Allogeneic Bone Marrow Derived Mesenchymal Stem Cells for the Treatment of Fistulas in Patients with Refractory Perianal Crohn*s Disease

Published: 15-03-2010
Last updated: 30-04-2024

In a dose escalation study we will determine the safety and preliminary efficacy of allogeneic bmMSCs in the induction of response for active fistulizing CD.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON36386

Source
ToetsingOnline

Brief title
allo bmMSCs CD fistula

Condition

- Gastrointestinal inflammatory conditions

Synonym
fistula, M. Crohn

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: grant van DigestScience

Intervention

Keyword: Bone marrow, Crohn disease, Fistula, MSC

Outcome measures

Primary outcome

1. To assess the safety (incidence of intervention related [serious] adverse events) and tolerability of the surgical intervention alone or the surgical intervent with local administration of different doses of allogeneic MSCs in fistula tracts of patients with refractory CD.

2. To document the efficacy of different doses of allogeneic bmMSCs in the induction of response for active fistulizing CD.

Secondary outcome

At 12 weeks

1. To assess changes in the Crohn*s Disease Activity Index (CDAI), the Perianal Disease Activity Index (PDAI) and the adapted Vaizey fecal incontinence score before and after MSC treatment;

2. To compare endoscopic changes before and after local bmMSC treatment using the Crohn*s Disease Endoscopic Index of Severity (CDEIS) and simplified endoscopic activity score for Crohn*s disease (SES-CD);

3. To evaluate the effect of local treatment with autologous bmMSCs on the quality of life of patients with fistulizing CD using the Inflammatory Bowel Disease Questionnaire (IBDQ) and Short Form (SF)-36 score;

4. To summarize the changes from baseline compared to 12 weeks in serum CRP.

At 12 and 24 weeks

5. To assess the incidence of surgical intervention and infections.

Study description

Background summary

Despite the introduction of anti-TNF therapy, perianal disease still accounts for a high rate of morbidity in patients diagnosed with CD. Recently, a phase II multicenter randomized study was reported showing that expanded adipose tissue derived MSCs (atMSCs) in combination with fibrin glue was an effective and safe treatment for complex perianal fistula. However, dose escalation of allogeneic bone marrow (bm) MSCs for the local treatment of perianal fistulas has not been studied.

Study objective

In a dose escalation study we will determine the safety and preliminary efficacy of allogeneic bmMSCs in the induction of response for active fistulizing CD.

Study design

This is a prospective, dose-escalating therapeutic exploratory study.

Intervention

MSC implantation will be preceded by surgical localization, curettage of the fistulous tract and closure of the internal opening. Three escalating doses will be tested, in a total of three cohorts. MSC implantation will be preceded by surgical localization, curettage of the fistulous tract and closure of the internal opening. Per cohort, patients will be randomized in a 5:2 fashion to receive either 10x10^6 (cohort 1), 30x10^6 (cohort 2) or 90x10^6 (cohort 3) bmMSCs or no cells (control group).

Study burden and risks

Crohn's Disease is a severe disorder with significant morbidity and impact on quality of life.
Perianal fistulas lead to substantial physical and emotional distress because of pain, discharge, incontinence, perianal and genital disfigurement, and slow resolution even with treatment.

Promising results have been seen in studies on intravenous MSC administration

in patients with severe steroid resistant Graft versus Host Disease69, including GvHD of the gut. These data is supported by encouraging results from studies with locally administered adipose tissue derived MSCs to treat complex perianal fistula in Crohn*s disease. Patients who can participate in this study have debilitating fistulizing disease not responding to medical therapy and other therapeutic options are limited. We think that these results, which suggest a beneficial effect from MSC administration for patients with fistulizing CD, and the expected limited possibility on adverse side effects, justify participation in this study.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

a) Men and women of at least 18 years of age;

b) Patient must have had CD (for at least 3 months from the time of initial diagnosis). The diagnosis of CD must have been confirmed by endoscopic and histologic evidence;
c) CDAI score of <250 at screening and baseline;
d) Peri-anal fistulas must be refractory to conventional medical therapy. Which means that at some time during the course of the disease, patient must have received both steroids and immunosuppressive agents (for example, azathioprine, 6-mercaptopurine, methotrexate, or infliximab) which did not result in an adequate response to treatment;
e) Patients with previous surgical attempts to eradicate perianal fistulas are eligible for inclusion as are patients with setons in situ. Setons will be removed during the surgical procedure
f) Patients included in the study might be receiving 5-aminosalicylic acid (5-ASA), steroids, azathioprine, 6-mercaptopurine (6-MP), methotrexate, infliximab or any similar drug at the time of enrolment, provided the following conditions are fulfilled at screening:
The dose of 5-ASA (both oral and rectal) must have been stable for at least 4 weeks prior to enrolment.
The dose of steroids must be stable for at least 4 weeks prior to enrolment.
The dose of immunosuppressants (for example azathioprine, 6MP, or methotrexate) must have been stable for at least 8 weeks prior to enrolment and the patient on therapy for at least three months prior to enrolment.
The dose of infliximab or other anti-TNF drug must have been stable for at least 8 weeks prior to enrolment;
g) No need for immediate surgery (obstruction, strictures or abscess);
h) If female and of child-bearing age, patient must be non-pregnant, non-breastfeeding, and use adequate contraception;
i) Patient is willing to participate in the study and has signed the informed consent. Consent must be obtained prior to any study procedure.

Exclusion criteria

a) Patients with evidence of acute peri-anal infection, presence of peri-anal abscesses larger than 2 cm, and anal or rectal stricture;
b) Patients with evidence of any infections needing antibiotic treatment.
c) Rectovaginal fistulas, or complex peri-anal fistulas with more than two internal openings;
d) Patients suffering from renal- or hepatic failure.
e) Use of any investigational drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer;
f) Patient is allergic to gadolinium (MRI contrast agent);
g) Patient with severe renal insufficiency defined as patients with a glomerular filtration rate (GFR) below 60 mL/min/1.73 m2. GFR = 186.3 x (serum creatinine)-1.154 x (age in years)-0.203 x 1.212 (if patient is black) x 0.742 (if female);
h) Due to the high strength electromagnetic fields that will be used during MRI there is a risk of interference with any metallic implants in the body. The following conditions will disqualify patients from having an MRI and will be excluded from this study:
* electronically, magnetically, and mechanically activated implants
* ferromagnetic or electronically operated stapedial implants

* cardiac pacemakers/carotid sinus pacemaker implant
* hemostatic clips
* metallic splinters in the orbit
* insulin pumps and nerve stimulators
* lead wires or similar wires
* metal intrauterine device
i)Change in concomitant medication:
*Steroids must be stable for at least 4 weeks prior to enrolment,
*5-ASA should be on a stable dose > 4 weeks prior to enrolment,
*Immunosuppressants (e.g. azathioprine, 6MP or methotrexate) should be on a stable dose > 8 weeks prior to enrolment,
*Infliximab or other anti-TNF antibody therapy should be on a stable dose > 8 weeks prior to enrolment.
j) Clausterphobia;
k) Documented HIV infection. Active hepatitis B, hepatitis C or TB;
l) Patients who currently have or who have had an opportunistic infection (e.g., herpes zoster [shingles], cytomegalovirus, Pneumocystis carinii, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening;
m) Serious infections (such as pneumonia or pyelonephritis) in the previous 3 months. Less serious infections (such as acute upper respiratory tract infection [colds] or simple urinary tract infection) need not be considered exclusions at the discretion of the investigator;
n) Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence);
o) History of lymphoproliferative disease including lymphoma;
p) Patient is unwilling or unable to comply with the study procedures.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	03-02-2011
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	15-03-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-05-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-01-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-06-2016

Application type:	Amendment
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015680-14-NL
ClinicalTrials.gov	NCT01144962
CCMO	NL29565.000.10