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Treatment of Perianal Fistulas in Crohn's Disease with Injection of Freshly Harvested Autologous Adipose Tissue: A placebocontrolled and randomized study

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Aim

To investigate the effects of injection of freshly harvested autologous adipose tissue in 140 patients with Crohn´s Disease (CD) and complex perianal fistulas.

Primary endpoint

Number of patients who have achieve complete clinical healing 6 months after treatment with freshly harvested adipose tissue. Complete clinical healing is defined as i) if the patient has no symptoms of discharge; (ii) no visible external fistula opening in the perineum; (iii) no internal opening can be palpated with rectal digital examination (iiii) no signs of a fluid conducting tract at the location of the former fistula.

Secondary endpoints

a) Number of patients who have achieve complete clinical healing 3 months after treatment with freshly harvested adipose tissue.
b) Number of patients with complete or partial healing 6 months after treatment.
c) Reduction of symptoms evaluated by the Perianal Disease Activity Index (PDAI) 3 months after treatment.
d) Reduction of symptoms evaluated by the Perianal Disease Activity Index (PDAI) 6 months after treatment.
e) Changes in fecal inconsistency evaluated by St. Marks score

Background

Perianal fistulas are frequently present in Crohn´s Disease (CD). The cumulative incidence of CD patients who develop perianal fistulas is as high as 26% during 20 years of follow-up, with the greatest risk present in the first 10 years after diagnosis.

Treatment of perianal fistulas with cultured mesenchymal stem cells derived from adipose tissue marrow has shown efficacy in CD patients. The use of cultured autologous cells, however, has the disadvantage of being time consuming, as it involves a harvesting procedure and weeks of *in vitro* stem cell expansion.

The injection of freshly harvested autologous adipose tissue is an easily accessible alternative to *in vitro* expanded autologous adipose-derived stem cells.

Present study investigate the effects of injection of freshly harvested autologous adipose tissue in 140 CD patients with complex fistulas.

Methods

Design

The study is a randomized double-blinded and placebo-controlled interventional study. It will be conducted as a national multicenter study. Based on a power-calculation 140 patients will be included. An interim analysis will be performed after the inclusion of 80 patients.

Patients

Inclusion Criteria

a) Diagnosed with Crohn´s Disease

b) Perianal fistula with out branching or cavities with one external and one internal opening, which due to the risk for development of incontinence is not suitable for lay-open procedure, meaning: 1) all anterior interspinchteric and low transpinchteric (involving<1/3 of spinchter) in women 2) high interspinchteric fistulas 3) high

transspinchteric (>1/3 of sphincter), suprasphincteric and ekstrasphincteric fistulas 4) intersphincteric or low transsphincteric fistula in patients with fecal incontinence and/or fecal urge.

c) no or minimal luminal disease activity by colonoscopy < 3 months before treatment defined by Simple Endoscopic Severity for Crohn´s Disease<3

d) Prior optimal medical treatment for fistulas (immunmodulators, antibiotics and/or anti-TNF-alfa treatment) with out achieving fistula healing

e) Treatment with seton for a minimum of 6 weeks

f) Speaks and understand Danish

Exclusion Criteria

a) Pregnancy

b) Changes in immunmodulator or anti-TNFalfa treatment < 12 weeks

c) Anovaginal fistulas

d) Rectal or anal stenosis

e) Active proctitis

f) Stoma

g) Previous surgery for fistulas besides simpel drainage or seton

h) Smoker

i) Insulin-dependent diabetes, conditions inducing defective immunity, previous pelvic radiation

j) pelvic MRI contraindicated

Study course

Included patients will in the period before treatment with freshly collcted adipose tissue or placebo receive standard surgical (regular curettage and seton) and/or medical treatment for their fistula(s). When the treating surgeon estimates (reduced secretion and fistula shrinkage) that the patients can achieve fistula healing by injection with freshly collected adipose tissue patients will be referred to pelvic MRI for exact fistula classification. The patient will only be included if pelvic MRI confirms that the fistula is applicable for treatment with freshly collected adipose tissue.

The surgical procedure is performed in general anaestesia. An abdominal liposuction will be performed and thereafter patients will be randomized 1:1 to either injection with freshly collected adipose tissue or saline (placebo). At least two experienced surgeons will be affiliated to the study at each study center. One will perform the surgical procedure and the other will be blinded for whether the patient receives active or placebo treatment. The blinded surgeon will be responsible for the subsequently clinical clinical evaluations of the treatment effects. Clinical evaluation of the treatment response will be performed 3 months after the procedure. If healing has not been achieved the initial treatment (adipose tissue/placebo) will be repeated and the treatment response will be evaluated following another 3 months. Patients with clinical healing after 3 months will be evaluated again 6 months after treatment. In case patients also present clinical healing 6 months after treatment a pelvic MRI will be performed to confirm complete fistula healing. All pelvic MRI scans will be reviewed centrally and the evaluating radiologist is blinded to what treatment the patients have received. Placebo treated patients who do not achieve healing from 2 placebo treatments will subsequently be offered treatment with injection with adipose tissue. Patients who achieves fistula healing will be followed for a total of 2 years.

Patients who receive immunomodulators or biological treatment at the time for inclusion will continue this treatment in the study period. However, the treatment will be paused 2 weeks before and 3 weeks after treatment.

Surgical procedure

The surgical procedure will be performed as previously described (Gastroenterology 2019 Feb 14. pii: S0016-5085(19)30375-0. doi: 10.1053/j.gastro.2019.02.005. [Epub ahead of print]

Randomization

A randomizationlist has been generated by use of the webpage randomization.com The randomization will be performed en bloc (5 adipose tissue/ 5 placebo)

Statistical considerations

Data analysis will be performed as intention-to-treat. A power-calculation has shown a power of 80 % based on the assumptions that 55% of the patients receiving active treatment and 30 % of the patients receiving placebo achieves clinical healing 6 months after treatment with a level of 0.05 for significance, when including 60 patients in each group. We have chosen to include a total of 140 patients who will be randomized 1:1. An interim analysis will be performed after 80 included patients. In case this interim analysis demonstrates a clear and statistical significant effect of the treatment compared to placebo further inclusion in the study be terminated.