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Genital Lichen Sclerosus in Male Patients: A New Treatment with Polydeoxyribonucleotide

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Key Words
Lichen sclerosus treatment · Polydeoxyribonucleotides · Dermatology life quality index

Abstract
Lichen sclerosus (LS) is an inflammatory and chronic disease that causes itching, pain, dysuria, urinary retention, dyspareunia and sexual dysfunction, in both men and women. The first line pharmacological treatment is based on the use of topical steroids, which have proved their efficacy in 60–70% of cases but with a high rate of relapses in time (50–80% of the patients of both sexes). The purpose of our non-randomised prospective pilot study was to evaluate the efficacy and tolerability of a new loco regional therapy with polydeoxyribonucleotides (PDRN) in the treatment of male genital LS. PDRN is an healing and anti-dystrophic drug with anti-inflammatory effects, through the reduction of cytokine. Twenty one male patients suffering from genital LS were recruited. All the patients were submitted to treatment using loco-regional intradermal injections with PDRN. Dermatology Life Quality Index (DLQI), International Index of Erectile Function (IIEF-5) and PGI-I questionnaires were administered at baseline and at the end of treatment in order to evaluate the results of this treatment. The statistical evaluation of the data obtained with the DLQI questionnaire showed a marked improvement of the overall conditions in terms of quality of life, with an average change of scores from 15 to 4 ($p < 0.0001$). PGI-I questionnaire showed that 80% of the patients treated considered their post-treatment conditions as 'improved'. There was no significant change in terms of sexual function according to the IIEF questionnaire ($p = 0.189$). The results obtained show the excellent tolerability and the therapeutic efficacy of PDRN, with clear improvement of the local symptoms and of the quality of life.

Introduction

Lichen sclerosus (LS) is a chronic and relapsing inflammatory skin disease that causes tissue atrophy, destructive scarring and functional impairment, and that sometimes may undergo malignant evolution. LS is a debilitating disease that causes itching, pain, dysuria and, in the more serious cases, urinary retention, dyspareunia and sexual dysfunction, in both men and women.

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In women, the etiopathogenesis of LS is very probably linked to autoimmune mechanisms, while in the men, this hypothesis seems less plausible [1, 2]. A broad study conducted on 350 women with LS highlighted that 21.5% had one or more diseases of an autoimmune type, 21% a family history of autoimmune diseases and 42% autoantibodies [3]. The most common autoimmune diseases were thyroiditis (12%), alopecia areata (9%), vitiligo (6%) and pernicious anaemia (2%) [4–8]. IgG1 autoantibodies directed against the glycoprotein of an extracellular matrix (ECM1) were found in the serum of about 70% of women with LS; however, even in the males, the concentration of anti-ECM1 antibodies was higher than in the controls in some recent clinical records reported in literature [9, 10]. There are, however, conflicting opinions concerning the true pathogenetic mechanism, since it would seem that the trigger is actually the local chronic irritation and that the auto-antibodies develop only later.

It is well known that the anatomical presence of the foreskin facilitates the creation of a 'damp' environment and, consequently, the onset of local chronic irritative condition that, in turn, could lead to the formation of LS (LS is found only rarely in circumcised patients). The formation of autoantibodies would therefore more probably be a reactive 'epiphenomenon' (a secondary, accompanying occurrence) rather than a direct cause of the problem.

Other triggering factors could consist of some infectious agents (Borrelia) or traumatic events and/or outcomes of genital surgery [11–15].

Further etiopathogenetic theories are based on hormonal factors and, in this respect, significantly lower levels of dihydrotestosterone were found in some LS patients [16]. Furthermore, a histochemical assessment of androgen receptors, carried out on the skins of patients with LS, showed a reduction of these receptors [17].

Psychosomatic inductions are also identifiable as the trigger in the widespread erupting or episodically relapsing forms.

The standard pharmacological treatment is based on the use of topical steroids, which have proved their efficacy in 60–70% of cases but with a high rate of relapses in time (50–80% of the patients of both sexes) [18–20]. The topical calcineurin inhibitors pimecrolimus and tacrolimus have a significant anti-inflammatory activity, immunomodulatory effects and a low systemic immunosuppressive potential; however, they are off-label and considered dangerous to develop tumours [21, 22]. Treatment of LS with topical testosterone was dropped out due to its very limited efficacy and to the noticeable superiority, in terms of clinical results, of corticosteroids [23, 24].

The purpose of our non-randomised prospective pilot study was to evaluate the efficacy and tolerability of a new loco-regional therapy with polydeoxyribonucleotides (PDRN) in the treatment of male genital LS. PDRN is a natural product obtained by means of selective extraction from fish for use as food; it has a documented effect in the repair of wounds and in favouring the trophism of connective tissues.

Materials and Methods

We carried out a non-randomised prospective pilot study on male patients with LS of the genitals. The diagnosis of this disease was based on clinical data and on an objective examination showing persistently discoloured areas of the foreskin or of the glans, with the presence of sclerotic and scar tissue with a lack of elasticity, small cracks in the skin and of the mucous membrane, desquamation and itching.

All the patients reported the onset of these symptoms at about 6 months earlier; however, none of the patients considered the first clinical signs of the disease to be important in the period before clinical evaluation by an Andrology consultant. In all the patients, the symptoms worsened over time even causing stiffness of the tissue of the foreskin and causing sometimes a secondary phimosis.

None of the patients had undergone loco-regional medical treatment of any other type earlier.

Before treatment all the patients were evaluated by physical examination, the Dermatology Life Quality Index (DLQI) is a specific questionnaire that assesses the impact of the skin disease on the quality of life of the patients [25] – and the International Index of Erectile Function (IIEF-5) to evaluate the sexual function.

All the patients provided a written informed consent and the study was approved by our Institutional Review Board (Perugia University Ethics Committee).

PDRN is the active fraction of a registered formulation (Placentex Integro; Mastelli s.r.l., Sanremo, Italy) a cicatrisation and antidystrophic preparation.

All the patients were treated with loco-regional intradermal (prepuce) or submucosal (corona sulcus/glans) injections with PDRN (5.625 mg in a 3 ml vial) carried out by means of a 5 ml syringe with a needle usually used for insulin or mesotherapy (Gauge 27–30), after application of a local anaesthetic cream about 20 min prior to the treatment. The injection of different dosage of drug could range from 5 to 10 mg (1 or 2 vials) per session, until the whole area affected by the disease was treated (fig. 1). The cycle of therapy called for weekly treatments for 10 weeks; in all cases, after a pause lasting for about 30 days, a second cycle of therapy of 10 sessions was carried out.

All the patients were evaluated again at the end of the treatment by physical examination, a DLQI and IIEF questionnaires. Furthermore, the patients underwent a PGI-I questionnaire for a 'subjective' evaluation of the results: the PGI-I asked the patient to best describe how his condition is now, compared with how it was before the treatment. The patient entered his answer on a 7-point scale scored as: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, or (7) very much worse [26, 27].

Fig. 1. Treatment with PDRN of Lichen sclerosus of the subcoronal sulcus: before and after injection of the drug.

Table 1. Site of disease in the patients tested

Site	Frequency	Valid percent
Coronal sulcus	5	23.8
Prepuce	9	42.9
Glans	1	4.8
Urethra meatus	1	4.8
Glans + prepuce	5	23.8
Total	21	100.0

Table 2. Results of DLQI questionnaires before and after treatment

	Age	DLQI pre-treatment	DLQI post-treatment	p value
n	21	21	21	<0.0001
Median	60.0	15.0	4.0	
Minimum	34.0	5.0	2.0	
Maximum	77.0	30.0	30.0	
Mean	56.95	17.14	9.57	
SD	11.34	8.16	9.21	

Table 3. Results of IIEF questionnaires before and after treatment

	Age	IIEF-5 pre	IIEF-5 post	p value
n	21	21	21	0.189
Median	60.0	21.0	21.0	
Minimum	34.0	7.0	7.0	
Maximum	77.0	28.0	29.0	
Mean	56.95	19.62	20.24	
SD	11.34	6.99	7.69	

Results

Between December 2013 and December 2014, we enrolled 21 patients with an average age of 56 (range 34–77); the mean follow-up was 16 months (range 12–24 months). According to their case histories, 5 patients had type 2 diabetes mellitus for which they were receiving pharmacological treatment, 6 patients had vascular disease and/or hypertension, 4 patients – as already described above – had already undergone surgery (circumcision) for LS, in other public hospitals.

In 43% of the cases, the disease was located on the foreskin: 23.8% in the coronal sulcus, 23.8% in glans and prepuce, 4.8% in glans only and 4.8% in urethral meatus (table 1).

Statistical evaluation of the data obtained with the DLQI questionnaire showed clearly that there was a marked improvement of the overall conditions of the patients treated, in terms of quality of life, with an average change of their scores from 15 (range 5–30) to 4 (range 2–30; $p < 0.0001$).

There was no significant change, on the other hand, in terms of sexual function according to the IIEF questionnaire ($p = 0.189$; tables 2 and 3).

The evaluation of the results, obtained with the PGI-I questionnaire about personal opinion and treatment satisfaction, showed that 80% of the patients treated considered their post-treatment conditions as 'improved': 17 patients reported a subjective improvement featuring increased suppleness of the foreskin and reduction of the local irritative symptoms (itching, stinging and pain), unlike 3 patients who reported worsening of their condition and 1 patient who did refer any change.

Lastly, no adverse reactions to the drug used and no intolerance to the active ingredient were noted till now; furthermore, no pain was referred by patients during or after the treatment in the site of injection.

Discussion

Genital LS is a dystrophic disease of the skin presenting clinically in the form of single or multiple whitish scaly and scleroatrophic areas in a mosaic-like arrangement; the lesions tend to extend from the coronal sulcus, from the foreskin or from the glans as far as the external urethral meatus causing, depending on the cases, phimosis and urethral stenosis.

Clinical medicine is often silent or features non-specific symptoms such as itching, stinging and local pain, which often last for many years. The diagnosis of LS is, however, based mainly on the clinical data and on the peculiar morphological characteristics of the actual lesion [28], although a histology test can confirm the diagnosis.

Until now it has often been found that the treatments used are not very effective. A review of the literature highlighted that steroids, considered the gold standard for treating LS, were effective only for short periods of time and featured a high percentage of relapses during the long-term follow-up period (50–80%) [18–20]. Chronic treatment with a steroid could moreover cause serious side effects that at times were even serious, such as skin atrophy, rebound effects, fungal infections, re-activation of the papilloma virus (HPV), infections due to the Herpes simplex virus and systemic absorption [24, 29].

In our experience, intradermal injection therapy with PDRN showed a high level of efficacy and safety, and was therefore classed as a therapeutic novelty for treating genital LS. PDRN (Placentex Integro – Mastelli), made from fractions of DNA with a molecular weight of less than 2,000 base pairs, is a product of natural origin obtained from fish intended for use as food, and since it is not a protein it does not need allergy testing.

In practice, this drug improves the trophism of the dermal tissues by means of 4 actions:

(1) Metabolic stimulation of the fibroblasts through a link that activates the A2 purinergic receptors. This leads to an increase in the number of fibroblasts (35%) and in the production of all the components of the dermal matrix (30%): collagenous and non-collagenous proteins, hyaluronic acid, elastin, fibronectin, and so on. [30–32].

(2) Activation of the salvage pathways of the nucleic acids: this metabolic pathway consists of the re-use of preformed nucleotides, which are necessary for synthesizing new DNA and for cell duplication. This alternative metabolic pathway enables considerable energy to be saved compared with the 'ex novo' pathway, which synthesises the nucleotides starting from the amino acids and using a higher quantity of energy [30–32].

(3) In addition to the tissue regeneration activity, PDRN occupies an important role in the inflammatory mechanism, reducing the release of cytokines with a pro-inflammatory activity at the site of inoculation, as documented by the studies conducted by Bitto et al. [33].

(4) It increases the production and presence in the skin of vascular endothelial growth factor: this is reflected in an increase of local vascularisation, with a consequent increase of the circulation flow rate and of district tissue oxygenation [32].

Thanks to the above properties, PDRN acts on the tissue damaged by LS modifying its structure: prolonged therapy with this drug improves in time the trophism and the elasticity of the skin and of the genital mucous membranes, reducing the scleroatrophic component.

In a recent paper by Laino et al. [29] the authors proposed for the first time the use of PDRN in the treatment of genital LS. The patients with LS were split up into 2 groups and treated either with steroid therapy alone or with steroid therapy plus PDRN. The authors showed that in the PDRN plus steroids group the short- and long-term results had been decidedly better than in the control group (steroid therapy alone) in terms of reduction of the symptoms and of overall improvement of the quality of life. Furthermore, the same authors showed improvement of the IIEF after pharmacological treatment in all the patients treated. The improvement was even more evident in the patients treated with the combined therapy (PDRN plus steroids). Although the results achieved in that study were considerable, we wish to stress, however, that they were invalidated by the fact that all the patients were in any case treated with steroids, which does not enable us to understand clearly the true efficacy of PDRN.

Although our pilot study with PDRN was carried out on a limited number of patients, it was the first and the only one using a single therapy. Our results show clearly the therapeutic efficacy and excellent tolerability of PDRN, with evident improvement of the local symptoms and of the quality of life, even over time. However, in our experience, there were no statistically significant changes in terms of IIEF (average pre and post-operative scores of 21), and it could be explained because our patients did not have severe disease (LS) and had not suffered of important sexual dysfunction related to this disease before treatment (all of them had good IIEF before treatment with a median score of 21).

Conclusion

LS is an underrated clinical disease and its etiopathogenetic mechanism is not completely known. Due to the availability of only limited data in the current literature, and also from a therapeutic point of view, a multi-disciplinary approach would appear to be necessary to treat this disease.

Use of PDRN is certainly a valid alternative to the drugs used till now and, in any case, it does not preclude the use of the standard therapy as it can be employed alongside a topical steroid.

In the future, the goal will be to evaluate the effectiveness of PDRN in clinical trials featuring a large numbers of cases and in randomised studies, necessary to confirm the good results achieved in our experience.

Authors' Contributions

A.Z. participated in protocolling, project development of the study, made the data analysis and drafted the manuscript. T.C. participated in protocolling and in project development of the study and also made the data analysis. G.C., G.D., A.L.P., G.F., L.L. participated in collecting the data. E.C. participated in protocolling, project development of the study and drafted the manuscript. All authors read and approved the final manuscript.

Competing Interest

All authors declare no competing financial interest.

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Disclosure Statement

None.

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