Bijlagen
Lichen sclerosus
richtlijn 2021

Colofon

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Inhoudsopgave

Bijlage 1: Belangenverklaringen

De KNMG-Code ter voorkoming van oneigenlijke beïnvloeding door belangenverstrengeling is gevolgd. Alle werkgroepleden hebben schriftelijk verklaard of ze in de laatste drie jaar directe financiële belangen (betrekking bij een commercieel bedrijf, persoonlijke financiële belangen, onderzoeksfinanciering) of indirecte belangen (persoonlijke relaties, reputatie management, kennisvalorisatie) hebben gehad. Een overzicht van de belangen van werkgroepleden en het oordeel over het omgaan met eventuele belangen vindt u in onderstaande tabel. De ondertekende belangenverklaringen zijn op te vragen bij het secretariaat van de Nederlandse Vereniging voor Dermatologie en Venereologie.

Werkgroep-lid	Functie	Nevenfuncties	Persoonlijke financiële belangen	Persoonlijke relaties	Reputatie management	Extern gefinancierd onderzoek	Overige belangen	Getekend op	Acties (voorstel)
Drs. C.L.M. van Hees, voorzitter	Dermatoloog	Voorzitter bestuur NVDV (bezoldigd) Docent landelijke vulvacursus (bezoldigd)	Geen	Geen	Vulvapoli ErasmusMC/Dermahaven	Geen	Geen	06-12-2018	Geen
Drs. M.L. Bandell	Gynaecoloog, seksuoloog NVVS/FECSM	Geen	Geen	Geen	Geen	Geen	Geen	07-01-2020	Geen
E. Bol-van den Hil	Mondhygiënist	Directeur Nederlandse Vereniging van Mondhygiënisten Bestuurslid (bezoldigd), Stichting Geschilleninstantie Mondzorg (betaald), Bestuurslid Stichting de Mond Niet Vergeten (onbezoldigd), Vice-voorzitter European Dental	Geen	Geen	Geen	Geen	Geen	17-10-2019	Geen

		Hygienists Federation (onbezoldigd)							
C.W.L. van den Bos	Bekkenfysiotherapeut, MSPT	Geen	Geen	Geen	Geen	Geen	Geen	06-12-2018	Geen
Drs. T. Breedveld	Tandarts	Lid lichen planus vereniging Nederland (LPVN)	Geen	Geen	Geen	Geen	Geen	03-12-2018	Geen
Dr. G.R. Dohle	Uroloog	Medisch adviseur Veduma (bezoldigd)	Geen	Geen	Geen	Geen	Geen	29-06-2019	Geen
Dr. J.J.E. van Everdingen	Dermatoloog n.p., directeur NVDV		Geen	Geen	Geen	Geen	Geen	?	Geen
Drs. A. Glansdorp	Huisarts en kaderhuisarts urogynaecologie	Geen	Geen	Geen	Geen	Geen	Geen	15-12-2018	Geen
S. Groot	Patiëtnvertegenwoordiger, secretaris Lichen Planus Vereniging Nederland	Vrijwilliger hospice Duurstede (onbezoldigd)	Geen	Geen	Bestuurslid patiëntenorganisatie	Geen	Geen	05-12-2018	Geen
Dr. W.A. ter Harmsel	Gyneacoloog	Docent colposcopie cursus, docent vulvapathologie cursus (bezoldigd). Lid medische adviesraad lichen sclerosus vereniging, lichen planus vereniging, bekkenbodem 4all (onbezoldigd).	Geen	Geen	Behandeling van patiënten met vulva problematiek in Rooseveldt kliniek waar dr. Ter Harmsel mede-eigenaar van is.	Geen	Geen	17-05-2019	Geen

Drs. I. Hendriks	Dermatoloog	Deelname richtlijnherzienin g VIN (onbezoldigd)	Geen	Geen	Geen	Geen	Geen	06-12-2018	Geen
J. Janssens	Verpleegkundi g specialist	Geen	Geen	Geen	Geen	Geen	Geen	06-12-2018	Geen
Dr. M.J. ten Kate-Booij	Gyneacoloog	Bestuurslid Federatie Medisch Specialisten	Geen	Geen	Geen	Mogelijk geringe mate indien in 2019 de (door METC goedgekeurde) RCT naar behandeling van LS met PDT in vergelijking met clobetasol van start gaat.	Geen	15-01-2019	Besproken tijdens eerste vergadering
Dr. E.H. van der Meij	MKA-chirurg	Geen	Geen	Geen	Geen	Geen	Geen	04-12-2018	Geen
Drs. E.J. Mendels	Dermatoloog	Lid werkgroep richtlijn infantiele hemangiomen (onbezoldigd) Auteur Zalfje, voorleesboek voor kinderen met eczeem (onbezoldigd)	Geen	Geen	Geen	Geen	Geen	22-04-2020	Geen
Dr. J.M. Oldhoff	Dermatoloog	Lid NVDV domeingroep SOA (onbezoldigd), organisator refereeravonden dermatologie OOR-NNL welke gesponsord worden door Abbvie BV, Galderma, Leo Pharma BV, Lilly	Geen	Geen	Geen	Geen	Geen	12-03-2018	Geen

		Nederland BV (onbezoldigd).							
Drs. M.C. Raadgers	Bekkenfysiotherapeut, bewegingswetenschapper	Nevenwerkzaamheden NVFB (bezoldigd)	Geen	Geen	Geen	Geen	Geen	04-12-2018	Geen
Drs. M.J. Ramakers	Arts-seksuoloog NVVS	Lid medische adviesraad patiëntenvereniging lichen sclerosus, lichen planus (onbezoldigd). Bestuurslid NVvVP (onbezoldigd), Docent vulvapathologie cursus (bezoldigd), Lid Pelvic Floor Network (onbezoldigd).	Geen	Geen	Geen	Geen	Geen	03-12-2018	Geen
Drs. L.M.T. van der Spek-Keijser	Dermatoloog	Geen	Geen	Geen	Geen	Geen	Geen	06-12-2018	Geen
E. Swanborn	Patiëntvertegenwoordiger, voorzitter stichting Lichen Sclerosus	Geen	Geen	Geen	Geen	Geen	Geen	03-12-2018	Geen
Drs. H. Vermaat	Dermatoloog	Geen	Geen	Geen	Geen	Betrokken bij aanvraag onderzoek naar LS geassocieerd vulvacarcinoom. Geen persoonlijke financiële belangen.	Geen	04-12-2018	Geen
Drs. A.H.I. Witterland	Ziekenhuisapotheker	Geen	Geen	Geen	Geen	Geen	Geen	06-12-2018	Geen

Drs S.A.A. Wolt-Plompen	Kinderarts	Instructeur kindermishandeling cursus Stichting Spoedeisende hulp bij kinderen (onbezoldigd), Kwaliteitsvisiteur NVK (onbezoldigd).	Geen	Geen	Geen	Geen	Geen	14-05-2019	Geen
M. Hofhuis	Arts-onderzoeker (secretaris t/m oktober 2019)	Geen	Geen	Geen	Geen	Geen	Geen	07-12-2018	Geen
L.S. van der Schoot	Arts-onderzoeker (secretaris t/m november 2019)	Geen	Geen	Geen	Geen	Geen	Geen	07-12-2018	Geen
E. de Booij	Arts-onderzoeker (secretaris vanaf november 2019)	Geen	Geen	Geen	Geen	Geen	Geen	01-12-2019	Geen

Bijlage 2: Zoekstrategieën

Zoekstrategie 2019

Er werd één systematische zoekstrategie uitgevoerd in de elektronische databases EMBASE, Medline en de Cochrane library. Experts op het gebied van lichen sclerosus werden geraadpleegd voor eventuele ontbrekende artikelen. Verder werden de studies uit de richtlijn 2012 nagelopen indien deze ontbraken bij de zoekstrategie. De search is geüpdatet tot 03-04-2019.
De zoekactie is met behulp van de PICO-systematiek opgebouwd. De zoekvragen hebben de P als gemeenschappelijke onderdeel. De overige onderdelen van de PICO werden geformuleerd op basis van de uitgangsvraag.

De volgende afbakening is gebruikt:
Voor de P: Patiënten met lichen sclerosus
Voor de I: elke behandeling voor lichen sclerosus
Voor de C: geen behandeling, placebo behandeling, andere behandelingen voor lichen sclerosus
Voor de O: zie hieronder.

Per uitgangsvraag zijn klinisch relevante uitkomstmaten opgesteld, waarbij zowel naar gewenste als ongewenste effecten is gekeken. De werkgroep heeft deze uitkomstmaten gewaardeerd volgens hun relatieve klinisch belang bij de besluitvorming rondom aanbevelingen. De werkgroep definieerde de uitkomstmaten als volgt en hanteerde de in de studies gebruikte definities.

Primair:
1. Verandering in kwaliteit van leven aan het eind van de studie (cruciaal)
2. Verandering in ernst van lichen sclerosus volgens patiënten aan het eind van de studie (cruciaal)
3. Proportie patiënten die een bijwerking rapporteerde gedurende de studie (cruciaal)

Secundair:
4. Verandering in ernst van lichen sclerosus volgens behandelaars aan het eind van de studie (belangrijk)
5. Behandelingstevredenheid volgens patiënten (belangrijk)
6. Duur van remissie (belangrijk)

Er is geen leeftijd limitatie aangehouden. Uitgesloten werden studies zonder originele gegevens (reviews), case control studies en studies met minder dan tien deelnemers (N<10). Er is een restrictie aangehouden voor Nederlandstalige en Engelstalige publicaties. Voor therapeutische uitgangsvragen werden vergelijkende, gecontroleerde studies geïncludeerd. Studies die geen spreidingsmaten rapporteren of die middelen beschrijven die in Nederland niet beschikbaar zijn werden geëxcludeerd.

EMBASE (datum 03-04-2019)

Zoektermen

#9. #6 OR #7 OR #8	638
#8. #1 AND #4 AND #5	411
#7. #1 AND #3 AND #5	243
#6. #1 AND #2 AND #5	68
#5. [dutch]/lim OR [english]/lim	29,322,984
#4. 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de)	2,212,723

	OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (case:ab,ti AND ((control NEAR/1 (study OR studies)):ab,ti)) OR (follow:ab,ti AND ((up NEAR/1 (study OR studies)):ab,ti)) OR ((observational NEAR/1 (study OR studies)):ab,ti) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	
#3.	('clinical trial'/exp OR 'randomization'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp OR rct:ab,ti OR random*:ab,ti OR 'single blind':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial'/exp OR placebo*:ab,ti) NOT 'conference abstract':it	2,218,326
#2.	('meta analysis'/de OR cochrane:ab OR embase:ab OR psycinfo:ab OR cinahl:ab OR medline:ab OR ((systematic NEAR/1 (review OR overview)):ab,ti) OR ((meta NEAR/1 analy*):ab,ti) OR metaanalys*:ab,ti OR 'data extraction':ab OR cochrane:jt OR 'systematic review'/de) NOT (('animal experiment'/exp OR 'animal model'/exp OR 'nonhuman'/exp) NOT 'human'/exp)	422,097
#1.	'lichen sclerosus et atrophicus'/exp OR 'lichen sclerosus et atrophicus' OR 'vulva kraurosis'/exp OR 'vulva kraurosis' OR (extragenital AND ('lichen' OR 'lichen'/exp OR lichen) AND sclerosus)	4,191

Resultaten = 638

MEDLINE (datum 03-04-2019)

Zoektermen

1 exp Lichen Sclerosus et Atrophicus/ or exp Vulvar Lichen Sclerosus/ or exp Balanitis Xerotica Obliterans/ or (lichen sclero* or kraurosis vulvae or kraurosis penis or extragenital lichen sclerosus).ti,ab,kw. (2508)

2 (meta-analysis/ or meta-analysis as topic/ or (meta adj analy$).tw. or ((systematic* or literature) adj2 review$1).tw. or (systematic adj overview$1).tw. or exp "Review Literature as Topic"/ or cochrane.ab. or cochrane.jw. or embase.ab. or medline.ab. or (psychlit or psyclit).ab. or (cinahl or cinhal).ab. or cancerlit.ab. or ((selection criteria or data extraction).ab. and "review"/)) not (Comment/ or Editorial/ or Letter/ or (animals/ not humans/)) (388246)

3 (exp clinical trial/ or randomized controlled trial/ or exp clinical trials as topic/ or randomized controlled trials as topic/ or Random Allocation/ or Double-Blind Method/ or Single-Blind Method/ or (clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomized controlled trial or multicenter study or clinical trial).pt. or random*.ti,ab. or (clinic* adj trial*).tw. or ((singl* or doubl* or treb* or tripl*) adj (blind$3 or mask$3)).tw. or Placebos/ or placebo*.tw.) not (animals/ not humans/) (1844291)

4 Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ (3154718)

5 limit 1 to (dutch or english) (2002)

6 2 and 5 (73)

7 3 and 5 (131)

8 4 and 5 (444)

9 6 or 7 or 8 (572)

Resultaten = 572

Cochrane (datum 04-04-2019)

Zoektermen

#1 MeSH descriptor: [Lichen Sclerosus et Atrophicus] explode all trees (24)
#2 MeSH descriptor: [Vulvar Lichen Sclerosus] explode all trees (26)
#3 MeSH descriptor: [Balanitis Xerotica Obliterans] explode all trees (1)
#4 #1 or #2 or #3 (39)

Resultaten = 39

Alle resultaten

Database	**Datum**	**# hits op filter**
EMBASE	03-04-2019	SRs (68), RCTs (243), Obs (411)
MEDLINE	03-04-2019	SRs (73), RCTs (131), Obs (444)
Cochrane	04-04-2019	39 (1 cochrane review, 38 trials)
Totaal		1409 (SRs (141), RCTs (374), Obs (855), Cochrane (39))
Duplicates		490
Netto aantal		**919** (SRs (69), RCTs (201), Obs (646), Cochranetrials (3))

Zoekstrategie 2012

Relevante artikelen werden gezocht door systematische zoekacties in de Cochrane Library, Medline en EMBASE in 2010. Er werd niet beperkt op publicatiedatum, tijdschrift, leeftijd of geslacht. De artikelen werden geselecteerd op grond van de volgende criteria: (a) Engelstalige, Duitstalige, Franstalige of Nederlandstalige publicaties en (b) gepubliceerd als 'full paper'. Vanwege het veelal ontbreken van randomized controlled trials werd er voor de meeste zoekacties niet beperkt op de fundamentele opzet van de studie.
Algemene exclusiecriteria waren:

- Dubbele publicaties
- Taal anders dan Nederlands, Engels, Duits en Frans
- Case series met minder dan 5 patiënten

Algemeen – RCT's en meta-analyses

EMBASE <1980 to 2010 Week 20>
1 exp lichen sclerosus et atrophicus/ (1505)
2 (lichen sclero* or kraurosis vulvae or kraurosis penis or balanitis xerotica obliterans).ti. or lichen sclero*.ab. or kraurosis vulvae.ab. or kraurosis penis.ab. or balanitis xerotica obliterans.ab. (1234)
3 1 or 2 (1666)
4 meta analysis/exp or cochrane.ab. or embase.ab. or psychlit.ab. or cinahl.ab. or (systematic and review).ab. or (systematic and review).ti. or data extraction.ab. (36358)
5 clinical trial/exp or randomization/exp or single blind procedure/exp or double blind procedure/exp or crossover procedure/exp or placebo/exp or prospective study/exp or rct.ab. or rct.ti. or random*.ab. or random*.ti. or single blind.ab. or single blind.ti. or randomised controlled trial.ab. or randomised controlled trail.ti. or randomized controlled trial/exp or placebo*.ab. or placebo*.ti. (492117)
6 3 and 4 (5)
7 3 and 5 (33)
8 6 or 7 (37)

9 limit 8 to (human and (dutch or english or french or german)) (31)
10 from 9 keep 1-31 (31)

Resultaten = 31

Epidemiologie (2010)

EMBASE

1. exp lichen sclerosus et atrophicus (1958)
2. (lichen slero* or kraurosis vulvae or kraurosis penis or balanitis xerotica obliterans).ti. or lichen sclero*.ab. or kraurosis vulvae.ab. or kraurosis penis.ab. or balanitis xerotica obliterans.ab (1286)
3. 1 or 2 (2204)
4. incidence (mesh) (165036)
5. prevalence (mesh) (240204)
6. epidemiology (mesh) (123306)
7. 4 or 5 or 6 limit to (human and (dutch or English or French or german)) (375780)
8. 3 and 7 (80)

Resultaten = 80

Medline

#12 Search (#11) AND #4 Limits: Humans, English, French, German, Dutch
#11 Search ((#10) OR #8) OR #6 Limits: Humans, English, French, German, Dutch
#10 Search "Epidemiology"[Mesh] Limits: Humans, English, French, German, Dutch
#8 Search "Prevalence"[Mesh] Limits: Humans, English, French, German, Dutch
#6 Search "Incidence"[Mesh] Limits: Humans, English, French, German, Dutch
#4 Search (#3) OR #2 Limits: Humans, English, French, German, Dutch
#3 Search (((lichen sclero*[Title/Abstract]) OR kraurosis vulvae[Title/Abstract]) OR kraurosis penis[Title/Abstract]) OR balanitis xerotica obliterans[Title/Abstract] Limits: Humans, English, French, German, Dutch
#2 Search "Lichen Sclerosus et Atrophicus"[Mesh] Limits: Humans, English, French, German, Dutch

Resultaten = 36

Epidemiologie - Leeftijd, geslacht, ras (2010)

EMBASE

1. exp lichen sclerosus et atrophicus (1958)
2. (lichen slero* or kraurosis vulvae or kraurosis penis or balanitis xerotica obliterans).ti. or lichen sclero*.ab. or kraurosis vulvae.ab. or kraurosis penis.ab. or balanitis xerotica obliterans.ab (1286)
3. 1 or 2 (2204)
4. age (mesh) (31332)
5. ethnology (mesh) (47617)
6. sex difference (mesh) (212940)
7. 4 or 5 or 6 limit to (human and (dutch or English or French or german)) (359857)
8. 3 and 7 (31)

Resultaten = 31

Medline

#17 Search (#16) AND #4 Limits: Humans, English, French, German, Dutch
#16 Search ((#15) OR #13) OR #11 Limits: Humans, English, French, German, Dutch
#15 Search "Sex Characteristics"[Mesh] Limits: Humans, English, French, German, Dutch
#13 Search "Ethnology"[Mesh] Limits: Humans, English, French, German, Dutch

#11 Search "Age Determination by Skeleton"[Mesh] Limits: Humans, English, French, German, Dutch
#4 Search (#3) OR #2 Limits: Humans, English, French, German, Dutch
#3 Search (((lichen sclero*[Title/Abstract]) OR kraurosis vulvae[Title/Abstract]) OR kraurosis penis[Title/Abstract]) OR balanitis xerotica obliterans[Title/Abstract] Limits: Humans, English, French, German, Dutch
#2 Search "Lichen Sclerosus et Atrophicus"[Mesh] Limits: Humans, English, French, German, Dutch

Resultaten = 1

Diagnostiek – Differentiaal diagnose (2010)

EMBASE

1. exp lichen sclerosus et atrophicus (1958)
2. (lichen slero* or kraurosis vulvae or kraurosis penis or balanitis xerotica obliterans).ti. or lichen sclero*.ab. or kraurosis vulvae.ab. or kraurosis penis.ab. or balanitis xerotica obliterans.ab (1286)
3. 1 or 2 (2204)
4. Differential diagnosis (mesh) (266101)
5. 3 and 4 (212)

Resultaten = 212

Medline

#17 Search (#16) AND #4 Limits: Humans, English, French, German, Dutch
#16 Search "Diagnosis, Differential"[Mesh] Limits: Humans, English, French, German, Dutch
#4 Search (#3) OR #2 Limits: Humans, English, French, German, Dutch
#3 Search (((lichen sclero*[Title/Abstract]) OR kraurosis vulvae[Title/Abstract]) OR kraurosis penis[Title/Abstract]) OR balanitis xerotica obliterans[Title/Abstract] Limits: Humans, English, French, German, Dutch
#2 Search "Lichen Sclerosus et Atrophicus"[Mesh] Limits: Humans, English, French, German, Dutch

Resultaten = 162

Kwaliteit van leven en seksualiteit (2010)

PsychInfo (datum 01-11-2010)

1 (lichen adj scleros*).ti,ab. (3)
2 (lichen adj planus).ti,ab. (14)
3 lichen.ti,ab. (23)
4 1 or 2 or 3 (23)
5 limit 4 to (dutch or english or french or german) (17)

Resultaten = 17

Medline (datum 01-11-2010)

1 Lichen Sclerosus et Atrophicus/ (587)
2 exp Lichen Planus/ (5300)
3 (lichen adj scleros*).ti,ab. (1195)
4 (lichen adj planus).ti,ab. (4315)
5 1 or 2 or 3 or 4 (7413)
6 "Concept-filter patiÃ«ntenperspectief dd. 03-08-2010".ti. (0)
7 Patient Participation/ (14501)
8 (patient* adj (participation or decisi* or decid*)).tw. (2764)
9 "Patient Acceptance of Health Care"/ (24442)

10 *patient satisfaction/ or patient preference/ (15901)
11 (patient adj2 preference*).tw. (3558)
12 (patient? adj2 view?).tw. (3201)
13 (patient adj3 attitude?).tw. (1437)
14 (patient* and (acceptance or perspective* or satisfaction)).ti. (8536)
15 (collaborat* adj3 patient?).tw. (1354)
16 exp Adaptation, Psychological/ (85015)
17 coping.ti,ab. (25665)
18 vignette.tw. (1924)
19 (patient* adj choice?).tw. (1319)
20 (patient* adj2 decision?).tw. (3943)
21 exp *health education/ or *patient education as topic/ (59954)
22 exp *attitude to health/ or health knowledge, attitudes, practice/ (134561)
23 or/6-17,19-22 (301287)
24 ("informed choice*" adj3 (patient* or parent* or famil* or spouse*)).ti,ab. (111)
25 empowerment.tw. (4405)
26 focus groups/ or narration/ (14204)
27 ("focus group*" adj3 (patient* or parent* or famil* or spouse*)).ti,ab. (763)
28 (perception* adj3 (patient* or parent* or famil* or spouse*)).ti,ab. (10995)
29 qualitative.ti. (13976)
30 *"Quality of Life"/ or "Quality of Life"/px [Psychology] (40944)
31 (QoL or "Quality of life").ti. (28543)
32 or/24-31 (85305)
33 23 or 32 (366756)
34 5 and 33 (25)
35 exp Sexual Behavior/ (66020)
36 exp Sexual Dysfunction, Physiological/ (20017)
37 exp Sexual Dysfunctions, Psychological/ (23514)
38 35 or 36 or 37 (89479)
39 sexual*.ti,ab. (130038)
40 38 or 39 (177028)
41 40 and 5 (89)
42 34 or 41 (110)
43 limit 42 to (dutch or english or french or german) (104)
Exclusie child abuse

Resultaten = 83

Kindermishandeling (2010)

Medline (01-11-2010)
1 Lichen Sclerosus et Atrophicus/ (587)
2 exp Lichen Planus/ (5300)
3 (lichen adj scleros*).ti,ab. (1195)
4 (lichen adj planus).ti,ab. (4315)
5 1 or 2 or 3 or 4 (7413)
6 (child* adj3 abuse*).ti,ab. (11704)
7 exp Child Abuse/ (21435)
8 6 or 7 (23620)
9 5 and 8 (33)

Resultaten = 33

Bijlage 3: Exclusietabellen

Lokale therapie

Exclusies na full tekst screening:

RCTs en vergelijkende studies

Artikel	Reden van exclusie
Bracco 1993	Geen full tekst, inclusie testosteron en progesteron
Diakomanolis 2002	Geen full tekst, retrospectieve cohortstudie zonder randomisatie
Goldstein 2015	Middel niet in NL (fibroblast lysate cream), pilotstudie
Maretti 2018	Middel niet in NL (neomercurocromo), geen full tekst
Murina 2015	Observationeel, corticosteroïden, vergelijking al in RCT
Origoni 1996	Middel niet in NL (oxatomide), geen randomisatie
Patsatsi 2013	Indirecte vergelijking, retrospectief
Kyriaku 2013	Middel niet in NL (Methylprednisolonaceponaat)

Observationele studies

Artikel	Reden van exclusie
Borghi 2018	Gaat niet over effect behandeling
Borghi 2015	Middel niet in NL, observationeel
Borghi 2015	Observationele studie tretinoine
Burrows 2011	Ongeschikte uitkomstmaten
Cattaneo 1991	Geen full tekst, testosteron
Cattaneo 2003	Mometason, observationeel

Clark 1999	Corticosteroïden, observationeel
Currò 2018	OZOILE (middel niet in NL), ongeschikte uitkomstmaten.
Dahlman 1999	Ongeschikte uitkomstmaten
Hengge 2006	Fase 2 studie, ongeschikte uitkomstmaten
LeFevre 2011	Triamcinolon, retrospectief
Lorenz 1998	Clobetasol, retrospectief
Nissi 2007	Pimecrolimus, observationeel
Oskay 2007	Pimecrolimus, observationeel
Potts 2016	Ongeschikte uitkomstmaten (kans van slagen procedure intra-urethrale corticosteroïden)
Virgili 2014	Mometason tapering dosering, observationeel
Virgili 2015	Mometason, observationeel

Overige designs

Artikel	Reden van exclusie
Andreassi 2003	Review
Chari 1994	Geen full tekst, case series
Chi 2011	Systematic review, andere inclusiecriteria
Edey 2006	Letter zonder originele data
Kaya 2005	N=1
Maassen 2012	Review

Onderhoudstherapie

Exclusies na full tekst screening:

Artikel	Reden van exclusie

Bradford 2010	Retrospectief, mogelijk zelfde cohort als Lee 2015
Dalziel 1993	N=9
Dalziel 1991	Geen full text
Sinha 1999	Geen full text
Ventolini 2012	Retrospectief, onduidelijk wat voor patiëntenpopulatie (geen karakteristieken beschreven), onduidelijke toewijzing interventies
Virgili 1995	Geen full text

Systemische therapie

Exclusies na full tekst screening:

Artikel	Reden van exclusie
Baggish 2006	Ongeschikte uitkomstmaten, niet-vergelijkende studie
Basak 2002	Case report
Buxton 1990	Para-aminobenzoaat, middel niet in NL, observationeel
Formiga 2014	Geen full tekst
Romppanen 1987	Geen full tekst, ongeschikte uitkomstmaten o.b.v. abstract
Shelley 2006	N<10 voor de verschillende therapeutische opties en per geslacht

Fotodynamische therapie

Exclusies na full tekst screening:

Artikel	Reden van exclusie

Biniszkiewicz 2005	Follow up 4 weken, voor lange termijn follow up n<10. Verschillend aantal cycli PDT per patiënt, niet beschreven hoeveel per patiënt.
Criscuolo 2017	Geen full tekst, PDT selectief toegepast op patiënten met gevorderde ziekte
Olejek 2009	Ongeschikte uitkomstmaten
Passeron 2009	Case report n=1
Prodromidou 2018	Systematisch review zonder risk of bias assessment
Skrzypulec 2009	Ongeschikte uitkomstmaten
Zawislak 2009	N<10

Overige therapie

Exclusies na full tekst screening:

Artikel	Reden van exclusie
Almadori 2017	Geen full tekst
Arena 2016	Letter zonder originele gegevens
Behnia-Willison 2016	Platelet rich plasma, ongeschikte uitkomstmaten
Goldstein 2019	Ongeschikte uitkomstmaten
Zucchi 2016	Middel niet gebruikt in NL (Polydeoxyribonucleotide)

Kichen sclerosus bij kinderen

Exclusies na full tekst screening:

Artikel	Reden van exclusie
Barbagli 2008	Commentaar op fase 2 studie Ebert et al. 2008

Ebert 2008	Ongeschikte populatie patiënten (jongens met LS die postoperatief na circumcisie lokaal tacrolimus gebruikten)
Ellis 2015	Retrospectief, verschillende middelen en follow up duur maar uitkomsten voor alle patiënten samen weergegeven
Folaranmi 2018	Systematisch review zonder meta-analyse of risico op bias beoordeling, kleine studies met N<10 geïncludeerd, ongeschikte uitkomstmaat (circumcisie)
Garzon 1999	Case series n=10, verschillende soorten corticosteroïden gebruikt

Bijlage 4: Tabllen karakteristieken geïncludeerde studies

Karakteristieken en resultaten van geïncludeerde studies 2012

Chirurgische behandeling

Auteur jaartal	Aantal patiënten geïncludeerd	Gemiddelde leeftijd patiënten (range)	Maximale duur behandeling	Start effect	Evaluatie datum	Studieopzet/Dosering	Resultaten	Uitkomstmaten/Definitie van succes	Duur remissie	Bijwerkingen genoemd Zo ja, welke?	Aantal uitvallers	Aantal uitval door bijwerkingen	Randomisatie Zo ja. Concealment of allocation?	Blindering	NNT versus placebo
Chirurgie															
Kulkarni 2009	215 (215/ 0)	50 (11-85)	-	-	gem. 56 mnd (12-170)	Chirurgie (circumcisie, meatotomie, urethro-plastiek, urethrostomie), retrospectief dossieronderzoek	87% succes, 100% bij circumcisie, combinatie circumcisie en meatotomie en 'one-stage' urethroplastiek	falen, heroperatie, terugkeer van de ziekte	zie follow-up	n.s.	-	-	-	-	-
Cryochirurgie															
Kastner 2003	31 (0/31)	9 meisjes (gem. 9 jr) 22 vrouwen (gem. 54 jr)	-	-	1-69 mnd	Eenmalig cryochirurgie met één vriescyclus gedurende 4-8 seconden. Daarna desinfecterende baden en paracetamol	16 ptn duidelijke klinische verbetering. Na behandeling geen sclerose, sec. huidverande-ringen en bloedingen meer. Minder jeuk en pijn. 2 meisjes en 3 vrouwen recidiveerden. Na 2e of 3e behandeling succesvol	klinische en subjectieve verbetering/ remissie	zie follow-up	-	14	n.s.	-	-	-

Stücker 2005	22 (0/22)	65 (42-85)	-	-	27,8 +/- 14,6 mnd	Follow-up na cryochirurgie met één vriescyclus. Retrospectieve opzet	14/22 recidief na behandeling. Ptn bevelen behandeling matig tot niet aan. Jeuk en pijn significant verminderd.	pijn, jeuk, patiënttevredenheid, dermatologische kwaliteit van leven	recidief na gem 11,7 mnd	langdurige hersteltijd na behandeling	-	-	-	-	-

Karakteristieken en resultaten van geïncludeerde studies 2019

Corticosteroïden

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Borghi 2015	Type of study: single-centre, randomized, investigator-blinded, comparative trial Country: Italy Source of funding: none	Inclusion criteria: adult female patients with a clinical and, when available, histological diagnosis of VLS Exclusion criteria: clinical or histological features showing possible resemblance to other diseases, such as lichen planus or plasma-cell	Tapering dose Mometasone furoate once daily for 5 days per week for 4 weeks, then on alternate days for 4 weeks, then twice weekly for 4 weeks All of the study subjects were instructed to apply a pea-sized quantity of the ointment to the affected vulvar	Continuous dose MMF for five consecutive days per week for the entire treatment duration	Length of follow-up: 12 weeks Loss-to-follow-up: I: 1 C: 3 Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Responders (score ≤ 3 for each evaluable subjective symptom and a GOS ≤ 4): I: n=27 (84%) C: n=25 (78%) RR non response in I vs C: 0.94 (95% CI 0.26-3.40) GSS75 (improvement of	Randomization: computer-generated simple randomization Schedule. The randomization schedule was prepared prior to enrolment to ensure allocation concealment. Objective and subjective patient assessment was performed in consensus by the same two experienced investigators (A.V.

		vulvitis; lack of agreement between clinical and histological features; systemic and/or topical VLS treatments during the 4 weeks before enrolment; known hypersensitivity to any component of the study drug, confirmed by patch tests; active vulvar infectious diseases or vulvar dermatoses or carcinoma; pregnancy or breastfeeding. <u>N total at baseline</u>: 64 Intervention: 32 Control: 32 <u>Important prognostic factors</u>[1]: mean GOS was significantly higher in intervention group than in control group (P = 0.006)	surfaces. Throughout the study duration no additional local or systemic treatments, nor cosmetics expected to relieve VLS, were allowed.			75%, GSS is max 20, sum symptom parameters): I: n=22 (69%) C: n=20 (62%) GOS75 (improvement 75%, GOS = max 12, summing clinical parameters score 0-3 for erythema, hyperkeratosis, pallor, pururic lesions, excoriations): I: n=15 (47%) C: n=9 (28%) No sign differences between groups. Adherence (adherent is never or sometimes (<25%) missing applications): Not adherent: I: 1 C: 2 The relative risk of poor adherence among group B patients was 214 (95% confidence interval 020–2234) compared with group A. Adverse events: none.	and M.C.) blinded to treatments at baseline and at the 12-week control visit. Other investigators (S.M. and G.T.), unblinded to treatment allocation and not involved in patient assessment, prescribed the study drugs in accordance with the randomization. Patients were not blinded to their group allocation. The main limitation of this study is that univocal and validated methods to assess VLS severity, as well as univocal definition of clinical response, are not available in the literature.

Virgili 2014	Type of study: Single centre, randomized, parallel-group, open-label, comparative trial Setting: Single centre Country: Italy Source of funding: none	Inclusion criteria: clinical and, when available, histological diagnosis of VLS Exclusion criteria: systemic treatment witlh steroids, retinoids or hormonal replacement therapies and oestroprogestinic drugs during the 4 weeks before enrolment; treatment with topical therapy (e.g. corticosteroids, tacrolimus, pimecrolimus, hormonal therapy) at the affected area during the 4 weeks before enrolment; hypersensitivity to any component of the study drugs; active vulvar infectious diseases or vulvar dermatoses or carcinoma; or pregnancy or breastfeeding. N total at baseline: 54	Clobetasol propionate 0.05% for 12 weeks initially once daily for 5 days a week for 4 weeks in order to avoid tachyphylaxis and reduce the risk of dose-dependent side-effects, then on alternate days for 4 weeks and, for the third month, twice weekly.	Mometasone furoate 0.1% ointment for 12 weeks initially once daily for 5 days a week for 4 weeks in order to avoid tachyphylaxis and reduce the risk of dose-dependent side-effects, then on alternate days for 4 weeks and, for the third month, twice weekly.	Length of follow-up: 12 weeks Loss-to-follow-up: Intervention: 2 Control: 1 Incomplete outcome data: ITT population used for analyses	Outcome measures and effect size (include 95%CI and p-value if available): Responders at 12 weeks (patients who achieved both a score ≤ 3 for each evaluable subjective symptom and a GOS ≤ 4 were arbitrarily judged as 'treatment responsive'): I: n=24 (88.9%) C: n=24 (88.9%) Non responder (patients who failed to improve at the end of the 12-week ATP were considered unresponsive and underwent a further treatment course with topical corticosteroids. Any worsening in sclerosis scarring was also arbitrarily considered as no response.): I: n=1 (3.7%) C: n=2 (7.4%) Global subjective score (GSS, max 20; based on itch, burning, signs of	Randomization: computer generated simple randomization schedule. The randomization schedule was prepared prior to enrolment to ensure allocation concealment. Efficacy analyses based on intent-to-treat (ITT) population, defined as all randomized patients enrolled in the ATP.

		Intervention: 27 Control:27 <u>Important prognostic factors</u>[1]: Groups comparable at baseline? Yes				VLS), 75% improvement: I: n=16 (59.3%) C: n=18 (66.7%) Global objective score (GOS, max 12, based on score 0-3 for erythema, leucoderma (pallor), hyperkeratosis, and purpuric lesions and itching-related excoriations) 75: I: n=10 (37%) C: n=13 (48.2%) Adherence: all pt. Treatment satisfaction: satisfied/dissatisfied I: n=2 (8%) dissatisfied C: n=4 (15%) dissatisfied. P=0.24 No adverse events.	

Calcineurineremmers

Study reference	Study characteristics	Patient characteristics [1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Funaro 2014	Type of study: double-blind, randomized	<u>Inclusion criteria</u>: aged 2 years or	Tacrolimus 0.1% If lesions resolved before the end	Clobetasol propionate 0.05%	<u>Length of follow-up</u>: 3 months	Outcome measures and effect size	recruitment through vulvar disease referral

	prospective study Setting: single centre Country: Canada Source of funding: Sponsored by an Astellas Pharma research grant for an investigator-initiated study. Disclosure: Dr Powell served on the advisory board for Astellas Pharma and Dr Funaro received from Astellas Pharma a grant for an investigator-initiated study and received a bursary in a research competition.	older with newly diagnosed vulvar lichen sclerosus or untreated lichen sclerosus for at least 1 month <u>Exclusion criteria</u>: absence of lichen sclerosus after biopsy, known hypersensitivity to the studied products or their vehicle, a history of vulvar intraepithelial neoplasia or anogenital epidermoid carcinoma, presence of condyloma, hyperkeratotic lichen sclerosus, physical limitation preventing application of the study ointment, children in diapers, and finally the use of topical corticosteroids or a calcineurin inhibitor the month	of the 3-month period, participants were still followed up until the end of the study and used their treatment as maintenance therapy, ie, twice weekly application of their ointment.		<u>Loss-to-follow-up</u>: C: 2 withdrew after first visit <u>Incomplete outcome data</u>: treatment readjustment due to possible reaction: I: n=3 C: n=2 ITT population: I: 28 C: 27	(include 95%CI and p-value if available): Clinical improvement as determined by investigator (white papules, patches, atrophy, erosion, ulcerated lesions, erythematous patches, lichenification; score 0-3): No clinical signs at 12 weeks: I: n=4 (14,3%) C: n=15 (55,6%) P=0.002 Mean VAS pruritus at 3 months: I: 3 C: 1 Mean VAS burning/pain: I: 2.2 C: 0.7 Adverse events: side effects related to treatment ≥1: I: n=24 C: n=20 Burning sensation: I: n=22 C: n=13 P=0.014 Side effects that led to treatment	center, prospective. 5 children included, age not reported > risk of indirectness Only p-value reported for efficacy scores, mean VAS only displayed in figure. Both participants and iinvestigators were blinded to the administered treatment. The hospital's pharmacy department prepared the ointment tubes and insured double-blindness and randomization. Block randomization was used (blocks of 4) to control for the numbers of participants allocated to each group during the enrollment phase of the study.

		before the study N total at baseline: 58 Intervention: 29(1 excluded, no LS) Control: 29 Important prognostic factors[1]: *More pt with atrophy in clobetasol group* *Five participants were younger than 18 years: 1 in the tacrolimus group and 4 in the clobetasol group.* Groups comparable at baseline? yes				readjustment: I: n=3 C: n=2	
Goldstein 2011	Type of study: double-blind randomized controlled trial Setting: single center Country: US Source of funding: Novartis Pharmaceuticals	Inclusion criteria: women who were 18 years or older with a diagnosis of biopsy-proven active vulvar LS, the ability to sign written informed consent, willingness and ability to comply with the	Pimecrolimus cream 1% twice daily for 12 weeks Safety assessments consisted of monitoring serum levels of pimecrolimus and clobetasol and evaluating total white blood cell count, lymphocytes, platelets, aspartate aminotransferase, alanine aminotransferase,	unmedicated vehicle cream in the morning daily and clobetasol cream 0.05% in the evening daily for 12 weeks.	Length of follow-up: 12 weeks Loss-to-follow-up: -) Incomplete outcome data: 1 excluded due to no LS in biopsy. 1 excluded due to loss of biopsy. Analyses population: n=36	Outcome measures and effect size (include 95%CI and p-value if available): change in inflammation, as determined by a dermatopathologist, on the biopsy specimens obtained at screening and at the week 12 visit:	www.clinicaltrials.gov (NCT00393263) Allocation: Randomized Intervention: Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

	Corp, East Hanover, NJ. Disclosure: Dr Goldstein has received research funding from Novartis Pharmaceuticals and Neocutis, Inc; he is a consultant for Boehinger Ingelheim. Novartis is producent of pimecrolimus.	study requirements, negative urine pregnancy test results for all women of childbearing potential before enrollment, two forms of birth control for women with childbearing potential, IGA at baseline of 1 or greater, and a score of 4 or greater (on a 0- to 10-point scale) on at least one of the two visual analog scales (VAS-PR, VAS-BP). Exclusion criteria:receiving systemic immunosuppressants (eg, corticosteroids) within 4 weeks before participation in the study; treatment with topical therapy (eg, topical corticosteroids,	creatinine, and blood urea nitrogen, and urinalysis at each visit. A urine pregnancy test was administered at screening and at each visit.		I: 17 C: 19	The improvement in inflammation as assessed by a dermatopathologist (primary efficacy variable) was significant both for the clobetasol and pimecrolimus groups (P = .001 and .008, respectively). Non responders (no improvement inflammation): I: n=8 C: n=1 patients assessed mean change in VAS pruritus: I: 3.5 C: 4.5 Not stat sign. patients assessed mean change in VAS and burning/pain: I: 3.8 C: 3.7 IGA severity of the disease (0-3 scale), clinical evaluation of lichenification (0-3 scale), and clinical evaluation of ulceration/fissuring (0-3 scale).: Both clobetasol and pimecrolimus cream were found to be effective in decreasing	Participants were assigned blinded treatment with consecutive numbers. Only p-value or mean without standard deviation reported for efficacy scores.

		pimecrolimus, and tacrolimus) at the affected area within 4 weeks before participation in the study; immunocompromise (eg, lymphoma, AIDS,Wiskott-Aldrich syndrome) or uncontrolled malignant disease; a history of lymphoma, lymphadenopathy, active vulvar herpes, olluscum, or condyloma; systemic or generalized infections (bacterial, viral, or fungal); a diagnosis of other vulvar dermatoses or carcinoma; a diagnosis of diabetes mellitus or Netherton syndrome; nursing mothers; known hypersensitivity				both the total score on the IGA (P = .001) and all 3 subscales (severity of disease, P = .001; lichenification, P = .001; and ulceration, P = .025). adverse events: Serum levels of pimecrolimus and clobetasol did not approach pre-established cut-off levels for safety at any point during the study period. In addition, none of the serum laboratory parameters changed significantly during the study period. No adverse events were reported and no herpetic events occurred.	

		to pimecrolimus or clobetasol or any of the components of the creams; severe medical conditions that, in the view of the investigator, prohibited participation in the study; and a history of substance abuse or any factor that would limit the participant's ability to cooperate with the study procedures. <u>N total at baseline</u>: 38 Intervention: 18 Control: 20 <u>Important prognostic factors</u>[1]: Groups comparable at baseline? yes					

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Borghi 2017	Type of study: single-center, retrospective, open label, nonrandomized, comparative cohort study Setting: single center Country: Italy Source of funding: no external:	Inclusion criteria: Adult female patients with a clinical and, when available, histological diagnosis of VLS treated between April 2015 and April 2016 at our Vulva unit were retrospectively evaluated for inclusion in the present study. In those not submitted to histological confirmation, the diagnosis of VLS was clinically evident beyond any doubt. Exclusion criteria: clinical or histological features showing possible resemblance with other diseases, such as lichen planus or plasma cell	Describe intervention (treatment/procedure/test): Tretinoin 0.05% cream in short contact therapy in the morning and mometasone furoate 0.1% ointment in the evening for 5 consecutive days a week for 12 weeks. Tretinoin cream was washed off with water after 1 h. .	Describe control (treatment/procedure/test): Cold cream in the morning and MMF in the evening for 5 consecutive days/week for 12 weeks	Length of follow-up: 12 weeks Loss-to-follow-up: I: n=3 (1 lost to follow up, 2 discontinued due to side effects) C: n =1 Incomplete outcome data: Patients were excluded from the study if any single data necessary for our analysis was incomplete.	Outcome measures and effect size (include 95%CI and p-value if available): Responders (score ≤3 for each subjective symptom that could be evaluated and a GOS ≤3): I: 13 patients (75.2%) C: 15 patients (78.9%) OR 0.6933 (95%CI from 0.1532 to 3.1388) (p=0.505) GSS75 (max 20, summing each symptom parameter): I: n=8 (50% because 2 pt were asymptomatic at baseline and 3 dropped out) C: 15 (100%, 4 were asymptomatic at baseline and 1 dropout).	Retrospective Not randomized, not blinded. Outcome assessors not blinded

		vulvitis; lack of agreement between clinical and histological features; systemic and/or topical VLS treatments during the 4 weeks before starting the study treatment; treatment regimens other than those assessed in the present survey; use of additional treatments, including cosmetics, expected to relieve VLS, throughout the study duration; active vulvar infectious diseases or vulvar dermatoses or carcinoma. Pregnant patients as well as those with known hypersensitivity to any component of the study drugs, confirmed by patch tests, were not treated with the study actives. Patients were excluded from the study if any single data necessary for our analysis was incomplete.				The rate of patients achieving GSS75 was significantly higher among patients belonging to group B compared with those in group A (p=0.0024, Fisher's test) GOS75 (max 9, summing scores 0-3 leukoderma, hyperkeratosis, pupuric lesions and excoriations): I: n=11 (61.1%) C: n=12 (63.1%) Not stat sign different. Safety: Local side effects I: n=6 (30%) C: n=2 (15%) The occurrence of side effects in group A was higher when compared with that of patients in group B (odds ratio 3.6429, 95% CI 0.6332–20.9569), without significant differences (p¼.147, Fisher's test).	

		N total at baseline: Intervention: 21 Control: 20 Important prognostic factors[1]: Groups comparable at baseline? yes				Treatment satisfaction: very satisfied: I: n=9 (45%) C: n=13 (68.4%) (odds ratio 2.648, 95%CI 0.7157–9.7986, p=0.145). Symptom scores: table 2.	

Calcipotriol

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Gupta 2005	Type of study: Open label trial, letter Setting: single center Country: India Source of funding:	Inclusion criteria: Genital LS (histopathologically confirmed) Exclusion criteria: N total at baseline: 23 Intervention: Control: Important prognostic factors[1]: Male: n=15 Female: n=8 Groups comparable at baseline? Yes	Describe intervention (treatment/procedure/test): Calcipotriol ointment 0,005% once a day for the first week, if no irritation occurred twice a day thereafter. Max 15 g /month 16 weeks 2 weeks wash out of previous treatment.	Describe control (treatment/procedure/test): -	Length of follow-up:16 weeks Loss-to-follow-up: 0 Incomplete outcome data: 0	Outcome measures and effect size (include 95%CI and p-value if available): The total sign score: adding the scores of depigmentation, sclerosis, and erosions. Score 0-3, after 16 weeks: Male: mean 2.5 Female: mean 2.0 Total symptom score: itching, soreness, and dyspareunia (women)/difficulty	Female group n=8 Results presented for male and female pt separately

		Unclear how many men were circumcised.				in retracting prepuce (men), score 0-3: male: 1.6 female: 1.8 Three patients (all uncircumcized men) reported lesional irritation and erythema within the first two weeks. These patients were successfully re-started on therapy after a brief discontinuation; however, they were advised to apply smaller amount of ointment.	

Onderhoudstherapie

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Corazza 2016	Type of study: Open label trial Setting: **extended** single-centre, open-label,	Inclusion criteria: judged as responders by the end of the 12-week active treatment phase (ATP) study (Virgili 2014) Exclusion criteria:	Describe intervention (treatment/procedure/test): Clobetasol propionate (CP) 0.05% ointment twice weekly during 52 weeks	Describe control (treatment/procedure/test): Mometasone furoate (MMF) 0.1% ointment Twice weekly during 52 weeks	Length of follow-up: 52 weeks Loss-to-follow-up: I: n=2 drop outs	Outcome measures and effect size (include 95%CI and p-value if available): VAS itching:	Follow up study Virgili 2014 Small sample size Open label Not double blind

	comparative trial conducted between June 2012 and July 2014 Country: Italy Source of funding: unclear.	Non responders from ATP study Virgili 2014 <u>N total at baseline</u>: 48 Clobetasol group: 24 Mometason group: 24 (= ITT population) <u>Important prognostic factors</u>[1]: *All enrolled patients entered this study directly after the previous trial, with no interruption in their treatment.* Groups comparable at baseline? Yes according to the authors. No large differences between groups (table 1).	Application on previously affected vulvar areas. No additional treatment nor cosmetics was allowed.		C: n=2 drop outs <u>Incomplete outcome data</u>: -	Baseline: I: n=11, mean 1.08 (1.25) C: n=6, mean 0.87 (2.01) At 52 weeks (0-10): I: n=8, mean 1.09 (SD 2.21) C: n=9, mean 1.18 (SD 2.21) VAS burning (0-10): Baseline: I: n=7, mean 0.06 (1.42) C: n=4, mean 0.54 (1.41) At 52 weeks: I: n=8, mean 1.04 (SD 2.18) C: n=6, mean 1.09 (SD 2.29) Global subjective score (GSS, 0-20): Baseline: I: n=12, mean 1.92 (2.25) C: n=7, mean 1.41 (2.53) At 52 weeks: I: n=10, mean 2.14 (SD 4.24) C: n=10, mean 2.18 (SD 4.27) GSS change at 52 weeks: I: mean 0.22 (2,79)	Per protocol analyses

						C: mean 0.77 (2.71) Global objective score (GOS, 0-12): Baseline: I: n=20, mean 1.54 (1.08) C: n=18, mean 1.54 (1.32) At 52 weeks: I: n=13, mean 1.27 (SD 1.74) C: n=11, mean 1.04 (SD 1.56) GOS change at 52 weeks: I: mean -0.27 (1.09) C: mean -0.50 (0.94) No sign differences between groups. Relapse (arbitrarily defined by a score ≥5 for at least one evaluable symptom and/or a score = 3 for any of the 4 signs considered reversible): I: n=2 (8.33%) C: n=1 (4.17%) P=1, RR=2 (95% CI 0.1940-20.6149)	

						The mean time to relapse was 30 weeks (range 20–38, median 32 weeks) (no difference between groups) Satisfaction: N=3 (relapsing patients were dissatisfied.) Safety: no side effects.	
Virgili 2013 BJD	Type of study: randomized, parallel-group, open-label, comparative study Setting: conducted between December 2009 and May 2012 at the Vulva Unit of the Dermatology Section of the University of Ferrara Country: Italy Source of funding: unclear	<u>Inclusion criteria</u>: clinical and, when available, histological diagnosis of VLS At 12 weeks after treatment with mometasone, patients who achieved both a score < 3 for each evaluable subjective symptom and a global OS ≤4 were judged as 'treatment responsive' and were eligible. <u>Exclusion criteria</u>: systemic treatment with steroids, retinoids or hormonal replacement therapies and oestroprogestinic drugs during the 4 weeks before enrolment; treatment with topical therapy	Describe intervention (treatment/procedure/test): proactive, twice-weekly application of mometasone furoate 0.1% ointment after 12 weeks of treatment with topical corticosteroid (mometason) (open label active phase study)	Describe control (treatment/procedure/test): Daily pure topical 100% vitamin E oil (tocopherol acetate, Vea Olio; Hulka, Rovigo, Italy) or Cold cream once daily (a dermatological oil-in-water emulsion containing white petrolatum, cetearyl alcohol, paraffinum liquidum, water, propylene glycol and ceteareth-20)	<u>Length of follow-up</u>: 52 weeks <u>Loss-to-follow-up</u>: Mometasone: n=1 <u>Incomplete outcome data</u>: Relapsing patients continued with daily application of topical steroid (total n=10) VAS displayed for non-relapsing patients only GSS and GOS not reported.	Outcome measures and effect size (include 95%CI and p-value if available): VAS burning (0-10, lower is better) VAS itching VAS dyspareunia (when applicable) Global subjective score (GSS, summing each VAS score, max 30): not reported. Global objective score (GOS: sum clinical parameters erythema, leukoderma, sclerosis scarring, hyperkeratosis,	Computer-generated simple randomization schedule Objective and subjective patient assessment was performed by the same two investigators (A.V. and M.C.), not blinded to treatments, at baseline and at all successive 12-week-interval visits. Very small number of patients per group. Incomplete outcome data. Similar efficacy results were found in the PP population.

		(e.g. corticosteroids, tacrolimus, pimecrolimus, hormonal therapy) at the affected area during the 4 weeks before enrolment; hypersensitivity to any component of the study drugs; active vulvar infectious diseases or vulvar dermatoses or carcinoma; pregnancy or breastfeeding. <u>N total at baseline</u>: 25 Mometasone: 8 Vit E: 9 Cold cream: 8 (=ITT population for efficacy analyses) <u>Important prognostic factors</u>[1]: *age ± SD:* *60.53 +/- 11.89* Groups comparable at baseline? Lower duration of disease in mometasone group.				purpuric lesions, score 0-4, lower is better): not reported. Relapse (defined by a score ≥ 5 for at least one evaluable subjective symptom and/or a score = 3 for any of the four signs considered reversible. Or any worsening in sclerosis scarring): Mometasone: 0 Cold cream: 5 Vit E: 5 >patients withdrew from study and continued with daily application of topical steroid. The calculation of confidence intervals (CIs) of the odds ratios (ORs) shows that mometasone furoate 01% twice a week protects from relapse (OR = 0.0951, 95% CI 0.0177–0.5106). Time to relapse:	

						Relapses were observed during the first 6 months of maintenance therapy in 80% of cases (8/10), while only two patients (20%) experienced the relapse in the course of the second semester of the MP. The median time to relapse was 216 weeks for patients in both the vitamin E and cold cream groups. Patient satisfaction (interview, convenient or inconvenient): patients in the proactive corticosteroid maintenance group were found to be more satisfied with treatment (seven out of eight patients) than those in the vitamin E and cold cream groups (eight of seventeen patients), even	

						though the difference did not reach statistical significance (P = 0.0967, Fisher's test). Safety: No side effects	
Virgili 2013 EJD	Type of study: Randomized, open-label study Setting: single centre, 2002-2010 Country: Italy Source of funding: not stated. No conflicts of interest.	Inclusion criteria: VLS Exclusion criteria: systemic treatments with steroids, hormones or retinoids within 4 weeks before enrolment in the study, treatment with topical therapy (e.g. corticosteroids, tacrolimus, pimecrolimus) on the affected area within 4 weeks before enrolment, hypersensivity to any component of the study drugs, active vulvar herpes, molluscum or condiloma, diagnosis of other vulvar dermatoses or carcinoma, pregnancy and breast-feeding. N total at baseline: 80 Vit E: 36 Emollient: 44	Describe intervention (treatment/procedure/test): 12-week active treatment phase on topical 0.1% mometasone furoate ointment once daily. Vitamin E (pure tocopherol acetate, VEA oil® Ulka, Rovigo, Italy) Once daily	Describe control (treatment/procedure/test): Emollient (cold cream) once daily	Length of follow-up: 52 weeks Efficacy was assessed every 12 weeks. Loss-to-follow-up: ATP: 76 subjects did not enter this second phase of the study, in 27 cases (35.5%) due to an unsatisfactory therapeutic outcome of the topical corticosteroid treatment. 49 patients (64.5%) dropped-out at the first stage of the study as they did not come to the 12-week	Outcome measures and effect size (include 95%CI and p-value if available): Global subjective score (sum VAS itching, burning, dyspareunia, max 30): not reported IGA (clinical response vulvar signs; 1) total healing (complete resolution of all reversible signs), 2) almost total healing, 3) partial healing, 4) no change, or 5) worsening.): not reported. Relapse rate at 52 weeks (any worsening in clinical features and/or symptoms requiring a new treatment course	Clinical assessments were performed and recorded by the same investigators (AV and MC) at baseline and at all successive visits. computer-generated simple randomization schedule open label study > high RoB Large number of patients were lost to follow up Incomplete outcome data: VAS scores after 52 weeks and global subjective score/IGA not reported.

		Active treatment phase: n=156 At 12 weeks, patients who achieved a symptomatological VAS global score ≤5/30 and an IGA score ≤2 (total or almost total healing) were judged as "treatment responsive" and were eligible for the MP → n=80 <u>Important prognostic factors</u>[1]: *Considering the demographics and clinical features of the dropped-out patients in comparison with those who had completed the study or experienced a relapse, the two groups did not differ in age (P = 0.9), severity of symptoms, such as itching (P = 0.6) and burning (P = 0.06), at the beginning of the maintenance phase, or place of residence (inside versus outside the city) (P = 0.18).*			control visit at the end of the AP. MP: At 26 weeks: Vit E: n=16 (44.4%) Emollient: n=18 (40.9%) At 52 weeks: Vit E: n=2 Emollient: n=6 <u>Incomplete outcome data</u>: VAS scores after 52 weeks and global subjective score/IGA were not reported.	with topical corticosteroids were arbitrarily considered relapse): vit E: n=4/12 (33.3%) emollient: 3/13 (23%) (p=0.7) Cumulative crude relapse rate = ITT: vit E: n=10/36 (27.8%) emollient: 10/44 (22.7%) Time to relapse: vit E: median 20 weeks emollient: median 18.7 weeks	
Lee 2015	Type of study: Prospective longitudinal cohort study Setting: Private practice	<u>Inclusion criteria</u>: age older than 18 years, biopsy-proved VLS, and having been followed up for a minimumof 2 years	Describe intervention (treatment/procedure/test): Initial treatment regimens were individualized, with the	Describe control (treatment/procedure/test): -	<u>Length of follow-up</u>: at least 2 years; every 3 to 6 months for the first 2 years	Outcome measures and effect size (include 95%CI and p-value if available):	To detect a decrease to 1.0% incidence of VSN in the compliant group compared with the partially compliant group

	Country: Australia Source of funding: Dermatology Department of Royal North Shore Hospital	Exclusion criteria: not mentioned. N total at baseline: 507 Important prognostic factors[1]: 158 (31.2%) patients were premenopausal, 307 (60.6%) were postmenopausal and not using hormone therapy, and 42 (8.3%) were postmenopausal and using either topical or systemic hormone therapy most pt had mild to moderate disease. Severe disease: n=151 (29.8%) Groups comparable at baseline?	target outcome being an objective return of the vulvar skin to normal color and texture. Patients were initially treated with a single TCS agent, applied daily, to achieve symptom control. Betamethasone dipropionate: 325 (64.1%) methylprednisolone aceponate: 156 (30.8%) Clobetasol: 17 (3.4%) hydrocortisone: 9 (1.8%) Once disease and symptom suppression had been achieved, long-term preventive management was initiated. A gradual reduction of TCS potency, titrated to the clinical response, was attempted in all patients. Treatment was outcome based, with the target being as close as possible to normal skin color and texture. As long as there were no adverse effects, this treatment was maintained. If atrophy or corticosteroid dermatitis developed, the potency of the TCS was reduced. If hyperkeratosis returned, the potency of		and then at least yearly mean duration of follow-up for all patients was 4.7 years (range, 2.0-6.8 years) Loss-to-follow-up: - Incomplete outcome data: -	Patients were considered compliant if they self-reported that they followed treatment instructions “most of the time” or “all of the time” and partially compliant if they self-reported that they followed treatment instructions “some of the time,” “little of the time,” or “none of the time,” Compliant pt: n=357 (70.4%) Non-compliant pt: n=150 (29.6%) Development SCC: Compliant pt: 0 Non-compliant pt: n=7 (4.7%) (p<0.001) Suppression of symptoms (itching, pain): Compliant pt: n=333 (93.3%) Non-compliant pt: n=87 (58%) (p<0.001) Adhesions and scarring: Baseline: Structural changes in the	with 80% power at 5% significance, we required a total of 504 patients

			the TCS was increased. Patients used the treatment at least 3 times per week. For patients with very severe disease, a potent to superpotent TCS was used daily.			vulvar architecture were found in approximately half the patients (262 [51.7%]) at presentation (173 [48.5%] compliant vs 89 [59.3%] partially compliant; P = .03); After follow up: Compliant pt: n=12 (3.4%) Non-compliant pt: N=60 (40%) (p<0.001) Side effects: Atrophy: Compliant pt: n=4 (1.1%) Non-compliant pt: n=3 (2%) P=0.43 Corticosteroid dermatitis: Compliant pt: n=8 (2.2%) Non-compliant: n=6 (4%). P=0.37	
Cooper 2004	Type of study: Descriptive cohort study Setting: single centre Country:	<u>Inclusion criteria</u>: In women, diagnosis was based on the typical clinical appearances of VLS plus confirmatory histologic	Describe intervention (treatment/procedure/test): Women: Clobetasol: 208 (89%) Clobetasone butyrate: 10 (4%)	Describe control (treatment/procedure/test): -	<u>Length of follow-up</u>: Every 3 months mean follow-up time for women and	Outcome measures and effect size (include 95%CI and p-value if available):	Outcomes were reported for all women in total, not adjusted per type of topical steroid. Unclear how long patients used

	England Source of funding: unclear	studies; in girls, it was based on typical clinical appearances alone. Childhood onset of disease was defined as onset of symptoms prior to menarche and a definite diagnosis at or before the age of 16 years. <u>Exclusion criteria</u>: Unclear <u>N total at baseline</u>: 327 <u>Important prognostic factors</u>[1]: *Women: 253* *Girls: 74* None of the 74 girls (23%) had reached menarche, and 55 (17%) of the women were in their reproductive years and 194 (60%) were postmenopausal. Groups comparable at baseline?	Betamethasone: 7 (3%) Beclomethasone dipropionate: 7 (3%) No topical steroid: 1 Most patients were given topical steroid for intermittent maintenance selftreatment after the initial treatment period.		girls was similar (65 vs 69 months). <u>Loss-to-follow-up</u>: - <u>Incomplete outcome data</u>: Reported response of symptoms to topical treatment was available for 255 patients, 36 girls and 219 women. Response of the vulvar physical signs to treatment was determined in 253 patients, 36 girls and 217 women.	Symptomatic response: good (symptomfree status reached during the treatment); partial (improvement and/or partial resolution of individual symptoms); or poor (no change or worsening): symptom free: 142 women (65%) partial: 67 women (31%) poor: 10 women (5%). Response of vulvar signs: total (complete resolution of all signs and return to normal color and texture—architectural changes, of course, remained); partial (complete resolution of purpura, hyperkeratosis, fissures, and erosions, but persistence of pallor or textural change); minor	which topical steroid. Most patients were given topical steroids for intermittent maintenance selftreatment after initial treatment period.

						(partial resolution of some signs); or poor (no change or worsening). Total resolution: 50 women (23%) Partial resolution: 149 women (69%) Minor resolution: 14 women (6%) No improvement: 4 women Thirteen women had undergone surgical treatment (the Fenton procedure) for introital stenosis. SCC: VIN: 4 SCC: 6 SCC on grade 3 VIN: 1	
Renaud-Vilmer 2004	Type of study: Prospective study Setting: 1981-2001 Country: France Source of funding:	Inclusion criteria: aged 20 years and older who had VLS and attended the vulvar clinic of the Hopital Saint-Louis Department of Dermatology, Paris, France, between January 1981 and June 2001. The lesions had to be confirmed histologically and were not to have been previously treated.	Describe intervention (treatment/procedure/test): 0.05% clobetasol propionate ointment, once daily for 3 months and then 3 times per week until complete remission. The treatment was ended only when CR was obtained. In the absence of remission after 12 to 18 months, the frequency of applications was	Describe control (treatment/procedure/test): -	Length of follow-up: Median 4.7 years Loss-to-follow-up: N=4 Incomplete outcome data:	Outcome measures and effect size (include 95%CI and p-value if available): Remission Complete (Complete remission was defined clinically as an absence of clinical signs of VLS (ie, no pruritus and a regression	

		Exclusion criteria: N total at baseline: 83 Important prognostic factors[1]: *mean age was 59.4 years (range, 30-92 years)* Groups comparable at baseline?	gradually tapered to twice per week.			of white and sclerotic lesions), and histologically as the disappearance of the infiltrate and hyalinized collagen in the dermis (with the persistence of a slight, mostly subepidermal fibrosis with some improvement of the elastic network): n=45 54%) Relapse incidence rate (clinically as new VLS lesions (areas of pallor with or without pruritus or pain), and histologically when histologic examination showed the reappearance of hyalinized foci of collagen with decreased numbers of elastic fibers with or without lymphocyte infiltrate): 50% at 16 months (95% confidence interval, 30%-64%)	

						84% at 4 years (95% confidence interval, 57%-94%). Development SCC: N=8 (9.6%) (6 at presentation without treatment until presentation) Adverse events: In 2 cases, treatment was interrrupted for 1 month because of local inflammation due to steroid application, and then resumed	
Simonart 2008	Type of study: Prospective open trial Setting: 1995-2006 Country: Belgium Source of funding: unclear	Inclusion criteria: Vulvar LS with typical appearance plus confirmatory histologic studies. No previous treatment. Exclusion criteria: Not reported. N total at baseline: 34 Important prognostic factors[1]: *All patients are postmenopausal* Groups comparable at baseline?	Describe intervention (treatment/procedure/test): 1 month of treatment with topical betamethasone valerate once daily followed by maintenance therapy with moisturizer (cold cream) once daily only	Describe control (treatment/procedure/test): -	Length of follow-up: After 1 month end then twice per year median follow-up time was 58 months (range, 12-139 m) Loss-to-follow-up: N=9 Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): After 1 month active therapy: N=24 symptom free N=10 partial response. Symptoms: Pruritus: Baseline: n=24 End of follow up: n=3 Pain: Baseline: 9	Symptoms and signs reported for all patients with different durations of follow up. Not only effect from moisturizer, also from previous used betamethasone

						End of follow up: 2 Response at last follow up visit (good: symptom-free status reached during treatment; partial: improvement and/or partial resolution of individual symptoms; poor: no change or worsening) total n=34 after therapy with a topical steroid once daily for 1 month. Twenty-four (71%) became symptom free, and 10 (29%) experienced partial response. Among the 24 women who became symptom free, 18 remained symptom free while treated with an emollient cream alone. Among the 10 women who exhibited a partial response, 6 reported no worsening of their symptoms while	

						treated with a cold cream alone. Response of the vulvar signs (total: complete resolution of all signs and return to normal color and texture; partial: complete resolution of erythema, purpura, hyper-keratosis, and fissures but persistence of pallor and textural changes; no change; or worsening) after 1 month betamethasone: total resolution: n=6 (18%) partial resolution: n=22 (64%) no change: n=6 (18%) Compliance (total n=18, self-reporting): Compliant: n=12 Partial: n=6 Noncompliant: n=0 Safety: No adverse events No SCC.	

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Bousema 1994	Type of study: RCT Setting: 5 centres Country: Netherlands, France, Turkey, Finland Source of funding: Roche International Clinical Research Center, Strasbourg, France.	Inclusion criteria: Women, 18 to 80 years of age, with severe, histologically confirmed LSA of the vulva. The disease had to be present for at least 3 months before entry into the study and refractory to previous treatment. Women of childbearing potential were included only if the pregnancytest before participation was negative and if they agreed to use an effective contraceptive method during and for at least 2 months after termination of treatment. During the study, the posttherapy contraception period was extended to 2 years because of new findings on the possible metabolic conversion of acitretin into etretinate. Exclusion criteria:	Describe intervention (treatment/procedure/test): acitretin (30 mg) once daily for 16 weeks. After 4 weeks, the dose could be reduced to 20 mg in case of adverse reactions. only emollient ointments and nonalkaline anti-septics were allowed for local treatment during the study.	Describe control (treatment/procedure/test): Placebo 1dd, identical capsules	Length of follow-up: 16 weeks The standard efficacy population included patients with more than 12 weeks of treatment and patients who had stopped treatment before this time point because of lack of efficacy. All 78 patients were included in the tolerability evaluations as well as in the overall assessment of treatment.	Outcome measures and effect size (include 95% CI and p-value if available): Symptoms: improvement at least one grade (scale 0-3, lower is better): Pruritus: I: 22 (100%) C: 19 (79%) (P<0.05) Burning: I: 18 (100%) C: 17 (85%) (non-significant) Signs (scale 0-3, lower is better): improvement at least one grade; Atrophic features: I: 19 (86%) C: 13 (54%) (P<0.05) Hyperkeratotic features: I: 16 (76%) C: 6 (27%) (P<0.05) Secondary features: I: 12 (57%)	Small number of patients Method of randomization not mentioned. (study not in clinical trial registry) Randomization was performed before inclusion criteria were checked. >high RoB High number of drop outs; efficacy population without pt who followed <12 weeks of treatment and pt who stopped because of lack of efficacy. This might influence the efficacy scores. Unclear if the 26 patients with dose reduction were in efficacy analyses

		severe hepatic, renal, cardiovascular, metabolic (hypertriglyceridemia or hypercholesterolemia), or neurologic disease. <u>N total at baseline</u>: 78 25 pt did not meet inclusion criteria for required intensity. I: 39 C: 39 Efficacy population: I: 22 C: 24 Patients were randomly allocated. <u>Important prognostic factors</u>[1]: *Of these 78 women, 58 were postmenopausal.* Groups comparable at baseline? Yes			<u>Loss-to-follow-up</u>: 12 did not complete the study: seven because of adverse reactions, two (receiving placebo) because of insufficient therapeutic response, two patients refused to continue, and one patient receiving acitretin did not appear at the week 16 visit <u>Incomplete outcome data</u>: Signs and symptom scores were only displayed if the parameter was present at baseline.	C: 9 (39%) (non-significant) Responder: defined as a patient who showed a decrease of at least two grades in one of the symptoms (pruritus or burning), without any worsening in any other symptom, a decrease of at least one grade in two of the signs (atrophy, hyperkeratosis, and secondary features) without any worsening in the other sign, and no increase in the extent of the lesions: I: n=14 (64%) C: n=6 (25%) <u>Adverse events:</u> No of pt who experienced at least one adverse event: I: 100% C: 56% Cheilitis and dry skin were noted in all patients who had received acitretin and in one third of patients who received	

						placebo. The most bothersome adverse reaction that occurred in the acitretin-treatment group was severe peeling of the palms and the sales (11 patients). The frequency of increased hair loss was higher in the acitretin-treatrnent group (23 patients) than in the placebo-treatment group (2 patients). 6 pt stopped treatment in acitretin group due to AEs: Abnormal hepatic tests (n=1), hypertriglyceridemia (n=1), abdominal pain (N=1), dizziness (n=1), hemorrhoidal pain (n=1), increased hair loss (n=1). 1 pt stopped placebo treatment due to AEs: hypertriglyceridemia The daily dose had to be reduced in 26 patients in the acitretin-treatment group	

						and in three patients in the placebo-treatment group. <u>Treatment satisfaction</u> (scale completely satisfied, partially satisfied, not satisfied, not done): no pt completely satisfied: I: 15 (38%) C: 7 (18%)	
Ioannides 2010	Type of study: RCT Setting: two centres Country: Greece Source of funding: not mentioned.	<u>Inclusion criteria</u>: histologically confirmed, severe genital LS, resistant to topical treatment with ultra potent steroids (at least 1 therapeutic cycle of 3 months) and age older than 18 years. Severe LS was arbitrarily defined as a TCS of 9 or greater <u>Exclusion criteria</u>: renal or hepatic function impairment, alcohol consumption, metabolic disorders (intractable hyperlipidemia, diabetes mellitus), history of pancreatitis and hypervitaminosis A. Patients on medications	Describe intervention (treatment/procedure/test): Acitretin 35 mg 1dd for 20 weeks Topical emollient was allowed. All previous medications for LS were discontinued at least 30 days before baseline	Describe control (treatment/procedure/test): Placebo capsules identical in size and color to the acitretin.	Length of follow-up: 36 weeks <u>Loss-to-follow-up:</u> Intervention: N=1 (surgical treatment) Control: N=1 (underwent surgical treatment) <u>Incomplete outcome data:</u> The withdrawn pt were not included in analyses.	Outcome measures and effect size (include 95%CI and p-value if available): Complete response: I: N=12 (33%) C: N=1 (6.3%) Total clinical score (TCS represented the sum of 6 different rates which were the result of the assessment of 3 individual parameters (symptoms, signs, extent of lesions); range 0-18. Mean (SD) at baseline: I: 9.39 (0.747) C: 9.25 (0.577)	Bias during clinical evaluation considering the expected side effects of acitretin. Blinding: Same masked physician recorded disease severity at every visit. An individual not involved in the trial performed randomization using a computer generated randomization scheme. The control group received placebo capsules identical in size and color to the acitretin.

		that interact with retinoids or interfere with the immune system were also excluded from study. <u>N total at baseline</u>: 51 Intervention: 34 Control: 17 A total of 49 patients (33 of the acitretin and 16 of the controls) completed the study and were eligible for statistical analysis. <u>Important prognostic factors</u>[1]: *Patient age was between 39 and 74 years (mean SD 56.56 -11.419) for the control group, and between 38 and 75 years (57.79 - 10.585) for the treatment group.* Groups comparable at baseline?				Mean at 16 weeks: I: 4.55 (SD 3.969, 95% CI 3.14–5.95). C: 9.25 (SD 1.732, 95% CI 8.33–10.17) Mean at 20 weeks: I: 4.55 (SD 3.969, 95% CI 3.14–5.95). C: 9.31 (SD 3.321, 95% CI 7.54 –11.08) Mean TCS of the acitretin group at a 0.05 level of significance was significantly lower than that of the control group at week 20 [t (47) = -4.146, p = 0.00 <0.5]. Quality of life (DLQI): Baseline (mean, SD): I: 12.27 (2.335) C: 11.94 (2.407) 16 weeks: I: 8.12 (2.619) C: 11.13 (2.277) 20 weeks:	Small number of pt

						I: 6.76 (SD 3.913, 95% CI 5.37–8.15) C: 10.63 (SD 2.482, 95% CI 8.85–2.40) Adverse events: No severe AEs. Total No of AEs for each group not reported.	

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Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Shi 2016	Type of study: open-label, randomized controlled prospective study Setting: single centre Country: China Source of funding: National Natural Science Foundation (81272990,	<u>Inclusion criteria</u>: Age >18 years; biopsy-proven vulvar LS; not planning to conceive or breastfeed during the study; consent to participate and willingness to comply with the study requirements <u>Exclusion criteria</u>:	Describe intervention (treatment/procedure/test): Freshly prepared 10% 5-ALA cream was applied to the lesions with a 1-cm margin and incubated for 3 h. The lesions were irradiated with 100 J/cm2 633 nm red light at 100 mW/cm2. The same PDT procedure was repeated 3 times at 2-week intervals. (total amount of sessions 4) No other treatments were allowed during	Describe control (treatment/procedure/test): Clobetasol 0,05% propionate ointment every night during 8 weeks	<u>Length of follow-up</u>: 6 months <u>Loss-to-follow-up</u>: Intervention:1 Control: 2 (drop outs due to relocation) Efficacy population: I: n=20 C: n=20 <u>Incomplete outcome data</u>: -	Outcome measures and effect size (include 95%CI and p-value if available): Lesion size; horizontal visual analogue scale (VAS) for disease extent (including lesion scale and signs); clinical response to symptoms; severity of	Small sample size Open label All eligible patients were randomized to either ALA-PDT or clobetasol propionate group using sequentially numbered envelopes. The random sequence in the envelopes was produced by computer programme. The sequentially numbered opaque envelopes were opened only

	81472538) and the Key Project of Shanghai Municipal Commission of Health and Family Planning (20124034).	subjects who received systemic or local treatment within the past 6 months, those diagnosed with other vulvar dermatoses or carcinoma, and those hypersensitive to clobetasol propionate, ALA or any of the components of the ointments <u>N total at baseline</u>: 43 Intervention: 21 Control: 22 <u>Important prognostic factors[1]</u>: Mean age 51.4 ± 15.6. N=28 postmenopausal Groups comparable at baseline? Yes according to the authors.	the treatment and follow-up.			treatment related pain. Lesion size reduction (week 8 after start treatment) Complete response (VAS) (complete response=100% lesion disappeared; partial response = >60% lesion clearance; minimal response =20–59% lesion clearance; and poor or no response =<20% clearance): I: 14/20 (70%) patients complete response, 4 (20%) partial response, 2 (10%) minimal response. C: 7/20 (35%) complete response, 6 (30%) partial response, 7 (35%) minimal response. Clinical signs:	after each patient agreed to participate. Evaluations were performed by the same examiners, who did not know which treatment was received by patients.

						The severity of clinical signs of hyperkeratosis, atrophy, sclerosis, and depigmentation were each graded as: 0=absent, 1= mild, 2=moderate, 3=severe): baseline: hyperkeratosis: I: 0 (n=4), 1 (n=13), 2 (n=3), C: 0 (n=3), 1 (n=12), 2 (n=3), 3 (n=2) Atrophy: I: 1 (n=7), 2 (n=11), 3 (n=2) C: 1 (n=9), 2 (n=10), 3 (n=1) Sclerosis: I: 1 (n=7), 2 (n=9), 3 (n=4) C: 1 (n=7), 2 (n=12), 3 (n=1) Depigmentation: I: 1 (n=7), 2 (n=11), 3 (n=2) C: 1 (n=8), 2 (n=11), 3 (n=1) week 8: hyperkeratosis: I: 0 (n=20) C: 0 (n=15), 1 (n=5) Atrophy: I: 0 (n=19), 1 (n=1)	

						C: 0 (n=13), 1 (n=7) Sclerosis: I: 0 (n=18), 1 (n=2) C: 0 (n=12), 1 (n=8) Depigmentation: I: 0 (n=14), 1 (n=6) C: 0 (n=7), 1 (n=13) 6 months: Hyperkeratosis: I: 0 (n=18), 1 (n=2) C: 1 (n=18), 2 (n=2) Atrophy: I: 0 (n=16), 1 (n=4) C: 1 (n=12), 2 (n=7), 3 (n=1) Sclerosis; I: 0 (n=16), 1 (n=4) C: 1 (n=15), 2 (n=5) Depigmentation: I: 0 (n=13), 1 (n=7) C: 1 (n=13), 2 (n=4), 3 (n=3) The severity of symptoms (pruritus, burning and pain feeling) was also graded as: 0 = absent, 1 = mild, 2	

						=moderate, 3 = severe): baseline: I: score 1 (n=5), score 2 (n=10), score 3 (n=5) C: score 1 (n=4), score 2 (n=15), score 3 (n=2) week 8: I: score 0 (n=14), score 1 (n=5), score 3 (n=1) C: score 0 (n=7), score 2 (n=11), score 3 (n=2) month 6: I: score 0 (n=13), score 1 (n=4), score 2 (n=3) C: score 1 (n=2), score 2 (n=10), score 3 (n=8) (p=0,000) Relapse: I: 1/14 (7.1%) patients with signs of recurrence 1 month after completion of treatment C: 7/7 (100%) Adverse events: I: n=1 erosion, successfully treated with mupirocin ointment; n=5	

						redness and swelling which faded away C: none	
Hillemans 1999	Type of study: Prospective single arm pilot study Setting: Country: Germany Source of funding: grant from the Friedrich Baur Stiftung.	Inclusion criteria: Biopsy-proven vulvar LS; pronounced pruritus; without taking any medication for LS no malignancies; no cardiovascular disease or diabetes; patients not preferred corticoid therapy Exclusion criteria: - N total at baseline: 12 Important prognostic factors[1]: *Mean age 55 yrs (range 24-80)* Groups comparable at baseline?	Describe intervention (treatment/procedure/test): Four to 5 hours before photodynamic therapy, 10 mL of a 20% solution of 5-aminolevulinic acid was applied topically to the vulva. Photodynamic therapy was administered with an irradiation of 80 J/cm2 at an irradiance of 40–70 mW/cm2. Light with a wavelength of 635 nm was delivered by an argon ion–pumped dye laser. Patients with persistent pruritus were offered a second cycle of photodynamic therapy after 1–3 weeks. 2 cycles; n=2 3 cycles; n=1 1 cycle: n=9	Describe control (treatment/procedure/test):	Length of follow-up: 6 months Loss-to-follow-up: Unclear Incomplete outcome data: Unclear	Outcome measures and effect size (include 95%CI and p-value if available): Clinical appearance of treated area; local and systemic toxicity and therapeutic effect; VAS for pruritus or burning; symptomatic relief VAS pruritus/burning ((0=no complaints, 1=slight pain, 2= moderate pain, and 3=strong pain). 6-8 weeks: The mean values for pruritus decreased from 2.6 +/- 0.4 to 1.0 +/- 0.6. 6 months; 7 of 10 women still had	Very small sample size Different amount of cycles, results reported for all patients together

						symptomatic relief. Duration of remission: The duration of symptom reduction was 3–9 months (mean 6.1). Adverse events: n=5 mild burning for 4-8 hours after treatment. N=3 treated with iv opioids during treatment N=1 separation of adhesions under general anesthesia	
Mazdziarz 2017	Type of study: Prospective cohort Setting: Single centre Country: Poland Source of funding: unclear	Inclusion criteria: Biopsy-proven vulvar LS; no response to previous therapy with clobetasol propionate (0.05% ointment); patients not preferred corticoid therapy Exclusion criteria: - N total at baseline: 102 Important prognostic factors[1]:	Describe intervention (treatment/procedure/test): 5% 5 - aminolevulinic acid (ALA) was used in gel form, with the 2% concentration of DMSO (dimethyl sulfoxide). After three hours the affected areas were irradiated with a halogenic lamp PhotoDyn 501 (590–760 nm) with power density of 204 mW/cm2, which generates a dose of 120 J/cm2 during a 10-min radiation treatment. The treatment was repeated once-a-week for 10 weeks.	Describe control (treatment/procedure/test): None	Length of follow-up: 3 months (12 months for vulvoscopy) Loss-to-follow-up: - Incomplete outcome data: All patients completed the entire cycle of ten PDT courses.	Outcome measures and effect size (include 95%CI and p-value if available): vulvoscopic evaluation of lichen appearance Patients' assessment of effectiveness of treatment (1. I am very satisfied. I do not experience any discomfort, or I experience	The addition of DMSO facilitates and speeds up transportation (absorption) of the ALA to the deeper layers of skin, which increases the effectiveness of therapy.

		Age average 55.08 (19–85 range): *76 patients (74.50%) were post-menopausal.* 38 patients used clobetasol and achieved a partial remission of disease, but overall they were not satisfied with the final outcome. 15 patients stopped treatment due to the worsening of their symptoms or inflammation. 49 patients refused to use topical corticosteroids.				it sporadically. Photodynamic therapy helped me 100–70%. 2. I am satisfied. My improvement rate is around 50%. PDT helped me 50%. 3. I feel some improvement. PDT has helped me 30%. 4. I am not satisfied. I do not feel any improvement, or my improvement is less than 30%. PDT has not helped me. 5. My condition has worsened after PDT): **At 3 months:** Complete or partial remission: n=89 (87.25%) Score 1: n=62 (60.78) Score 2: n=17 (16.67%) Score 3: n=10 (9.8%) Score 4: n=13 (12.75%) At the 12-month check-up,	

						vulvoscopic assessment did not show any cases of disease progression or transformation into VIN or cancer. 17 patients missed their check-ups. side effects: n=39 paresthesia during therapy n=12 swelling that subsided	
Olejek 2017	Type of study: Prospective cohort Setting: Poland Source of funding: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	Inclusion criteria: diagnosed with Lichen sclerosus (both clinical and histological confirmation) treated without improve-ment at the Outpatient Clinic for Vulvar Diseases, MedicalUniversity of Silesia, Poland. All women signed a written, informed consent Exclusion criteria: - N total at baseline: 100	Describe intervention (treatment/procedure/test): ALA PDT 10-procedures cycle in two-weeks intervals Group 1: At the beginning of the experiment, when patients were hospitalized (40 women), we used DIOMED light source (DIOMED, Andover, USA, 630 nm wavelength) Energy density of light irradiation- 100 J/cm2 at an irradiance of 40–80 mW/cm2	Describe control (treatment/procedure/test): Group 2: when patients were treated on an outpatient basis, women (60 women) were treated with light source PhotoDyn®- combination with either visible light (VIS) + water-filtered infrared A (wIRA)® light (PhotoDyn(®) 750 (PD750), 580–1400 nm Heine.Med GmbH & Co. K G)	Length of follow-up: 24 months Loss-to-follow-up: Incomplete outcome data: All patients completed 10 cycles	Outcome measures and effect size (include 95%CI and p-value if available): Symptoms intensity (0=no, 1=moderate, 2=severe): Before: Group 1: mean 1.77 (SD 0.87) Group 2: mean 1.73 (SD 0.68) After PDT 10 cycles (20 weeks): Group 1: mean 0.6 (SD 0.16) Group 2: mean 0.60 (SD 0.13)	Subgroups based on concomitant autoimmune disease. Only use symptom scores for all patients together.

		Group 1: n=60 without concomitant autoimmune disease; Group 2: n=40 with autoimmune disease <u>Important prognostic factors</u>[1]: the mean age in the group I was 57 yo and the mean age in the group II was 58.5 yo.				Before PDT treatment, 60% of total patients had severe symptoms. After 10 cycles of PDT, 51% of patients was symptoms-free (n=51), 41% (n=41) of patients had decreased symptoms (from severe to moderate or moderate to mild) patients and 8% (n=8) had persistent or worsened symptoms (continuous moderate or severe or from moderate to severe) During 24 months the increased severity of symptoms (itching) in 8% of patients with no symptoms after PDT in first 12 months and 12% of patients with no symptoms after completion of 24 months-	

						obser-vation period. Side effects: No visible side effects.	
Osiecka 2017	Type of study: Prospective cohort Setting: Country: Poland Source of funding: unclear	Inclusion criteria: LS of the vulva confirmed by a routine histopathologic examination. Exclusion criteria: - N total at baseline: 11 Important prognostic factors[1]: *Age 30 to 66 years (mean: 48)* Groups comparable at baseline?	Describe intervention (treatment/procedure/test): after cleansing the area with 0.9% saline solution, 20% 5-ALA (Sigma-Aldrich) in a cream (Nanobase®, Astel-las Pharma) was applied topically on the lesions with a wide margin beyond the affected area, sealed with cellophane wrap and left for 5 h. Then, the vulva was irradiated using the green light at the wavelength 540 nm ± 15 nm from the halogen lamp (Penta Lamps,Teclas) achieved with a bandpass filter each patient was treated with three sessions of PDT at two-week intervals.	Describe control (treatment/procedure/test): -	Length of follow-up: 2,4,6 months Loss-to-follow-up: - Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Appearance of erosions; itching score (Verbal rating score); burning; pain. Baseline: Itching: Moderate: n=4 (36.4%) Severe: n=7 (63.6%) Burning: N=5 (45.5%) Erosions: N=5 (45.5%) Pain: n=3 (27.3%) After 6 months: Itching: Lack: n=7 (63.6%) Weak: n=3 (23.3%) Moderate: n=1 (9.1%) Burning: N=2 (18.2%) Erosions: N=2 (18.2%)	Very small sample size

						Pain: N=2 (18.2%) Side effects: The main symptom during PDT notified by patients was an itching of different intensity. Any reported pain was weak or moderate. No patient required interruption of irradiation or local application of analgesics. Furthermore, immediately after the session of PDT we observed a slight swelling and erythema, which was not a significant side symptom reported by the patients.	
Sotiriou 2008	Type of study: Case series Setting: Country: Greece Source of funding: unclear	Inclusion criteria: N/A Exclusion criteria: - N total at baseline: 10	Describe intervention (treatment/procedure/test): 20% 5-aminolevulinic acid was applied topically to the entire labia and sealed with cellophane wrap. Lesions were treated 4 h after ALA application with red	Describe control (treatment/procedure/test):	Length of follow-up: 2, 4 months Loss-to-follow-up: - Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Total objective score (summing 4 objective parameters	No improvement of LS Inclusion criteria not reported. Very small sample size (case series) Objective score only reported

		Important prognostic factors[1]: *Mean age 54.6 mean disease duration 3.9 years.* *Previous treatments consisted of intermittent topical applications of potent and ultrapotent corticosteroids that lead to temporary improvement. Patients nos. 2, 5, 8, and 9 were also treated with pimecrolimus ointment with no symptom reduction*	light (570–670 nm) by a noncoherent light source (Waldmann PDT 1200, Waldmann-Medizin-Technik, Villingen-Schwenningen, Germany) at a light dose of 40 J/cm2 and a fluence rate of 80 mW/cm2. Each treatment cycle consisted of two sessions of PDT with a 2-weeks interval. .			(hyperkeratosis, atrophy, sclerosis and depigmentation); scale: 0=absent, 1=mild, 2=moderate, 3=severe): baseline: mean 8.05 after 8 weeks: mean 7.1 Subjective score (0=no symptoms, 1= slight pruritus, burning and pain, 2=moderate pruritus, burning and pain, 3=strong pruritus, burning and pain): baseline: mean 2.6 after 16 weeks: mean 1.35 Adverse events: all patients developed erythema for 1 week after therapy. All patients had burning and stinging sensation during irradiation.	after 8 weeks, not after 16 weeks No effect sizes reported of mean values.

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Eshtiaghi 2019	Type of study: SR Setting: - Country: USA Source of funding: not stated. No conflicts of interest.	Inclusion criteria: if they were written in English, published in a peer-review journal, and reported either ADSC or PRP for the treatment of vulvar LS The search strategy combined the terms "platelet-rich plasma" or "adipose-derived stem cells" with "lichen sclerosus" and "vulva*." Exclusion criteria: If not meeting inclusion criteria. N total at baseline: 7 studies between 2010 and 2018 (2 case reports, 5 case series/cohort studies) 98 patients Important prognostic factors[1]:	Describe intervention (treatment/procedure/test): One study used both ADSCs and PRP, 3 studies used ADSCs, and 3 used PRP to treat vulvar LS.	Describe control (treatment/procedure/test): -	Length of follow-up: Range from 2 – 24 months Loss-to-follow-up: - Incomplete outcome data: No meta-analysis was performed	Table 1 Both ADSCs and PRP administration im Proved patient symptoms, quality of life measures, and clinical and histological signs of vulvar LS—many of whom were re ported to be refractory to steroid treatment. However, the quality of the reviewed evidence is weak.	AMSTAR-2 assessment: Low confidence in results of the review: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review? NO Not mentioned if the review authors perform study selection and data extraction in duplicate. No list of excluded studies provided. No RoB assessment performed. No meta analysis performed.

		Studies included mostly postmenopausal women					
Study reference	**Study characteristics**	**Patient characteristics[1]**	**Intervention (I)**	**Comparison / control (C) [2]**	**Follow-up**	**Outcome measures and effect size [3]**	**Comments**
Casabona 2017	Type of study: Retrospective Setting: Single centre Country: Italy Source of funding: unknown	Inclusion criteria: chronic penile LS, failed to improve after at least 6 months of standard topical ultra-potent steroid therapy (clobetasol propionate), or requested an alternative treatment to steroid therapy and/ or circumcision. without systemic disorders (platelet disorders, thrombocytopenia, bone marrow aplasia, cancer), or local disorders (infection, suspicious areas for squamous cell carcinoma) Exclusion criteria: - N total at baseline: 45 Important prognostic factors[1]: *mean age at the first PRP treatment was 42.96 ± 11.32 years*	Describe intervention (treatment/procedure/test): PRP injections A blood sample of 50 ml was drawn from the patient to obtain approximately 5 ml of platelet-rich plasma (PRP). The blood, according to the transfusion service procedure, was centrifuged at 293.475g (1000 rpm for 6 min, centrifuge diameter 52.5 cm) to obtain platelet-poor plasma, followed by a second centrifugation at 2641.275g (3000 rpm for 12 min, centrifuge diameter 52.5 cm) to obtain platelet rich plasma (PRP). Topical anesthetic (lidocaine 2.5% and prilocaine 2.5%)	Describe control (treatment/procedure/test): No control	Length of follow-up: Mean follow-up was 17.60 ± 5.63 months (median: 18; range 12–24). Loss-to-follow-up: None Incomplete outcome data: None	Outcome measures and effect size (include 95%CI and p-value if available): The number of treatments performed on each patient varied from 2 to 10 (median: 4), with an average of 4.38 ± 1.86. The mean interval between two consecutive treatments was about 3 months (94.20 ± 46.64 days), ranged from 40 to 240 days. IGA (6 pt likert scale: = cleared no inflammatory signs; 1 = minimal disease— minimal erythema, infiltration,	Retrospective design with mean follow up Uncontrolled Outcomes also corrected for several patient characteristics Varying number of treatments performed on each patient

		(median: 44; range 17–66 *N=3 underwent previous circumcision*	was applied half an hour before the treatment; 1–2 ml of an anesthetic solution of mepivacaine 2% with adrenaline 1:100.000 was then injected to improve the anesthetic effect and to obtain vasoconstriction (to reduce bleeding and to concentrate the PRP in the infiltration). About 2 cc (range 1–3 cc) of PRP per treatment was injected byp mean of a 30-gauge needle in the affected areas (scar and/ or splitting, depending on the dimension of defect). Before injection, PRP was added with 0.5 ml of CaCl2 to stimulate platelet degranulation and growth factors activation An antibiotic ointment was placed in all the treated areas. The number of treatments to be performed was decided from time to time based on the improvement obtained in each patient.			lichenification, and excoriation; 2 = mild disease—mild erythema, infiltration, lichenification, and excoriation; 3 = moderate disease—moderate erythema, infiltration, lichenification, and excoriation; 4 = marked—marked disease, erythema, infiltration, lichenification, and excoriation; 5 = severe—severe erythema, infiltration, lichenification, and excoriation) The difference in the IGA score before and after PRP treatment (Δ IGA) was 2.04 ± 0.71 (median: 2; range 1–4). The IGA score before PRP treatment was 3.24 ± 0.77 (median: 3; range 2–5); when compared to IGA score post-treatment (1.20 ± 0.69; median: 1;	

						range 0–2), a statistically significant difference ($p < 0.001$) was found DLQI: The difference in the DLQI score before and after PRP treatment (Δ DLQI) was 7.73 ± 4.92 (median: 6; range 2–23). The DLQI score showed a significant reduction ($p < 0.001$) after PRP treatment (1.69 ± 1.20; median: 2; range 0–5), when compared with pre-treatment values (9.42 ± 4.75; median: 7; range 5–25).	

Lichen sclerosus bij kinderen

Jongens

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size [3]	Comments
Kiss 2001	Type of study: RCT Setting: single centre Country: Hungary Source of funding: unclear	Inclusion criteria: Boys with preputial balanitis xerotica obliterans. Exclusion criteria: N/A N total at baseline: 40 Intervention: 20 Control: 20 Important prognostic factors[1]: *Age 5-15 years (mean 8.9)* All patients underwent circumcision after the treatment.	Describe intervention (treatment/procedure/test): Steroid therapy was prepared by mixing 0.1% mometasone furoate ointment with a vehicle for a final steroid concentration of 0.05%. applied by parents once daily for 5 weeks on the tip of the prepuce exposed during gentle retraction.	Describe control (treatment/procedure/test): Vehicle	Length of follow-up: Loss-to-follow-up: I: 3 C: 4 (4 lost to follow up and 3 without biologically confirmed diagnosis) Incomplete outcome data: See above.	Outcome measures and effect size (include 95%CI and p-value if available): Total clinical score after 5 weeks: I: mean decrease from 3.35 ± 0.15 to 2.94 ± 0.18 points (mean decrease=0.41 +/- 0.11) (clinical symptoms improved in 41% of patients with no worsening in remainder) C: mean decrease from 3.00 ± 0.20 to 3.38 ±0.20 points (mean increase=0.38 +/- 0.13) (no improvement, in 31% of cases worsening) Safety: No local or systemic side effects.	Unclear how clinical score was obtained. Randomization procedure not described. Study not in clinical trial registries. Open label?

Vincent 2005	Type of study: Noncontrolled observational study Setting: single centre Country: UK Source of funding: unclear	Inclusion criteria: clinically diagnosed BXO affecting the foreskin with or without glanular involvement using various preparations of randomly chosen topical steroid-based creams for at least 3 months. Because conservative treatment was intended, histological confirmation of the diagnosis could not be established before treatment. However, all were supervised in clinic by the senior author (A.E.M.) and were included in the study on the basis of the typical clinical features of BXO. Exclusion criteria: N/A N total at baseline: 56 Important prognostic factors[1]: *Mean age 8.9 (3-15) years*	Describe intervention (treatment/procedure/test): Application topical steroid 3 times daily. Initial choice: 2.5% hydrocortisone (n=18) Tri-Adcortyl (triamcinolone acetonide 0.1%, neomycin 0.25%, gramicidin 0.025%, and nystatin 100,000U/g) when signs of infection (n=3) 2.5% hydrocortisone and Tri-Adcortyl on alternate weeks (n=29) Later: Betamethasone (n=2) Betamethasone and hydrocortisone on alternate weeks (n=4)	Describe control (treatment/procedure/test): -	Length of follow-up: 3 months Loss-to-follow-up: - Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Clinical resolution: N=10 (18%) Substantial improvement: N=7 (12%), all resolved after further treatment. Minimal improvement: N=10 (18%) No improvement: N=29 (52%) Duration of remission: No relapse was reported after 13-66 (average 33) months.	If there had been significant improvement but not resolution at 3 months, a further period of treatment was offered until resolution had been attained. In case of relapse after resolution: retreatment. Different treatment regimens. Clinical improvement reported for all patients together, not per treatment regimen.

Meisjes

Study reference	Study characteristics	Patient characteristics[1]	Intervention (I)	Comparison / control (C) [2]	Follow-up	Outcome measures and effect size 3	Comments
Anderson 2016	Type of study: Retrospective case series Setting: single centre Country: USA Source of funding: unclear	Inclusion criteria: 18 years of age or younger seen in the Pediatric Dermatology Clinic at Wake Forest School of Medicine Department of Dermatology from January 2005 to January 2010 with a diagnosis of LS treated with clobetasol 0.05% ointment and tacrolimus 0.1% ointment. Exclusion criteria: N/A N total at baseline: 14 Important prognostic factors[1]: *Age 2-10 years* *N=2 with extragenital involvement*	Describe intervention (treatment/procedure/test): clobetasol 0.05% ointment applied to affected mucosa, and, in some cases, carefully to cutaneous areas, twice daily. Bridging: tacrolimus 0,1%once daily on weekdays, Clobetasol twice daily in weekends. If clearance was maintained, clobetasol application was tapered to once daily on weekends. With maintained clearance of lesions, clobetasol application was discontinued and tacrolimus was tapered to once daily on weekends only, and continued through the entire observation period. If the disease flared, patients were	Describe control (treatment/procedure/test): -	Length of follow-up: Varying Loss-to-follow-up: Unclear Incomplete outcome data: Unclear	Outcome measures and effect size (include 95%CI and p-value if available): ‘‘clear’’ when they reported complete relief of symptoms and examination showed no clinical signs of inflammation: complete clearance n=13 (93%) significant clearance of 75% n=1 (7%) Time to complete clearance: 4-156 weeks (average 43.1)	No side effects monitored despite possible burning sensation tacrolimus Unclear how long patients used clobetasol until bridging to tacrolimus Very small sample size

			advised to either start reapplying or increase use of clobetasol, depending on their current level of use. Once clearance was obtained again, they were advised to re-start the aforementioned tapering regimen.				
Casey 2015	Type of study: Retrospective and prospective cohort Setting: 10 year period, single centre Country: UK Source of funding: unclear	Inclusion criteria: 72 children with VLS in the paediatric vulvar clinic of Oxford University Hospitals NHS Trust. VLS was diagnosed by clinical appearance in girls who were pre-menarche and aged ≤ 14 years. Exclusion criteria: N/A N total at baseline: 62 N=31 treated with hydrocortisone 1% or clobetasol butyrate 0.05% were studied retrospectively. N=21 from this cohort and n=41 new patients were studied prospectively. Important prognostic factors[1]: *Age mean 6.7 (3–14)*	Describe intervention (treatment/procedure/test): clobetasol propionate 0.05% ointment daily for 3 months and then as necessary One adult fingertip unit was applied to the vulvar and perianal areas at each application, and 30 g tubes were supplied for the 3-month treatment course. Treatment frequencies: After 1 year: Twice weekly or more: n=3 (5%) Less than weekly: n=24 (40%) Nil: n=33 (55%) After 4 years or puberty: Twice weekly or more: n=1 (2.1%) Less than weekly: n=18 (37.5%) Nil: n=29 (60.4%)	Describe control (treatment/procedure/test): -	Length of follow-up: 3, 6, 12 months and annually during 4-8 years or until puberty Loss-to-follow-up: After 1 year: n=2 After 4 years: N=14 Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Symptom response at 3 months: Clear: n=45 (72.6%) Moderate: n=15 (24,2%) Poor: n=2 (3.2%) Symptom response at 1 year: Clear: n=33 (55%) Moderate: n=26 (43.3%) Poor: n=1 (1.6%) Symptom response at 4 years or puberty (total n=48): Clear: n=29 (60.4%) Moderate: n=18 (37.5%) Poor: n=1 (2.1%)	Results not stratified for treatment frequencies.

						Resolution of signs at 3 months: Total: n=14 (22.6%) Partial: n=42 (67.7%) Nil: n=6 (9.7%) Resolution of signs at 1 year: Total: n=15 (25%) Partial: n=42 (70%) Nil: n=3 (5%) Resolution of signs at 4 years or puberty: Total: n=14 (29.2%) Partial: n=34 (70.8%) Side effects after 3 months: Difficulty of application n=7 (11.3%) Teleangiectasia n=12 (19.4%) Reversible erythema n=8 (12.9%)	
Cooper 2004	Type of study: Descriptive cohort study Setting: single centre Country: England	<u>Inclusion criteria</u>: In women, diagnosis was based on the typical clinical appearances of VLS plus confirmatory histologic	Describe intervention (treatment/procedure/test): Girls: 31 (50%) girls: 0.05% clobetasol propionate ointment. Other topical steroids	Describe control (treatment/procedure/test): -	<u>Length of follow-up</u>: Every 3 months mean follow-up time for women and	Outcome measures and effect size (include 95%CI and p-value if available):	Outcomes were reported for all girls in total, not adjusted per type of topical steroid. Unclear how long patients used which topical steroid. Most

	Source of funding: unclear	studies; in girls, it was based on typical clinical appearances alone. Childhood onset of disease was defined as onset of symptoms prior to menarche and a definite diagnosis at or before the age of 16 years. Exclusion criteria: Unclear N total at baseline: 327 Important prognostic factors[1]: *Women: 253* *Girls: 74* None of the 74 girls (23%) had reached menarche, and 55 (17%) of the women were in their reproductive years and 194 (60%) were postmenopausal. Groups comparable at baseline?	prescribed were 0.05% clobetasone butyrate in 20 girls (32%), 0.1% betamethasone in 4 (7%), 0.025% beclometasone dipropionate in 3 (5%), and 1.0% hydrocortisone in 4 (7%). One child had no topical steroid prescribed. Most patients were given topical steroid for intermittent maintenance selftreatment after the initial treatment period.		girls was similar (65 vs 69 months). Loss-to-follow-up: - Incomplete outcome data: Reported response of symptoms to topical treatment was available for 255 patients, 36 girls and 219 women. Response of the vulvar physical signs to treatment was determined in 253 patients, 36 girls and 217 women.	Symptomatic response: good (symptomfree status reached during the treatment); partial (improvement and/or partial resolution of individual symptoms); or poor (no change or worsening): symptom free: 26 (72%) partial: 9 (25%) poor: 1 (3%) Response of vulvar signs: total (complete resolution of all signs and return to normal color and texture—architectural changes, of course, remained); partial (complete resolution of purpura, hyperkeratosis, fissures, and erosions, but persistence of pallor or textural change); minor (partial resolution of some signs);	patients were given topical steroids for intermittent maintenance selftreatment after initial treatment period.

						or poor (no change or worsening). Total resolution: 8 (22%) Partial resolution: 24 (67%) Minor resolution: 4 (11%)	
Focsenean u 2013	Type of study: Retrospective chart review and follow up interview Setting: Single centre Follow up phone calls Country: USA Source of funding: unclear	<u>Inclusion criteria:</u> premenarchal girls diagnosed with vulvar lichen sclerosus from 1989 to 2010. The diagnosis of lichen sclerosus was made by experienced clinicians based on characteristic history and clinical appearance. <u>Exclusion criteria: -</u> <u>N total at baseline:</u>36 <u>Important prognostic factors1:</u> mean age at LS diagnosis was 7 years (range: 3-14 years).	Describe intervention (treatment/procedure/test): For 26 patients, first-choice therapy was a high potency topical steroid (0.05% clobetasol propionate ointment). Other initial therapies included hydrocortisone 1% ointment (n=5), fluticasone 0.05% cream (n=1), fluocinonide 0.05% ointment (n=3), and tacrolimus (n=1).	Describe control (treatment/procedure/test): -	<u>Length of follow-up:</u> Mean 5.3 years (range: 2 months-15 years). <u>Loss-to-follow-up:</u> N/A <u>Incomplete outcome data:</u> N/A	Outcome measures and effect size (include 95%CI and p-value if available): Clinical response: Improvement in symptoms: Total 92% Duration of remission: Mean 3.6 years (range 1 months-10 years) Remission: N=30 after initial treatment Relapse: N=16 after 3.1 years (range 3 months-7 years) intermittent maintenance therapy	Retrospective Outcomes reported for al patients on different therapies but mostly on clobetasol
Ismail 2019	Type of study: Retrospective Setting: Referral centre	<u>Inclusion criteria:</u> patients aged < 18 years attending a local specialist dermatology	Describe intervention (treatment/procedure/test): 3-month	Describe control (treatment/procedure/test): -	<u>Length of follow-up:</u> 3 months <u>Loss-to-follow-up:</u>	Outcome measures and effect size (include 95%CI and p-value if available):	Retrospective Mostly information on clinical features

	Country: UK Source of funding: unclear	service who had a diagnosis of prepubertal onset VLS. Exclusion criteria:- N total at baseline: 26 Important prognostic factors1: Median age at onset of LS symptoms was 5 years (age range 2–8.5 years); median age at diagnosis of LS was 8 years (age range 3–17 years). The most common presenting symptoms were itching and soreness. Most patients initially presented with pallor, atrophy and fissures. One patient presented with extragenital LS.	induction regimen (superpotent topical steroid daily for 1 month initially, on alternate days for 1 month then twice weekly plus emollient).		N/A Incomplete outcome data: N/A	7 patients (27%) did not achieve disease control or experienced disease progression and required potent or superpotent steroid more than twice weekly, while the remaining 19 patients were managed with maintenance therapy of a potent/superpotent steroid twice weekly or less, plus emollient.	
Li 2013	Type of study: Observational cohort study Setting: single centre, 2006-2010 Country: China Source of funding: unclear	Inclusion criteria: Age between 2 and 12 years, and with typical clinical vulvar lichen sclerosus. Exclusion criteria: concomitant severe chronic disease, allergy to macrolides, contraindications for tacrolimus, other dermatologic diseases, viral systemic disease	Describe intervention (treatment/procedure/test): 0.03% tacrolimus ointment (Protopic, Astellas Toyama Co, Toyama, Japan) was applied twice daily in a thin layer to the affected areas for 16 weeks, then 2 times per week for 6 months (maintenance	Describe control (treatment/procedure/test): None	Length of follow-up: week 4, 8, 12, and 16 of the therapy, and at month 1, 3, and 6 of maintenance treatment, then at 1, 3, and12 months in the post-therapy follow-up period	Outcome measures and effect size (include 95%CI and p-value if available): Response (Complete response (CR): more than 75% improvement of clinical signs (erythema, erosion, fissuring,	Some patients had been misdiagnosed with eczematous dermatitis (n 5 3), fungal infection (n 5 2), vitiligo (n 5 2) maintenance treatment: n=9 (not included for guideline)

		N total at baseline: 14 Important prognostic factors1: age ± SD: 4 to 11 years 5 patients had been treated with topical steroids and 2 patients had been treated with topical antifungal agents, but the effect was not remarkable	treatment); no other topical or systemic therapy was allowed.		Loss-to-follow-up: - Incomplete outcome data: Only 9 patients continued treatment (maintenance)	crusting, and ulceration, except sclerosis and atrophy; score 0-3), and subjective symptoms (burning pain, pruritus, dysuria; score 0-3) attributable to lichen sclerosus. Partial response (PR)): 30%-75% improvement in the severity of clinical signs, and subjective symptoms attributable to lichen sclerosus. No response (NR): less than 30% improvement in clinical signs and symptoms.): 8 weeks: CR: n=5 (36%) PR: n=7 (50%) NR: n=2 (14%) 16 weeks: CR: n=9 (64%) PR: n=5 (36%) NR: n=0 AEs: transitory mild burning and itching at the initiation of treatment on 5 patients and	

						disappeared after 1 week. N=1 had bacterial folliculitis locally at week 20; n=1 hyperpigmentation in vulvar area at 6 months	
Mazzilli 2018	Type of study: Case series, prospective Setting: Country: Italy Source of funding: none	Inclusion criteria: affected by vulvar LS Exclusion criteria:- N total at baseline: 10 Important prognostic factors1: Age 4-9 years mean duration of symptoms from 6 to 9 months.	Describe intervention (treatment/procedure/test): tacrolimus 0.03% ointment twice daily for 6 weeks in association with emollient cream	Describe control (treatment/procedure/test): -	Length of follow-up: 12 weeks Loss-to-follow-up: - Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Itching and burning completely disappeared after 2 weeks, while skin lesions were in remission at 1 week after beginning treatment, with residual milia. No local and systemic side effects were recorded.	Open label Case series No systematic outcome reporting
Patrizi 2010	Type of study: Case series Setting: single centre, dermatology unit, 1999-2007 Country: Italy	Inclusion criteria: genital LS clinically (presence of ivory white sharply demarcated plaques) (14 cases) and clinically and histologically (one case) diagnosed, with onset before the	Describe intervention (treatment/procedure/test): clobetasol propionate 0.05% ointment or cream with nightly application The treatment was reduced first to every two nights for 4 weeks,	Describe control (treatment/procedure/test): -	Length of follow-up: Mean 4.7 years Loss-to-follow-up: Not described. Incomplete outcome data: -	Outcome measures and effect size (include 95%CI and p-value if available): Remission was obtained in all patients after 2–16 weeks.	No systematic outcome reporting Patients were evaluated every 2 weeks. Not described how many treatment cycles patients received during follow up; only total number

	Source of funding: unclear	menarcheal age and treated with potent topical steroids with at least 1-year follow-up. <u>Exclusion criteria:</u> - <u>N total at baseline:</u> 15 <u>Important prognostic factors1:</u> mean age at diagnosis was 7.1 years (range: 4–11)	and then to twiceweekly for at least 8 week in case of remission.			relapses in nine patients (60%) after approximately 1 year from the first clearing. In two cases more than three relapses per year occurred. The same treatment regimen was successfully re-applied for relapses. At the end of the study, a new physical examination showed plaques of LS in two cases (13.33%) with soreness and itching. Scarring, such as minor labial adhesion and clitoris atrophy, was detected in three cases (20%) and in two of them a history of relapses was reported. No AEs.	of relapses and results of physical examination at the end of the study.
Smith 2010	Type of study: Retrospective chart review Setting: pediatric and adolescent	<u>Inclusion criteria:</u> Premenarchal girls with vulvar lichen sclerosus. the provider noted the typical clinical appearance including	Describe intervention (treatment/procedure/test): topical clobetasol propionate ointment	Describe control (treatment/procedure/test): -	<u>Length of follow-up:</u> 2 months – 6 years	Outcome measures and effect size (include 95%CI and p-value if available):	All examinations were performed by one or both of the authors.

	gynecology clinic, 1995-2000 Country: US Source of funding: unclear	whitening, atrophy, erythema, erosion, and fissures in a perineal and perianal distribution, or if the subject had biopsy-proven lichen sclerosus, and the subject was treated with clobetasol <u>Exclusion criteria:</u> no clobetasol use or no follow-up by either a clinic visit or a phone survey <u>N total at baseline: 15</u> <u>Important prognostic factors1:</u> Age at the onset of symptoms was 5.7 years (range 3–11 years)	0.05% for 2–4 weeks, frequency of application depending on severity of the disease. Twice daily application for 2 weeks then once daily for 2 weeks in 11 children, daily in 4 children for 2 weeks. After 2-4 weeks tapering: Initially, they were changed to triamcinolone ointment 0.1%, most commonly twice daily for 2 weeks and then daily for 2 weeks. After this taper, they received hydrocortisone 2% (if necessary).		<u>Loss-to-follow-up: -</u> <u>Incomplete outcome data:</u> At least 1 year follow up available in 11 girls.	significant improvement (subjects reporting complete or almost complete resolution of the presenting symptoms and complete or almost complete regression of vulvar abnormalities (if examined), except whitened skin.): within 4–7 weeks in 14 girls (93%). After at least 1 year follow up (average 2.2 years, range 1–6 years): Total n=11. Two girls had no further vulvar symptoms after the initial treatment, five had one or two total flares, three reported three to eight flares per year, and one girl continues to be unresponsive to therapy. Overall, there was a mean of 2.19 flares per year of follow-up	

						(95% CI interval 0.07– 4.32) in the ten girls who had follow-up at least 1 year and who responded to clobetasol therapy. Flares were generally successfully selftreated with short courses of triamcinolone or hydrocortisone. AEs: One girl developed a yeast superinfection and one developed transient erythema.	

Bijlage 5: Risk of bias tabellen

Risk of bias tabellen lokale therapie 2019

Corticosteroïden

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Random sequence generation (selection bias)[2]** (high/unclear/low risk)	**Allocation concealment (selection bias)[3]** (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)[4,6]** *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)[5,6]** *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)[7]** *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)[8]** (high/unclear/low risk)	**Other bias[9]** (high/unclear/low risk)	**Total RoB**
Borghi 2015	computer-generated simple randomization Schedule	computer-generated simple randomization Schedule Low risk	The randomization schedule was prepared prior to enrolment to ensure allocation concealment. Low risk	Patients were not blinded to their group allocation. Other investigators (S.M. and G.T.), unblinded to treatment allocation and not involved in patient assessment, prescribed the study drugs in accordance with the randomization. High risk	Objective and subjective patient assessment was performed in consensus by the same two experienced investigators (A.V. and M.C.) blinded to treatments at baseline and at the 12-week control visit. Low risk	Unlikely, no missing data. Low risk	Unclear	Unclear	High risk of bias for patient reported outcome due to unblinded patients. low risk of bias for physician's reported outcomes

Virgili 2014	computer generated simple randomization schedule.	Low risk	The randomization schedule was prepared prior to enrolment to ensure allocation concealment. Low risk	Open label High risk	Objective and subjective patient assessment was performed by the same two experienced investigators (A.V., M.C.), who were not blinded to treatments at baseline and at the 12-week control visit. High risk	Low number of drop outs Low risk	Unclear	Unclear	High risk of bias for patient reported outcome due to unblinded patients. low risk of bias for physician's reported outcomes

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2. Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence. Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
3. Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment. Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
4. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.
5. Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
6. Detection bias due to knowledge of the allocated interventions by outcome assessors. Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
7. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has "soft" (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
8. Attrition bias due to amount, nature or handling of incomplete outcome data: dropout ≤ 10% low, > 20% high, in between is judged as unclear risk. If for example drop out is 15% and unbalanced then judged as high risk. Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear. Describe if there is bias due to violation of

intention to treat analysis: participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.

9. Reporting bias due to selective outcome reporting. State how the possibility of selective outcome reporting was examined by the review authors, and what was found. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
10. Other bias: State any important concerns about bias not addressed in the other domains in the tool: baseline imbalance in disease severity, co-medication such as use of emollients and information about wash-out period from topical corticosteroid use.

Calcineurineremmers

RCT's

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Random sequence generation (selection bias)[2]** (high/unclear/low risk)	**Allocation concealment (selection bias)[3]** (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)[4,6]** *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)[5,6]** *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)[7]** *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)[8]** (high/unclear/low risk)	**Other bias[9]** (high/unclear/low risk)	**Total RoB**
Funaro 2014	Block randomization was used (blocks of 4) to control for the numbers of participants allocated to each group during the enrollment phase of the study.	Low risk	Low risk	Both participants and investigators were blinded to the administered treatment. The hospital's pharmacy department prepared the ointment tubes and insured double-blindness and randomization. Low risk	Low risk	Only mean values or p-values reported for efficacy scores. High risk	Unclear	Sponsored by an Astellas Pharma research grant for an investigator-initiated study. Disclosure: Dr Powell served on the advisory board for Astellas Pharma and Dr Funaro received from Astellas Pharma a grant for an investigator-initiated study and received a	High risk but already downgraded for impresicion

								bursary in a research competition risk of publication bias	
Goldstein 2011	Allocation: Randomized Intervention: Model: Parallel Assignment www.clinicaltrials.gov (NCT00393263)	Unclear	Unclear	Participants were assigned blinded treatment with consecutive numbers. Low risk	Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Low risk	Only p-value or mean without standard deviation reported for efficacy scores. High risk	Unclear	Novartis Pharmaceuticals Corp, East Hanover, NJ. Disclosure: Dr Goldstein has received research funding from Novartis Pharmaceuticals and Neocutis, Inc; he is a consultant for Boehinger Ingelheim. Novartis is producent of pimecrolimus risk of publication bias	High risk but already downgraded for imprecison

Observationele studies

Beoordeling risk of bias middels Newcastle-Ottawa scale (NOS).

		Selection				Comparability	Outcomes			
Studie	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Borghi 2017	Retrospective, comparative	★	★	★	★	-	-	★	★	Adequate selection of patients with LS. Study does not control for possible confounding factors.
Gupta 2005	Prospective, non comparative	★	-	★	★	-	-	★	★	Some male patients were already circumcised.
Kyriakou 2013	Retrospective, non comparative	★	-	★	★	-	-	-	★	genital LS accompanied by pruritus and the disease activity at baseline was required to be at least moderate

RCT's

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Random sequence generation (selection bias)[2]** (high/unclear/low risk)	**Allocation concealment (selection bias)[3]** (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)[4,6]** *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)[5,6]** *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)[7]** *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)[8]** (high/unclear/low risk)	**Other bias[9]** (high/unclear/low risk)	**Total RoB**
Corazza 2015	In original study computer generated randomization schedule	Low risk	The randomization schedule was prepared prior to enrolment to ensure allocation concealment. Low risk	Open label High risk	Objective and subjective patient assessment was performed by the same two experienced investigators who were not blinded to treatments at baseline and at the 12-week control visit. Unclear if outcome assessors were the same at 52 weeks. High risk	Low number of dropouts. Unclear how subjective scores were measured, low number of patients who reported scores? Unclear risk	Unclear risk	Low risk	High RoB due to opel label design

Virgili 2013 BJD	computer generated randomization schedule	Low risk	Unclear	Open label High risk	Objective and subjective patient assessment was performed by the same two investigators who were not blinded to treatments High risk	VAS displayed for non-relapsing patients only Relapsing patients continued with daily application of topical steroids High risk	Unclear risk	Low risk	High RoB due to opel label design
Virgili 2013 EJD	computer generated randomization schedule	Low risk	Unclear	Open label High risk	Objective and subjective patient assessment was performed by the same two investigators who were not blinded to treatments High risk	Large number of patients lost to follow up High risk	VAS scores after 52 weeks and global subjective score/IGA not reported. High risk	Low risk	High RoB

Observationele studies

Risk of bias van observationele studies werd beoordeeld met de Newcastle-Ottawa scale.

		Selection				Comparability	Outcomes			
Study	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Lee 2015	Prospective longitudinal cohort study	★	-	★	★	-	-	★	★	
Cooper 2004	Descriptive cohort study	★	-	★	★	-	-	★	-	Incomplete outcome data
Renaud-Vilmer 2004	Prospective study	★	-	★	-	-	-	★	★	6/8 SCC were already present at baseline
Simonart 2008	Prospective open trial	★	-	★	★	-	-	★	-	9/34 patients were lost

										to follow up
Ventolini 2012	Retrospective clinical medical records review	★	-	★	-	-	-	★	-	No baseline charac-teristics reported.

Systemische therapie

Vulvar LS

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Random sequence generation (selection bias)[2]** (high/unclear/low risk)	**Allocation concealment (selection bias)[3]** (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)[4,6]** *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)[5,6]** *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)[7]** *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)[8]** (high/unclear/low risk)	**Other bias[9]** (high/unclear/low risk)	**Total RoB**
Bousema 2014	Method of randomization not mentioned.	Unclear	Unclear Patients were randomly allocated. Method not described.	Low risk Placebo capsules were identical as acitretin capsules.	Unclear	High risk of bias High number of drop outs; efficacy population without pt who followed <12 weeks of treatment and pt who stopped because of lack of efficacy. This might influence the efficacy scores.	Unclear	Low risk Only emollient ointments and nonalkaline anti-septics were allowed for local treatment during the study. This might not influence treatment efficacy.	High RoB

						Unclear if patients with dose modification were included in efficacy analyses.			

Male genital LS

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Random sequence generation (selection bias)[2]** (high/unclear/low risk)	**Allocation concealment (selection bias)[3]** (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)[4,6]** *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)[5,6]** *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)[7]** *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)[8]** (high/unclear/low risk)	**Other bias[9]** (high/unclear/low risk)	**Total RoB**
Ioannides 2010	An individual not involved in the trial performed randomization using a computer generated randomization scheme.	Low risk	Low risk	Low risk The control group received placebo capsules identical in size and color to the acitretin.	Low risk Same masked physician recorded disease severity at every visit. Considering the expected side effects of acitretin, the observer might have been biased.	High risk The withdrawn pt were not included in analyses (n=2).	Unclear risk	Low risk Topical emollient was allowed. All previous medications for LS were discontinued at least 30 days before baseline	Low RoB

PDT

Vulvar LS

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Random sequence generation (selection bias)**[2] (high/unclear/low risk)	**Allocation concealment (selection bias)**[3] (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)**[4,6] *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)**[5,6] *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)**[7] *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)**[8] (high/unclear/low risk)	**Other bias**[9] (high/unclear/low risk)	**Total RoB**
Shi 2016	Open label All eligible patients were randomized to either ALA-PDT or clobetasol propionate group using sequentially numbered envelopes. The random sequence in the envelopes was produced by computer programme. The sequentially numbered opaque envelopes were opened only after each patient agreed to participate. Evaluations were performed by the same examiners, who	Low risk	Low risk	Patients were not blinded. High risk for patient reported outcomes (symptom scores)	Physicians who performed evaluations were blinded. Low risk	Low number of patients lost to follow up Low risk	Unclear risk	Unclear risk	Low risk High risk for patient reported outcomes

	did not know which treatment was received by patients.								

Observationele studies

Risk of bias van observationele studies werd beoordeeld met de Newcastle-Ottawa scale.

		Selection				Comparability	Outcomes			
Studie	**Study design**	**Representativeness of the intervention cohort**	**Selection of the non intervention cohort**	**Ascertainment of intervention**	**Demonstration that outcome of interest was not present at start of study**	**Comparability of cohorts on the basis of the design or analysis**	**Assessment of outcome**	**Was follow up long enough for outcomes to occur**	**Adequacy of follow up of cohorts**	**Explanations**
Hillemanns 1999	Prospective single arm pilot study	★	-	★	★	-	-	★	★	Different amount of treatment cycles, results reported for all patients together

Mazdziarz 2017	Prospective, non comparative	★	-	★	★	-	-	★	★	Patient reported outcome
Olejek 2017	Prospective, non comparative	★	★	★	★	-	-	★	★	Patients with concomitant autoimmune diseases compared with patients without; comparison not of interest for our guideline
Osiecka 2017	Prospective, non comparative	★	-	★	★	-	-	★	★	
Sotiriou 2008	Case series	-	-	-	★	-	-	★	-	Inclusion criteria not reported. Not mentioned how intervention was allocated. Objective score only reported after 8 weeks. No effect sizes reported of mean values.

Observationele studies

Risk of bias van observationele studies werd beoordeeld met de Newcastle-Ottawa scale.

		Selection				Comparability	Outcomes			
Studie	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Casabona 2017	Retrospective cohort study	★	-	-	★	-	-	★	-	Adequate selection of male patients with LS. Varying number of treatments performed on each patient. Outcomes were self-reported or investigator-reported, not blinded. Large range in follow up duration.
Zucchi 2016	Non-randomized	-	-	-	★	-	-	★	-	Population not well described.

	prospective pilot study									Small number of patients Large range in follow up duration; unclear when outcomes were measured. Subjective self-reporting outcome measures.

Kinderen

Boys with LS

Study reference (first author, publication year)	**Describe method of randomisation[1]**	**Random sequence generation (selection bias)[2]** (high/unclear/low risk)	**Allocation concealment (selection bias)[3]** (high/unclear/low risk)	**Blinding of participants and personnel (performance bias)[4,6]** *All outcomes* (high/unclear/low risk)	**Blinding of outcome assessor (detection bias)[5,6]** *All outcomes* (high/unclear/low risk)	**Incomplete outcome data (attrition bias)[7]** *All outcomes* (high/unclear/low risk)	**Selective reporting (reporting bias)[8]** (high/unclear/low risk)	**Other bias[9]** (high/unclear/low risk)	**Total RoB**
Kiss 2001	Unclear	Unclear risk	Unclear risk	Patients were not blinded. Unclear if personnel was blinded. High risk for patient reported outcomes (symptom scores)	Unclear risk	Low number of patients lost to follow up Low risk	The authors did not describe how outcome measures were measured. Unclear risk	Unclear risk	High risk of bias due to lack of information.

Observationele studies

Risk of bias van observationele studies werd beoordeeld met de Newcastle-Ottawa scale.

		Selection				Comparability	Outcomes			
Study	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Vincent 2005	Prospective single arm pilot study	★	-	-	★	-	-	★	★	Different amount of treatment cycles, results reported for all patients together

Observational studies

Risk of bias van observationele studies werd beoordeeld met de Newcastle-Ottawa scale.

		Selection				Comparability	Outcomes			
Study	Study design	Representativeness of the intervention cohort	Selection of the non intervention cohort	Ascertainment of intervention	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur	Adequacy of follow up of cohorts	Explanations
Anderson 2016	Retrospective case series	★	-	-	★	-	-	-	-	Varying length of follow up. No side effects monitored. Unclear how long pt used clobetasol until bridging to tacrolimus.
Casey 2015	Prospective cohortstudy	★	-	-	★	-	-	★	-	>10% lost to long term follow up

Cooper 2004	Descriptive cohortstudy	★	-	★	-	-	-	★	★	Incomplete outcome data
Focseanu 2013	Retrospective chart and follow up review	★	-	-	★	-	-	-	-	Large range of follow up.
Ismail 2019	Retrospective	★	-	-	★	-	-	-	★	Retrospective
Li 2013	Cohort study	★	-	-	★	-	-	★	★	Follow up complete until 16 weeks. Outcome assessment not blinded, performed by 2 same investigators.
Mazzilli 2018	Case series	★	-	-	-	-	-	★	★	No systematic outcome reporting. Open label.
Patrizi 2010	Case series	★	-	-	-	-	-	★	-	No systematic outcome reporting. Open label. Not described how many treatment cycles patients received during follow up. Mean follow up of 4.7 years.

Smith 2010	Retrospective	★	-	-	★	-	-	★	-	Mean follow up with large range. All examinations were performed by one or both of the authors.

Bijlage 6: Summary of Findings tabellen GRADE

GRADE Summary of Findings (SoF) tabellen onderhoudstherapie LS 2019

Clobetasol propionate 0.05% twice weekly compared to mometasone furoate 0.1% twice weekly for 52 weeks for lichen sclerosus

Patient or population: lichen sclerosus
Setting:
Intervention: Clobetasol propionate 0.05% twice weekly
Comparison: mometasone furoate 0.1% twice weekly for 52 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with mometasone furoate 0.1% twice weekly for 52 weeks	**Risk with Clobetasol propionate 0.05% twice weekly**				
Relapse follow up: 52 weeks	3 per 100	**7 per 100** (1 to 68)	**RR 2.00** (0.20 to 20.49)	52 (2 RCTs) [1,2]	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of clobetasol propionate 0.05% vs mometasone furoate 0.1% twice weekly during 52 weeks on relapse.
Duration of remission follow up: 52 weeks	The mean time to relapse was 30 weeks (median 32 weeks, range 20–38) (no difference between groups)			52 (1 RCT) [2]	⨁◯◯◯ VERY LOW [a,c]	Clobetasol propionate 0.05% twice weekly may result in little to no difference in duration of remission when compared with mometasone furoate 0.1%. Mean time to relapse was 30 weeks (range 20-38), but we are very uncertain.
Quality of life - not measured	No study adressed this outcome.			-	-	

Clobetasol propionate 0.05% twice weekly compared to mometasone furoate 0.1% twice weekly for 52 weeks for lichen sclerosus

Patient or population: lichen sclerosus
Setting:
Intervention: Clobetasol propionate 0.05% twice weekly
Comparison: mometasone furoate 0.1% twice weekly for 52 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with mometasone furoate 0.1% twice weekly for 52 weeks	**Risk with Clobetasol propionate 0.05% twice weekly**				
Participant-assessed improvement in lichen sclerosus severity assessed with: Global Subjective Score change Scale from: 0 to 20 follow up: 52 weeks	The mean participant-assessed improvement in lichen sclerosus severity was **0.77**	MD **0.55 lower** (2.96 lower to 1.86 higher)	-	20 (1 RCT) [2]	⨁◯◯◯ VERY LOW [a,c]	Clobetasol propionate 0.05% twice weekly may result in little to no difference in participant-assessed improvement in lichen sclerosus severity when compared with mometasone furoate 0.01% but the evidence is very uncertain. The global subjective score did not change significantly after 52 weeks when compared with baseline.
Proportion of patients with adverse event follow up: 52 weeks	No adverse events reported.			52 (2 RCTs) [1,2]	⨁⨁◯◯ LOW [a,d]	Clobetasol propionate 0.05% and mometasone furoate 0.1% twice weekly for 52 weeks may not cause adverse events.

Clobetasol propionate 0.05% twice weekly compared to mometasone furoate 0.1% twice weekly for 52 weeks for lichen sclerosus

Patient or population: lichen sclerosus
Setting:
Intervention: Clobetasol propionate 0.05% twice weekly
Comparison: mometasone furoate 0.1% twice weekly for 52 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with mometasone furoate 0.1% twice weekly for 52 weeks	**Risk with Clobetasol propionate 0.05% twice weekly**				
Physician-assessed improvement in lichen sclerosus severity assessed with: Global Objective Score change Scale from: 0 to 12 follow up: 52 weeks	The mean physician-assessed improvement in lichen sclerosus severity was **-0.50**	MD **0.23 higher** (0.58 lower to 1.04 higher)	-	24 (1 RCT) [2]	⨁◯◯◯ VERY LOW [a,c]	Clobetasol propionate 0.05% twice weekly may result in little to no difference in physician-assessed improvement in lichen sclerosus severity when compared with mometasone furoate 0.1% but the evidence is very uncertain. The global objective score did not change significantly after 52 weeks when compared with baseline.
Treatment satisfaction (dissatisfied) follow up: 52 weeks	7 per 100	**13 per 100** (1 to 100)	**RR 2.00** (0.20 to 20.49)	52 (2 RCTs) [1,2]	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of clobetasol propionate 0.05% vs mometasone furoate 0.1% twice weekly on treatment satisfaction (dissatisfied).
Proportion of patients with SCC - not measured	No study addressed this outcome.			-	-	

Clobetasol propionate 0.05% twice weekly compared to mometasone furoate 0.1% twice weekly for 52 weeks for lichen sclerosus

Patient or population: lichen sclerosus

Setting:

Intervention: Clobetasol propionate 0.05% twice weekly

Comparison: mometasone furoate 0.1% twice weekly for 52 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with mometasone furoate 0.1% twice weekly for 52 weeks	**Risk with Clobetasol propionate 0.05% twice weekly**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for serious risk of bias due to open label design studies.

b. Downgraded two levels for very serious imprecision due to small sample size and wide confidence interval.

c. Downgraded two levels for very serious imprecision due to very small sample size.

d. Dowgraded one level for serious imprecision due to small sample size.

References

1. Virgili, BJD; 2013.

2. Corazza, 2016.

Vitamin E oil compared to Cold cream once daily for 52 weeks for lichen sclerosus

Patient or population: lichen sclerosus
Setting:
Intervention: Vitamin E oil
Comparison: Cold cream once daily for 52 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Cold cream once daily for 52 weeks	**Risk with Vitamin E oil**				
Relapse follow up: 52 weeks	29 per 100	**30 per 100** (18 to 53)	**RR 1.05** (0.61 to 1.82)	97 (2 RCTs) [1,2]	⨁◯◯◯ VERY LOW [a,b]	Vitamin E oil may have little to no effect on relapse when compared with cold cream but the evidence is very uncertain.
Duration of remission follow up: 52 weeks	The median duration of remission was **18.7** weeks	median **1.3 weeks higher** (0 to 0)	-	80 (1 RCT) [1]	⨁◯◯◯ VERY LOW [a,c]	Vitamin E oil may result in little to no difference in duration of remission when compared with cold cream.
Proportion of patients with SCC - not measured	No study addressed this outcome.			-	-	
Quality of life - not measured	No study addressed this outcome.			-	-	
Participant-assessed improvement in lichen sclerosus severity - not measured	No study addressed this outcome.			-	-	

Vitamin E oil compared to Cold cream once daily for 52 weeks for lichen sclerosus

Patient or population: lichen sclerosus
Setting:
Intervention: Vitamin E oil
Comparison: Cold cream once daily for 52 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Cold cream once daily for 52 weeks	Risk with Vitamin E oil				
Proportion of patients with adverse event	No adverse events were reported.			17 (1 RCT) [2]	⨁◯◯◯ VERY LOW [a,d]	The evidence is very uncertain about the effect of vitamin E oil on proportion of patients with adverse events when compared with cold cream. There were no adverse events reported in the study.
Physician-assessed improvement in lichen sclerosus severity - not measured	No study addressed this outcome.			-	-	
Treatment satisfaction - not measured	No study addressed this outcome.			-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for serious risk of bias due to open label design.

b. Downgraded two levels for very serious imprecision due to wide confidence interval (the lower boundary indicates appreciable harm (0.75), whilst the upper boundary of the CI indicates appreciable benefit (1.25))

c. Downgraded two levels for serious imprecision (small sample size and lack of distribution data)

d. Downgraded two levels for very serious imprecision due to very small sample size.

References

1. Virgili EJD; 2013.

2. Virgili BJD; 2013.

GRADE Summary of Findings (SoF) tabellen systemische therapie LS 2019

Acitretin 30 mg compared to placebo for vulvar lichen sclerosus

Patient or population: vulvar lichen sclerosus

Setting:

Intervention: acitretin 30 mg

Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 30 mg				
Quality of life - not measured	No study addressed this outcome.			-	-	We are uncertain about the effect of acitretin on quality of life. No study addressed this outcome.

Acitretin 30 mg compared to placebo for vulvar lichen sclerosus

Patient or population: vulvar lichen sclerosus
Setting:
Intervention: acitretin 30 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 30 mg				
Participant-assessed improvement in lichen sclerosus severity assessed with: Symptom score pruritus (present) follow up: 16 weeks	79 per 100	**99 per 100** (80 to 100)	**RR 1.25** (1.01 to 1.56)	46 (1 RCT) [1]	⨁⨁◯◯ LOW [a,b]	Acitretin 30 mg may increase participant-assessed improvement in lichen sclerosus pruritus severity slightly when compared with placebo.

Acitretin 30 mg compared to placebo for vulvar lichen sclerosus

Patient or population: vulvar lichen sclerosus
Setting:
Intervention: acitretin 30 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 30 mg				
Participant-assessed improvement in lichen sclerosus severity assessed with: Symptom score burning (present) follow up: 16 weeks	85 per 100	**99 per 100** (81 to 100)	**RR 1.17** (0.95 to 1.43)	38 (1 RCT) [1]	⨁⨁◯◯ LOW [a,b]	Acitretin 30 mg may increase participant-assessed improvement in lichen sclerosus burning severity slightly when compared with placebo.
Proportion of patients with at least one adverse event	56 per 100	**99 per 100** (75 to 100)	**RR 1.76** (1.33 to 2.31)	78 (1 RCT) [1]	⨁⨁◯◯ LOW [b,c]	Acitretin 30 mg may increase proportion of patients with at least one adverse event when compared with placebo.

Acitretin 30 mg compared to placebo for vulvar lichen sclerosus

Patient or population: vulvar lichen sclerosus
Setting:
Intervention: acitretin 30 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 30 mg				
Physician-assessed improvement in lichen sclerosus severity assessed with: No of responders follow up: 16 weeks	25 per 100	**64 per 100** (30 to 100)	**RR 2.55** (1.19 to 5.45)	46 (1 RCT) [1]	⨁⨁◯◯ LOW [a,b]	Acitretin 30 mg may result in a increase in total number of responders when compared with placebo.
Treatment satisfaction assessed with: No of patients who were completely satisfied follow up: 16 weeks	18 per 100	**38 per 100** (18 to 84)	**RR 2.14** (0.98 to 4.67)	78 (1 RCT) [1]	⨁◯◯◯ VERY LOW [c,d]	Acitretin 30 mg may increase treatment satisfaction but the evidence is very uncertain.
Duration of remission - not measured	No study addressed this outcome.			-	-	We are uncertain about the effect of acitretin on duration of remission. No study addressed this outcome.

Acitretin 30 mg compared to placebo for vulvar lichen sclerosus

Patient or population: vulvar lichen sclerosus
Setting:
Intervention: acitretin 30 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with acitretin 30 mg**				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for risk of bias (randomization was performed before the inclusion criteria were checked, incomplete outcome data)
b. Downgraded one level for imprecision (small sample size)
c. Downgraded one level for risk of bias (randomization was performed before the inclusion criteria were checked)
d. Downgraded two levels for very serious imprecision (small sample size and wide confidence interval)

References

1. Bousema 1994.

Acitretin 35 mg compared to placebo for male genital lichen sclerosus

Patient or population: male genital lichen sclerosus
Setting:
Intervention: acitretin 35 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 35 mg				
Quality of life assessed with: DLQI (lower is better) follow up: 20 weeks	The mean quality of life was **10.63**	The mean quality of life in the intervention group was 3,87 lower (5,68 lower to 2,06 lower)	-	49 (1 RCT) [1]	⨁⨁⨁◯ MODERATE [a]	Acitretin 25 mg probably improves quality of life slightly.
Participant-assessed improvement in lichen sclerosus severity - not measured	No study addressed this outcome.			-	-	We are very uncertain about the effect of acitretin 25 mg on participant-assessed improvement in lichen sclerosus severity. No study addressed this outcome.
Proportion of patients with adverse event follow up: 20 weeks	Only the proportion of patients for each adverse event were reported. Overall there were more adverse events in the acitretin group (in total 99 adverse events in the acitretin group vs 14 in the placebo group).			49 (1 RCT) [1]	⨁⨁⨁◯ MODERATE [a]	Acitretin 25 mg probably increases the proportion of patients with adverse events.

Acitretin 35 mg compared to placebo for male genital lichen sclerosus

Patient or population: male genital lichen sclerosus
Setting:
Intervention: acitretin 35 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 35 mg				
Physician-assessed improvement in lichen sclerosus severity assessed with: Total clinical score (the sum of 6 different rates which were the result of the assessment of 3 individual parameters (symptoms, signs, extent of lesions)), lower is better Scale from: 0 to 18 follow up: 20 weeks	The mean physician-assessed improvement in lichen sclerosus severity was **9.31**	The mean physician-assessed improvement in lichen sclerosus severity in the intervention group was 4,76 lower (6,88 lower to 2,64 lower)	-	49 (1 RCT) [1]	⨁⨁⨁◯ MODERATE [a]	Acitretin 25 mg probably improves physician-assessed improvement in lichen sclerosus severity.

Acitretin 35 mg compared to placebo for male genital lichen sclerosus

Patient or population: male genital lichen sclerosus
Setting:
Intervention: acitretin 35 mg
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with acitretin 35 mg				
Treatment satisfaction - not measured	No study addressed this outcome.			-	-	We are very uncertain about the effect of acitretin 25 mg on treatment satisfaction. No study addressed this outcome.
Duration of remission - not measured	No study addressed this outcome.			-	-	We are very uncertain about the effect of acitretin 25 mg on duration of remission. No study addressed this outcome.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for imprecision (small sample size)

References

1. Ioannides 2010.

Summary of findings:

ALA-PDT compared to clobetasol propionate 0,05% for vulvar LS

Patient or population: vulvar lichen sclerosus
Intervention: ALA-PDT
Comparison: clobetasol propionate 0,05%

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with clobetasol propionate 0,05% for vulvar LS	**Risk with ALA-PDT**				
Quality of life - not measured				-	-	
Participant-assessed improvement in lichen sclerosus assessed with: Subjective symptom score (range 0-3) follow up: 6 months	After 6 months 13 patients in the PDT group reported a score of 0 (symptoms absent), 4 patients scored 1 (mild symptoms), 3 patients scored 2 (moderate symptoms). In the clobetasol group no patients scored 0, 2 patients scored 1, 10 patients scored 2 and 8 patients scored 3.			40 (1 RCT) [1]	⨁◯◯◯ VERY LOW [a,b]	The evidence is very uncertain about the effect of ALA-PDT on participant-assessed improvement in lichen sclerosus.
Proportion of patients with adverse events follow up: 6 months	No adverse events occured in the clobetasol group. In de PDT group 1 patient developed an erosion and 5 patients reported redness and swelling which faded away.			40 (1 RCT) [1]	⨁⨁◯◯ LOW [a,c]	ALA-PDT may increase the proportion of patients with adverse events slightly when compared with clobetasol propionate.

Summary of findings:

ALA-PDT compared to clobetasol propionate 0,05% for vulvar LS

Physician-assessed improvent in lichen sclerosus severity assessed with: Score clinical signs of hyperkeratosis, atrophy, sclerosis, and depigmentation; each graded as: 0=absent, 1= mild, 2=moderate, 3=severe follow up: 6 months	ALA-PDT group: n=18 score of 0 for hyperkeratosis, n=16 for atrophy, n=16 for sclerosis and n=13 for hyperpigmentation. In the clobetasol group no patients had a score of 0 for any clinical sign.	40 (1 RCT) [1]	⊕⊕◯◯ LOW [b]	ALA-PDT may result in a slight increase in physician-assessed improvent in lichen sclerosus severity when compared with clobetasol propionate.
Treatment satisfaction - not measured		-	-	
Duration of remission - not measured		-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for serious risk of bias, patients were not blinded.
b. Downgraded two levels for very serious imprecision (small sample size and surrogate outcome)
c. Downgraded one level for serious imprecision (small sample size)

References

1. Shi 2016.

Summary of findings:

Mometasone furoate 0,05% compared to placebo for 5 weeks in boys with LS

Patient or population: boys with LS
Setting:
Intervention: Mometasone furoate 0,05%
Comparison: placebo for 5 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo for 5 weeks	**Risk with Mometasone furoate 0,05%**				
Physician assessed improvement of LS assessed with: Mean decrease in total clinical score follow up: 5 weeks	The mean physician assessed improvement of LS was **+0.38**	MD **0.79 lower** (0.87 lower to 0.71 lower)	-	33 (1 RCT) [1]	⨁◯◯◯ VERY LOW [a,b,c]	Mometasone furoate 0,05% may have little effect on physician assessed improvement of LS but the evidence is very uncertain.
Proportion of patients with adverse events (Safety)	No adverse events occured during the study.			33 (1 RCT) [1]	⨁◯◯◯ VERY LOW [a,d]	The evidence is very uncertain about the effect of mometasone furoate 0,05% on proportion of patients with adverse events.
Duration of remission - not measured	No study addressed this outcome.			-	-	

Summary of findings:

Mometasone furoate 0,05% compared to placebo for 5 weeks in boys with LS

Patient or population: boys with LS
Setting:
Intervention: Mometasone furoate 0,05%
Comparison: placebo for 5 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo for 5 weeks	Risk with Mometasone furoate 0,05%				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Downgraded one level for serious risk of bias due to unclear method of randomization and blinding.
b. Downgraded one level for serious indirectness due to short follow up period.
c. Downgraded one level for serious imprecision (unclear how outcome was measured)
d. Downgraded two levels for very serious indirectness (short follow up period for adverse events to occur)

References

1. Kiss, . . 2001.

Bijlage 7: Kennislacunes

Bij de modulaire herziening van de richtlijn Lichen sclerosus is geconstateerd dat er een aantal vragen zijn die niet beantwoord kunnen worden omdat er onvoldoende bewijs beschikbaar is. Er zijn met name onvoldoende RCT's uitgevoerd op het gebied van de behandeling van lichen sclerosus.

1. Wat is het ideale smeerschema van tacrolimus als onderhoudstherapie bij lichen sclerosus?
2. Wat is de effectiviteit van fotodynamische therapie bij lichen sclerosus en is het veilig?
3. Wat is de effectiviteit van onderstaande systemische middelen bij lichen sclerosus en zijn deze veilig?
    - Isotretinoïne
    - Methotrexaat
    - Fumaarzuur
    - Prednison
4. Wat is de incidentie van anogenitale lichen sclerosus bij jongens? Er worden veel circumcisies uitgevoerd zonder dat er histologisch onderzoek wordt gedaan. Hierdoor is met moeilijk te achterhalen wat de oorzaak van de klacht was die aanleiding gaf voor het uitvoeren van een circumcisie.
5. Wat is het effect van chirurgische behandeling op seksuele problematiek bij LS?

Bijlage 8: Organisatie van zorg

Lichen sclerosus is een aandoening die huisartsen, dermatologen, gynaecologen en urologen regelmatig zien. Samenwerking is van belang met als doel het beleid van deze disciplines op elkaar af te stemmen.

Diagnostiek
De diagnose lichen sclerosus kan meestal worden gesteld op basis van anamnese en lichamelijk onderzoek. Bij twijfel over diagnose (of bij verdenking op neoplasie) kan de huisarts naar de tweede lijn verwijzen voor beoordeling en zo nodig (aanvullende) diagnostiek.

Behandeling
De huisarts verwijst de patiënt met lichen sclerosus zo nodig naar de tweede lijn indien de klachten van de patiënt niet voldoende verbeteren na behandeling met lokale therapie. Binnen de tweede lijn kan onderling worden verwezen, bijvoorbeeld naar centra waar bepaalde behandelingen (zoals systemische therapie en chirurgische behandelingen) plaatsvinden.

Begeleiding door een seksuoloog NVVS kan zinvol zijn om vragen en problemen op gebied van seksualiteit te inventariseren, patiënt (en partner) daarin te begeleiden en seksuele dysfuncties te behandelen. Seksuoloog is geen beschermde titel in Nederland. Zorgverleners die voldoen aan kwaliteitseisen hebben een registratie als seksuoloog NVVS en zijn opgenomen in het kwaliteitsregister van de Nederlandse Vereniging voor Seksuologie (NVVS). Bij psychologische klachten (zoals angst of depressie) kan begeleiding door een gezondheidszorgpsycholoog nuttig zijn. Als er problemen zijn met mictie en/of defaecatie of als er sprake is van dyspareunie kan er verwezen worden naar een bekkenfysiotherapeut. Deze adviezen gelden voor zowel mannelijke als vrouwelijk patiënten met anogenitale lichen sclerosus.

Terugverwijzing
Een patiënt met lichen sclerosus kan worden terugverwezen naar de huisarts indien de lichen sclerosus onder controle is. Patiënten worden meestal jaarlijks voor controle gezien. Om te voorkomen dat een patiënt bij terugverwijzing naar de 1^{e} lijn pas na lange tijd wordt gezien en om ervoor te zorgen dat de huisarts snel op de hoogste is van de huidige situatie en het beleid is het aan te bevelen dat de huisarts patiënt bij terugverwijzing op korte termijn (< 6 weken) ziet. Dit advies dient door de dermatoloog of gynaecoloog te worden vermeld in de brief aan de huisarts.

Controle
Gezien de chroniciteit van de aandoening en het risico op anatomische veranderingen en maligne ontaarding dienen patiënten met anogenitale LS levenslang vervolgd te worden. Controle vindt in principe jaarlijks plaats. Afhankelijk van de ernst van de ziekte kan het interval tussen controles verlengd of verkort worden.

Voorlichting
Het is belangrijk dat de voorlichting van verschillende zorgverleners (huisarts, dermatoloog, gynaecoloog uroloog, seksuoloog en bekkenfysiotherapeut) aan patiënten met lichen sclerosus op elkaar zijn afgestemd. Zorgverleners dienen iedere patiënt met lichen sclerosus pro-actief en uitgebreid informatie te geven over de aandoening en over de consequenties op de korte en lange termijn. Deze voorlichting kan schriftelijk ondersteund worden door bijvoorbeeld een informatiefolder of een verwijzing naar de websites van de patiëntenvereniging en de beroepsverenigingen.

Bijlage 9: Implementatiestrategie

Inleiding
Dit plan is opgesteld ter bevordering van de implementatie van de richtlijn lichen sclerosus. Voor het opstellen van dit plan is een inventarisatie gedaan van de mogelijk bevorderende en belemmerende factoren voor het naleven van de aanbevelingen. Daarbij heeft de richtlijnwerkgroep een advies uitgebracht over het tijdspad voor implementatie, de daarvoor benodigde randvoorwaarden en de acties die door verschillende partijen ondernomen dienen te worden

Werkwijze

Om tot dit plan te komen heeft de werkgroep per aanbeveling in de richtlijn nagedacht over:

- Het tijdstip per wanneer de aanbeveling de implementatie gerealiseerd zou moeten zijn;
- De verwachtte impact van implementatie van de aanbeveling op de zorgkosten;
- Randvoorwaarden om de aanbeveling te kunnen implementeren;
- Mogelijk barrières om de aanbeveling te kunnen implementeren;
- Mogelijke acties om de implementatie van de aanbeveling te bevorderen;
- Welke partijen aan zet zijn.

Lezers van dit implementatieplan dienen rekening te houden met het feit dat er verschillen zijn tussen ‘sterke aanbevelingen’ en ‘zwakke aanbevelingen’. In het eerste geval doet de richtlijncommissie een duidelijke uitspraak over iets dat wel of niet gedaan moet worden. In het tweede geval wordt de aanbeveling minder zeker gesteld en spreekt de werkgroep haar voorkeur of advies uit, maar laat zij meer ruimte voor alternatieven. Een reden hiervoor is bijvoorbeeld dat er onvoldoende wetenschappelijk bewijs is om de aanbeveling te onderbouwen. Een zwakke aanbeveling is te herkennen aan de formulering en begint bijvoorbeeld met ‘Overweeg om…’. Zowel voor de sterke als voor de zwakke aanbevelingen heeft de werkgroep nagedacht over de implementatie. Alleen voor sterk geformuleerde aanbevelingen worden implementatietermijnen gegeven.

Implementatietermijnen

Voor de volgende aanbevelingen geldt dat implementatie op korte termijn gerealiseerd zouden moeten worden. In de meeste gevallen geldt hiervoor de termijn van 1-3 jaar. In onderstaande aanbeveling is dat 1 jaar.

Aanbeveling	**Toelichting**
Onderhoudsbehandeling	
Wij bevelen onderhoudsbehandeling van 1-4 keer per week met sterk tot zeer sterk (klasse 3-4) werkende corticosteroïd zalf aan bij patiënten met anogenitale LS.	In tegenstelling tot eerdere aanbevelingen wordt in de nieuwe richtlijn gezien de chroniciteit van de ziekte en het risico op anatomische veranderingen en maligne ontaarding, levenslange onderhoudstherapie aanbevolen. Het is belangrijk dat dit advies actief wordt verspreid onder dermatologen, gynaecologen, urologen en huisartsen.

Voor sommige aanbevelingen geldt echter dat zij niet direct overal kunnen worden ingevoerd, bijvoorbeeld vanwege een gebrek aan middelen, expertise of de juiste organisatievormen. In sommige gevallen dient ook rekening te worden gehouden met een leercurve. Daarnaast kan de aanwezigheid van personeel of faciliteiten of de afstemming tussen professionals een belemmering zijn om de aanbevelingen op korte termijn in te voeren. Voor de volgende aanbevelingen geldt daarom een implementatietermijn van één tot drie jaar:

Aanbeveling	Toelichting
Chirurgie bij mannen	
Verwijs mannelijke patiënten met LS en seksuele problemen naar een uroloog-seksuoloog of seksuoloog.	Het is belangrijk dat behandelaars van patiënten met LS inventariseren welke uroloog-seksuologen en seksuologen er in de regio werkzaam zijn en waar patiënten naar verwezen kunnen worden.
Chirurgie bij vrouwen	
Bij chirurgisch ingrijpen dient een preoperatief consult bij een seksuoloog NVVS en/of geregistreerd bekkenfysiotherapeut plaats te vinden.	Dit preoperatieve consult kan helpen bij het in kaart brengen van mogelijk seksuologische problemen, zoals bekkenhypertonie, die invloed hebben op de kans van slagen en de keuze voor het wel of niet uitvoeren van een operatie.
Overige therapie	
Bij patiënten met cutane lichen sclerosus die zeer uitgebreid is of die niet of onvoldoende reageert op behandeling met corticosteroïden of tacrolimus, kan lichttherapie overwogen worden.	Lichttherapie wordt ingezet als behandeling voor cutane LS. Omdat in de vorige versie van deze richtlijn alleen anogenitale LS werd beschreven ontbrak deze aanbeveling.
Behandeling bij kinderen	
Bij circumcisie vanwege een phimosis wordt histologisch onderzoek aanbevolen.	Er worden veel circumcisies bij phimosis uitgevoerd zonder dat er histologisch onderzoek wordt gedaan. Het implementeren van deze aanbeveling zal ervoor zorgen dat de diagnose LS bij jongens vaker gesteld wordt. Omdat de ziekte chronisch van aard is, is het belangrijk dat deze groep in kaart wordt gebracht zodat terugkerende ziekte vroeg herkend en behandeld kan worden.

Impact op zorgkosten

Veel aanbevelingen brengen geen of nauwelijks gevolgen met zich mee voor de zorgkosten. Een aantal aanbevelingen doet dit echter wel. In onderstaande tabel wordt per module beschreven welke aanbevelingen volgens de richtlijncommissie een belangrijk effect met zich meebrengen op de zorgkosten en welk effect dit is.

Aanbeveling	Toelichting
Onderhoudsbehandeling	
Wij bevelen onderhoudsbehandeling van 1-4 keer per week met sterk tot zeer sterk (klasse 3-4) werkende corticosteroïd zalf aan bij patiënten met anogenitale LS.	Mogelijk kostenstijgend door toenemende zorgvraag. Mogelijk kostenreducerend wegens voorkomen van verergering van de ziekte en/of maligne ontaarding.
Chirurgie bij mannen	
Verwijs mannelijke patiënten met LS en seksuele problemen naar een uroloog-seksuoloog of seksuoloog.	Kostenstijgend voor de patiënt aangezien seksuologische zorg niet vanuit de basisverzekering vergoed wordt.
Chirurgie bij vrouwen	
Bij chirurgisch ingrijpen dient een preoperatief consult bij een seksuoloog NVVS en/of geregistreerd bekkenfysiotherapeut plaats te vinden.	Kostenstijgend voor de patiënt aangezien seksuologische zorg niet vanuit de basisverzekering vergoed wordt. Mogelijk kostendalend omdat niet-noodzakelijke ingrepen worden voorkomen.

Overige therapie	
Bij patiënten met cutane lichen sclerosus die zeer uitgebreid is of die niet of onvoldoende reageert op behandeling met corticosteroïden of tacrolimus, kan lichttherapie overwogen worden.	Mogelijk kostenstijgend omdat de verspreiding van deze richtlijn zal zorgen voor meer bekendheid over het gebruik van lichttherapie bij LS.
Behandeling bij kinderen	
Bij circumcisie vanwege een phimosis wordt histologisch onderzoek aanbevolen.	Kostenstijgend omdat er meer biopsieën worden verricht. Mogelijk kostenreducerend omdat patiënten onder controle blijven en terugkerende ziekte eerder wordt herkend en adequaat kan worden behandeld.

Te ondernemen acties per partij

Hieronder wordt per partij toegelicht welke acties zij volgens de richtlijncommissie zouden moeten ondernemen om de implementatie van de richtlijn te bevorderen.

Alle direct betrokken wetenschappelijk verenigingen/beroepsorganisaties (NHG, NVDV, NVFB, NVK, NVOG, NVU, NVVS, NVvVP, NVZA en V&VN) bekend maken van de richtlijn onder de leden;

- publiciteit voor de richtlijn maken door over de richtlijn te publiceren in tijdschriften en te vertellen op congressen;
- verzorgen van (bij)scholing en training om ervoor te zorgen dat de gewenste expertise geleverd kan worden voor het naleven van de richtlijn;
- controleren van de toepassing van de aanbevelingen middels audits en de kwaliteitsvisitatie;

Initiatiefnemende wetenschappelijke vereniging (NVDV)

- bekend maken van de richtlijn onder de andere betrokken wetenschappelijke – en beroepsverenigingen.

De lokale vakgroepen/individuele medisch professionals

- het bespreken van de aanbevelingen in de vakgroepsvergadering en lokale werkgroepen;
- het afstemmen van lokale protocollen op de aanbevelingen in de richtlijn;
- aanpassen lokale patiënteninformatie op grond van de materialen die door de verenigingen beschikbaar gesteld zullen worden;
- afstemmen en afspraken maken met andere betrokken disciplines om de toepassing van de aanbevelingen in de praktijk te borgen;

De systeemstakeholders (onder andere zorgverzekeraars, NZA, (koepelorganisaties van) ziekenhuisbestuurders, IGZ)

Van zorgverzekeraars wordt verwacht dat zij fer mede toezien op implementatie van de zorg die in deze richtlijn wordt aanbevolen. Over het algemeen is het waarschijnlijk dat noodzakelijke investeringen voor de baat uit gaan. De ‘sterk geformuleerde aanbevelingen’ in deze richtlijn kunnen, na verloop van de aangegeven implementatietermijnen door zorgverzekeraars worden gebruikt voor de inkoop van zorg.

Wetenschappers en subsidieverstrekkers

Onderzoek initiëren naar de kennislacunes.

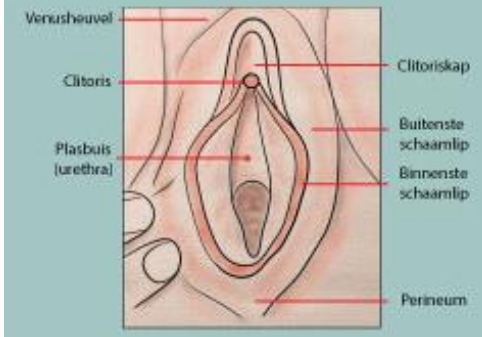
Toevoegen van richtlijn aan richtlijnendatabase. Opnemen van dit implementatieplan op een voor alle partijen goed te vinden plaats.

Bijlage 10: Zelfonderzoek van de vulva*

**Stichting Lichen Sclerosus (SLS) folder 'Zelfonderzoek van de vulva'*

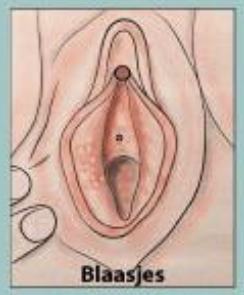
Hoe kun je de vulva zelf onderzoeken?

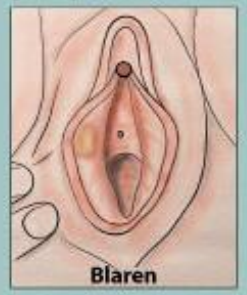
Allereerst leggen we uit wat een vulva is!
De vulva is de huid rondom de schede
(de schede of vagina is het inwendige deel
van het geslachtsorgaan).
De vulva bestaat uit:

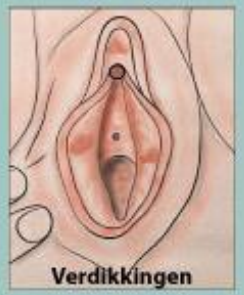


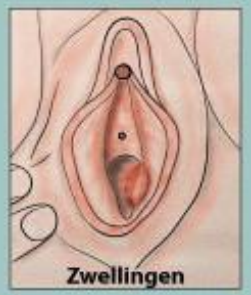
Om de vulva zelf te onderzoeken ga je in een voor jouw makkelijke houding staan of zitten. Met één hand spreid je de schaamlippen vervolgens kun je nu met een spiegel in de andere hand de vulva bekijken.
Het kan ook handig zijn om een foto te maken met je mobieltje.
Doe wat je het prettigst vindt.

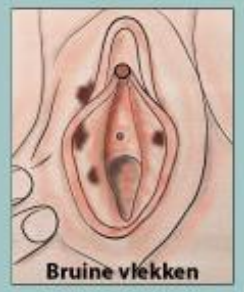
Waar moet u vervolgens op letten

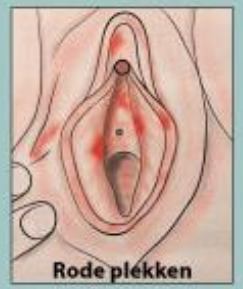

Blaasjes

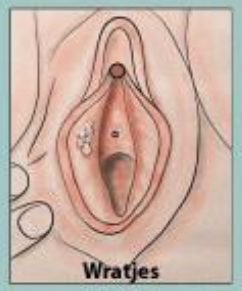

Blaren

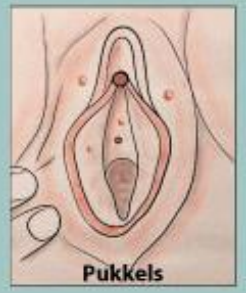

Verdikkingen

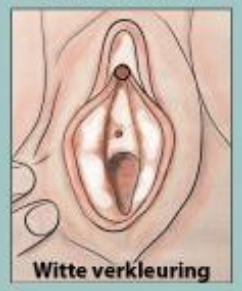

Zwellingen


Bruine vlekken

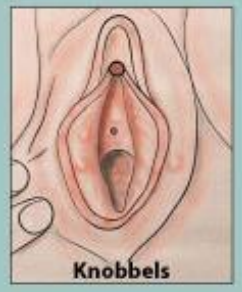

Rode plekken

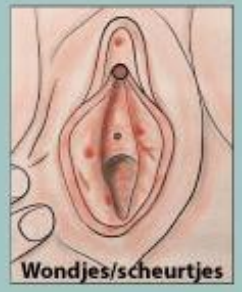

Wratjes


Pukkels


Witte verkleuring


Kleiner wordende binnenste schaamlippen


Knobbels


Wondjes/scheurtjes

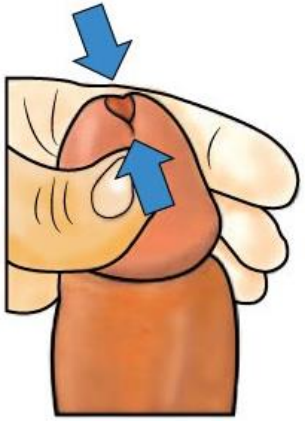
Doe dit zelfonderzoek 1 x in de 1 á 2 maanden.
Het belangrijkste doel is dat u verschil kunt opmerken!
Zo kunt u zelf in de gaten houden of er veranderingen zijn.

Als u één van bovenstaande afwijkingen ziet, schroom dan niet om naar de huisarts te gaan.

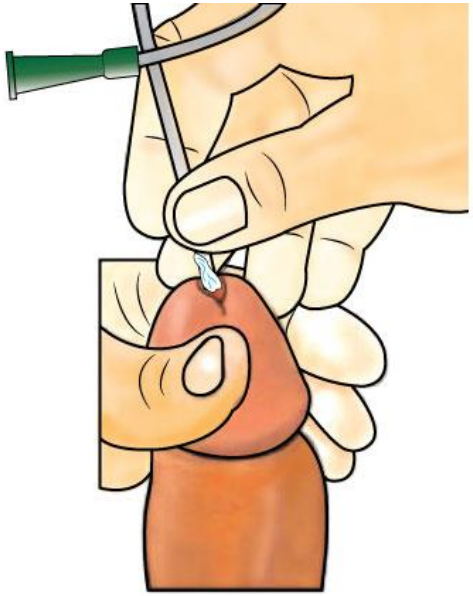
Mocht de huid anders aanvoelen dan je gewend bent en zijn er geen zichtbare veranderingen, ga ook dan naar de huisarts.

Bijlage 11: Topicale behandeling intra-urethraal, mannen

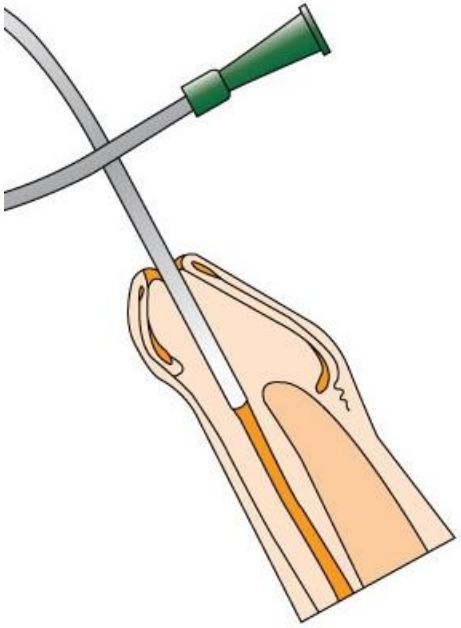
Illustraties: Ellen Swanborn

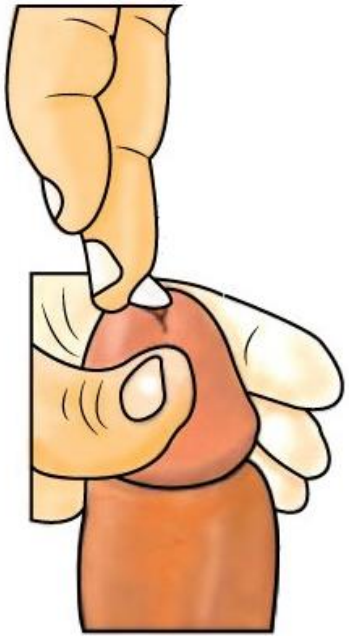


1) Knijp voorzichtig om de opening van de plasbuis te vergroten



2) Breng de katheter met de zalf in de opening van de plasbuis tot aan het punt wat vooraf met de arts is afgesproken



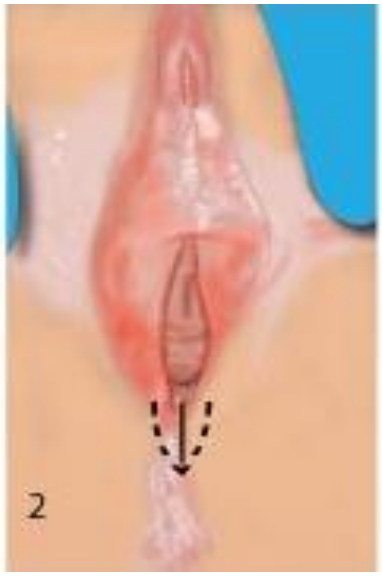


3) Smeer de overgebleven zalf voorzichtig in de opening van de plasbuis

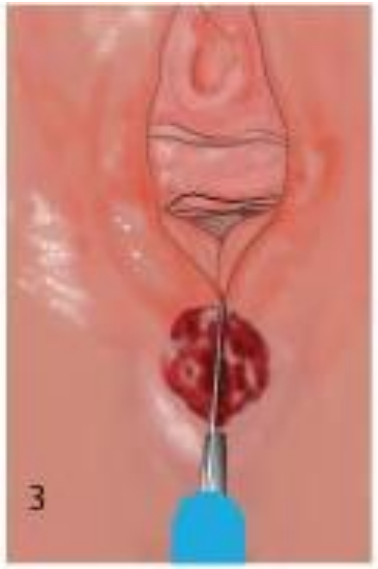
Bijlage 12: Introïtusplastiek*

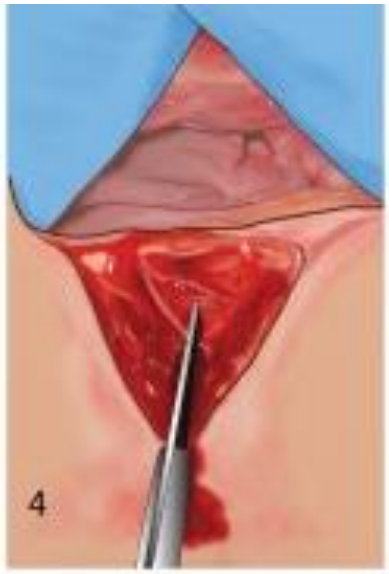
** Stichting Lichen Sclerosus (SLS) folder 'Introïtusplastiek'*

1) Vulva

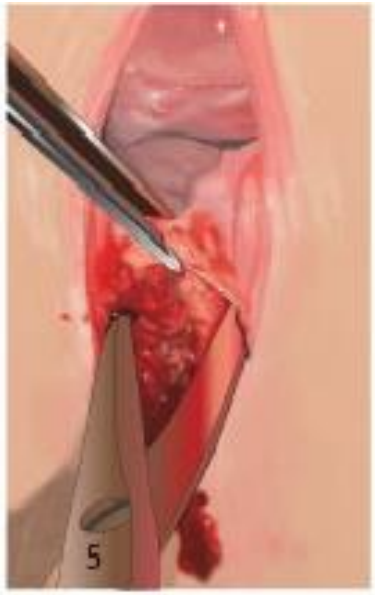


2) In te snijden huid en gestippeld de nieuwe situatie

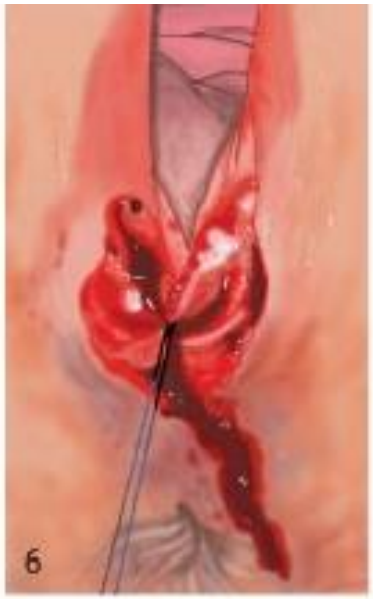




3/4) Na de plaatselijke verdoving wordt in de lengte richting ingesneden



5) De vagina-achterwand wordt losgemaakt om deze later iets naar buiten te brengen

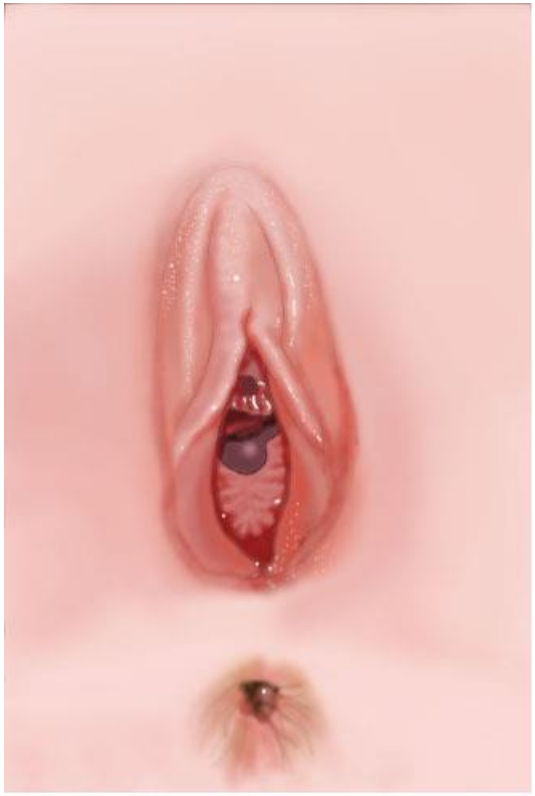


6) De eerste hechting word onder de huid geplaatst

7) De wond wordt doorlopend dwars geslotenen. Dit is het eindresultaat direct na de ingreep.

Bijlage 13: Genitaal kinderen

Illustraties: Ellen Swanborn



Meisje zonder lichen sclerosus

Meisje met lichen sclerosus