Injection of Autologous Stromal Vascular Fraction enriched lipoaspirate for the treatment of vulvar Lichen Sclerosus - a pilot study

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To quantify clinical and histological improvements in patients with vulvar lichen sclerosus after treatment with SVF enriched lipofilling.

Ethical review	Approved WMO
Status	Pending
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON48736

Source
ToetsingOnline

Brief title
Injection of aSVF enriched lipoaspirate for vulvar Lichen Sclerosus

Condition

- Epidermal and dermal conditions
- Skin and subcutaneous tissue therapeutic procedures

Synonym
Chronic inflammatory dermatosis, chronic skin disease, lichen sclerosus

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Lipofilling, Scars, Stromal vascular fraction, Vulvar Lichen Sclerosus

Outcome measures

Primary outcome

The primary objective of this study is to perform a pilot-study on the efficacy and safety of autologous injections of SVF enriched lipoaspirate for the treatment of therapy-resistant vulvar lichen sclerosus. Efficacy is determined by the quantification of improvement in patient*s symptoms by improvement in quality-of-life and sexual functioning three months, six months and one year after injection of SVF enriched lipoaspirate. Quality of life is evaluated using the validated Dermatology Life Quality Index (DLQI) and resumption of sexual activity and quality of sexual functioning is evaluated using the validated Female Sexual Function Index (FSFI).

Secondary outcome

Secondary objective is the quantification of improvements in clinical signs and architectural changes by physical examination findings and improvements of histopathological parameters.

To date, no agreed-on standard exists to measure lichen sclerosus disease severity for use in clinical practice or research trials. For this pilot study we developed a non standardized severity scale, based on the preliminary outcomes of an international expert consensus exercise for item generation for the development of a future adult vulvar lichen sclerosus severity scale. Each

parameter is scored by a five point Investigator Global Assessment (IGA) scale for severity of disease (0=clear; 1=minimal disease; 2=mild disease; 3=moderate disease; 4=severe disease)

Clinical signs in lichen sclerosus include parameters on extent of disease, erosions, excoriations or ulcerations, white lesions, hyperkeratosis,, lichenification, (loss of) elasticity and sclerosis. Architectural changes include caliber and elasticity of vaginal introitus (narrowing of introitus), clitoris burying degree (clitoral hood fusion), labial resorption/fusion, fusion below the clitoris,(urethral occlusion), posterior commisure bands (fourchette webs).

In order to reduce observer bias, standardised digital photographs are made before and at three months, six months and one year after SVF enriched lipofilling treatment. These digital registrations will be assessed by a panel of three independent expert consultant gynaecologists from the University Medical Center Groningen, whom are blinded-for-time before and after treatment.

To compare histological modi*cations of the vulvar skin before and after injection of SVF enriched lipofilling and assess the mechanism of SVF enriched lipofilling therapy, biopsies are taken at three times on the same locations of the perivulvar area: pre-operative (lichen sclerosus affected vulvar skin), 3 months postoperative and 1 year postoperative. Histological parameters of lichen sclerosus are evaluated by an expert pathologist. Using routine

Hematoxylin-Eosin and Masson*s Trichrome staining, epidermal atrophy, hyperkeratosis, dermo-epidermal detachment, dermal inflammation, dermal homogenization (fibrosis), presence of edema and presence of large caliber vessels in the superficial dermis are stained. Additionally, immunohistochemical analyses will be performed to quantify vascularisation, tissue regeneration and visualize immune cell influx.

To elucidate on the molecular mechanism of regeneration, the Luminex multiplex ELISA technique will be applied in one biopsy for every patient. Multiplex ELISA can quantify up to 30 cytokines from a single sample. In biopsies from lichen sclerosus patients, we will assess the tissue level of the immunorelated cytokines and regenerative factors.

Study description

Background summary

Lichen sclerosis (LS) is a chronic inflammatory dermatosis with a high prevalence in the genital area in peri- or postmenopausal women. Shame and ignorance often result in late reporting and hesitation to seek help. Vulvar LS presents with progressive pruritus and pain, sexual and urinary dysfunction, reduced quality of life and an increased risk of squamous cell carcinoma of the vulva.The lifetime risk for women with LS to develop vulvar squamous cell carcinoma is estimated at 5%. In patients treated for vulvar cancer, the presence of LS appears to affect the incidence of recurrence of squamous cell carcinoma. The true prevalence of LS is not known; estimates range from 1 in 30 elderly women and 1 in 59 women in a general gynecology practice. A Dutch historical cohort of 3038 woman indicates an increase of nearly 100% in the incidence of LS from 7.4 to 14.6 per 100,000 woman-years between 1991 and 2011.

LS typically begins as white, polygonal papules that coalesce into shiny porcelain-white plaques involving the perivaginal and perianal areas. Vulvar LS may progress to obliteration of the labia minora and stenosis of the introitus.

Diagnosis is often made on clinical appearance. Punch biopsy, followed by histological examination is the golden standard to confirm the diagnosis. The etiology and pathogenesis of LS are largely unknown and may include genetic, auto-immune, infectious, environmental and hormonal factors. Inflammation and fibroblast-to-myofibroblast transdifferentiation in the papillary dermis culminate in fibrogenesis in the upper dermis. Histological examinations of classic LS indicate epidermal atrophy, a typical band-like lympho-histiocytic infiltrate in the dermo-epidermal junction and compact hyperkeratosis with stratum corneum, which often is thicker than the greatly effaced epidermis. In time, edema in the papillary (upper) dermis is replaced by a dense, homogenous fibrotic tissue as the lesion matures. Histopathological findings of LS tissue include the occurrence of tissue hypoxia and ischemia, followed by inflammatory processes (T-cell infiltration and TH1-cytokine accumulation in the tissue), resulting in epithelial damage (reduced CD44 expression) and fibrogenesis (accumulation of extracellular matrix proteins and hyaluronic acid).

The preferred treatment for genital LS are very potent topical corticosteroids (e.g., clobetasol propionate), which may relief clinical symptoms (pruritus and pain) and reduce clinical indicators on physical examination (i.e. ulceration, hyperkeratosis, erythema, ecchymosis, atrophy and depigmentation). Although randomized trials that compare therapies for vulval LS are elusive, several other topical therapeutic options have been proposed (e.g. topical testosterone or progesterone), but proven not to be effective. In case of treatment-resistant LS, topical treatment with tacrolimus or pimecrolimus (inhibition of T-cell activation) can be considered, but evidence on its effectiveness is sparse. Tissue fibrosis and its associated disfigurement often cannot be prevented by topical treatment and result in persistent sexual and urinary dysfunction and reduction in quality of life. A surgical approach is only considered in severe vaginal introitus stenosis, urinary retention, and synechiae, yet surgery creates scars and is characterized by a high recurrence rate of the original pathology.

Transfer of adipose tissue, also known as lipofilling, is recognized as a promising and novel technique for the treatment of a range of pathologies. This is strongly supported by clinical trials as well as more fundamental studies in preclinical models. The white adipose tissue harbors a mesenchymal cell population with stem cell-like properties, which holds regenerative as well as angiogenetic, immunomodulatory and differentiative potential. These regenerative cells can be isolated from the adipose tissue through standard lipofilling procedures, after which the lipograft is fractionated using mechanical dissociation and subsequent isolation of Stromal Vascular Fraction (SVF) using density centrifugation. The advantage of the use of SVF is believed to be in two areas. Firstly, the so-called FAT-SVF procedure (Fractionation of Adipose Tissue to obtain Stromal Vascular Fraction with harvesting, processing and injection of the therapeutic product) can all be executed in a short *one stop* procedure in day surgery. Additionally, the distinctive heterogeneous cellular composition of SVF may be responsible for better therapeutic outcomes

observed in comparative pre-clinicall studies. Cells from the SVF are currently used for many medical indications: burns sequelae, radiotherapy tissue damage, reconstruction after oncological surgery, improvement of facial nerve function, the experimental treatment of ischaemic cardiomyopathy and intervertebrate disc regeneration.

To reduce fibrogenesis and adverse tissue remodeling in vulvar LS, pioneering studies have used lipofilling to treat women with therapy-resistant LS. In 2010 Casabona et al. proposed lipofilling in combination with injection of Platelet Rich Plasma (PRP) for the treatment of LS and reported favorable outcomes. A later study by Boero et al used lipofilling solely for the treatment of therapy-resistant LS. Vulvar tropism of the skin and mucosa improved in 34 out of 36 women (94%) and the routine usage of topical corticosteroids was stopped in 34 out of 36 women. More importantly, the quality-of-life and sexual functioning were improved as assessed by the validated DLQI and FSFI questionnaires. In addition, several small studies have evaluated the efficacy of lipofilling in the treatment of severe vulvar LS, confirming the reduction of symptoms, increased quality-of-life and increased sexual functioning without any report of adverse events. Hence, lipofilling might represent a promising alternative for current topical corticosteroid treatment in LS. Although clinical improvements have been reported from these studies, limitations should be mentioned: small sample sizes, short follow up period (maximum of two years) and no analysis included on the mechanism of regeneration of sclerosis at tissue levels.

Study objective

To quantify clinical and histological improvements in patients with vulvar lichen sclerosus after treatment with SVF enriched lipofilling.

Study design

A prospective pilot study.

Intervention

All patients will receive autologous SVF enriched lipoaspirate: 20 ml of lipoaspirate will be added to 2 ml of SVF resulting in a total of 22 ml of SVF enriched aspirate to be injected in the vulvar region (with 0,1 ml of volume for every 0,1 cm2 epithelium).

Study burden and risks

To-date, only minor complications have been noticed when performing lipoharvesting: swelling of the harvesting site, neuropraxy due to collision of the cannula against a sensible nerve and hypersensitivity of harvesting site.

There is a very low risk of fatembolism and risks related to the anaestetic procedure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Postmenopausal women up to 80 years with ASA Physical Status Classification 0-1
- Histopathological confirmed diagnosis of lichen sclerosus
- Moderate or severe lichen sclerosus (IGA scale 3 or 4), therapy resistant to conventional therapy with highly potent topical steroids (insufficient reduction in clinical symptoms and signs having used topical steroids for 6 months).

Exclusion criteria

- Women with history of vulvar cancer or vulva intraepitheliale neoplasie (VIN) in addition to lichen sclerosus
- An oncological event in the patient*s history < 5 years ago.
- A known systemic disease that will impair wound healing (e.g. diabetes mellitus type I, known atherosclerosis with an event that required hospitalization, collagen diseases, diseases of the skin, HIV).
- Systematic use of prednisone or other immunotherapy
- Use of anticoagulant therapy
- Smoking

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2018
Enrollment:	15
Type:	Anticipated

Ethics review

Approved WMO

Date:	15-04-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 23776
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL65403.000.18
OMON	NL-OMON23776