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Proposition of standardized protocol for photodynamic therapy for vulvar lichen sclerosus

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Abstract

Background: Photodynamic therapy (PDT) is an alternative treatment modality for vulvar lichen sclerosus (VLS) which is a chronic inflammatory mucosal condition. In literature, no consensus of optimal parameters of PDT for VLS are reached so far.

Objectives: The aim of this narrative review is to develop a standardized treatment protocol for PDT in VLS

Methods: A systematic literature search was conducted to identify studies reporting on PDT in VLS and used treatment parameters, side-effects and clinical outcome were summarized.

Results: Thirteen studies used 5-aminolevulinic acid (5-ALA) with concentrations of 20%, 10%, 5% and three studies used methyl aminolevulinate. Generally the light source was red light (median 630 nm). Light dose varied between 9 and 180 J/cm² and light intensity between 40 and 700 mW/cm². Incubation period with the photosensitizer ranged from two to six hours. All studies showed a substantial improvement of VLS-related pruritus, burning and pain.

Conclusion: Based on a literature review we suggest the following protocol for PDT in VLS: 5% 5-ALA as a photosensitizer applied for three hours under occlusion before irradiation at the dose of 120 J/cm² with red light (590-760 nm) and intensity of 204 mW/cm².

Keywords: protocol, photodynamic therapy, PDT, vulvar lichen sclerosus

Introduction

Vulvar lichen sclerosus (VLS) is a chronic progressive inflammatory dermatosis. Although it can occur at any age, a bimodal distribution was recorded with one peak in prepubertal girls and a second higher peak in peri- and postmenopausal women [1,2]. The incidence rate of VLS doubled from 7,4 to 14,1 per 100 000 woman-years between 1991 and 2011 [3]. Generally, VLS's main symptom is pruritus (93%), which frequently causes complications [4]. For instance scarring can lead to narrowing of vaginal introitus and clitoral hood adhesions. This might induce the formation of pseudocysts, which in turn might lead to dysuria, dyspareunia, pain during defecation, bleeding and a need for surgical reconstruction [5–7]. All these symptoms and malformations result in sexual and social dysfunction and distress, which negatively affects quality of life (QoL) [8,9]. Furthermore, VLS has been associated with the development of vulvar squamous cell carcinoma (VSCC) [10]. In women with VLS the cumulative risk of VSCC was found to be 14,8% while only 0,06% in the female general population [11]. In 3,2% to 57,9% of cases VLS shows to be asymptomatic and is only discovered by routine examinations [4,12]. Despite an initial asymptomatic appearance, malignancy can still occur, possibly leading to death [13].

To date, evidence-based data underpinning treatment of VLS are scarce [14]. Current guidelines recommend potent topical corticosteroids (TCS) as a first-line treatment [7,15]. Yet, TCS only act symptomatically. There is no evidence for TCS to influence or stop the course of disease [16]. Moreover, TCS can trigger a latent HPV infection and can suppress immunity leading to malignancy [17]. Especially in woman older than 70 years, resistance and recurrence of VLS is observed under TCS [18]. Furthermore, topical calcineurin inhibitors (TCI) have shown to be effective [15,19]. Nonetheless consensus on the safety profile for long-term use is lacking because of a potential increased risk of neoplasia [15,19,20]. Although not widely studied, other therapies such as testosterone, progesterone,

retinoids and cryotherapy have not proven to be more effective than TCS and TCI [15,21]. A safe and effective therapeutic alternative for VLS has yet to be found.

Photodynamical therapy (PDT) is a known treatment for actinic keratoses (AK), superficial and nodular basal cell carcinoma (BCC) and Bowen's disease (or in situ squamous cell carcinoma (SCC)) [22]. By topically applying a photosensitizer, containing light-sensitive molecules which accumulate in pathological tissue, and using a light source with the corresponding wavelength, cytotoxic reactive oxygen species will be produced and lead to cell death [23,24]. Recently, PDT was introduced as a treatment for infective and inflammatory dermatosis, including VLS. First results are promising [23,25]. In case of VLS, PDT has shown to reduce symptoms and histological aberrations [26]. Although PDT is increasingly used in VLS, standardization of PDT is lacking, which complicates the comparison of study results. The way PDT is applied differs widely. More specifically, different photosensitizers, light sources, ranges of irradiation dose and intensity are used.

So, a well-established and standardized protocol for PDT in VLS is needed [27]. The aim of this study was to propose a standardized protocol for the application of PDT in VLS in adult women. Therefore, we conducted a literature study on the application of PDT in VLS and its results. Our research questions were: 1) What are the characteristics of the population that has been treated with PDT in terms of age, duration of disease, VLS treatment in the past; 2) what are the procedural details of the application of PDT e.g. light source, wavelength, irradiation dose and intensity, photosensitizer and its concentration, occlusion method; 3) which procedural details are associated with favourable therapy results; 4) what are the side effects of PDT for VLS?

Methods

We conducted a narrative review to evaluate the procedure of PDT in VLS. Articles were identified using a computerized literature search in ClinicalTrials.gov, ISRCTN, ICTRP, Cochrane library, EudraCT database, MEDLINE and Embase until April 2019. MeSH terms and free-text words specifying each of the two components of the search question – PDT and VLS - were combined. A detailed overview of the search can be found in the appendices. A manual inspection of the results was done, which is presented in Figure 1. Articles were included if they described an empirical study assessing PDT as a treatment for VLS diagnosed female adults (18 years or older). The study outcome needed to contain the impact on symptomatic, clinical or histological features after treatment. Prospective cohort studies, case series, case reports and randomized controlled trails (RCT) were included. Ongoing trial, a completed trail without available results, a conference abstract and a guideline were excluded. After applying our in/exclusion criteria, we extracted the following data from the remaining body of studies: characteristics of patients who had been treated with PDT (age, duration of disease, previous VLS treatments), the procedural details of the application of PDT (light source, wavelength, irradiation dose and intensity, photosensitizer and its concentration, occlusion method, incubation time, management before and after PDT), therapy results and the side effects of PDT.

Results

We investigated relevant data concerning procedural details of the application of PDT. Overall, most of the studies used the photosensitizer 5-aminolevulinic acid (5-ALA) while a few studies applied methyl aminolevulinate (MAL). Data with regard to study type and patient characteristics are displayed in table 1 in a concise and stately manner. Table 2 gives more insight into the procedural details on how PDT was performed in the included articles.

Table 3 provides information about the side effects before and after treatment. In the appendices, the protocol can be found in more detail. The treatment of VLS with PDT remains a clinical challenge, untill now there is no standardized treatment protocol about parameters, such as concentration of ALA, incubation time, light source (power and wavelength), exposure time (energy density and power density), and number and frequency of treatment repetitions to treat VLS. This narrative review gives an overview of procedural details of the application of PDT in order to develop a standardized treatment protocol for PDT in VLS.

More than half of the studies with 5-ALA used 20% of 5-ALA for PDT in VLS (Table 2). The study of Hillemanns et al. [28], with 12 cases, was the first to introduce 20% of 5-ALA for PDT in VLS. When we look further at the parameters reported in the studies, Hillemanns et al. [28], Osiecka et al. [29] and Sotiriou et al. [30,31] used an incubation time of four hours, with different irradiation dose and intensity (80 J/cm², 150 J/cm², 40 J/cm² and 70mW/cm², 100 mW/cm², 80 mW/cm², respectively). While others, Biniszkiewics et al. [17] and Romero et al. [32] used a shorter incubation with various irradiation dose and intensity (180 J/cm², 30 J/cm² and 700 mW/cm², 80 mW/cm², respectively). Remarkably, only Biniszkiewicz et al. [17], in which 24 cases have been described used high irradiation parameters (180 J/cm² - 700 mW/cm²). Moreover in the two small cohort studies of Sotiriou et al. [30,31], lesions were sealed with cellophane wrap and Sotiriou et al. [31] was the only study who has demonstrated the effect of PDT with 20% 5-ALA in VLS histopathologically. According to this study no histopathological differences were observed after treatment. It should also be noted that Osiecka et al. [29] and Romero et al. [32] had only one case in the study. Within the 20% 5-ALA group, all studies reported a considerable reduction in subjective symptoms, described as pruritus, burning and pain after treatment. However, minor or no improvement was detected in clinical signs in the 20% 5-ALA group. In contrast to the

studies described above, Osiecka et al. [33] used green light. After cleaning the vulva with 0.9% saline solution, they applied 20% 5-ALA under cellophane wrap occlusion for five hours. A green halogen light (540 nm) with a bandpass filter at a dose of 62,5 J/cm² and an intensity of 85 mW/cm² was used in a fractioned mode: two minutes of irradiation followed by one minute pause. They also observed a clear improvement in pruritus using PDT with this green light.

Furthermore, Lan et al. [27], Shi et al. [34] and Olejek et al. [35] used a 10% concentration of 5-ALA. They all used the same protocol in their studies: lesions were treated three hours after 10% concentration of 5-ALA application -with or without occlusion- with red light (630-635 nm) at a total light dose of 100 J/cm². They all reported improvement in subjective symptoms, but histopathological differences were not demonstrated (Table 2). Olejek et al. [35], one of the largest studies (n=100) on the subject, used two light sources, group I was treated with red light (DIOMED 630 nm) as group II was treated with a combination of visible light and water-filtered infrared A (PhotoDyn® 750, 580–1400 nm). Only, in Shi et al. [34] erosions after PDT were treated with mupirocin ointment for one week. The other two articles did not reported any after-treatment [27,35]. In summary the three studies reported decrease in subjective symptoms. Olejek et al. [35] concluded a relevant subjective symptom reduction with both types of lamps, without significant difference in results between the two groups. The two smallest studies Lan et al. [27] (n=10) and Shi et al. [34] (n=20) also described a substantial improvement in objective lesion characteristics.

The two largest studies of Maździarz et al. and Olejek et al. (2010) (102 and 100 patients respectively) applied a 5% of 5-ALA with three hours incubation time and utilized a halogen lamp with orange to red (590 – 760 nm) and red light (Table 2). Maździarz et al. [36] added dimethyl sulfoxide (DSMO) in there applied product and reported an irradiation dose of 120 J/cm² at an intensity of 204 mW/cm², while Olejek et al. [37] did not reported the

irradiation dose and intensity. Maździarz et al. [36] showed that 61% of the patients had a total disappearance and 17% had a partial improvement of the subjective symptoms, while Olejek et al. [37] reported 51% and 41% respectively. In addition, Maździarz et al. [36] showed objective improvement of the clinical signs. Interestingly, Olejek et al. [37] performed a histopathologic examination. They established histopathologically that the 100 patients had VLS before treatment. And after treatment they found the histopathological characteristics of VLS only in 39% of the cases, which means that 61% of the patients no longer had lichen sclerosus after PDT treatment.

Remarkably, only Zawislak et al. [38] used a patch with 5-ALA for surface release. Lesions were treated with a non-laser red light (630nm) at an irradiation dose of 100 J/cm². The incubation time ranged from four to six hours, which is higher than the average time used in 5-ALA. Improvement of pruritus and discomfort were noticed after treatment.

Finally, Vano-Galvan et al. [39], Imbernon-Móya et al. [40] and Cabete et al. [41] applied methyl aminolevulinate (MAL) – the methyl ester of 5-ALA - and added an occlusive dressing immediately afterwards. Prior to a low irradiation of 9 J/cm², Vano-Galvan et al. [39] injected intralesional 2% mepivacaine for a local anesthetic effect after two hours of incubation. On the other hand the two other studies led MAL absorb for three hours followed by an irradiation dose of 37 J/cm². The authors reported a particular after-treatment management with TCS or daily topical amitriptyline [40,41]. After application of MAL-PDT, good responses on subjective symptoms were reported [39–41]. Clinical signs of VLS did not improve after treatment in the three studies, which are analogous results compared to 20% 5-ALA studies.

The side effects of PDT

During treatment sensations of burning, itching, warmth, pain, stinging ranging from weak to intense are described in 12 of 13 studies who were treated with 5-ALA (Table 3)

[17,27–34,36–38]. Also after treatment pain, burning, erythema, edema and erosion were reported, lasting from a few hours post-treatment till one week. Solely Olejek et al. [35] reported that no visible side effects were reported.

The study with green light of Osiecka et al. [33] described the same side effects as red light, but under green light the side effect lasted less long. Although, red light studies, such as Maździarz et al. [36] and Zawislak et al. [38], reported less side effects compared to the green light studies.

Anesthesia was used in the three studies which used MAL. Vano-Galvan et al. [39] applied intralesional mepivacaine to prevent pain. It is not clear if this analgesia was sufficient, but the injections were distressing too. As Imbernon-Móya et al. [40] and Cabete et al. [41] used sedation or general anesthesia, no side effects were reported during treatment. For Imbernon-Móya et al. [40] side effects after treatment were likewise the 5-ALA studies, with the exception of micturate difficulty and longer duration time.

Discussion

The aim of this review is to propose a standardized protocol for the application of PDT in VLS in adult women in our daily practice. In particular this study seeks to identify parameters, such as concentration of ALA, incubation time, light source, exposure time, number and frequency of treatment repetitions of PDT to treat VLS. Therefore we made an overview of the current data regarding the use of PDT in VLS. The literature was screened in order to obtain a broad dataset.

The results of this study have shown that PDT is studied especially in single-arm cohort studies with postmenopausal women. Mean age ranged from 48 to 68 years without taking into account the case reports. The majority of patients had unsatisfying treatment for VLS in the past while suffering from VLS for many years.

If we look to the procedural details of the application of PDT with photosensitizers 5-ALA, only a few studies have performed histopathological examination. Maździarz et al al. [36] with 5% 5-ALA have done a histopathologic examination but the changes on biopsies post- and pretreatment were not reported. Histopathological improvement is stated only in the study of Olejek et al. [37] with 5% 5-ALA. Sotiriou et al. [31] using 20% 5-ALA and Zawislak et al. [38] using a 5-ALA patch reported no significant differences in histopathological features between the post- and pretreatment biopsies. PDT in all studies showed a substantial improvement of pruritus, burning and pain. However improvement of clinical sings such as hyperkeratosis, sclerosis, atrophy and depigmentation, was only reported in the minority of cases. Minor or no improvement in clinical signs was detected in the 20% 5-ALA group. Interestingly, Lan et al. [27] and Shi et al. [34] with 10% 5-ALA in a small group of 10-20 patients and Maździarz et al. [36], with 5% 5-ALA in a sample of 102 patients did indeed observe objective clinical improvement. Although improvement of subjective symptoms are reported in every study, side effects were not reported consistently. Only the study of Olejek et al. [35] reported no visible side effects while almost all other studies without anesthesia reported side effects such as burning pain and erythema during and after treatment. Regarding the number of patients and the safety data of studies we opt for the use of low photosensitizer concentration, 5% 5-ALA. While the limited number of previous studies makes comparison difficult, the use of 20% and 10% 5-ALA have no clear added value. Therefore, we recommend to use of 5% 5-ALA in PDT for VLS.

Generally, the used light source was red. Interestingly, one study used green light with fractioned irradiation [33]. They stated that red light induces severe local pain during illumination while green light (495 nm - 570 nm), together with fractioned irradiation, could be effective and less painful in PDT setting. The results reported that improvement of symptoms was established in some patients and the side effects were categorized as weak to

moderate, but similar outcomes were seen in studies with red light. These results would seem to suggest that green light is not superior to red light. Subsequently, we commend red light (wavelength 590-760 nm) and light dose of 120 J/cm² and intensity of 204 mW/cm², corresponding with the methodology of the 5% 5-ALA studies which showed objective and histopathological improvement in a large population [36,37]. None of the studies reported the distance between the lamp and the skin surface. We opt a distance of 5 to 8 cm, likewise in the treatment of actinic keratosis [42].

The use of any other treatment than PDT for VLS was an exclusion criteria. Nevertheless TCS were prescribed during treatment in the study of Imbernón-Moya et al. [40]. Furthermore, Romero et al. [32] and Sotiriou et al. [31] reported that at three months follow-up mild symptoms of VLS recurred, but these could be controlled with TCS. According to Osiecka et al. [29], not only PDT was responsible for symptom relief in their patient with hypothyreosis, but also the added thyroid hormone therapy contributed to this success. Concerning DSMO, it is indicated that 20% DMSO may enhance the penetration of 5-ALA into the skin [43,44]. Olejek et al. [35] claimed as well that theoretically DSMO can have an analgesic effect if it used in a high concentration.This statement is not completely supported in literature [45]. Due to the limited number of studies included which used DMSO [35,36], no conclusions could be made. The number of PDT sessions performed per study is not discussed in this review. With the reason that a great variation was identified: from one session [31] to ten sessions [36,37], with a fixed interval of one week [36] to one month [39] or individualized and dependent of the duration of response of the previous session [38]. Therefore, the incoherent picture of the number of iterations and the interval fell beyond the scope of this review. The point in time of evaluation is an important factor in the light of correct interpretation of the results. Namely, the symptom reduction due to PDT changes over time. The best results are observed shortly after treatment. During follow-up, the symptoms

might recur. With this knowledge, we decided to use and interpret the results of the last follow-up whenever possible [29,33,34].

Regarding the application area of the photosensitizer, three groups can be found. First, a group applied the photosensitizer on the entire vulva [30–32,41]. Second, studies applied the photosensitizer topical on the lesions, with a 10 mm margin [27,33–35,39]. At last, a group of studies only described the total amount of photosensitizer used, which was 10 g and 10 ml [17,28]. Other studies, including the two 5% 5- ALA studies, did not specify their appliciation site [29,36,37,39,40]. As the three 10% 5- ALA studies applied the photosensitizer on the lesions with a margin of 10 mm with good subjective and objective results, we follow this application method [27,34,35]. Occlusion of the photosensitizer was reported in nine out of sixteen studies in form of plastic film [27], self-adhesive foil [35], cellophane wrap [30,31,33], patch [38] or not specified [39–41]. We cannot confirm that occlusion gave a better clinical outcome compared to studies without occlusion. Taken into account that women will close their legs, sit or walk around during incubation of the photosensitizer, we propose the use of a cellophane wrap. Also a variation in incubation time was reported. Corresponding with the methodology in which 5% 5-ALA was used, we suggest an incubation time of three hours.

The preparation of the skin before application is rarely reported in the included studies. To prevent removal or relocation of the photosensitizer, we recommend to urinate before application in order to avoid this act during incubation time. With the assumption that the photosensitizer should penetrate the affected skin equally, the vulva should be cleaned after urination with 0,9% saline solution.

The application of a photosensitizer is not only an approach for treatment in form of PDT, but also a way to diagnose VLS. Photodynamic diagnosis (PDD) was conducted in seven of sixteen included studies [17,28,33–35,38,39]. Solely Biniszkiewicz et al. [17] used

PDD as an outcome. We suggest to perform PDD in order to evaluate the treatment effectiveness and to estimate how many sessions the patient might need in the future.

Side effects related to the treatment are reported in all studies except in the study of Olejek et al. [35]. In literature, Warren et al. [46] reported conflicting results with regard to the relation between pain and irradiation dose. This is in line with what is observed in the studies included in this review. The two 5% 5-ALA studies did not use anesthesia. We suggest, analogous to treatment of PDT in actinic keratosis, side effects of pain or burning sensations during illumination could be treated with a xylocaine spray, applied before treatment, or a water spray during treatment. After illumination, a cold pack can be applied [46].

Protocol

We recommend a protocol for PDT in VLS. Regardless of previous treatment, all patients with VLS of 18 years and older can be included. We choose application of 5% 5-ALA. After three hours incubation time, illumination with red light (wavelength 590-760 nm) and light dose of 120 J/cm² and intensity of 204 mW/cm² is recommended.

As a preparation before application, we recommend that the patient should urinate and that the vulva should be cleaned after urination with 0,9% saline solution. The photosensitizer should be applied on the individual lesions with a margin of 10 mm and occluded with a cellophane wrap. We suggest a distance of five to eight centimeters between the lamp and skin surface during illumination. Right before illumination, we suggest to perform PDD with a blue light and pictures must be added to the patient's file. Side effects during illumination could be treated with a xylocaine spray or a water spray.

Conclusion

This summary provides a support for future research in PDT in VLS in order to establish evidence based medicine. Based on the clinical outcomes of the included studies, we described a protocol with the procedural details of PDT. Namely, 5% 5-ALA as a photosensitizer with red light (590-760 nm), an irradiation dose of 120 J/cm² at an intensity of 204mW/cm², an incubation time of three hours under occlusion with cellophane wrap. However, clinical outcomes of the individual studies were often difficult to compare because of the variation in used scoring systems of the symptoms. Therefore, further research regarding a standardized scoring system for VLS is required. This to accurately compare treatments methods in future research.

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Disclosure of interest

The authors report no conflict of interest

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Appendix 1: The following databases were searched:

1. ISRCTN [1] using "vulval lichen sclerosus AND (Interventions: PDT)"
2. ClinicalTrials.gov [2] using “PDT AND vulvar lichen sclerosus”
3. ICTRP [3] using “vulvar lichen sclerosus and PDT”
4. Cochrane Library [4] using “vulvar lichen sclerosus and PDT” .
5. EudraCT database via EU clinical trial register [5] using “vulvar lichen sclerosus AND PDT”
6. MEDLINE via Pubmed [6]:
    a. (("Vulvar Lichen Sclerosus"[Mesh]) AND "Photochemotherapy"[Mesh]) AND "Aminolevulinic Acid"[Mesh])
    b. (("methyl 5-aminolevulinate" [Supplementary Concept]) AND "Vulvar Lichen Sclerosus"[Mesh]) AND "Photochemotherapy"[Mesh]
    c. ("methyl 5-aminolevulinate" [Supplementary Concept]) AND "Vulvar Lichen Sclerosus"[Mesh]
    d. ("Photochemotherapy"[Mesh]) AND "Vulvar Lichen Sclerosus"[Mesh]
    e. ("Photochemotherapy"[Mesh]) AND "Lichen Sclerosus et Atrophicus"[Mesh]
    f. “MAL PDT vulvar lichen sclerosus”
    g. “Lichen sclerosus PDT”
7. Embase [7]: “lichen sclerosus et atrophicus” AND “photodynamic therapy”

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Appendix 2: Protocol

A. Preparation of patient and skin

1. Ask the patient to urinate before application.
2. After undressing, clean the vulvar area with a 0,9% saline-soaked cotton pad.

B. Pictures of treatment area

3. Take pictures of the vulva with a clear view of all the lesions.

C. Application of photosensitizer: 5% 5- ALA

4. Apply a layer of 5% 5- ALA evenly with a spatula or protected fingertips to every lesion with a thickness of 1 mm and a margin of 1 cm.

D. Occlusion

5. Place cellophane wrap in order to cover every applied lesion. The patient puts on her clothes gently.

E. Incubation time: 3 hours

6. The photosensitizer and its occlusion stay in place for 3 hours.
7. Afterwards remove the cellophane wrap and wipe off the remnant fluid of the photosensitizer with a 0,9% saline-soaked cotton pad.
8. Apply xylocaine spray on the lesions and let it air dry.

F. Illumination

9. Immediately after cleaning, install patient for illumination.
10. To conduct PDD, take pictures of all lesions and capture red fluorescence while shining with a blue halogen light source.
11. Distance between skin surface and lamp should be between 5 and 8 cm.
12. Start illumination with red light, approximately wavelength of 590-760 nm and a light dose of 120 J/cm² and intensity of 204 mW/cm².

13. Check whether all lesions are illuminated. If the size of the light field doesn't cover all lesions, a second illumination should be done for the lesions that were previously not illuminated.
14. During illumination: ask the patient about pain, burning or other symptoms. If necessary, ofer some cooling by spraying water.

G. After illumination

15. When in pain, wrap a cold pack in a cloth and apply on the lesions.

Table 1. The study and patients characteristics of the included articles (n=16).

Author, year, reference	Study type	Patient no.	Age	Duration of disease	Previous VLS treatment	Biopsy proven
Hillemanns et al., 1999 [28]	prospective, single-arm cohort	12	55	NR	NR	yes
Osiecka et al., 2012 [29]	case report	1	30	3	TCS TCI	yes
Sotiriou et al., 2008 [30]	case series - letter to editor	10	54.6	3.9	TCS TCI	yes
Sotiriou et al., 2008 [31]	case series - letter to editor	5	61.4	4.6	TCS TCI	yes
Biniszkiewicz et al., 2005 [17]	prospective, single-arm cohort	24	58	0.4 - 11*	NR	yes
Romero et al., 2007 [32]	case report - letter to editor	1	61	15	TCS TCI surgery[1]	yes
Osiecka et al., 2017 [33]	prospective, single arm cohort	11	48	1.5 - 4*	TCS TCI oestrogens	yes
Lan et al., 2018 [27]	case series	10	51	3.38	TCS TCI cryosurgery estrogens UVA1 local injection	yes
Shi et al., 2016 [34]	RCT	20 - 20 °	50.7	NR	NR	yes
Olejek et al., 2017 [35]	prospective, open, controlled cohort	100 (40 - 60)°°	57.6†	3.8 **	NR	yes
Maździarz et al., 2017 [36]	prospective, open, single-arm cohort	102	55,08	4.59	TCS	yes
Olejek et al., 2010 [37]	prospective, singel-arm cohort	100	54	NR	TCS	yes
Zawislak et al., 2009 [38]	prospective, single-arm cohort	8 - 2 °°°	NR	NR	NR	yes
Vano-Galvan et al., 2009 [39]	case report - letter to editor	1	68	5	TCS TCI	yes
Imbernón-Moya et al., 2017 [40]	case series - letter to editor	8	65	NR	TCS TCI	yes
Cabete et al., 2015 [41]	case report	1	75	15	TCS amitriptylin	yes

Age and duration of disease are mean values presented as numbers in years.

* Range of duration; [1] surgery specified as vulvectomie and reconstruction; ° number of patients respectively in group I (PDT) and group II (clobetasol treatment); °° number of patients respectively in group I (DIOMED 630 nm) and group II (PhotoDyn ® 750 (PD750), 580–1400 nm); † mean age of group I (57 years) and group II (58,5 years); ** mean duration of group I (3,6 years) and group II (4,2 years); °°° number of patients respectively diagnosed with vulvar lichen sclerosus and squamous hyperplasia.

Abbreviations: TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; NR, not reported; RCT, randomized controlled trial.

Table 2. Procedural details of the included studies (n=16).

Author, year, reference	Photosensitizer	Preparation before application	Occlusion	Incubation time	Light source	Light dose and intensity	Management after treatment
Hillemanns et al., 1999 [28]	20% 5-ALA	NR	NR	4 to 5	red - argon ion–pumped dye laser - 635 nm	80 J/cm² 70 mW/cm²	cream base
Osiecka et al., 2012 [29]	20% 5-ALA	NR	NR	4	red- HL - 630 nm	150 J/cm2 100 mW/cm2	NR
Sotiriou et al., 2008 [30]	20% 5-ALA	NR	yes	4	red - noncoherent light source - 570–670 nm	40 J/cm² 80 mW/cm²	NR
Sotiriou et al., 2008 [31]	20% 5-ALA	NR	yes	3	red - non-coherent light source - 570–670 nm	40 J/cm² 80 mW/cm²	NR
Biniszkiewicz et al., 2005 [17]	20% 5-ALA	NR	NR	2,5	red - laser - 630 nm	180 J/cm² 700mW/cm²	NR
Romero et al., 2007 [32]	20% 5- ALA	NR	NR	2	red - LED - 633 nm	30 J/cm² 80 mW/cm²	clobetasol oint. after 3-6 m
Osiecka et al., 2017 [33]	20% 5-ALA	cleansing the area with 0.9% saline solution	yes	5	green - HL - 540 nm ± 15 nm with a bandpass filter	62.5 J/cm² 85 mW/cm² fractionated: 2min irradiation -1min pause	NR
Lan et al., 2018 [27]	10% 5-ALA	NR	yes	3	red - LED - 635±15 nm	100 J/cm² 100 mW/cm² 20 m	NR
Shi et al., 2016 [34]	10% 5-ALA	urinate - cleaning	NR	3	red - diode laser - 633 nm	100 J/cm² 100 mW/cm²	mupirocin oint. for erosion for 1 w
Olejek et al., 2017 [35]	10% 5- ALA with 20% DSMO	NR	yes	3	group I: red - laser - 630 nm group II: red/orange - VIS + water-filtered infrared A, 580–1400 nm	100 J/cm² 40–80 mW/cm²	NR
Maździarz et al., 2017 [36]	5% 5- ALA with 2% DMSO	NR	NR	3	orange/red - HL - 590–760 nm	120 J/cm² 204 mW/cm² (10min)	NR
Olejek et al., 2010 [37]	5% 5-ALA	NR	NR	3	red - HL	NR	NR
Zawislak et al., 2009 [38]	5-ALA patch 38.0 mg per cm²	NR	yes	4 to 6	red - non-laser light source - 630 nm	100 J/cm²	NR
Vano-Galvan et al., 2009 [39]	MAL (Metvix®)	intralesional 2% mepivacaine	yes	2	red/orange - pulsed dye laser - 595-nm	7 mm, 6 ms, 9 J/cm²	NR
Imbernón-Moya et al., 2017 [40]	MAL (Metvix®)	NR	yes	3	red - noncoherent - 630 nm	37 J/cm² 70 mW/cm² (9min45s)	TCS
Cabete et al., 2015 [41]	MAL	NR	yes	3	red - 630nm	37 J/cm² (8min20s)	amitriptylin and emollient daily

(legend of table on next page)

Incubation time in hours. Light source is defined as: color of light - type of light source - wavelength. Irradiation parameters are presented as indicated in the articles with duration time between parentheses () if available.

Abbreviations: 5-ALA, 5-aminolevulinic acid; NR, not reported, HL, halogen lamp; LED, light-emitting diode; oint., oitment; DMSO, dimethyl sulfoxide; VIS, visible light; MAL, methyl aminolevulinate; m, month, w, week; s, seconds; min, minutes

Table 3. Side effects during and after treatment of the included articles (n=16).

Author, year, reference	During treatment	After treatment
Hillemanns et al., 1999 [28]	burning sensation	burning discomfort (mild) [4-8h], erythema [1-3 d]
Osiecka et al., 2012 [29]	itching	burning [24h]
Sotiriou et al., 2008a [30]	burning and stinging sensation	erythema [1w]
Sotiriou et al., 2008b [31]	burning sensation	erythema [3-5 d]
Biniszkiewicz et al., 2005 [17]	warmth and pain (intense), requiring 1-2min interruption of irradation	local toxicity (minimal) included vulvar erythema
Romero et al., 2007 [32]	pain (moderate)	pain (moderate) [3 - 4d]
Osiecka et al., 2017 [33]	itching, pain (weak to moderate)	swelling, erythema (immediately after treatment)
Lan et al., 2018 [27]	pain, burning sensation	pain (VAS ± 4/10) and burning sensation [3h] erythema and swelling [2-4d]
Shi et al., 2016 [34]	pain: PR-NRS ± 4/10*	erythema, edema and erosion
Olejek et al., 2017 [35]	no visible side effects	no visible side effects
Maździarz et al., 2017 [36]	paresthesia “pins and needles” [first 2–3 sessions], discomfort (minor)	swelling [few h]
Olejek et al., 2010 [37]	burning irritation (soft)	burning (soft) [2d]
Zawislak et al., 2009 [38]	burning sensation	pain [24h]
Vano-Galvan et al., 2009 [39]	pain (important - intense), needing distressing intralesional anesthesia before treatment	NR
Imbernón-Moya et al., 2017 [40]	no side effects, under sedation or general anesthesia	anogenital erythema (mild), edema (mild), burning sensation and micturition difficulties (mild to moderate-severe) [7-10d], treated with common analgesics
Cabete et al., 2015 [41]	no side effects, no need for local anesthesia under conscious sedation	NR

Side effects presented in words, intensity between parentheses () and duration of side effects between brackets [] if available.

* PR-NR score is a 11-point pain intensity numeric rating scale.

Abbreviations: h, hours; d, days; w, weeks; min, minutes

Figure 1. Flowchart of the study selection process. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097