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Feasibility study of stem-cell enriched autologous lipotransfer to treat oro-facial fibrosis in systemic sclerosis (Sys-Stem): Protocol for open-label randomised controlled trial

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ABSTRACT

Introduction: Oro-facial fibrosis is a common and disabling manifestation of systemic sclerosis (SSc), causing a plethora of functional, aesthetic and social compromise, yet is without effective treatment. Autologous lipotransfer is an established minimally invasive surgical procedure that is postulated to exert anti-fibrotic effects by adipose-derived stem cells, and presents a novel method in the treatment of fibrotic conditions. This study aims to assess the safety and efficacy of autologous lipotransfer for facial involvement in SSc.

Methods and analysis: This is the first randomised controlled study with an open label design to assess autologous lipotransfer for oro-facial involvement in systemic sclerosis. The goals of this study are to assess the feasibility of using a range of quantitative and qualitative outcome measures to effectively measure disease severity and treatment outcome, and to assess patient acceptability for future multi-centre trials. A total of 50 participants will be randomised to a treatment or control group. The treatment group will receive autologous fat transfer to the peri-oral region by a single surgeon. Dermal fibroblasts and adipose-derived stem cells will be isolated from tissue samples. All outcome measures will be taken at baseline, then at 6 weeks, 3 months and 6 months from the time of intervention in the treatment arm, or from baseline in the control arm.

Ethics and dissemination: The study has ethical approval (REC reference 19/LO/0718). Results will be available to patients, patient user groups, clinicians and the public through presentations at national and international rheumatology conferences and published in peer reviewed journals.

Trial registration: Registered on ISRCTN registry (ISRCTN17793055).

1. Introduction

1.1. Context

Systemic Sclerosis (SSc) is a complex multisystem disease characterised by autoimmune, microvascular and fibrotic components, affecting a predominantly female population aged 30 to 60 years at onset [1,2]. Skin fibrosis is present in nearly all patients, and often termed the clinical hallmark of SSc [3]. In particular, facial involvement presents a significant disease burden to patients due to its impact on aesthetic appearance and oro-facial function, leading to social disability, isolation and psychological distress. It ranked as the most worrying aspect of the disease by the majority of patients, overtaking even internal organ involvement [4]. Oro-facial manifestations include skin thickening and atrophy, skin induration, reduction in mouth opening (microstomia), thinning and retraction of the lips (microcheilia), peri-oral furrowing and telangiectasia. With disease progression this can lead to inability in achieving oral competence with breathing and chewing impairment. Involvement of the salivary and lacrimal glands can also lead to xerostomia and xerophthalmia [5].

There is yet no effective disease modifying therapy to reverse skin fibrosis [6]. Physiotherapy and self-administered exercises are suggested to improve mouth opening but relapse is common [7,8]. Autologous lipotransfer is a minimally invasive surgical tech-

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nique that is used for correcting volumetric deficits and soft tissue, however is now finding a role in fibrotic conditions [9,10]. Our group and others have suggested that it may improve skin fibrosis in different conditions including hypertrophic scars, burns, radiation-induced fibrosis, lichen sclerosis, and hemifacial atrophy [11–14]. Autologous lipotransfer has been also reported in small cohorts of SSc patients with facial or hand involvement [15–19]. A formal clinical trial assessing the safety and efficacy of autologous lipotransfer for facial involvement in SSc has not yet been reported and represents an unmet clinical need within the NHS.

1.2. Preliminary work

The Royal Free NHS Trust London is a national referral centre for SSc in the UK. We are the only site to treat SSc patients with autologous lipotransfer. Sixty-two patients with oro-facial fibrosis were retrospectively assessed following oro-facial lipotransfer [2]. Efficacy was assessed by volumetric augmentation, oro-facial function and psychological questionnaires. Results showed improvement in peri-oral volume, lip flexibility and aesthetics with fat retention in the cheeks (93.7%), nasolabial folds (81.9%) nose (67.4%) chin (68.2%), upper lips (35.5%) and lower lips (27.3%). The Mouth Handicap in Systemic Sclerosis (MHISS) scale and all psychological measures showed significant improvement.

2. Methods and design

2.1. Study design

This is a single centre, randomised controlled study with an open-label design. The control arm will be a no-treatment concurrent control receiving care-as-usual. The treatment arm will receive autologous lipotransfer as the intervention and therefore study participants will not be blinded. Randomisation will be carried out by the clinical research team using a centralized system, sealedenvelope.com, and a single surgeon will carry out the procedure. Patients will be assessed at 6 weeks, 3 months and 6 months (Fig. 1). Table 1 summarises the assessments at each time point. Participants in the control arm will be given the option of receiving the intervention at the end of the study to ensure treatment is offered to all.

2.2. Study aims and outcomes

The primary objective of this study is to assess the feasibility of using the Mouth Handicap in Systemic Sclerosis scale (MHISS) as our primary outcome measure. This was determined as being the most important outcome measure by our patient discussion group. Also, we will assess the feasibility of using the 3 subscales of the MHISS (Opening, Dryness and Aesthetic) as outcome measures.

Secondary objectives include the following:

- Estimate recruitment rate required for a multi-centre clinical trial;
- Estimate attrition rate required for a multi-centre clinical trial;
- Assess the willingness of participants to be randomised;
- Feasibility of obtaining patient-reported outcomes via psychological and quality of life questionnaires; Visual Analogue Scale (VAS) Derriford Appearance Scale (DAS24), Brief Fear of Negative Evaluation Scale (BFNE), Hospital Anxiety and Depression Scale (HADS), EuroQol (EQ-5D-5L);
- Feasibility of determining cost-effectiveness in main trial, by quality-adjusted life-years calculated from the EQ-5D-5L, and costs to the NHS according to Patient Resource Use questionnaires (Client service receipt inventory (CSRI));

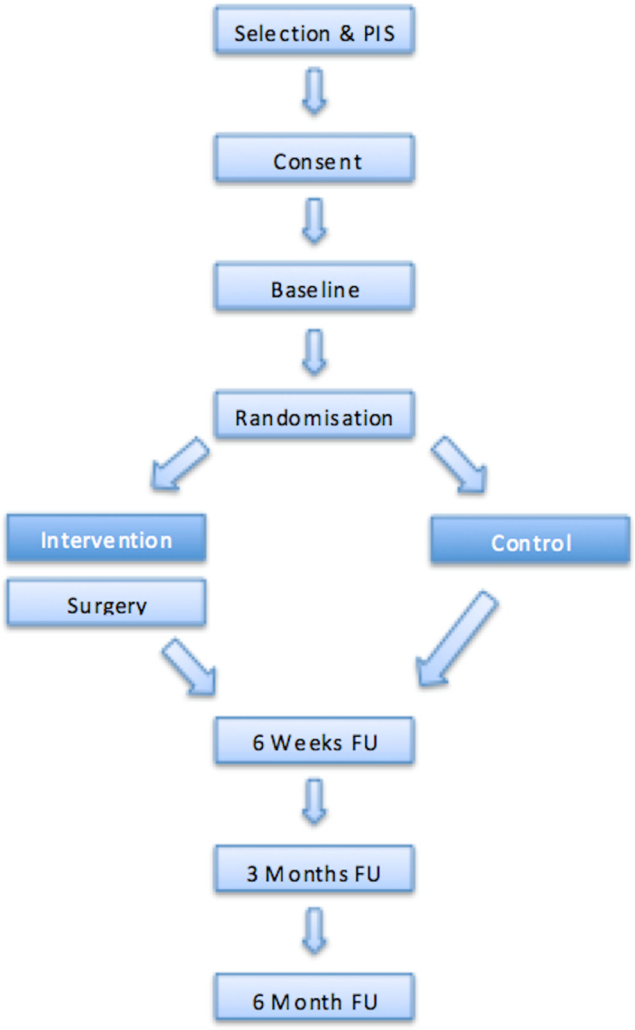

Fig. 1. Flow diagram of the Sys-Stem study design.

- Acceptability of a range of qualitative and quantitative outcome measures (mouth opening, salivary flow, ultrasound, thermography, videocapillaroscopy, cutometry, durometry, laser speckle contrast imaging, 3D photography)

Feasibility criteria are as follows:

- Minimum recruitment rate of 80%
- Maximum attrition rate of 10%

2.3. Trial population

The Royal Free London NHS Foundation Trust has the highest number of SSc patients on registry in the UK with currently 1700 patients with both limited and diffuse forms of the disease. Study participants will be recruited from the existing registry over a period of 12 months. Only patients who plan to have surgery as part of their standard of care will be approached. Surgery will not be carried out if there is no clinical need. The inclusion criteria are as follows:

2.3.1. Inclusion criteria

- Age > 18 and < 90 years
- Diagnosis of limited or diffuse forms of SSc in the established phase of the disease (>3 years)

Table 1
Summary of Sys-Stem study assessments.

Visit	T0 (Baseline)	T1 (Intervention)	T2 (6 weeks FU)	T3 (3 Months FU)	T4 (6 Months FU)
Screening	X				
Informed Consent	X				
Demographic data, past medical history	X				
Clinical measurements	X		X	X	X
Tissue collection		X			X

- A clinical relevant impact on facial function determined by an MHISS score of $\geq$ 20
- Able to give written consent for surgical intervention to the face

2.3.2. Exclusion criteria

- Body mass index < 18.5
- Pregnancy
- Deemed not fit for a general anaesthetic as per heart and lung function
- Active infection of the face or potential sites of fat harvest

2.4. Sample size

This feasibility study will consist of 25 patients in each arm, 50 patients in total. The sample size of 50 was chosen to fulfill one of the main objectives of this study which is to calculate the recruitment rate and rate of attrition for the main trial. We can estimate a recruitment rate of 80% with 95% CI (69% to 91%) and an attrition rate of 10% with 95% CI (1.5% to 18.5%). A difference of four points in the mean MHISS scores comparing control and intervention groups could be considered to be clinically significant, assuming a mean MHISS score of 29.3 (SD = 8) pre intervention (calculated from our retrospective data based on improvement in MHISS scores). This mean difference of 4 points can be estimated from the feasibility study with 95% CI (0.5 to 9.5).

2.5. Screening and enrolment

Subjects who match the inclusion criteria will be identified from the SSc registry by the clinical research team, and screened in clinic at their next scheduled visit, or telephoned and invited to clinic to discuss the study. The study will be described to the patient and they will be provided with a patient information sheet (PIS) detailing the specifics of the study and the risks and benefits involved. Subjects willing to participate in the study will be approached for informed consent at the next clinic visit, giving enough time to consider participation in the trial. The trial nurse will take informed consent and address all queries.

2.6. Consent

Subjects who sign the consent form will be deemed recruited into the study and will be assigned a unique subject number. A copy of the signed informed consent form will be given to the participant and the original signed form will be retained in the locked trial file on site and a copy placed in the medical notes.

2.7. Interventions and outcomes

The following non-invasive interventions will be undertaken by the participant at the Royal Free Hospital at baseline, 6 weeks, 3 months and 6 months following the autologous fat transfer in the intervention arm or following screening in the control arm:

2.7.1. Questionnaires

Assessment of patient-reported outcomes via psychological and quality of life questionnaires will be assessed VAS, DAS24, BFNE, HADS, and EQ-5D-5L.

2.7.2. Assessment of oral function

The MHISS scale will be supplemented with measurements of mouth opening. Salivary flow rate will also be measured to assess involvement of salivary glands in fibrosis.

2.7.3. Assessment of skin fibrosis

The modified Rodnan skin score and high frequency ultrasound will be used to give a measure of the degree of skin fibrosis.

2.7.4. Assessment of microcirculation

Videocapillaroscopy, thermal imaging and laser speckle imaging will be used as assessment tools for microcirculation of the skin.

2.7.5. Assessment of biomechanical properties

Durometry and cutometry will be used as quantitative measures to assess stiffness and elasticity of the skin respectively.

2.7.6. Photography

Standardised two-dimensional photographs will be taken. Three-dimensional photography will allow volumetric assessment of the face to calculate fat retention rates.

2.7.7. Intervention

Autologous lipotransfer is a minimally invasive clinical procedure and is considered a standard of care procedure in reconstructive surgery [9,10]. Adipose tissue is harvested from the abdomen or thighs and centrifuged to separate out the fraction rich in stem and progenitor cells. This is injected into the fibrotic oro-facial tissues using a minimally invasive technique [20]. Any surplus lipoaspirate to be discarded will be collected at the end of procedure. Two punch biopsies will be taken from the forearm in the same procedure and a single aliquot of autologous lipotransfer will be injected at a marked site. At 6 months follow up subsequent forearm biopsies will be taken from the injected site.

2.7.8. Tissue collection

The clinical research fellow will be responsible for collection, isolation procedures and storage of the participant's tissue and cells in accordance with informed consent and the detailed PIS. All samples will remain onsite and will be stored anonymised in the secure onsite storage facility. Samples will be processed, stored and disposed in accordance with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter.

2.7.9. Laboratory assessment

The tissue samples, collected at baseline and 6 months, and will be assessed by immunohistochemistry for features of SSc including fibrosis, vasculopathy and immuno-inflammatory markers. Dermal

fibroblasts will be isolated from the tissues using established methodologies. Fibroblasts will be analysed by quantitative PCR to assess the genetic phenotype. A 2 gene biomarker (THBS1 and MS4A4A) specific to SSc will be used to quantify the profibrotic signature of SSc fibroblasts before and after exposure to lipotransfer. We will also determine the benefit of genetically screening participants. Adipose-derived stem cells (ADSCs) will be isolated from discarded lipoaspirate using established fat digestion techniques and characterised for cell viability and DNA content.

2.8. Participant withdrawal

Participants may be withdrawn from the trial whenever continued participation is no longer in their best interests. This may include disease progression, interconcurrent illness; participant choice or persistent non-compliance to protocol requirements. The decision to withdraw a participant from treatment will be recorded in the CRF and medical notes.

2.9. Patient and public involvement

We have a patient representative who has made substantial contribution in research design including identifying and prioritising the research questions and receiving feedback from a dedicated patient discussion group in shaping these further. Wider involvement of the public and patients is through the social media discussion group (https://www.facebook.com/groups/205999563141399).

2.10. Data collection

All data will be handled in accordance with the UK Data protection Act 1998. Clinical data will be collected into case report forms (CRFs) which will not include the participant's name or other identifiable data. The participant's initials, date of birth and trial identification number will be used for identification. The clinical trial nurse and the clinical research fellow will be responsible for data collection. All source data from medical records and laboratory and clinical reports will be included in the CRFs. All data will be anonymised and encrypted and will be stored in a locked and dedicated filing cabinet.

Research data will be stored electronically on-site in REDCap, a secure and trusted resource. In the long term, data will be stored at Iron Mountain. Records will be stored over the lifetime of the patients, as they will continue to be under the care of the consultant.

2.11. Statistical analyses

Data on all key variables will be summarised using mean (SD), median (interquartile ranges) or proportions as appropriate. The difference in the mean MHISS scores between the intervention and control groups will be estimated using linear regression, adjusted for the baseline score and presented as an estimate with 95% confidence intervals. The secondary outcomes will be compared between the intervention and control groups using appropriate statistical methods and presented as estimates with 95% CI or just descriptive statistics.

2.12. Trial funding, organisation and administration

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by the National Institute for Health Research (NIHR), Research for Patient Benefit (RfPB) scheme (reference number PB-PG-1216–20042; funding amount £245,985; date of award 13th Nov 2017). This research is also supported by the Royal Free Charity to cover the salary costs of the clinical research nurse for the duration of the study (funding amount: £100,000; awarded Sept 2017).

2.13. Ethics and dissemination

The study received ethical approval from the London Camden and Kings Cross Research Ethics Committee (REC reference 19/LO/0718). The results of the study will be disseminated to a national and international audience of patients, patient user groups, public, clinicians and health services, with a goal of raising awareness and receiving patient and public feedback for the full multi-centre trial. The design and results of the study will be presented to national and international rheumatology conferences including the Scleroderma and Raynaud's UK (SRUK), and published in peer reviewed rheumatology journals.

2.14. Availability of data

The protocol, sample case report forms and participant information are available on upon request to the corresponding author.

2.15. Trial status

The trial opened to recruitment on 22nd October 2019.

2.16. Discussion

Oro-facial fibrosis is recognised as a cause of significant concern in SSc patients and yet there has been no effective treatment to target skin fibrosis. Emerging studies reporting clinical improvement after autologous lipotransfer are encouraging and support the use of this well-established surgical technique as a novel therapeutic approach in these patients [11–19]. It is postulated that antifibrotic effects are mediated by adipose-derived stem cells (ADSCs). Compared to other adult stem cell populations, ADSCs have drawn interest due to the ease of isolation, quick processing time and abundance of stores to harvest from [21]. ADSCs have been shown to secrete angiogenic, immunomodulatory and anti-apoptotic factors and can differentiate into adipogenic, chondrogenic and osteogenic lineages [22]. The mechanisms by which ADSCs exert their antifibrotic effects are not yet fully understood.

Dermal fibrosis in SSc is a complex process involving pathological deposition and accumulation of extracellular matrix in the dermis. Dermal fibroblasts show upregulated proliferation and collagen synthesis with decreased collagenase activity levels, as a result of alterations in several molecular regulators including cytokines and transcription factors. Transforming growth factor-beta-1 (TGF-β1) and connective tissue growth factor (CTCG) are implicated to exert a significant role by activating collagen synthesis and enhancing fibroblast action [1,3,11]. The TGF-β1 pathway has been explored as a potential mechanism by which ADSCs reverse fibrosis, as well as potential modulation of angiogenesis or immune response [23–25].

To date study cohorts remain limited by small sample size, limited outcome measures and short follow-ups. A formal clinical trial is necessary to assess the efficacy of autologous lipotransfer as a treatment for oro-facial fibrosis in SSc over time, and how this therapy may be optimised. Consdering the heterogeneity of disease presentation, involvement of auto-antibodies, overlap with other rheumatological diseases and variable disease progression and degree of fibrosis in SSc subsets, our data will enable subset anal-

yses that will allow assessment of treatment response to guide future therapy tailored to the specific patient. As we increase our understanding of the regulation and reversal of the fibrotic pathway, this can form a foundation upon which we can extrapolate to other fibrotic conditions, including hypertrophic scarring, radiation-induced fibrosis, burns, lichen sclerosis and Dupuytren's disease.

3. Please state any conflicts of interest

None to declare.

4. Please state any sources of funding for your research

This work was funded by the National Institute for Health Research (NIHR Research for Patient Benefit (RfPB) scheme (PB-PG-1216-20042).

5. Consent

Not applicable.

6. Registration of Research Studies

Registered on ISRCTN registry. Identifier: ISRCTN17793055.

7. Guarantor

Peter EM Butler.

Ethical Approval

REC approval was given on 17th June 2019 by London Camden and Kings Cross Research Ethics Committee. Ref: 19/LO/0718.

Declaration of Competing Interest

None to declare.

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