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Autologous Mesenchymal Stem Cells, Applied in a Bioabsorbable Matrix, for Treatment of Perianal Fistulas in Patients With Crohn's Disease'

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Abstract

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In patients with Crohn's disease (CD), perianal fistulas frequently recur, causing substantial morbidity. We performed a 12 patient, 6 month phase I trial to determine whether autologous mesenchymal stem cells (MSCs), applied in a bioabsorbable matrix, can heal the fistula. Fistula repair was not associated with any serious adverse events related to MSCs or plug placement. At 6 months, 10/12 patients (83%) had complete clinical healing and radiographic markers of response. We found placement of MSC-coated matrix fistula plugs in 12 patients with chronic perianal fistulas to be safe and lead to clinical healing and radiographic response in 10 patients.

Keywords

STOMP trial; IBD; cell therapy; clinical trial

Perianal fistulizing Crohn's Disease (CD), a particularly refractory disease complication, occurs in up to 20% of CD patients and has a cumulative risk of 26% over a 20 year period[1]. Novel therapies include the use of biologic and artificial matrices as well as other biological approaches such as MSC therapy. A recent Phase III trial demonstrated that injection of allogeneic MSCs into a fistula tract appears safe and efficacious (50% remission rate at week 24)[2]. We developed an approach to deliver concentrated MSC to the fistula via attachment of autologous MSCs to a bioabsorbable matrix for definitive surgical placement. Subsequently, we designed a Phase I clinical trial (STem cells On Matrix Plugs; STOMP) to test feasibility and safety of this therapy.

Details of product manufacturing and patient enrollment are available in supplemental methods. Briefly, approval for a Phase I study of autologous MSC-coated fistula plugs in patients with fistulizing CD was obtained through Mayo Clinic Institutional Review Board and the FDA (IND #15356). Patients with CD ages 18–65, with a single draining fistula for at least 3 months without proctitis, and who had failed anti-TNF therapy were eligible. Autologous adipose tissue was obtained and cells were processed and cryo-preserved in the Human Cell Therapy Lab. Upon scheduling of plug placement, MSCs were thawed and returned to culture in the presence of a Gore® Bio-A® Fistula Plug (MATRIX) in a polypropylene bioreactor for 3–6 days. The average dose was approximately 20×10^6 cells per plug. Patients underwent intraoperative placement of the stem cell loaded plug (MSC-MATRIX) 6 weeks following the MSC harvest by the same surgeon (EJD).

The primary endpoint of this study was to determine the safety and feasibility of using autologous MSC-MATRIX for treatment of refractory CD fistulas. The secondary endpoint of efficacy was defined in 2 ways: 1) clinically and 2) radiographically. Clinically, a partial response was defined as decreased drainage and symptoms as reported by the patient and complete clinical healing was defined as complete cessation of drainage both spontaneously and upon gentle compression upon physical exam at the Week 24 (6 month) visit. Radiographic response was defined by decrease in the diameter and length of the T2-weighted hyperintense fistula tract on T2-weighted fast spin-echo images (percent change from baseline), without development of abscess or additional ramifications off the treated fistula, and without increase in the Van Aasche MRI perianal fistula severity score[3].

Twelve of 18 screened patients were treated. Enrolled patients had diverse demographics (Table 1) and had persistent refractory disease (median of 5 years of perianal disease). All patients remained on biologic therapy through the 6 month study duration. There was 1 serious adverse event, which was related to underlying CD, and not related to study treatment. This serious event was debridement of granulation tissue in the fistula tract unrelated to the placement of MSC-MATRIX and did not result in study withdrawal. There were 2 non-serious adverse events related to seromas at the site of fat collection. In addition, there were 11 non-serious adverse events of which 4 were related to underlying CD and 5 were unrelated to underlying CD or the study interventions.

Nine of 12 patients had complete clinical healing by 3 months, and 10 of 12 patients (83.3%) had complete clinical healing at 6 months. Of the 2 patients without clinical healing, one developed an abscess at three months requiring seton placement, and the other experienced persistent drainage. Other than 1 patient switching from infliximab to adalimumab therapy (patient preference), no patients underwent a change in primary anti-Crohn's therapy throughout the 6 months; however 4 patients received antibiotics (<30-day course) at the discretion of the clinical management team.

MRI was used to define the characteristics of the treated fistula tracts at baseline and six months (Figure 1A, B). Changes in Van Assche Score, and the length and diameter of T2-weighted hyperintensity within the fistula are shown in Figure 1. Radiographic criteria for response were demonstrated in 10 of 12 patients (83%). Mean absolute changes for length and diameter of fistula tract decreased by a mean of 23.5 and 5.0 mm, respectively, in responding patients, and increased by a mean of 0.2 and 10 mm in treatment failures, respectively. There was a significant decrease in the length of T2-weighted hyperintensity within the fistula (median decrease 22%, range −5 to 100%, p=0.01), and a non-significant decrease in diameter (median decrease 57%, range −36 to 100%, p=0.307), with negative values representing an increase in fistula size in the treatment failures. Similarly, Van Assche perianal severity scores also decreased (median 13 to median 9, p=0.0008), without worsening in any patients. These data collectively demonstrate the therapeutic potential for MSC-MATRIX in this refractory disease. We now plan a larger study as the feasibility, safety and preliminary evidence of efficacy, suggest a promising new approach to the treatment of patients with fistulizing perianal CD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ABD	Allan B. Dietz
anti-TNF	*Anti*-tumor necrosis factor
CBC	complete blood count with differential
CD	Crohn's Disease
CRP	C reactive protein
D-PBS	Dulbecco's phosphate-buffered saline
EJD	Eric J. Dozois, colorectal surgeon
ESR	erythrocyte sedimentation rate
EUA	exam under anesthesia
GMP	Good Manufacturing Practices
GWB	Greg W. Butler
HIV	human immunodeficiency virus
IND	Investigational New Drug
IRB	Institutional Review Board
MATRIX	Gore® Bio-A® Fistula Plug
MRI	magnetic resonance imaging
MSC-MATRIX	stem cell loaded plug
MSCs	MSC, mesenchymal stem cell(s)
SOP	Standard Operating Procedure
STOMP	Stem cells On Matrix Plug

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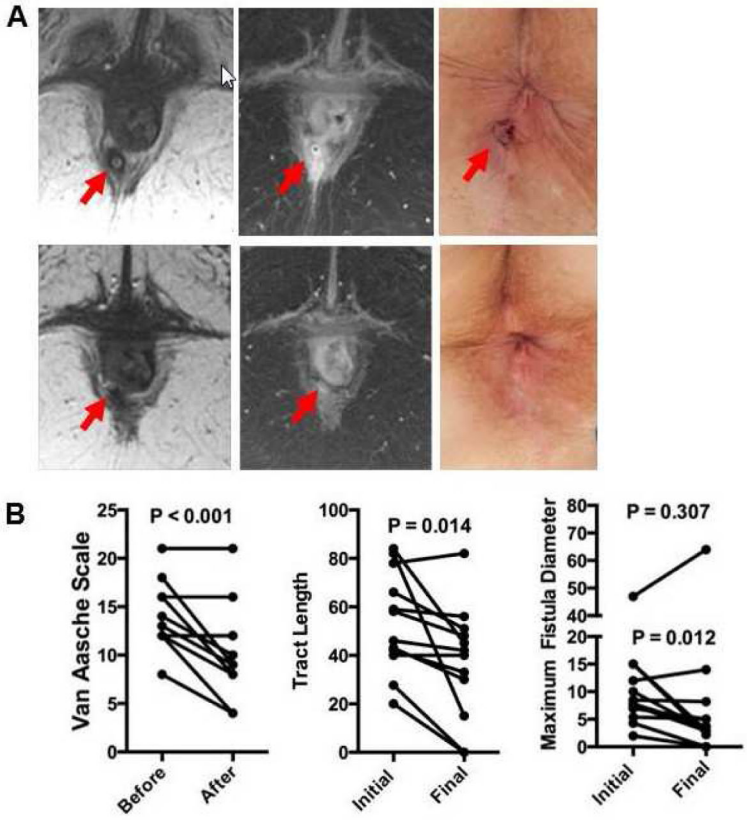

Figure 1. Fistula response upon treatment with MSC-MATRIX

(A) Pre and post treatment imaging in a representative patient. Red arrow indicates intersphincteric fistula in 39 year-old female Crohn's patient prior to treatment and six months after therapy, along with images from perianal examination at time of plug placement (top row) and follow-up MRI. (B) Cumulative results of the changes in Van Aasche score, tract length and fistula diameter. P values represent paired T test before and six months after plug placement. For the fistula diameter, the P value on the upper is representative of all samples while the P value below is for the 11 samples with a starting diameter less than 20 mm.

Table 1

Subject	Age	Sex	Disease Duration	Previous Management	Previous Surgical Management	No. Prior EUA	Clinic findings at EUA	Clinical response	Drainage	Incontinence
1	21	F	13	IFX, ADA, 6-MP, steroids	seton; fistulotomy	9 since 2011	Transsphincteric with puborectalis/levator plate extensions	yes	no	no
2	58	M	4	IFX, ADA; AZA	seton; fistulotomy	8 since 2012	Suprasphincteric	no	Yes	no
3	40	F	2	IFX; ADA	seton	7 since 2012	Intersphincteric fistula	yes	no	no
5	18	M	6	IFX; ADA	seton	12 since 2011	Intersphincteric fistula	yes	no	no
7	24	M	4	6-MP; ADA	seton; diversion	7 since 2012	Transsphincteric with puborectalis/levator extension	yes	no	no
8	25	F	7	IFX; Cimzia; steroids	seton	4 since 2008	Transsphincteric	yes	no	no
9	33	F	2	IFX; ADA; AZA; steroids	seton	5 since 2013	Transsphincteric	yes	no	no
12	51	F	6	IFX+6MP	seton	1 since 2009	Transsphincteric	no	Yes	no
13	31	M	17	ADA; AZA	I and D	5 since 1998	Transsphincteric	yes	no	no
14	56	M	10	IFX; AZA; steroids	none	none	Intersphincteric	yes	no	no
17	21	F	3	IFX; MTX; ADA;	seton	5 since 2014	Transsphincteric	yes	no	no
18	42	M	4	ADA	seton; I and D; fistulotomy	3 since 2013	Transsphincteric	yes	no	no

Mean Age	35
Median Age	32

Mean Disease Duration	6.5
Median Disease Duration	5

IFX: Infliximab

ADA: adalimumab

AZA: Azathioprine

6-MP: 6-Mercaptopurine

MXT: Methotrexate

EUA: Examination under Anesthesia

I and D: Incision and Drainage