Stem Cells in Perianal Crohn’s Disease (Fistula)

Damián García-Olmo, MD, PhD, Colorectal Surgeon
“Fundación Jimenez Díaz” University Hospital
Universidad Autónoma de Madrid
Madrid, Spain
Disclosure

- Member of Advisor Board of TiGenix SAU
- Inventor in a patent “Identification and isolation of multipotent cells from non-osteochondral mesenchymal tissue” (10157355957US), pending to TiGenix
- Inventor in a patent “Use of adipose tissue derived stromal stem cells in treating fistula” (US11/167061), pending to TiGenix
- Consulting fees from Takeda
Algorithm in Crohn’s Perianal Fistula

The role of the surgeon

- Antibiotics + drainage ± seton ± immunosuppressants
  - Remission
  - Relapse
    - Maintenance therapy
    - (Biologic) Anti-TNFαs ± immunosuppressants
      - Remission
      - Relapse
        - Maintenance therapy
        - (Biologic) Anti-TNFαs intensification or (Biologic) Anti-TNFαs + repair surgeries
          - Remission
          - Relapse
            - Maintenance therapy
            - (Biologic) Anti-TNFαs + palliative surgeries
              - Remission
              - Relapse
                - Maintenance therapy

- Chronic seton placement
- Fibrin glue
- Fistula plug
- Endorectal mucosal advancement flap
- Local perineal flaps
- Ligation on the intersphincteric tract (LIFT)
- Over the scope clip (OTSC)
- Video assisted fistula closure (VAAFT)
- Fistula-assisted laser closure (FiLaC™)

Complex Perianal Fistula is Amongst the Highest Unmet need in IBD

- Devastating impact on patients - social, sexual and employment restrictions (Falconi 2002)
- Highly burdensome symptoms: Anal pain and discharge (Mahadev 2011)
- QoL significantly reduced when undergoing repetitive surgical procedures (Riss et al., 2013)
- Anal fistula surgery is an important predictor for fecal incontinence (40% in the overall IBD population) (Norton et al., 2013).
- Patients are highly motivated to avoid complications of fistula:
  - >10% report feeling suicidal
  - Willing to trade 6.5% of life expectancy for cure (Mahadev et al., 2011)

We Need New Perspectives!
We Need New Perspectives!

Patient QoL – the heavy burden of perianal fistulas in CD

- Fistulas may occur in up to 25% of patients with CD\(^1\)
- 73% of patients with perianal fistulas in CD report depression\(^2\)
- 13% of patients with perianal fistulas in CD report suicidal thoughts\(^2\)

CD: Crohn's disease; QoL: quality of life.
The fistula Dilemma

RECURRENCE

INCONTINENCE
COMPARISON AMONG CURRENT SURGICAL PROCEDURES IN CD ANAL FISTULA

<table>
<thead>
<tr>
<th>INTO FISTULA TRACTS</th>
<th>RECURRENTITY</th>
<th>INCONTINENCE</th>
<th>TECHNICAL DIFFICULTY</th>
<th>POSTOP PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fibrin glue, Plug</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>• FilaC, VAAFT,…</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SETON</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>+++/+</td>
</tr>
<tr>
<td>FLAPS</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>SPHINCTEROPLASTY</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>LIFT</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>IDEAL TECHNIQUE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

No risk: -  Lower: +  Intermediate: ++  High: +++

**A personal evaluation.**
Prof. Garcia-Olmo, Colorectal Surgeon since 1989

May Stem Cells provide an effective procedure like a “Minimally Invasive Surgery”, easy to perform, and without Incontinence risk?
How do we expect cells work in Crohn’s Fistula?

• An immunomodulator effect of adipose derived stem cells has been described.

• These immunosuppressive properties lead to a potent anti-inflammatory effect

**Inflammation**
- Infiltration of lymphocytes (PBLs) in wound area
- Secretion of pro-inflammatory cytokines
- Sensation of pain

**Delivery of eASCs**
- Activation of eASC by a cytokine called IFN-γ
- Expression of an enzyme called IDO by eASCs
- Suppression of the proliferation of activated PBLs
- Suppression of production of inflammatory signals

**Healing**
- Elimination of activated PBLs
- Abrogation of pro-inflammatory cytokines
- Cessation of pain
- Repair of tissue
Mechanism of Action of ASCs

- ASCs are activated in an inflamed environment
- Activated ASCs suppress the proliferation of lymphocytes and suppress the inflammation
- Local treatment of inflammatory diseases with tissue damage/wounds: ASCs act at the source of the inflammation and establish an environment that will permit a healing
- Systemic treatment of diseases with acute inflammatory component: ASCs migrate to the inflammatory environment and suppress inflammation, avoiding tissue damage

Mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms

Ida RasmussenA, Olivia Ringerd, Berit Sundberg, Katarina Le Blanc

Mesenchymal stem cells induce apoptosis of activated T cells
J Plumas1, L Chaperon1, M J Richard2, L P Molems1, L C Bensal1, and M C Faverot1,2

1Faculté de Médecine de Grenoble, Grenoble, France; Centre d'innovation en biologie, Centre Hospitalier Universitaire Micheline, Grenoble, France; and the Unité Mixte de Therapie Cellulaire et Tissulaire, Grenoble, France

Human mesenchymal stem cells modulate allogeneic immune cell responses
Suresh Aggarwal and Mark F. Pithanar

Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells

Role for Interferon-γ in the Immunomodulatory Activity of Human Bone Marrow Mesenchymal Stem Cells
Fistulas in Crohn’s disease: A real problem of inflammation and wound healing

- Perianal discharge
- Pain
- Swelling
- Bleeding
- Diarrhoea
- Skin excoriation
- External opening
- …and SETON is the HERO!
Technologies involved in Adipose Derived Stem Cells

ASC Obtention
- Liposuction
- Isolation

ASC Manipulation
- In vitro culture
- Master Cell Bank

ASC Implant
- Cryopreservation
- Cell expansion
Mesenchymal stem cells for fistulising Crohn’s disease:
"The long and winding road" from the bench to the bedside.

Mesenchymal cells in perianal fistulas

- Garcia-Olmo (1)
  - Autologous Case report
- Garcia-Olmo (4)
  - Autologous Phase 1 Single arm
- Garcia-Olmo (14)
  - Autologous Phase 2b Open label MSC in fibrin glue
- de la Portilla (24)
  - Allogeneic Phase 1/2a Single arm
- Panes (212)
  - Allogeneic Phase 3 RCT
  - Allogeneic Phase 3 Long-Term
- Ciccocioppo (10)
  - Autologous Bone marrow Single arm
- Lee (33)
  - Autologous Phase 2 Single arm
- Molenkijk (21)
  - Allogeneic Bone marrow 4 arms
- Cho (10)
  - Autologous Phase 1

Garcia-Olmo (1)

Garcia-Olmo (4)

Garcia-Olmo (14)

de la Portilla (24)

Panes (212)

Ciccocioppo (10)

Lee (33)

Molenkijk (21)

Cho (10)

Autologous ASCs: Phase 1 and 2 studies

Administration of autologous ASCs was effective in inducing healing in patients with complex Crohn’s perianal fistula, and this procedure can be considered safe.

A Phase I Clinical Trial of the Treatment of Crohn’s Fistula by Adipose Mesenchymal Stem Cell Transplantation

Diseases of the Colon & Rectum

Expanded Adipose-Derived Stem Cells for the Treatment of Complex Perianal Fistula: a Phase II Clinical Trial


Red texts indicate the percentage of patients with complete fistula healing.

Good tolerability of ASCs and feasibility of allogeneic cell therapy

- ASCs are considered “immune privileged” because of:1-3
  - Low expression of HLA I (constitutively)
  - Lack of expression of HLA II (constitutively)
  - Lack of expression of classic co-stimulatory molecules (after priming)
  - Low expression of ligands for NK cell receptors (constitutively or after priming)
  - Delay of the maturation of terminally differentiated effector T cells

- Anergy of T lymphocytes and immune tolerance
- Delayed or reduced activation of the innate and adaptive immune responses
- Feasibility of allogeneic treatments without suppression of host immunity
  - Easily available cell therapy
  - Economically affordable

ASC, Adipose-derived mesenchymal stem cells. BM, bone marrow. HLA, human leukocyte antigen. MSC, mesenchymal stem cells. NK cell, natural killer cell.

Allogenic ASCs: phase 1 and phase 2 studies

Administration of Allogenic ASCs was effective in inducing healing in patients with complex Crohn’s perianal fistula, and this procedure can be considered safe.
Cumulative Evidence That Mesenchymal Stem Cells Promote Healing of Perianal Fistulas of Patients With Crohn’s Disease—Going From Bench to Bedside

Reprint requests
Address requests for reprints to: Damian Garcia-Olmo, MD, Department of Surgery (Fundacion Jimenez Diaz), Universidad Autonoma de Madrid, Reyes Catolicos 2, 28040 Madrid, Spain. e-mail: damian.garcia@uam.es.

© 2015 by the AGA Institute
0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.08.038
Designing a clinical trial process

- Phase 1: Screening for safety
- Phase 2: Establishing the efficacy of the drug, usually against a placebo
- Phase 3: Final confirmation of safety and efficacy
- Phase 4: Sentry studies during sales
Expanded allogenic ASCs (Cx601): ADMIRE-CD
a phase 3 clinical trial in Crohn’s perianal fistulas

Adipose Derived Mesenchymal Stem Cells for Induction and Maintenance of Remission in Perianal Fistulizing Crohn's Disease (ADMIRE-CD)

- Double-blind, placebo-controlled, randomized, multicenter, phase 3 study (NCT01541579)
- Single local injection of $120 \times 10^6$ eASCs (Cx601) or placebo

Primary endpoint:
- **Combined remission at week 24:** clinical assessment of closure of all treated external openings that were draining at baseline, and absence of collections $>2$ cm of the treated perianal fistulas confirmed by masked central MRI

Key secondary endpoints:
- Clinical remission and response at Weeks 24 and 52
- Combined remission at Week 52

Clinical assessment of closure: absence of draining despite gentle finger compression. Clinical remission: closure of all treated external openings that were draining despite gentle finger compression. Response: closure of $\geq 50\%$ of all treated external openings that were draining at baseline.
eASC, expanded allogeneic adipose-derived stem cells; MRI, magnetic resonance imaging; R, randomization.
The concept of “Minimally Invasive Surgery”
Surgical technique include...

1. Vigorous curettage of all tracts, especially in the IO area
2. Closure of the IO with absorbable, 2-3/0 stitches
52 Centers at 8 Countries

ADMIRE CD study design/objective
Combined remission (Clinical and MRI)* (mITT population, N= 204)

- Data at week 24 and 52 suggest that Cx601 superior to control arm in achieving combined remission
- Difference at week 52 is maintained from week 24 analysis

*Closure of all treated external openings that were draining at baseline assessed clinically, and absence of collections >2 cm in the area of the treated perianal fistulas by blinded central MRI reading.

CI, confidence interval; mITT, modified intention-to-treat (randomized, treated and ≥1 post-baseline efficacy assessment); MRI, magnetic resonance imaging.


---

**Week 24**

<table>
<thead>
<tr>
<th></th>
<th>Cx601</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>51.5</td>
<td>35.6</td>
</tr>
<tr>
<td>Patients, N</td>
<td>53/103</td>
<td>36/101</td>
</tr>
</tbody>
</table>

\[ \Delta = 15.8 \text{ percentage points} \quad P=0.021 \]

**Week 52**

<table>
<thead>
<tr>
<th></th>
<th>Cx601</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, %</td>
<td>56.3</td>
<td>38.6</td>
</tr>
<tr>
<td>Patients, N</td>
<td>58/103</td>
<td>39/101</td>
</tr>
</tbody>
</table>

\[ \Delta = 17.7 \text{ percentage points} \quad P=0.010 \]
Patients with relapse* at week 52
(ITT population – patients with combined remission at week 24)

No combined remission at week 52 in patients with combined remission at week 24 (No LOCF)

*Reopening of any of the treated external openings with active drainage as clinically assessed, or development of a perianal collection > 2 cm of the treated perianal fistulae confirmed by centrally blinded MRI assessment in patients with clinical remission at a previous visit combined remission at week 24

LOCF, Last observation carried forward.

ITT, intent-to-treat.

No Drainage after treatment

Infliximab (ACCENT II) \(^1\)

Delta week 54 = 11 pp

\(45\%\) to \(23\%\)

Darvadstrocel (ADMIRE CD) \(^2\)

Delta week 52= 18 pp

\(55\%\) to \(59\%\)

\(^1\) Sands et al 2004

\(^2\) Panés et al 2018
Time to clinical remission (A) and time to relapse (B) over a follow-up period of 52 weeks (ITT population, N=212)

(A) Time to clinical remission*

(B) Time to clinical relapse*

*Closure of all treated external openings.
ITT, intent-to-treat.
Speeding the healing!

**ACUTE Inflammation**
- 1 day
- 4 days
- 10 days
- > 1 month

**CRONIC**

- NEUTROPHILS
- MACROPHAGES
- MULTINUCLEATED

**ASCs**

**Original Research**


Stem Cells superior to control in achieving clinical remission* at any time point up to week 52

mITT population

- mITT, modified intention-to-treat.

*Closure of all treated external openings that were draining at baseline despite gentle finger compression.
Excellent Safety Profile to week 52
(Safety population, N=205)

**TEAEs in ≥5.0% of patients***

- Overall
- TEAEs leading to study withdrawal
- Proctalgia
- Anal abscess
- Nasopharyngitis
- Diarrhea
- Abdominal pain
- Fistula

**Treatment-related TEAEs in ≥ 2.0 of patients***

- Fistula discharge
- Induration

**Serious TEAEs‡**

- Anal abscess
- Proctalgia
- Procedural pain
- Fistula discharge
- Induration

**Serious treatment-related TEAEs***

- Liver abscess
- Anal inflammation

---

*In either treatment group. †Includes the following preferred terms: anal abscess, anal fistula, fistula discharge and infected fistula. ¶Defined as any adverse event that at any dose resulted in death, was life-threatening, caused permanent incapacity or disability, resulted in hospital admission or prolonged a hospital stay, was a medically significant event, or was a suspected transmission of an infectious agent.

TEAE, treatment-emergent adverse event.

The durable response that was observed with Cx601 over one-year suggests:

1. The need for major surgical interventions may be reduced: Less incontinence!
2. The need for systemic immunosuppression can be reduced: Less adverse events!
3. One year after a single administration in treatment-refractory Crohn’s disease patients: Why not repeat doses?
# Current technical options in CD anal fistulas

<table>
<thead>
<tr>
<th>INTO FISTULA TRACTS</th>
<th>RECURRENCE</th>
<th>INCONTINENCE</th>
<th>TECHNICAL DIFFICULTY</th>
<th>POSTOP PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrin glue, Plug, FilaC, VAAFT,...</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SETON</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>++/+</td>
</tr>
<tr>
<td>FLAPS</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>SPHINCTEROPLASTY</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>LIFT</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>IDEAL TECHNIQUE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Darvadstrocel (Cx601)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
The Revolution of Stem Cells

Antibiotics + drainage ± seton ± immunosuppressants

Remission  Relapse

Maintenance therapy

(Biologic) Anti-TNFαs ± immunosuppressants

Remission  Relapse

Maintenance therapy

(Biologic) Anti-TNFαs intensification or (Biologic) Anti-TNFαs + repair surgeries

Remission  Relapse

Maintenance therapy

(Biologic) Anti-TNFαs + palliative surgeries

Maintenance therapy

- Proctectomy
- Diverting STOMA

Injection sites:

a. Fistula internal opening
b. Fistula tract

CX601: DarVadstrocel

Pending Commercialization: ALOFISEL®

- May the Force be with you!

[Image of Star Wars comic with Darth Vader and a light saber, and a row of vials]
Thank you!