids are useful in the follow-up of patients with previously surgically excised dVIN to reduce the risk of further invasive malignancy and should thus be recommended to this patient group [13]. Ultimately, a systematic review was conducted to summarize the efficiency of various treatment modalities for genital LS.

2. Methods

We conducted a systematic review of the literature adhering to PRISMA reporting guidelines [14].

2.1. Search Strategy, Study Eligibility Criteria, and Study Selection

A literature search of the PubMed, MEDLINE, and Embase databases was performed on 23 April 2024 using the following search strategy: "lichen sclerosus" and ("genital" or "vulvar" or "vaginal" or "penile") and ("treatment" or "management"). All randomized controlled trials (RCTs) reporting treatment modalities and their associated outcomes for lichen sclerosus were included. In vitro, histological and animal studies were excluded. Non-English articles and non-RCT studies were also excluded. Finally, studies that did not distinguish treatment modalities used by sex were also excluded. Title and abstract screening was completed by three independent researchers (S.C., S.D.M., and M.S.) using Covidence online systematic review software (www.covidence.org). Full texts to identify relevant studies were assessed by six reviewers. Conflicts were resolved by the primary author (S.C.) and the senior author (I.M.).

2.2. Data Extraction and Synthesis

Three reviewers (S.C., S.D.M., and M.S.) independently extracted data from eligible studies using a standardized extraction form that included title, authors, year of publication, sample size, and key findings divided by sex, including mean age, age range, affected region(s), treatment modalities, treatment response, treatment-related adverse events, and follow-up duration. Three authors (S.C., S.D.M., and M.S.) evaluated the extracted data

and synthesized the available evidence in an iterative manner. A pooled analysis was performed for studies with available outcome data. A risk of bias analysis was conducted by two different authors for all included studies using the Cochrane risk-of-bias tool for randomized trials. This systematic review was not registered in a database and a review protocol was not prepared.

3. Results

3.1. Study and Patient Characteristics

Following the title and abstract screening of 66 studies, and full text screening of 33 studies, 31 studies ultimately met inclusion criteria (Figure 1). This pooled analysis reports on 1507 cases of LS, 1374 (91%) of which occurred in females, with available data on treatment outcomes. The mean age of females included in this review was 56.4 years (range 12 to 86), whereas only one of the three male-only studies noted mean age (57.4 years) and one was focused on LS in male children. All 1374 cases of LS presenting in females were noted to affect the vulva, while 58 male LS cases affected the penis, and 51 cases localized to the male genitalia, not otherwise specified (Tables 1 and 2).

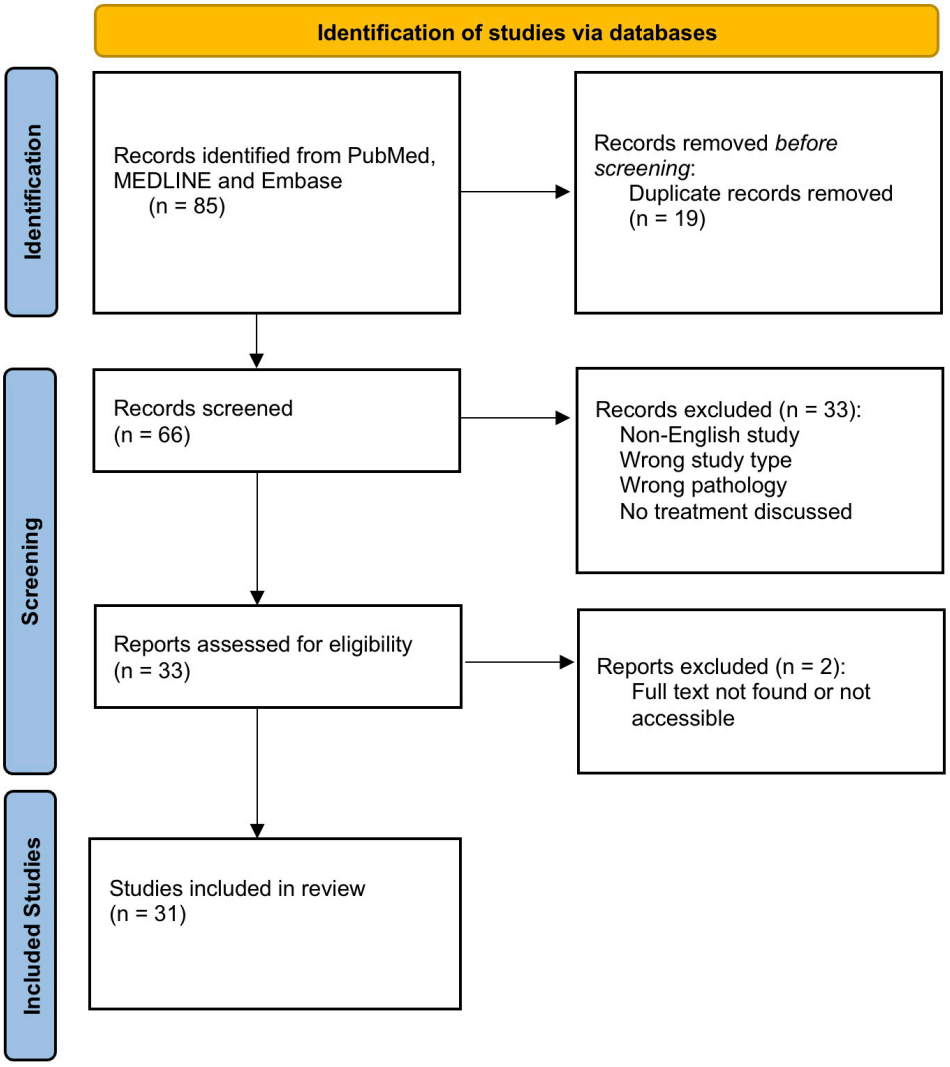


Figure 1. PRISMA flow diagram of included studies.

Table 1. Management of LS in female patients.

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Topical Steroids as a Single Modality									
Corazza 2016 [15]	48	64.14 (NR)	Vulva	Group 1 (24): Clobetasol propionate 0.05% ointment twice weekly for 52 weeks (CP) Group 2 (24): Mometasone furoate 0.1% ointment twice weekly for 52 weeks (MF)	Mean change in features: • Itching: 0.01 in CP, 0.31 in MF, no statistical difference between groups (p = 0.42) • Burning: 0.98 in CP, 0.55 in MF, no statistical difference between groups (p = 0.52) • Global Subjective Score: 0.22 in CP, 0.77 in MF, no statistical difference between groups (p = 0.48) • Global Objective Score: −0.27 in CP, −0.5 in MF, no statistical difference between groups (p = 0.14)	None	52 weeks	3 cases of relapse: 2 in CP, 1 in MF Mean time to relapse: 30 weeks (range 20–38)	Some concern
Virgili 2014 [16]	54	64.2 (NR)	Vulva	Group 1 (27): Clobetasol propionate 0.05% ointment five days per week for 4 weeks, then on alternate days for 4 weeks, then twice weekly for 4 weeks (CP) Group 2 (27): Mometasone furoate 0.1% ointment five days per week for 4 weeks, then on alternate days for 4 weeks, then twice weekly for 4 weeks (MF)	CP: • Responders (significant improvement in clinical picture and symptoms): 24 (88.9%) • Non-responders: 1 (3.7%) • >75% improvement in Global Subjective Score: 16 (59.3%) • >50% improvement in Global Subjective Score: 21 (77.8%) • >75% improvement in Global Objective Score: 10 (37.0%) • >50% improvement in Global Objective Score: 21 (77.8%) MF: • Responders: 24 (88.9%) • Non-responders 2 (7.4%) • >75% improvement in Global Subjective Score: 18 (66.7%) • >50% improvement in Global Subjective Score: 21 (77.8%) • >75% improvement in Global Objective Score: 13 (48.2%) • >50% improvement in Global Objective Score: 22 (81.5%)	None	12 weeks	24 patients responded, while 1 did not for CP 24 patients responded, while 2 did not for MF	Some concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Borghi 2015 [17]	64	60.95 (NR)	Vulva	Group A (32): Mometasone furoate 0.1% ointment daily for 5 days per week for 4 weeks, then on alternate days for 4 weeks, then twice weekly for 4 weeks Group B (32): Mometasone furoate 0.1% ointment 5 days weekly	• 27 patients (84%) in Group A experienced clinical resolution • 25 patients (78%) in Group B considered as responders • Difference in response between the two groups was not statistically significant • Relative risk of non-response Group A:Group B = 0.94 (CI 0.26–3.40) Change in mean. . . • Itching: 5.45 in Group A ($p < 0.001$), 5.29 in Group B ($p < 0.001$), no statistical difference between groups ($p = 0.15$) • Burning: 4.11 in Group A ($p < 0.001$), 3.28 in Group B ($p < 0.001$), no statistical difference between groups ($p = 0.41$) • Global Subjective Score: 9.43 in Group A ($p < 0.001$), 8.79 in Group B ($p = 0.002$), no statistical difference between groups ($p = 0.26$) • Global Objective Score: 3.95 in Group A ($p < 0.001$), 2.61 in Group B ($p < 0.001$), no statistical difference between groups ($p = 0.22$)	None	12 weeks	27 responders and 4 non-responders in MF1 25 responders and 4 non-responders in MF2	Some concern
Virgili 2013 [18]	27	60.53 (NR)	Vulva	Treatment Phase (12 weeks): • Mometasone furoate 0.1% ointment once daily Maintenance Phase (52 weeks), whereby all patients were assigned to one modality: • Mometasone furoate (MF) 0.1% ointment twice weekly (8) • Topical vitamin E oil (VitE) once daily (9) • Cold cream (CC) once daily (8)	Treatment Phase (27 patients): • 25/27 completely or almost completely healed on both objective and subjective protocol-defined scores • 1 patient dropped out, 1 patient discovered she was pregnant • Mean objective signs score (MOS): MF 8.5 → 0.0, VitE 6.75 → 0.0, CC 6.75 → 1.25 • Mean itching score (MIS): MF 5.75 → 0.0, VitE 8.0 → 0.0, CC 5.75 → 1.25 • Mean burning score (MBS): MF 6.75 → 2.0, VitE 4.75 → 1.0, CC 5.0 → 1.75 Maintenance Phase (25 patients): • MF (7): 0 relapses, MOS 0.0 → 0.2, MIS 0.0 → 1.0, MBS 2.0 → 1.75 • VitE (9): 5 relapses, MOS 0.0 → 1.5, MIS 0.0 → 0.5, MBS 1.0 → 0.5 • CC (8): 5 relapses, MOS 1.25 → 1.0, MIS 1.25 → 0.0, MBS 1.75 → 0.75	None	64 weeks	MF: 7 remission, 0 relapse VitE: 4 remission, 5 relapse CC: 3 remission, 5 relapse Median time to relapse for VitE and CC: 21.6 weeks	Some concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Topical Corticosteroids and Adjunct Therapies									
D'Antuono 2011 [19]	42	51.5 (22–79)	Vulva	Treatment Phase (6 months): • Clobetasol propionate 0.05% ointment once nightly • Standard moisturizer containing vitamin E once daily • White cotton (CT) (21) or Dermasilk fabric (DS) briefs (21)	CT Group: • Symptoms: Complete response (CR) = 0, good/partial response = 17, poor response = 4 • Clinical signs: CR = 0, GR = 12, PR = 9 DS Group: • Symptoms: CR = 1, GR = 20, PR = 0 • Clinical signs: CR = 2, GR = 19, PR 0	3 cases of Candida vulvovaginitis in CT group	6 months	CT: Remission in 0 patients, relapse not noted DS: Remission in 2 patients, relapse not noted	Some concern
Non-Steroid Topicals									
Cattaneo 1996 [14]	32	60 (28–85)	Vulva	First part of treatment (32): • Clobetasol propionate 0.5% cream twice daily for 4 weeks, once a day for 8 weeks and then twice a week for 12 weeks (both groups) Second part of treatment: • Experimental group (16): 2% topical testosterone propionate in a petrolatum-vehicle galenic preparation once daily for 24 weeks (TP) • Control group (16): Petrolatum vehicle placebo once daily for 24 weeks (PLA)	First part of treatment: • Symptomatic relief by all patients, reduction in cumulative score for symptoms from 58 to 9 ($p < 0.001$) • Reduction in cumulative score for gross aspects from 82 to 38 ($p < 0.001$) • Evident reduction in hyperkeratosis and sclerosus • Very little change in atrophy • Total disappearance in erosion and purpura • Complete regression of histological changes in 12 patients, with remaining patients showing some improvement; marked improvement in inflammatory infiltrate, edema and fibrosis Second part of treatment: • Cumulative score showed a statistically significant worsening with TP (6 to 23, $p < 0.05$) • Further improvements in symptoms in 3 PLA patients, recurrence of itching to a mild degree in 3 other PLA patients (score change insignificant) • Better response to PLA than TP for symptoms ($p < 0.01$), no difference for gross aspects (non-significant)	Burning (4) and itching (9) on application of testosterone ointment	48 weeks	Symptomatic relief in all patients in first phase Worsening of symptoms in patients in TP arm of study 3 patients maintained on placebo improved	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Funaro 2014 [20]	55	46.6 (NR)	Vulva	Group 1 (28): Tacrolimus 0.1% ointment daily for 3 months (CL) Control group (27): Clobetasol propionate 0.05% ointment daily for 3 months (CP)	• Change in pruritus: 2.0 in TL, 3.5 in CP • Change in burning/pain: 1.75 in TL, 2.5 in CP • Significant decrease in pruritus and burning/pain for all participants ($p < 0.001$) • Change in pruritus ($p = 0.108$) and burning ($p = 0.172$) not statistically different between the two groups, but CP more effective in reducing burning/pain and pruritus after 1 month than TL, but CP more effective in reducing burning/pain and pruritus after 1 month than TL • More significant decrease in papules and atrophic patches than TL (perineal 0 = 0.036, clitoral $p = 0.001$) • At end of study: 19 TL patients versus 9 CP patients still had some clinical signs of LS ($p = 0.015$) • Number of participants with no clinical signs or reported symptoms significantly higher in CP (15) than the TL (4) group	None	3 months	Remission in 9/28 (32%) of CP patients, only 19/27 (70%) of TL patients	Low concern
Goldstein 2011 [21]	38	NR (NR)	Vulva	Group 1 (17): Pimecrolimus 1% cream twice daily for 12 weeks (PIM) Group 2 (19): Clobetasol propionate 0.05% cream twice daily for 12 weeks (CP)	• Histopathological improvement in inflammation significant for both groups: $p = 0.001$ for CP, $p = 0.008$ for PIM, CP superior to PIM ($p = 0.015$) • More non-responders in PIM than CP group: 8 PIM, 1 CP • Mean change in pruritus: CP 4.5, PIM 3.5, difference not statistically significant ($p = 0.319$) • Mean change in burning and pain: CP 3.7, PIM 3.8, difference not statistically significant ($p = 0.932$) • Both CP and PIM were effective in decreasing Investigator Global Assessment scores ($p = 0.001$) and its 3 subscales (severity of disease [$p = 0.001$], lichenification [$p = 0.001$], ulceration [$p = 0.25$])	None	12 weeks	26 patients completed the follow-up period, where 24 showed improvement and 11 (42%) experienced remission (not broken down by treatment arm)	Low concern
Sideri 1994 [22]	58	56.5 (35–83)	Vulva	Group 1 (30): 2% Testosterone propionate in Vaseline Group 2 (28): Petroleum ointment	Symptom improvement (pruritus vulvae, burning): Testosterone propionate group: • Improved (66.6%, $n = 20$) • Unchanged (20%, $n = 6$) • Worsened (13.4%, $n = 4$) Placebo: • Improved (75%, $n = 21$) • Unchanged (17.8%, $n = 5$) • Worsened (7.1%, $n = 2$) No significant difference found between groups.	$n = 4$, adverse events not specified	12 months	Improvement in dystrophy in 17 patients (group not specified), but no histological demonstration of regression in any of the cases.	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Gunthert 2022 [23]	37	34.52 (NR)	Vulva	Group 1 (17): Progesterone 8% ointment, 2 g daily for 12 weeks (PRO) Group 2 (20): Clobetasol propionate 0.05% ointment, 2 g daily for 12 weeks (CP)	Change in: • Clinical severity: 0.1 in PRO, 1.7 in CP, difference 1.61 ($p = 0.0009$) • Symptom severity: 1.4 in PRO, 2.8 in CP, difference 1.32 ($p = 0.095$) • Short Form-12 physical component score: 0.1 in PRO, −0.4 in CP, difference −0.30 ($p = 0.151$) Short Form-12 mental component score: −0.2 in PRO, 0.3 in CP, difference 0.41 ($p = 0.169$)	CP: Genital herpes (2), mycotic genital infection (1), urinary tract infection (2) PRO: Mycotic genital infection (1), vulvitis (2), urinary tract infection (1), peritonitis (1)	24 weeks	Remission in 6/10 PRO patients, 13/16 CP patients	Low concern
Bracco 1993 [24]	79	57 (27–83)	Vulva	Group 1 (20): Clobetasol propionate 0.05% topical Group 2 (20): Testosterone 2% topical Group 3 (20): Progesterone 2% topical Group 4 (19): Cream-based preparation topical	Symptoms (itching, burning, pain and dyspareunia) were classified from 0–3, with 3 most severe. Symptom improvement: Clobetasol propionate: 15% Testosterone: 40% Progesterone: 40% Cream-based preparation: 21%. Symptom unchanged: Clobetasol propionate: 10% Testosterone: 40% Progesterone: 50% Cream-based preparation: 69% Gross changes: Significant difference in clobetasol group only ($p < 0.001$, CI 2.93–4.97) Gross appearance mean score, clobetasol: 5.8 to 1.9 Histological evaluation: Significant difference in clobetasol group only ($p < 0.001$, CI 2.29–4.65), mean score 7.1 to 3.7	None	3 months	Symptom remission (no symptoms and/or lesions remaining): Clobetasol propionate: 75% Testosterone: 20% Progesterone: 10% Cream-based preparation: 10.5%. Follow up encouraged for an additional 3 months for clobetasol group, in which patients encouraged to use it twice weekly for 3 more months. Of remaining 13 patients, 11 continued good response to therapy, 2 who discontinued had recurrence.	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Goldstein 2015 [25]	30	58 (NR)	Vulva	Treatment Group (TG) (15): Human fibroblast lysate cream twice daily for 12 weeks Control Group (CG) (15): Placebo cream with the same emollient base as the treatment cream twice daily for 12 weeks	• Significant improvement of Investigator Global Assessment (IGA) score at 12 weeks for both groups; 60% of TG showed a decrease of 1+ points, while only 33% of CG patients had improvement • Mean decrease in IGA points: TG 0.9, CG 0.5, $p > 0.2$ • Improvement in pruritus: TG 43% ($p = 0.005$), CG 51% ($p = 0.001$), $p = 0.226$ • Improvement in pain and burning: TG 51% ($p = 0.002$), CG 43% ($p = 0.005$), $p = 0.86$ • No significant difference in sexual function for either group: TG $p = 0.98$, CG $p = 0.89$ No significant change in histopathologic inflammation for both groups	None	12 weeks	No relapse noted	Some concern
Virgili 2013 [26]	80	61.85 (12.17–84.92)	Vulva	Maintenance therapy (following a 12-week active treatment phase on topical 0.1% mometasone furoate ointment daily; patients who achieved a symptomatologic VAS global score $\leq$ 5/30 and an IGA score $\leq$ 2 (total or almost total healing) were judged as "treatment responsive" and were eligible for the MP) with: • Topical vitamin E oil for 52 weeks (44) • Emollient (cold cream) for 52 weeks (36)	Primary efficacy point: relapse rate at both week 26 and 52 Second efficacy variable: mean time to relapse, defined as number of weeks from start of maintenance phase (MP) until LS relapse Total cumulative crude relapse rate (intention to treat): 25% (20/80) Total cumulative modified crude relapse rate: 52.36% (20/38) Crude relapse rates after 52 weeks of maintenance treatment: • Vitamin E: cumulative rate 27.8% (10/36), cumulative modified rate 55.6% (10/18) • Emollient: cumulative rate 22.7% (10/44), cumulative modified rate 50.0% (10/20) • Differences not statistically significant Median time to relapse: • Vitamin E: 20 weeks • Emollient: 18.7 weeks • Not statistically significant ($p = 0.7$).	No observed adverse events	52 weeks	Relapses • Vitamin E: $n = 6$ at 26 weeks, and an additional $n = 4$ at 52 weeks • Emollient: $n = 7$ at 26 weeks, and an additional $n = 3$ at 52 weeks Dropouts (total $n = 42$): • Vitamin E: $n = 16$ prior to 26 weeks, and an additional $n = 2$ prior to 52 weeks • Emollient: $n = 18$ prior to 26 weeks, and an additional $n = 6$ prior to 52 weeks	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Intradermal Injections									
Gutierrez-Ontalvilla 2022 [27]	19	55.17 (NR)	Vulva	Treatment Group (TG) (9): 24 mL of nanofat mixed with PRP, 2 infiltrations 3 months apart Control Group (CG) (10): Topical clobetasol propionate 0.05% cream once or twice weekly	Mean change in feature, standard deviation within brackets: • Gross elasticity: −0.01 (0.16) in TG, 0.01 (0.23) in CG, $p = 0.427$ • Net elasticity: 0.05 (0.17) in TG, 0.08 (0.26) in CG, $p = 0.860$ • Itching: −2.0 (2.7) in TG, −0.2 (2.3) in CG, $p = 0.035$ • Pain: −4.0 (3.5) in TG, 1.3 (3.5) in CG, $p = 0.077$ • Burning: −3.8 (2.9) in TG, −0.7 (5.7) in CG, $p = 0.004$ • Dyspareunia: −2.0 (4.0) in TG, −0.5 (4.3) in CG, $p = 0.022$ • Global Subjective Score: −11.8 (9.6) in TG, −0.1 (9.9) in CG, $p = 0.013$ • Cervical erosions: −0.7 (1.1) in TG, 0.1 (0.7) in CG, $p = 0.004$ • Hyperkeratosis: −0.1 (0.3) in TG, 0.0 (0.0) in CG, $p = 0.542$ • Cracks or fissures: −0.1 (0.3) in TG, 0.0 (0.0) in CG, $p = 0.017$ • Agglutination: −0.2 (0.4) in TG, −0.1 (0.3) in CG, $p = 0.075$ • Introitus stenosis: −0.6 (0.5) in TG, 0.0 (0.0) in CG, $p = 0.043$ • Atrophy: −0.1 (0.3) in TG, −0.1 (0.3) in CG, $p = 0.081$ • Pallor: −1.1 (0.6) in TG, 0.2 (0.6) in CG, $p < 0.001$ • Global Objective Score: −1.1 (0.6) in TG, 0.2 (0.6) in CG, $p < 0.001$ • T lymphocytes: −1.1 (0.3) in TG *, 0.1 (0.8) in CG • Melanophages: −1.3 (1.5) in TG *, 0.2 (0.6) in CG • Eosinophils: −2.9 (1.6) in TG *, 1.6 (−0.3) in CG * • Mast cells: −7.0 (6.1) in TG *, −1.9 (22.8) in CG	None	12 months	3 cases of relapse, all patients in control group	Some concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Goldstein 2019 [28]	30	52.6 (NR)	Vulva	Group 1 (20): Platelet-rich plasma intradermal injections, separated by 6 weeks (PRP) Group 2 (10): Placebo saline injections (PLA)	Change in histopathologic inflammation: • PRP: 5 patients had improvement, 10 had no change, and 4 had more inflammation • PLA: 5 patients had improvement, 4 had no change, and 1 had more inflammation • $p = 0.542$ Change in Clinical Scoring System for Vulvar LS: −7.74 in PRP, −9.44 in PLA, $p = 0.654$	Bruising	12 weeks	Not specified	Low concern
Energy-Based Devices									
Guo 2022 [29]	50	NR (NR)	Vulva	Experimental group: CO_2 laser once monthly for 3 months (CO_2) Control group 1: Radiofrequency treatment with 5-aminolevulinic acid as a photosensitizer once weekly for 10 weeks (RF) Control group 2: Clobetasol propionate 0.05% ointment with traditional Chinese medicine soaking and washing for 3–4 months, then once every other day for 4 weeks, then twice weekly for 4 weeks (CP)	Change in scores at 1 month after treatment: • Pruritus degree: 0.26 in CO_2, 0.33 in RF, 0.25 in CP ($p = 0.865$) • Skin elasticity: 0.57 in CO_2, 1.00 in RF, 0.75 in CP ($p = 0.122$) • Skin color: 1.13 in CO_2, 1.33 in RF, 1.75 in CP ($p = 0.025$) • Lesion scope: 1.61 in CO_2, 4.13 in RF, 4.42 in CP ($p = 0.097$) • Total score: 3.57 in CO_2, 4.13 in RF, 4.42 in CP ($p = 0.097$) Change in scores at 3 months after treatment: • Pruritus degree: 0.17 in CO_2, 0.33 in RF, 1.50 in CP ($p = 0.057$) • Skin elasticity: 0.57 in CO_2, 0.93 in RF, 1.08 in CP ($p = 0.002$) • Skin color: 1.09 in CO_2, 1.33 in RF, 1.83 in CP ($p = 0.003$) • Lesion scope: 1.30 in CO_2, 1.47 in RF, 1.75 in CP ($p = 0.095$) Total score: 3.13 in CO_2, 4.07 in RF, 5.58 in CP ($p = 0.000$)	None reported	3 months	Not specified	Some concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Burkett 2021 [30]	52	64.5 (NR)	Vulva	Group 1 (19): Fractionated CO_2 laser therapy, 5 courses 4–6 weeks apart (CO_2) Group 2 (18): Clobetasol propionate 0.05% ointment nightly for 1 month, then three times weekly for 2 months, then as needed (CP)	Change in... • Skindex-29 score: −16.83 in CO_2, −5.92 in CP, treatment effect of 10.91 (p = 0.007) • Itching: −3.26 in CO_2, −1.83 in CP, treatment effect of 1.43 (p = 0.136) • Burning: −2.78 in CO_2, −1.00 in CP, treatment effect of 1.78 (p = 0.081) • Irritation or tearing: −4.15 in CO_2, −1.32 in CP, treatment effect of 2.79 (p = 0.009) • Dyspareunia: −0.69 in CO_2, −0.14 in CP, treatment effect of 0.55 (p = 0.535) • White plaque: −1.81 in CO_2, −1.30 in CP, treatment effect of 0.51 (p = 0.341) • Cigarette paper: −2.58 in CO_2, −1.50 in CP, treatment effect of 1.08 (p = 0.058) • Introital narrowing: −1.73 in CO_2, −0.70 in CP, treatment effect of 0.18 (p = 0.160) • Loss of labia minora: −0.96 in CO_2, −0.78 in CP, treatment effect of 1.50 (p = 0.792) • Fusion of labia minora: −0.50 in CO_2, 0.35 in CP, treatment effect of 0.34 (p = 0.279) • Phimosis: −1.28 in CO_2, 0.22 in CP, treatment effect of 1.5 (p = 0.022) • Fissure: −2.12 in CO_2, −1.78 in CP, treatment effect of 0.34 (p = 0.634) • Erosion: −2.08 in CO_2, −0.57 in CP, treatment effect of 1.51 (p = 0.036) • Vulvovaginal Symptom Questionnaire: −3.92 in CO_2, −0.58 in CP, treatment effect of 3.34 (p = 0.014) • Vaginal Health Index: 1.92 in CO_2, −0.43 in CP, treatment effect of −2.35 (p = 0.046) • Patient Global Impression of Improvement: 23 in CO_2, 13 in CP, treatment effect of 4.72 (p = 0.073) Patient Global Impression of Satisfaction: 21 in CO_2, 9 in CP, treatment effect of 6.07 (p = 0.011)	Minor burning and blistering with CO_2 (1); reactivation of genital herpes 1 week after starting CP (1)	6 months	Not specified	Some concern
Mitchell 2021 [31]	37	59 (51–64)	Vulva	Group 1 (19): Fractionated CO_2 laser therapy, 5 courses in 24 weeks (CO_2) Group 2 (18): Placebo laser (PLA)	Change in... • Histopathology scale on biopsy: −0.2 in CO_2 (p = 0.74), 0.1 in PLA (p = 0.91), no statistical difference between groups (p = 0.76) • Patients' Clinical Scoring System for Vulvar LS: −7.1 in CO_2 (p = 0.02), −4.8 in PLA (p = 0.04), no statistical difference between groups (p = 0.60) Providers' Clinical Scoring System for Vulvar LS: 0.7 in CO_2 (p = 0.36), −0.3 in PLA (p = 0.70), no statistical difference between groups (p = 0.36)	Transient, mild discomfort (n not specified)	24 weeks	No remission achieved	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Krause 2023 [32]	67	Low dose group: 53 (21–80) Normal dose group: 52 (20–79)	Vulva	Microablative CO_2 laser low dose group (LDG) (29): three laser applications in three subsequent sessions of three weeks. Microablative CO_2 laser normal dose group (NDG) (34): three laser applications in three subsequent sessions of three weeks.	Mean change in total VAS score at 18 weeks • LDG: − 2.7 (±2.8) ($p < 0.0001$) • NDG: − 2.4 (±2.3) ($p < 0.0001$) The difference in mean VAS scores between two groups was not significant at 18 weeks ($p = 0.6244$) Mean change in total LS score at 18 weeks: • LDG: −3.3 ($p < 0.0001$) • NDG: −3.4 ($p < 0.0001$) The difference in total LS scores between two groups was not significant at 18 weeks ($p = 0.88$) Regarding sexual activity: • LDG: pre-treatment: 13 were sexually active, 11 were not sexually active due to LS, 5 were not sexually active due to other reasons; post-treatment: 16 were sexually active, 7 were not sexually active due to LS and 6 for other reasons. • NDG: pre-treatment: 18 were sexually active, 10 were not sexually active due to LS, 6 were not sexually active due to other reasons; post-treatment: 23 were sexually active, 5 were not sexually active due to LS and 6 for other reasons. The improvement in sexual activity is not significantly different between two groups at 18 weeks ($p = 0.61$) Regarding quality of life (QoL): • LDG: pre-treatment: 15 reported severe limitations and 13 indicated intermittent restrictions; post-treatment: 1 had no more restrictions, 7 patients reported severe and 20 intermittent restrictions. There was an improvement in 8 patients (53%). • NDG: pre-treatment: 17 reported severe and 14 intermittent limitations; post-treatment: 7 reported severe and 24 intermittent restrictions. There was an improvement in 10 patients (58%). • The difference between the number of patients showing an improvement in QoL for NDG vs. LDG was not significant ($p = 0.80$).	Burning sensation during laser application, not requiring intervention: 31 No other adverse events or side effects reported.	18 weeks	No reported relapses or remissions.	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Bizjak Ogrinc 2019 [33]	40	58 (NR)	Vulva	Experimental group (20): 3 neodymium-doped yttrium aluminium garnet (Nd:YAG) laser treatments every 14 days (Nd:YAG) Control group (20): Topical betamethasone twice daily for 2 weeks, then once daily for one week, then every second day for one week (BM)	Change in scores at 3 months after treatment: • Burning: 5.0 in Nd:YAG ($p < 0.001$), 3.6 in BM ($p = 0.002$), 3.3 in Nd:YAG vs. BM ($p = 0.001$) • Itching: 6.4 in Nd:YAG ($p < 0.001$), 3.4 in BM ($p = 0.001$), 4.1 in Nd:YAG vs. BM ($p < 0.001$) • Pain: 6.1 in Nd:YAG ($p < 0.001$), 2.2 in BM ($p = 0.037$), 3.3 in Nd:YAG vs. BM ($p = 0.001$) • Total score: 17.5 in Nd:YAG ($p < 0.001$), 9.1 in BM ($p < 0.001$), 10.2 in Nd:YAG vs. BM ($p < 0.001$) Change in scores at 6 months after treatment: • Burning: 4.4 in Nd:YAG ($p < 0.001$), 1.7 in BM ($p = 0.038$), 3.9 in Nd:YAG vs. BM ($p = 0.008$) • Itching: 4.9 in Nd:YAG ($p = 0.001$), 3.0 in BM ($p = 0.095$), 3.5 in Nd:YAG vs. BM ($p = 0.066$) • Pain: 5.4 in Nd:YAG ($p < 0.001$), 2.0 in BM ($p = 0.225$), 0.6 in Nd:YAG vs. BM ($p = 0.793$) • Total score: 14.7 in Nd:YAG ($p < 0.001$), 5.7 in BM ($p = 0.042$), 7.6 in Nd:YAG vs. BM ($p = 0.080$)	None	6 months	8/20 Nd:YAG-treated patients were free of symptoms at 3-month follow up, compared with none of the 16 patients in the control group; 4/16 Nd:YAG-treated patients were free of symptoms at 6-month follow up.	High concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Zivanovic 2024 [34]	66	59.3 (22–86)	Vulva	Group 1 (44): l dual neodymium:yttrium–aluminium–garnet (Nd:YAG)/erbium:yttrium–aluminium–gar-net (Er:YAG) laser at baseline, months 1, 2 and 4 Group 2 (22): topical clobetasol propionate (17 patients used 0.05% oitment and 5 preferred 0.05% cream) first 4 days/week for 8 weeks (phase I) then 4 days/week every 2nd week for 8 weeks (phase II) and finally 4 days/week every 4th week for 8 weeks (phase III)	• In Group 1: 3 did not complete allocated intervention (2 became pregnant and 1 could not come due to COVID-19) • In group 2: 1 did not complete allocated intervention (did not want to participate anymore) • No patients were lost to FU or had discontinued intervention at 6 month FU Mean change in total LS score and subcategories at 6 months: • Group 1: −2.34 ±1.20 (95% CI −2.71 to −1.98, $p < 0.001$) with significant improvement in erosion ($p = 0.011$), hyperkeratosis ($p < 0.001$), fissures ($p = 0.005$) and atrophy ($p < 0.001$). Architectural changes such as agglutination ($p = 0.197$) and stenosis ($p = 0.467$) were not improved by laser therapy. • Group 2: −0.95 ± 0.90 (95% CI −1.35 to −0.56, $p = 0.014$) with significant improvement in erosion ($p = 0.003$), hyperkeratosis ($p = 0.035$) and fissures ($p = 0.046$). Changes in agglutination ($p = 1.0$) and stenosis ($p = 1.0$) were not significant. Atrophy did not change as opposed to the laser group. • Total LS score and atrophy at 6 months were both significantly different between two groups ($p < 0.001$)	Pain/discomfort during laser sessions: • 5 reported pain in laser session 1, 3 in session 2, 5 in session 3 and 4 in session 4. • No local anaesthetic was necessary. Topical anesthetics were needed in 4.5% (8/176) of all treatments (never in in session 1, once in session 2, thrice in session 3, and four times in session 4). Within the first week of laser: • Urinary tract infection (1) • Vulvar itching (2) Vulvar pain (1)	6 months total with 2 months follow up	No reported relapses or remissions	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Zivanovic 2024 [34]	66	59.3 (22–86)	Vulva	Group 1 (44): 1 dual neodymium:yttrium–aluminium–garnet (Nd:YAG)/erbium:yttrium–aluminium–gar-net (Er:YAG) laser at baseline, months 1, 2 and 4 Group 2 (22): topical clobetasol propionate (17 patients used 0.05% oitment and 5 preferred 0.05% cream) first 4 days/week for 8 weeks (phase I) then 4 days/week every 2nd week for 8 weeks (phase II) and finally 4 days/week every 4th week for 8 weeks (phase III)	Mean change in total VAS score (itching, burning and pain) and subcategories at 6 months: • Group 1: total VAS -5.84 ± 6.19 ($p < 0.001$) with significant improvement in: itching -2.89 ± 2.56 ($p < 0.001$), burning -1.91 ± 2.86 ($p < 0.001$). Changes in unprokoved vulvar pain -1.05 ± 2.48 ($p = 0.052$) and pain at intercourse -1.74 ± 2.36 ($p = 0.053$) were not significant *. • Group 2: total VAS -5.36 ± 6.33 ($p = 0.001$) with significant improvement in: itching -2.36 ± 3.36 ($p = 0.008$) and burning -2.23 ± 3.39 ($p = 0.012$). • Total VAS scores did not differ significantly between two groups ($p = 0.881$). Changes in unprokoved vulvar pain -0.77 ± 1.95 ($p = 0.253$) and pain at intercourse -1.78 ± 1.39 ($p = 0.088$) were not significant *. Mean change in total VSQ score and subcategories at 6 months: • Group 1: total VSQ -3.23 ± 3.21 ($p < 0.001$) with significant improvement in: symptoms -1.91 ± 2.37 ($p < 0.001$) and emotions -0.86 ± 1.41 ($p = 0.011$). Changes in life impact (-0.45 ± 1.02, $p = 0.176$) and intercourse (-0.44 ± 1.05, $p = 0.275$) were not significant. • Group 2: total VSQ -2.32 ± 3.43 ($p = 0.043$) with significant changes in symptoms only -1.23 ± 1.69 ($p = 0.010$). Changes in emotions (-0.68 ± 1.55, $p = 0.180$), life impact (-0.41 ± 1.59, $p = 0.229$) and intercourse (-0.56 ± 0.73, $p = 0.320$) were not significant. • Changes in total VSQ scores and in subcategories were not significant between two groups.	Pain/discomfort during laser sessions: • 5 reported pain in laser session 1, 3 in session 2, 5 in session 3 and 4 in session 4. • No local anaesthetic was necessary. Topical anesthetics were needed in 4.5% (8/176) of all treatments (never in in session 1, once in session 2, thrice in session 3, and four times in session 4). Within the first week of laser: • Urinary tract infection (1) • Vulvar itching (2) Vulvar pain (1)	6 months total with 2 months follow up	No reported relapses or remissions	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Zivanovic 2024 [34]	66	59.3 (22–86)	Vulva	Group 1 (44): l dual neodymium:yttrium–aluminium–garnet (Nd:YAG)/erbium:yttrium–aluminium–gar-net (Er:YAG) laser at baseline, months 1, 2 and 4 Group 2 (22): topical clobetasol propionate (17 patients used 0.05% oitment and 5 preferred 0.05% cream) first 4 days/week for 8 weeks (phase I) then 4 days/week every 2nd week for 8 weeks (phase II) and finally 4 days/week every 4th week for 8 weeks (phase III)	Regarding reported patient satisfaction (PGI-I) for laser vs. steroid groups respectively: • Very much better: 32% (14/44) vs. 4.5% (1/22) • Much better: 32% (14/44) vs. 41% (9/22) • A little better: 27% (12/44) vs. 36% (8/22) • No change or worsening: 9.0% (4/44) vs. 18.5% (4/22) • The differences for those experiencing no change or worsening is significant between both groups ($p = 0.035$). * $p < 0.05$ considered statistically significant	Pain/discomfort during laser sessions: • 5 reported pain in laser session 1, 3 in session 2, 5 in session 3 and 4 in session 4. • No local anaesthetic was necessary. Topical anesthetics were needed in 4.5% (8/176) of all treatments (never in in session 1, once in session 2, thrice in session 3, and four times in session 4). Within the first week of laser: • Urinary tract infection (1) • Vulvar itching (2) Vulvar pain (1)	6 months total with 2 months follow up	No reported relapses or remissions	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Salgado 2023 [35]	20	Not reported	Vulva	Fractional CO_2 laser (11): three sessions, with the following settings: 25 watts/ Stack 1/ime 700 microseconds/Spacing 700 micromillimeters. Clobetasol propionate ointment 0.05% (9): nightly in the first month, followed by nightly on alternate days in the second month, then nightly on two consecutive days of the same week (Saturdays and Sundays) in the third month, as needed afterwards without exceeding twice weekly	Mean change in WHOQOL-BREF domains after 3 months of treatment: • No statistically significant differences between the treatment groups, except for the social domain in favor of treatment with clobetasol (3.26 SD 0.88 pretreatment; 2.92 SD 0.70, $p < 0.05$ for clobetasol vs. 3.12 SD 0.95 → 2.88 SD 0.40 for laser) Regarding self-perceived itch, dysuria, pain/sting, sexual activity, appearance, difficulty and patient satisfaction at 3 months: • Higher degree of satisfaction in laser group in terms of self-perception ($p = 0.006$), but not maintained at 12 months At 12 months: • Higher occurrence of mild cases of hyperkeratosis and lichenifcation ($p = 0.02$), in addition to excoriation ($p < 0.03$) in the laser group. WHOQOL-BREF domains did not differ between the groups	No reported adverse events	12 months	No reported relapses or remissions at 12 months, however higher occurrence of mild hyperkeratosis and lichenification and excoriations in laser groups	Low concern
Terras 2014 [36]	26	60.83 (20–81)	Vulva	Group 1 (13): Clobetasol propionate 0.05% ointment once daily for 3 months (CP) Group 2 (13): Medium-dose ultraviolet A1 (50 J/cm^2) home-based phototherapy, performed 4 times weekly for 3 months (UVA)	Change in mean. . . • Total Clinician's Score: 5.0 in CP ($p < 0.001$), 4.5 in UVA ($p = 0.006$), no statistical difference between groups ($p > 0.05$) • Itching: 4.6 in CP ($p = 0.005$), 2.1 in UVA ($p = 0.16$), statistical difference between groups ($p < 0.05$) • Burning and/or pain: 4.2 in CP ($p = 0.001$), 3.2 in UVA ($p = 0.01$), statistical difference between groups ($p < 0.05$) • Skindex-29 Score: 29.6 in CP ($p = 0.009$), 4.9 in UVA ($p > 0.99$), statistical difference between groups ($p < 0.05$) • Histological infiltrate: 0.9 in CP ($p = 0.02$), 0.2 in UVA ($p = 0.51$), statistical difference between groups ($p < 0.05$) • Corium thickness on 20-MHx sonography: −786 in CP ($p = 0.003$), −282 in UVA ($p = 0.41$), statistical difference between groups ($p < 0.05$) • Dermal density on 20-MHx sonography: 15.0 in CP ($p < 0.001$), −0.1 in UVA ($p = 0.97$), statistical difference between groups ($p < 0.05$)	Initial increase in pruritus for UVA-treated patients, treated with petroleum jelly applied within 30 min of radiation to prevent dehydration, which led to marked improvement	6 months	Three months after end of therapy, all primary and secondary outcomes points returned to baseline levels in all patients, suggesting only transient benefit from these therapies	Some concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Shi 2016 [37]	40	51.4 ± 15.6 (range not reported)	Vulva	ALA-PDT (20): 10% 5-aminolevulinic acid photodynamic therapy (ALA-PDT) cream applied to the lesions with a 1-cm margin and incubated for 3 h. The lesions were irradiated with 100 J/cm^2 633 nm red light at 100 mW/cm^2. The same PDT procedure was repeated 3 times at 2-week intervals. CP (20): Topical 0.05% clobetasol propionate ointment applied by the patient nightly for 8 weeks.	Changes in clinical scores (hyperkeratosis, sclerosis, atrophy, depigmentation) Scores: 0 = absent, 1 = mild, 2 = moderate, 3 = severe Mean changes not reported. Hyperkeratosis: • ALA-PDT: Pre-treatment: score 0 (4), score 1 (13), score 2 (3); Post-treatment: score 0 (20) • CP: Pre-treatment: score 0 (3), score 1 (12), score 2 (3), score 3 (2); Post-treatment: score 0 (15), score 1 (5) • No significant difference between the 2 groups before treatment • At end of treatment, CP scores were higher, but both groups showed improvement; significant differences between groups ($p < 0.05$) • At 6 months: ALA-PDT: score 0 (18), score 1 (2); CP score 1 (18), score 2 (2), significant difference between groups Atrophy: • ALA-PDT: Pre-treatment: score 1 (7), score 2 (11), score 3 (2); Post-treatment: score 0 (19), score 1 (1) • CP: Pre-treatment: score 1 (9), score 2 (10), score 3 (1); Post-treatment: score 0 (13), score 1 (7) • No significant difference between the 2 groups before treatment • At end of treatment, scores of CP were higher, but both groups showed improvement, difference significant ($p < 0.05$) • At 6 months: ALA-PDT: score 0 (16), score 1 (4); CP: score 1 (12), score 2 (7), score 3 (1), significant difference between groups	ALA-PDT: • Pain (*n* not reported) • Redness and swelling (6) after light irradiation in the first session, gradually faded away in 3 days for all cases except 1 which developed into erosion the following day. Treated with mupirocin ointment for 1 week. CP: • No observed adverse events	6 months	ALA-PDT: 14/20 (70%) complete response 4 (20%) partial response 2 (10%) minimal response Clobetasol propionate: 7/20 (35%) complete response 6 (30%) partial response 7 (35%) minimal response. Rate of complete response in the ALA-PDT group was much higher than that in the CP group ($p < 0.05$, $\chi^2 = 4.912$) Rate of relapse: All patients finished the 6-month follow-up. In ALA-PDT group: 1 out of 14 (7.1%) patients relapsed one month after completion of treatment. The remaining 13 patients showed no signs of recurrence during follow-up. In CP group, 7 out of 7 (100%) patients relapsed one month after treatment.	Some concerns

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Shi 2016 [37]	40	51.4 ± 15.6 (range not reported)	Vulva	ALA-PDT (20): 10% 5-aminolevulinic acid photodynamic therapy (ALA-PDT) cream applied to the lesions with a 1-cm margin and incubated for 3 h. The lesions were irradiated with 100 J/cm^2 633 nm red light at 100 mW/cm^2. The same PDT procedure was repeated 3 times at 2-week intervals. CP (20): Topical 0.05% clobetasol propionate ointment applied by the patient nightly for 8 weeks.	Sclerosis: • ALA-PDT: Pre-treatment: score 1 (7), score 2 (9), score 3 (4); Post-treatment: score 0 (18), score 1 (2) • CP: Pre-treatment: score 1 (7), score 2 (12), score 3 (1); Post-treatment: score 0 (12), score 1 (8) • No significant difference between the 2 groups before treatment • At end of treatment, scores of CP were higher, but both groups showed improvement, with significant difference between the groups ($p < 0.05$) • At 6 months: ALA-PDT: score 0 (16), score 1 (4); CP: score 1 (15), score 2 (5), significant difference between groups Depigmentation: • ALA-PDT: Pre-treatment: score 1 (7), score 2 (11), score 3 (2); Post-treatment: score 0 (14), score 1 (6) • CP: Pre-treatment: score 1 (8), score 2 (11), score 3 (1); Post-treatment: score 0 (7), score 1 (13) • No significant difference between the 2 groups before treatment • At end of treatment, scores of CP were higher, but both groups showed improvement with significant difference between both groups ($p < 0.05$) • 6 months: ALA-PDT: score 0 (13), score 1 (7); CP: score 1 (13), score 2 (4), score 3 (3), significant difference between groups	ALA-PDT: • Pain (*n* not reported) • Redness and swelling (6) after light irradiation in the first session, gradually faded away in 3 days for all cases except 1 which developed into erosion the following day. Treated with mupirocin ointment for 1 week. CP: • No observed adverse events	6 months	ALA-PDT: 14/20 (70%) complete response 4 (20%) partial response 2 (10%) minimal response Clobetasol propionate: 7/20 (35%) complete response 6 (30%) partial response 7 (35%) minimal response. Rate of complete response in the ALA-PDT group was much higher than that in the CP group ($p < 0.05$, $\chi^2 = 4.912$) Rate of relapse: All patients finished the 6-month follow-up. In ALA-PDT group: 1 out of 14 (7.1%) patients relapsed one month after completion of treatment. The remaining 13 patients showed no signs of recurrence during follow-up. In CP group, 7 out of 7 (100%) patients relapsed one month after treatment.	Some concerns

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Shi 2016 [37]	40	51.4 ± 15.6 (range not reported)	Vulva	ALA-PDT (20): 10% 5-aminolevulinic acid photodynamic therapy (ALA-PDT) cream applied to the lesions with a 1-cm margin and incubated for 3 h. The lesions were irradiated with 100 J/cm^2 633 nm red light at 100 mW/cm^2. The same PDT procedure was repeated 3 times at 2-week intervals. CP (20): Topical 0.05% clobetasol propionate ointment applied by the patient nightly for 8 weeks.	Changes in symptom scores (pruritus, burning and pain feeling) • ALA-PDT: Pre-treatment: score 1 (5), score 2 (10), score 3 (5); Post-treatment: score 0 (14), score 1 (4), score 2 (1) • CP: Pre-treatment: score 1 (4), score 2 (14), score 3 (2); Post-treatment: score 0 (7), score 1 (11), score 2 (2) • No significant difference between the 2 groups before treatment • At end of treatment, CP scores were higher, but both groups showed improvement with significant differences between both groups (p = 0.035) • 6 months: ALA-PDT: score 0 (13), score 1 (4), score 2 (3); CP: score 1 (2), score 2 (10), score 3 (8), with significant differences between the groups Mean reduction in lesion size: • ALA-PDT: 35.18 ± 3.51 cm^2 → 5.38 ± 8.98 cm^2 (p = 0.000) • CP: 36.29 ± 13.23 cm^2 → 9.83 ± 8.51 cm^2 (p = 0.000) • Both groups showed significant reduction in lesion size initially, although there was no difference between the 2 groups (p = 0.116) • 6 months: no significant change in ALA-PDT (p = 0.523), but increase in CP (p = 0.000), with the difference between the 2 groups statistically significant (5.66 ± 8.73 cm^2 vs. 32.49 ± 12.71 cm^2) (p = 0.000)	ALA-PDT: • Pain (n not reported) • Redness and swelling (6) after light irradiation in the first session, gradually faded away in 3 days for all cases except 1 which developed into erosion the following day. Treated with mupirocin ointment for 1 week. CP: • No observed adverse events	6 months	ALA-PDT: 14/20 (70%) complete response 4 (20%) partial response 2 (10%) minimal response Clobetasol propionate: 7/20 (35%) complete response 6 (30%) partial response 7 (35%) minimal response. Rate of complete response in the ALA-PDT group was much higher than that in the CP group ($p < 0.05$, χ^2 = 4.912) Rate of relapse: All patients finished the 6-month follow-up. In ALA-PDT group: 1 out of 14 (7.1%) patients relapsed one month after completion of treatment. The remaining 13 patients showed no signs of recurrence during follow-up. In CP group, 7 out of 7 (100%) patients relapsed one month after treatment.	Some concerns

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Shi 2016 [37]	40	51.4 ± 15.6 (range not reported)	Vulva	ALA-PDT (20): 10% 5-aminolevulinic acid photodynamic therapy (ALA-PDT) cream applied to the lesions with a 1-cm margin and incubated for 3 h. The lesions were irradiated with 100 J/cm^2 633 nm red light at 100 mW/cm^2. The same PDT procedure was repeated 3 times at 2-week intervals. CP (20): Topical 0.05% clobetasol propionate ointment applied by the patient nightly for 8 weeks.	Change in ratios of the vulvar surface affected by VLS: Scored as 0 = none, 1 = less than 25%, 2 = 25–50%, 3 = more than 75% of the vulvar surface affected • ALA-PDT: Pre-treatment: score 1 (2), score 2 (8), score 3 (5), score 4 (5); Post-treatment: score 0 (14), score 1 (4), score 2 (2) • CP: Pre-treatment: score 1 (1), score 2 (7), score 3 (10), score 4 (2); Post-treatment: score 0 (7), score 1 (11), score 2 (2) • Overall, ALA-PDT was more effective in reducing the ratios of vulvar surface affected by VLS after 8 weeks of treatment; however the difference between both groups was not significant ($p = 0.057$) • 6 months: CP scores much higher than ALA-PDT and returned to a distribution profile similar to that seen before treatment ($p = 0.414$). The scores of the ALA-PDT group was similar to those at the end of treatment ($p = 0.317$) and lower than those before treatment ($p = 0.000$).	ALA-PDT: • Pain (*n* not reported) • Redness and swelling (6) after light irradiation in the first session, gradually faded away in 3 days for all cases except 1 which developed into erosion the following day. Treated with mupirocin ointment for 1 week. CP: • No observed adverse events	6 months	ALA-PDT: 14/20 (70%) complete response 4 (20%) partial response 2 (10%) minimal response Clobetasol propionate: 7/20 (35%) complete response 6 (30%) partial response 7 (35%) minimal response. Rate of complete response in the ALA-PDT group was much higher than that in the CP group ($p < 0.05$, $\chi^2 = 4.912$) Rate of relapse: All patients finished the 6-month follow-up. In ALA-PDT group: 1 out of 14 (7.1%) patients relapsed one month after completion of treatment. The remaining 13 patients showed no signs of recurrence during follow-up. In CP group, 7 out of 7 (100%) patients relapsed one month after treatment.	Some concerns

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Li 2004 [38]	31	38.5	Vulva	Focused ultrasound therapy • Frequencies of the transducer ranged from 5 to 8 MHz • Number of sessions not specified	Response measured based on the reduction of pruritus, changes of the skin elasticity and color, decreased percentage of the involved area, and changes in histological findings Cured: (17/31, 54.84%) Improvement: (12/31, 38.71%) Persistent disease: (2/31, 6.45%) Overall response rate: (29/31, 93.55%)	None	2 years	17 patients in remission	Some concerns
Oral Therapies									

Bousema 1994 [39]	78	NR (18-83)	Vulva	Experimental group (22): Acitretin 30 mg once daily for 16 weeks, could be reduced to 20 mg once daily in case of adverse reactions after 4 weeks (AC)
				
				Control group (24): Placebo (PLA)
					Improvement in. . .
					• Pruritus: 1.0 in AC, 0.79 in PLA ($p < 0.05$)
					• Burning: 1.0 in AC, 0.85 in PLA (not significant)
					• Atrophic features: 0.86 in AC, 0.54 in PLA ($p < 0.05$)
					• Hyperkeratotic features: 0.76 in AC, 0.27 in PLA ($p < 0.05$)
					• Secondary features: 0.57 in AC, 0.39 in PLA (not significant)
					• Extent of lesions: 0.36 in AC, 0.08 in PLA ($p < 0.05$)
					
					• Higher number of responders in AC (0.64) than PLA (0.25) ($p < 0.05$)
					• Greater degree of patient satisfaction in AC ($p < 0.05$):
					  ○ Completely satisfied: 0.38 in AC, 0.18 in PLA
					  ○ Partially satisfied: 0.51 in AC, 0.41 in PLA
					  ○ Not satisfied: 0.08 in AC, 0.38 in PLA
						Cheilitis and xerosis in all AC patients, 1/3 of PLA patients
						
						Severe peeling of palms and soles in AC group (11)
						
						Increased hair loss higher in AC (23) than PLA (2)
							16 weeks	None	Low concern

Table 1. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Psychological Counselling									
Vittrup 2022 [40]	158	Median, IQR Intervention group: 53 (33.2–60.5) Median, IQR Treatment Group: 50.5 (30.8–57.0)	Vulva	Control group: usual management where woman would receive oral instruction at diagnosis, treatment, and consultation with nurse specialized in vulvar diseases to follow-up regarding compliance, adherence and support (80) Usual treatment + psychosexual counselling group offered 8 individual sessions of 45 min of counselling based on individual needs (78)	Female Sexual Function Index-FSFI Scores: • Control group effect size, difference from baseline to follow up: 0.4 (−1.2 to 2.0) • Intervention group effect size, difference from baseline to follow up: 5.4 (3.2 to 7.7) Dermatology Life Quality Index-DLQI Scores: • Control group effect size, difference from baseline to follow up: −0.4 (−1.5 to 8.0) • Intervention group effect size, difference from baseline to follow up: −2.5 (−3.7 to −1.3) WHO-5 Wellbeing Index Scores: • Control group effect size, difference from baseline to follow up: 1.0 (−3.2 to 5.1) • Intervention group effect size, difference from baseline to follow up: 6.4 (2.3 to 10.5) Effect size of sexual counselling on sexual activity: • Control, sexually active-effect size difference: −0.6 (−2.7 to 1.6) • Intervention, sexually active–effect size difference: 3.5 (0.5 to 6.4) • Control, non-sexually active–effect size difference: 2.0 (−0.5 to 4.4) • Intervention, non-sexually active–effect size difference 8.2 (4.8 to 11.5)	None	6 months	Not applicable to this study	Low concern

* Signifies statistical significance.

3.2. Risk of Bias

A risk of bias analysis showed that 16 of the included studies had a low risk of bias, 14 had a moderate risk of bias, and 1 had a high risk of bias (Figure 2).

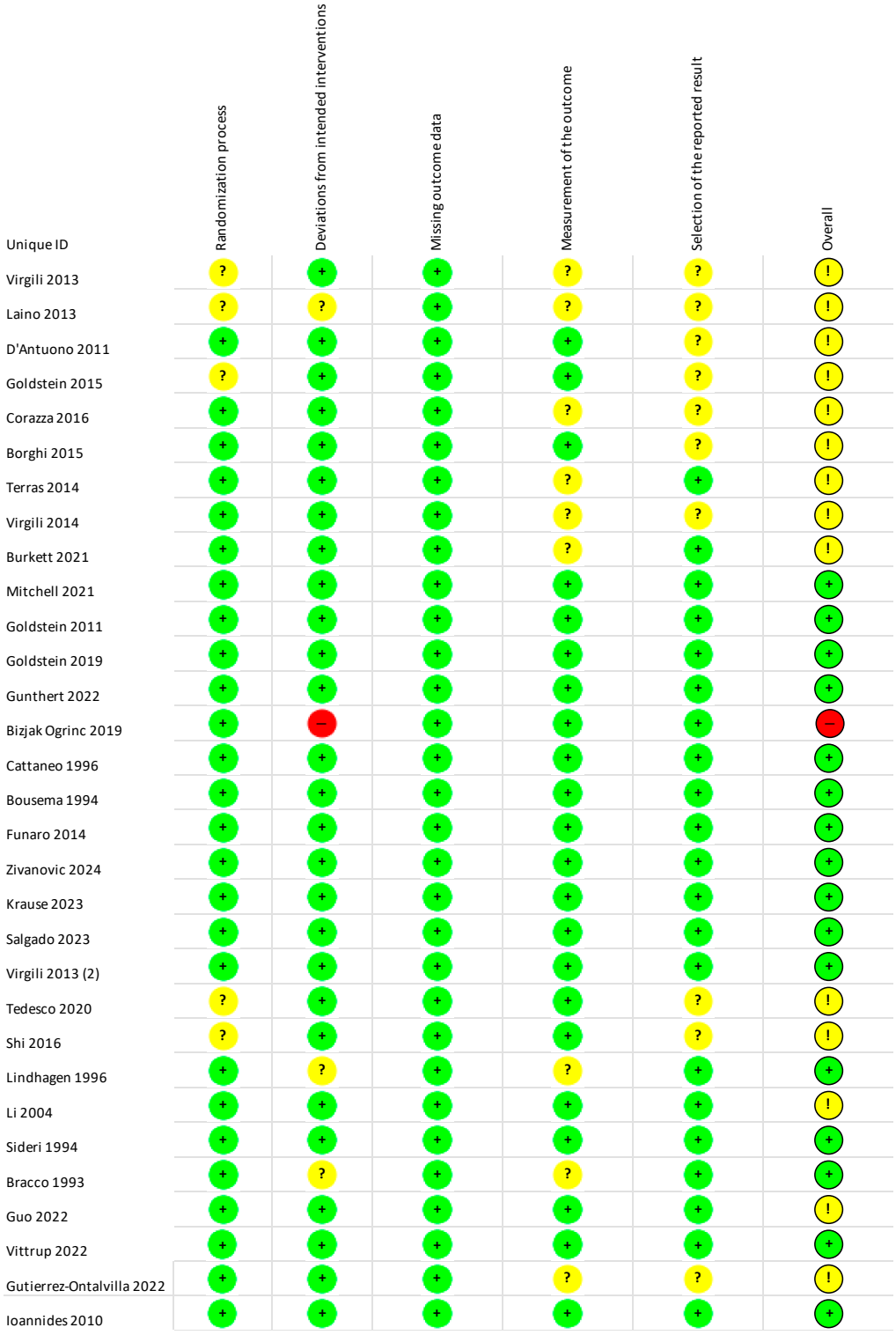


Figure 2. Risk-of-bias assessment of included studies. Low risk of bias is represented by a green circle, moderate risk of bias by a yellow circle, and high risk of bias by a red circle [14–44].

Table 2. Management of LS in Male Patients.

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Recurrence	Risk of Bias
Lindhagen 1996 [41]	30	NR	Penis	Group 1 (15): Clobetasol propionate Group 2 (15): Placebo	Clobetasol Propionate: Improvement: *n* = 10 (+7 from placebo group who were switched) No effect: *n* = 3 Withdrawal: *n* = 2 Placebo: Improvement: *n* = 7 No effect: *n* = 7 (subsequently given clobetasol propionate and improved) Withdrawal: *n* = 1	NR	6 months	No information about relapse or complete remission provided.	Low concern
Laino 2013 [42]	28	NR (25–65)	Penis	Group 1 (14): Subdermal polydeoxyribonucleotide infiltration, 8 sessions total, in association with nightly clobetasol propionate 0.05% (PDRN) for 4 months Group 2 (14): Clobetasol propionate 0.05% nightly (CP) for 4 months	Change in median value of. . . • Investigator Global Assessment (IGA): 4 in PDRN (p = 0.001), 1 in CP (p = 0.001) • Dermatology Life Quality Index (DLQI): 8 in PDRN (p = 0.001), 4 in CP (p = 0.003) • In PDRN, 9 patients (64.3%) had a reduction of at least 50% in IGA after therapy (p = 0.007); in CP, only 2 patients (14.3%) had a reduction of at least 50% • In PDRN, 7 patients (50%) had a reduction of at least 50% in DLQI after therapy; in CP, 0 patients had a reduction of at least 50%	None	6 months	PDRN: 14 remission, 0 relapse CP: 8 remission, 6 relapse	Some concerns

Table 2. *Cont.*

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Recurrence	Risk of Bias
Ioannides 2010 [43]	51	For control group: 57.79 (38–75) For treatment group: 56.56 (38–74)	Male genitalia	Treatment (34): systemic acitretin 35 mg daily for 20 weeks Control (17): placebo capsules (identical in size and color to acitretin) for 20 weeks	Two patients, 1 on acitretin and 1 on placebo, withdrew from the study due to disease associated complications (phimosis) which demanded surgical management Mean change in total clinician score (TCS) • Acitretin group (33): 9.39 (95% CI 9.13–9.66) at baseline → 7.94 (95% CI 7.52–8.35) at week 8, and 6.00 (95% CI 5.12–6.88) and 4.55 (95% CI 3.14–5.95) at weeks 16 and 20. Treatment cessation resulted in a subsequent increase in mean TCS from 4.55 to 6.24 (95% CI 4.96– 7.52) after 16 weeks • Control group (16): 9.25 (95% CI 8.94 –9.56), 9.56 (95% CI 9.05–10.08), 9.25 (95% CI 8.33–10.17) and 9.31 (95% CI 7.54 –11.08) at weeks 0, 8, 16 and 20. • The mean TCS of the acitretin group was significantly lower than that of the control group at week 20 (p= 0.00 < 0.5). Mean change in total quality of life • Acitretin group: 12.27 (95% CI 11.44 –13.10) at week 0 → 6.76 (95% CI 5.37– 8.15) at week 20, which reflects a statistically significant difference ($p < 0.05$) • Control group: 11.94 (95% CI 10.65–13.22) at week 0 → 10.63 (95% CI 8.85–12.40) at week 20, which is not statistically significant	Acitretin group: • Cheilitis (25/33) • Skin peeling (16/33) • Pruritus (10/33) • Paronychia (8/33) • Hair shedding (7/33) • Rhinitis (7/33) • GI disturbances (3/33) • Moderate hyperlipidemia (14/33) • Slight increase in liver enzymes (9/33) Control group: • GI disturbances (4/16) • Headaches (3/16) • Pruritus (2/16) • Fatigue (2/16) • Dizziness (2/16) • Arthralgias (1/16)	36 weeks	Complete response: 36.4% (12 of 33) of the subjects on acitretin and 6.3% (12 of 16) of controls Partial response: 36.4% (12 of 33) of the treatment group and in 12.5% (2 of 16) of the control group. Disease remained stable in: 21.2% (7 of 33) of the acitretin group and 31.3% (5 of 16) of the control groups Disease progression: 6.1% (2 of 33) of individuals on acitretin and 50.0% (8 of 16) on placebo	Low concern

3.3. Topical Corticosteroids as a Single Modality

Unimodal topical corticosteroid therapy was the most commonly reported treatment modality for LS, with one male and four female studies uniquely discussing its usage. All studies noted the usage of high or very high potency topical corticosteroids, notably mometasone furoate 0.1% (MF) and clobetasol propionate 0.05% (CP). Each of the studies that evaluated the efficacy of topical corticosteroids for the treatment of LS interpreted response as clinical or symptomatic improvement of the affected areas. For instance, Cattaneo et al. described significant improvements in a cohort of 32 patients with vulvar LS, whereby 24 weeks of treatment with CP led to significant reductions in the cumulative symptom and gross aspect scores, evident reductions in hyperkeratosis and sclerosis, and the disappearance of erosions and purpura. Histological parameters were also significantly improved, with twelve biopsies showing complete regression of LS findings with improvement in the remaining patients, and overall improvements in inflammatory infiltrates, edema, and fibrosis [41]. Moreover, Lindhagen examined the efficacy of CP in male children with penile LS, and found that, at baseline, patients were more likely to respond to CP than placebo, and that patients initially in the placebo arm then treated with CP responded to CP therapy [15].

Three studies performed comparisons of topical corticosteroid therapy in the treatment of females with LS. Corazza et al. compared CP and MF, two high potency topical steroids, as twice weekly maintenance therapy in patients who had already achieved disease stability with a course of topical corticosteroids, and found no significant differences in outcomes between the two groups over a 52-week period [16]. Virgili et al. also compared CP and MF, and similarly concluded that CP and MF were equally effective for treatment of LS, with the decrease in mean sign and symptom scores significant amongst both groups without significant differences between the groups [17]. Finally, Borghi et al. looked at MF alone, either in the form of a tapering (five days weekly for four weeks, alternate days for four weeks, twice weekly for four weeks) or continuous (five days per week) regimen, and found no statistically significant difference between the two treatment cohorts, concluding that both a tapering and continuous regimen were effective [19].

Overall, high potency topical corticosteroids recurrently proved to be effective in the symptomatic and physical management of LS in both males and females, and should remain the gold standard of therapy for genital LS therapy. There were no significant differences between corticosteroid subtypes, as well as no differences in patient outcomes with regards to varying treatment regimens, allowing physicians to prescribe the course of therapy that the patient feels most comfortable with.

3.4. Topical Corticosteroids and Adjunct Agents

An additional three studies (two female studies, one male study) discussed the use of topical corticosteroids, however these studies attempted to use steroid therapy in conjunction with adjunct agents. A study by D'Antuono et al. analyzed the potential for clothing therapy in the management of vulvar LS, comparing Dermasilk or cotton briefs in conjunction with CP and a vitamin E moisturizer [29]. While both groups had relief from soreness and pruritus, the Dermasilk group showed significant improvement in burning soreness and pruritus. The Dermasilk was also noted to have a greater, non-significant improvement in dyspareunia. Moreover, the severity of these symptoms was in favour of the Dermasilk group with regards to overall improvement and speed of reduction within four weeks. In terms of clinical signs, there was a significantly better improvement in erythema and a non-significant greater improvement in whitening in the Dermasilk group.

Another study analyzed the impact of CP, this time in conjunction with traditional Chinese medicine soaking and washing for 3–4 months, whereby the combination of Chinese and Western medicine has been shown to enhance curative effects, decrease adverse events, and improve the quality of life of vulvar LS patients [45]. More specifically, the traditional Chinese medicine soaking and washing regimen consisted of *Fructus cnidii* and sweet wormwood, however, elaboration pertaining to the specifics of the treatment plan

was not provided [46]. *Fructuss cnidii* is commonly used in the treatment of chronic itch [46], while sweet wormwood has a therapeutic value in inflammatory diseases and autoimmune disorders [42]. Guo et al. found that there was a statistically significant reduction in pruritus when CP was combined with traditional Chinese medicine. Differences in skin elasticity, colour, and disease extent were not significant, with easy relapse after treatment completion [45]. Overall, patients were found to have better outcomes with multi-focused laser treatment (see "Energy-Based Devices" section).

Laino et al. evaluated the efficacy of polydeoxyribonucleotide (PDRN) administered intradermally in conjunction with topical CP, as compared to CP monotherapy [42]. The study found that PDRN + CP patients achieved better improvements than the CP monotherapy group, as well as better improvements in elasticity and decreased ecchymoses, infiltrating areas, erythematous areas, fissures, and lichenification. Moreover, PDRN + CP patients saw a significant reduction in Investigator Global Assessment (IGA) scores and Dermatology Life Quality Index (DLQI) scores, and maintained disease control at six months, while the CP patients demonstrated more signs of disease relapse at the 4–6 months follow up [20].

Altogether, while topical corticosteroids continuously prove to be efficacious in the management of LS, certain adjunct therapies have also proven to improve patient outcomes, and should be utilized in the clinical setting. Notably, silk briefs, traditional Chinese medicine soaks, and PDRN can be used in conjunction with high potency topical corticosteroids to provide patients with additional relief from their LS-associated symptoms.

3.5. Steroid-Sparing Topical Agents

Seven studies reported on the use of steroid-sparing topical therapies for the treatment of female patients with LS. Two reported on topical calcineurin inhibitors. Funaro et al. compared the efficacy of topical tacrolimus 0.1% to CP in patients with vulvar LS [21], and found significant decreases in papules, atrophic and erythematous patches, erosions, and ulcerations across in both groups. The CP group saw a more significant decrease in papules and atrophic patches than the tacrolimus group, and by the end of the study the number of patients with no clinical signs or reported symptoms was significantly higher in the CP group in comparison to the tacrolimus group, with Visual Analog Scale (VAS) scores reporting that CP was more effective than tacrolimus in reducing burning, pain, and pruritus [21]. Similar to tacrolimus, while pimecrolimus also appeared to be effective in the management of LS, CP showed a more robust clinical response [22]. While histopathological improvement in inflammation was significant for both CP and pimecrolimus groups, a comparison demonstrated a superior improvement in the CP group, and numerically more non-responders in the pimecrolimus group ($n = 8$) than the CP group ($n = 1$) [22]. However, VAS scores showed improvement in both groups, with a numerically greater improvement in the CP group, while IGA scores and subscales denoting disease severity, lichenification, and ulceration were equivalent between the two groups [22].

The efficacy of topical hormonal therapy was also investigated. Testosterone 2% ointment as maintenance therapy for vulvar LS, in patients who had already achieved disease control with CP, showed less-than-promising results [41]. Four (25%) patients experienced burning upon ointment application, while nine (56%) noted symptom recurrence, mainly pruritus. Overall, there was a statistically significant worsening of symptoms, whereby patients kept on CP reported further improvements in symptoms [41]. A study by Sideri et al. found that topical testosterone propionate was as effective as petroleum ointment in the management of vulvar LS, with no significant differences between the two groups [23]. Topical progesterone 8% ointment was also found to be inferior to CP treatment in managing LS clinical signs and symptoms [24]. Notably, there was less improvement in standardized LS clinical ($p < 0.05$), symptom ($p = 0.095$), and physical scores in progesterone patients as opposed to CP patients, and biopsies proved that more CP patients (81%) achieved disease remission in comparison to progesterone patients (60%) [24]. Interestingly, there were no randomized controlled trials investigating the efficacy of topical estrogen cream in the treatment of vulvar LS, despite being a widely recommended modality. Finally, a study con-

ducted by Bracco et al. compared topical CP, testosterone, progesterone, and a cream-based preparation, and concluded that significant differences in gross and histologic changes before and after treatment were only observed with CP, and that CP-treated patients noted a much lower degree of patients with unchanged symptoms (CP 10%, testosterone 40%, progesterone 50%, cream-based preparation 69%), reinforcing CP as the mainstay of therapy for vulvar LS [25].

Human fibroblast lysate (HFL) cream, which contains multiple anti-inflammatory cytokines and wound-healing growth factors, did not show statistically significant differences in comparison to placebo [18]. Histopathological analysis revealed no significant changes after 12 weeks of therapy. Finally, Virgili et al. analyzed a cohort of patients who had achieved LS disease remission with the once-daily application of MF, who now sought disease maintenance with either MF twice weekly, topical vitamin E oil once daily, or cold cream once daily [26]. The study showed that MF applied twice weekly protected patients from relapsing in comparison to daily topical vitamin E or cold cream applications over three months [26]. Further studies by Virgili et al. showed that vulvar LS in remission from topical corticosteroid treatment may be managed with either vitamin E or emollient therapy, however, relapse rates are high at 52 weeks, with cumulative modified crude relapse rates between 50 and 55% [27].

In summary, while certain steroid-sparing topical agents may prove to be effective in the management of genital LS, they are suboptimal in comparison to topical corticosteroids, and should thus not be used as a first-line treatment. Other modalities, namely topical hormonal therapies, HFL cream, and vitamin E oils, are not effective tools in managing genital LS and should not be used.

3.6. Intradermal Injections

Intradermal injections were reported by three studies in the literature. Platelet-rich plasma (PRP) and nanofat infiltrations delivered twice at a three-month interval for patients with moderate-to-severe vulvar LS were noted to have no significant improvement in vulvar skin elasticity, however, patients noted a significant improvement in symptoms such as itching, pain, burning, and dyspareunia [28]. Objectively, there was noted improvement in clinical signs such as cervical erosions, fissures, stenosis, and leukoderma, and a significant decrease in all inflammatory cell types upon analysis of skin biopsies [28]. Importantly, when Gutierrez-Ontalvilla et al. compared the PRP group to the CP group, they found significant improvements in the PRP group with regards to fissures, stenosis, pallor, itching, burning, and dyspareunia, which were not achieved in the CP group, and treatment outcomes continued to be significantly more effective in the PRP group with regards to reduction in erosions, fissures, stenosis, and pallor at one-year follow-up, with no cases of relapse [28]. Moreover, histological evaluations and quality-of-life assessments (using the Skindex-29 questionnaire) also revealed statistically significant positive findings for the PRP group in comparison to the CP group [28]. However, Goldstein et al. also investigated the potential for PRP injections administered twice, six weeks apart, in the management of vulvar LS, but found more variable results, whereby 5 patients saw improvement in the histopathologic inflammation between pre- and post-treatment biopsies, 10 had no change, and 4 had more inflammation [44]. The mean difference in the Clinical Scoring System for Vulvar Lichen Sclerosus for the PRP and placebo groups was insignificant [44]. Finally, Tedesco et al. evaluated the efficacy of intradermally injected adipose tissue-derived stromal vascular fraction either as monotherapy or in conjunction with PRP, and found that both treatments were equally efficacious in all patients with the exception of those with late-stage disease (Table 3) [30].

Table 3. Management of LS in both female and male patients.

	# Patients	Mean Age (Age Range)	Affected Region	Treatment Modality	Response	Adverse Events	Follow Up Duration	Remission or Relapse	Risk of Bias
Tedesco 2020 [44]	40 (24 M, 16 F)	Entire sample: 43 (18–78) Female patients: 59 (29–78) Male patients: 49 (18–76)	Female and male genitalia, not otherwise specified	Group 1 (20 total, 5F and 15M): Intradermal injection of adipose tissue derived-stromal vascular fraction; 2 surgical procedures 4 months apart Group 2 (20 total, 11F and 9M): Intradermal injection of combined purified AD-SVF and platelet rich plasma (PRP); 2 surgical procedures 4 months apart	Mean clinical score at 6 months post-second injection (score ranging from 0 (disease stability) to 3 (great functional improvement with reduction of symptoms until their disappearance) based on subjective itch, pain, burning sensation and dyspareunia on 10 level VAS) • AD-SVF: 2.0 +/− 0.8, AD-SVF + PRP: 1.8 +/− 1.1 • No statistically significant difference between both groups (p = 0.42) • Separate analysis of both arms based on patients with early vs. late LS revealed significant difference for AD-SVF + PRP but not for AD-SVF. ○ For AD-SVF + PRP: patients with early LS (7: 3F, 4M) had mean score of 2.6 +/− 0.7 of compared to patients with late LS (13, 8F, 5M) who had mean score of 1.3 +/− 1.0 (p = 0.011) ○ For AD-SVF: patients with early LS (10, 1F and 9M) had mean score of 2.0 +/− 0.8 compared to patients with late LS (10, 4F and 6M) who had mean score of 2.0 +/− 0.9 (p = 0.77) • Analysis of patients with early vs. late LS also revealed significantly higher clinical scores compared to late-stage patients (early = 2.2 +/− 0.8, late = 1.6 +/− 1.0, p = 0.046) • No significant differences in clinical score between male and female patients (F = 2.0 +/− 1.1; M = 1.79 +/− 0.9, p = 0.52) Mean change in QoL (based on DLQI questionnaire) • Significant improvement in QoL after 6 months for both groups (p = 0.0002) with median DLQI value decreased from 5.0 +/− 3.9 (moderate impact) to 2.32 +/− 1.85.· • Individual subgroup analysis also revealed significant improvement of QoL for each group· • Separate analysis based on disease stage revealed better results in patients with early LS treated with AD-SVF + PRP than in AD-SVF-treated patients (−4.7 +/− 2.8 vs. −1.7 +/− 2.2, p = 0.036) • Overall significant difference in QoL among early and late-stage patients treated with combinatory therapy (−4.7 +/− 2.8 vs. −1.3 +/− 2.0, p = 0.0083)	None	6 months	13 patients had complete resolution of symptoms 23 showed significant improvement in symptoms 4 showed no changes 2 reported a reduction of white lesions	Some concerns

Overall, the efficacy of PRP in the management of LS would require further investigation given the variability of data currently available in the literature among only two randomized controlled trials, while adipose tissue-derived stromal vascular fractions as either monotherapy or in conjunction with PRP have the potential to provide early stage LS patients with symptomatic relief.

3.7. Energy-Based Devices

The use of energy-based devices was reported by 10 studies in females with LS. Guo et al. compared carbon dioxide (CO_2) laser therapy and photodynamic therapy (PDT) using 5% 5-aminolevulinic acid (5-ALA) as a photosensitizer, and found that CO_2 treatment led to statistically significant improvements in pruritus, skin elasticity and colour, lesion size, and total clinical scores, while 5-ALA PDT produced significant improvements in the degree of pruritus, skin colour, and total clinical scores [45]. Notably, significant differences were observed between the groups at three months post-treatment, with the study indicating that CO_2 laser therapy has the most potential to improve clinical signs and symptoms and prevent relapse within two months [45]. CO_2 lasers were used on two other occasions in the literature, and also demonstrated good efficacy in comparison to CP. Burkett et al. showed that patients treated with a CO_2 laser had greater improvement in their Skindex-29 scores at six months in comparison to CP treatment [31]. The patients also viewed their treatment outcomes more positively, with more CO_2-treated patients feeling a better improvement in their symptoms (89% vs. 62%) and feeling satisfied with their treatment (81% vs. 41%) [31]. Differently, Mitchell et al. placebo-controlled their CO_2 laser therapy trial, and found insignificant improvements in LS upon histopathological examination when comparing the CO_2 and placebo lasers [32]. Similarly, patient scores according to the Clinical Scoring System for Vulvar Lichen Sclerosus showed improvement, but the difference in comparison to the placebo group was insignificant, while physician scoring scales also did not demonstrate significant change in either treatment arm [32]. Additionally, Krause et al. investigated the impact of a CO_2 laser's dose on clinical improvement in LS scores, and found that higher dosages show no significant benefit with regards to LS scores, visual analog scores, sexual activity, or quality of life when compared to lower doses [33].

Other energy-based devices reported for LS include the non-ablative neodymium:yttrium aluminum garnet (Nd:YAG) laser and ultraviolet A (UVA) phototherapy. Bizjak Ogrinc et al. studied the efficacy of the Nd:YAG laser in comparison to topical corticosteroids, and found that while patients in both groups experienced a reduction in itching, burning, and pain intensity, the reduction was statistically significantly better for patients in the Nd:YAG laser group amongst all symptoms, and numerically more patients treated with the Nd:YAG laser remained disease-free at a three-month follow up (40% vs. 0%) [33]. Patients also experienced a greater degree of satisfaction when treated with laser therapy (100% very satisfied, compared to 12.5% in the topical steroid group). Zivanovic et al. assessed the efficacy of a combined Nd:YAG/Er:YAG laser in comparison to topical CP, concluding that total LS scores decreased significantly in both groups [35]. CO_2 lasers were also compared to topical CP by Salgado et al., who noted similar findings: post-treatment vulvar characteristics and impact on quality of life did not differ significantly between the two groups, while laser-treated patients had a greater degree of satisfaction [36]. Light was also tried as a treatment modality for LS in two studies. Terras et al. investigated the efficacy of UVA phototherapy compared to CP in the management of LS, and found that both therapies resulted in significant decreases in total clinician's scores, which took into account hypopigmentation, sclerosis, atrophy, hyperkeratosis, erosions, edema, and erythema, but the difference between the groups was not significant [37]. With regards to VAS scores, CP had more parameters that achieved statistically significant results, notably decreases in pruritus, burning and/or pain, and the Skindex-29 score, however, only the score for burning and/or pain significantly decreased for UVA-treated patients. Ultrasound and histopathological assessments also noted improvements in both groups, however, only the values in the CP group reached significance. Shi et al. investigated the use of PDT with

10% 5-ALA cream as compared to CP, and found that PDT resulted in twice the response elicited by CP in terms of hyperkeratosis, atrophy, sclerosis, and depigmentation [38]. Finally, Li et al. attempted to use focused ultrasound therapy for the treatment of vulvar dystrophy, including LS, with a transducer range between 5 and 8 MHz, and noted a dramatic improvement in the patients' total response rates and the tissues' return to normal appearance by 3–6 months, with continued response/clearance of disease at the two-year follow-up [39].

Generally, CO_2 laser was often effective in comparison to other laser types and high potency topical corticosteroids, serving as an adjunct in the genital LS treatment armamentarium. Importantly, higher laser doses did not prove to be more effective than lower doses. Moreover, the Nd:YAG or Er:YAG lasers or UVA therapy also proved to be either equally effective or more effective than topical corticosteroids with regards to objective findings, while patients treated with laser modalities typically had greater treatment satisfaction. Finally, PDT-treated patients also had greater responses in their physical LS findings than patients treated with topical steroids. Of great importance, laser therapy is often costly and comes with a great out of pocket expense to patients, and thus might not be a feasible option for all.

3.8. Oral Therapies

Two studies analyzed the impact of oral therapy in the treatment of LS. Bousema et al. investigated acitretin, a second-generation retinoid dosed at 20 to 30 mg daily for 16 weeks [43]. While symptoms and signs improved in both the acitretin- and placebo-treated groups, sign and symptom intensity was statistically significantly lower for pruritus, atrophy, and hyperkeratosis in the acitretin group. The number of treatment-responsive patients was also noted to be significantly higher in the acitretin group (64%) as compared to the placebo (25%) ($p < 0.05$). Ioannides et al. also investigated the use of acitretin in the management of LS compared to the placebo, but instead in cases involving the male genitalia [40]. A larger number of acitretin-treated patients achieved complete or partial response compared to placebo-treated patients (36.4% and 36.4% vs. 6.3% and 12.5%). Finally, there was a significant improvement in the mean DLQI score for the acitretin group [40].

Overall, while acitretin proved to be effective in the management of genital LS, no direct comparisons with topical corticosteroids were noted in the literature. Such a comparison would be needed to further note the efficacy of acitretin as compared to the gold standard in LS management, while being cognizant of the fact that only topical corticosteroids prevent malignant progression of the disease.

3.9. Psychological Counselling

Vittrup et al. analyzed the impact of psychosexual counselling in addition to usual care with ultrapotent topical corticosteroids in combination with a fatty cream and oil massage of the vulva [47]. After six months of therapy, the patients who had underwent psychosexual counselling had a statistically significant improvement in their sexual functioning, as opposed to a non-significant improvement in the control group. The counselled group achieved better improvements in their sexual function indices, mean DLQI scores, and a higher degree of quality of life when compared to the controls, reinforcing the significant impact that psychosexual counselling has on outcomes in LS patients [47].

4. Discussion

In 2018 the British Association of Dermatologists published the first guidelines for the management of LS, in which a strong recommendation was made to start all female and male patients on topical CP [48]. In accordance with this guideline, topical corticosteroids remain the cornerstone of LS treatment, with high potency CP and MF demonstrating significant efficacy in improving cumulative symptoms and gross aspect scores in four RCTs [16,17,19,41]. Importantly, results from two RCTs, which compared CP and MF,

showed no significant differences in effectiveness, suggesting that the two high-potency corticosteroids could be considered interchangeable for vulvar LS management, however, the above-mentioned guidelines do not mention the use of MF as an alternative to CP [16,17,48]. As for penile LS, despite the current guideline recommendation to initiate CP in males, only one RCT, which looked at the efficacy of unimodal therapy with CP compared to that of CP combined with subdermal injections of PDRN, was identified [20]. Finally, CP combined with other modalities, such as Dermasilk briefs and vitamin E moisturizers, showed promising results in symptom relief and clinical outcomes [26,29].

This review also identified several steroid-sparing topical agents and alternative therapies for LS management. Topical calcineurin inhibitors demonstrated some efficacy comparable to corticosteroids in improving symptoms and clinical signs, providing alternative treatment options, especially for patients who may be intolerant to corticosteroids or require long-term maintenance therapy. However, results from two RCTs suggest topical steroids remain superior [21,22]. Current guidelines conclude there is insufficient evidence to recommend the use of these therapies [48], and, thus, further research is warranted. An additional important consideration is the relatively high cost of these medications compared to that of topical corticosteroids.

The efficacy of hormonal therapies, such as testosterone and progesterone ointments, was also investigated in four RCTs. However, the results appeared less promising compared to corticosteroids [24,25,41]. Importantly, one study showed significant worsening of symptoms with topical testosterone, suggesting limited utility in LS management [41]. Similarly, current guidelines do not recommend the use of topical hormonal therapy [48]. However, topical estrogen has been successfully used in conjunction with CP for treatment of LS [49–51], and this is commonly recommended by clinicians for well-controlled LS.

Importantly, various studies demonstrated therapies with outcomes superior to those of CP. Energy-based devices, namely CO_2 and Nd:YAG lasers, showed promising results in improving symptoms and clinical outcomes, with the CO_2 laser improving symptoms and quality of life more than CP, and Nd:YAG leading to a greater improvement in remission rates at three months compared to CP [31,34]. Importantly, these RCTs were all published following the release of the 2018 guidelines. PRP injections also demonstrated superior efficacy compared to corticosteroids, with sustained benefits and minimal adverse effects observed over long-term follow-up in one study [28], however, results were variable in another [44]. Given the variability in the reproducibility of the results, the generalization of the results is limited, and further research is warranted.

In one RCT, oral acitretin demonstrated significant efficacy in improving symptoms and clinical signs, suggesting its potential role as an alternative or adjunctive therapy [43]. Current guidelines report insufficient evidence to recommend this intervention [48]. Finally, given that multiple studies have proven that LS is associated with increased psychological distress, decreased quality of life and overall negative health outcomes, more studies evaluating the efficacy and importance of psychological intervention are paramount to improving patients' quality of life, in addition to pharmacologic therapies [8,52].

Despite the comprehensive nature of this systematic review, there are several limitations. Firstly, the inclusion criteria focused exclusively on RCTs, potentially excluding relevant studies published in other study designs. This may have resulted in the omission of valuable data on different treatment modalities for LS. Moreover, although only RCTs were included to provide a summary of the highest level of evidence, when analyzed using the revised Cochrane tool for risk of bias, eleven studies out of nineteen were associated with "moderate risk" and one study with "high risk" of bias, which underscores the need for cautious interpretation of the findings and highlights potential systematic errors that can influence the validity and reliability of the results [53]. Moreover, the heterogeneity in treatment regimens and outcome measures across studies hindered direct comparisons between different modalities via a meta-analysis. Importantly, the predominance of female-focused studies in the RCT literature suggests a gap in the current understanding of LS management in males, in addition to limiting conclusions that can be made from this

review for this population. Finally, comparisons of the efficacies associated with various treatment modalities proved to be a challenge across different studies, given that a plethora of investigator scores were used to objectify LS findings.

Despite these limitations, this systematic review provides a comprehensive synthesis of the current evidence on treatment modalities for LS, serving as a valuable resource for clinicians and researchers in guiding clinical decision-making and future research endeavors, and reinforcing high potency topical corticosteroids as the mainstay of treatment for LS with regards to the prevention of malignant progression, symptomatic management, and improvement in architectural changes. While we strongly reinforce the importance of topical corticosteroids as the cornerstone of treatment for genital LS, more extensive research is needed to better formulate therapeutic algorithms based on a multitude of factors.

5. Conclusions

In conclusion, while LS is reportedly difficult to treat and is known to have a significant impact on patients' quality of life, the literature contains a plethora of potential treatment modalities with varying outcomes. Physicians should be aware that while topical corticosteroids are the mainstay of treatment, they are not the sole modality available to manage this condition, and that multimodal therapies that combine topical steroids, clothing therapy, and procedural interventions for long-term management also prove to be effective and tolerable.

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