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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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**In patients with Crohn's disease, perianal fistulas recur frequently, causing substantial morbidity. We performed a 12-patient, 6-month, phase 1 trial to determine whether autologous mesenchymal stem cells, applied in a bioabsorbable matrix, can heal the fistula. Fistula repair was not associated with any serious adverse events related to mesenchymal stem cells or plug placement. At 6 months, 10 of 12 patients (83%) had complete clinical healing and radiographic markers of response. We found placement of mesenchymal stem cell−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. ClinicalTrials.gov Identifier: NCT01915927.**

*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 biologic approaches, such as mesenchymal stem cell (MSC) therapy. A recent phase 3 trial found that injection of allogeneic MSCs into a fistula tract appears to be safe and efficacious (50% remission rate at week 24).[2] We developed an approach to deliver concentrated MSCs to the fistula via attachment of autologous MSCs to a bioabsorbable matrix for definitive surgical placement. Subsequently, we designed STOMP (Stem Cells on Matrix Plugs), a phase 1 clinical trial, to test the feasibility and safety of this therapy.

Details of product manufacturing and patient enrollment are available in the Supplementary Material. Briefly, approval for a phase 1 study of autologous MSC-coated fistula plugs in patients with fistulizing CD was obtained through the Mayo Clinic Institutional Review Board and the Food and Drug Administration (Investigational New Drug #15356). Patients aged 18 to 65 years with CD, with a single draining fistula for at least 3 months without proctitis, and who had failed anti−tumor necrosis factor therapy, were eligible. Autologous adipose tissue was obtained and cells were processed and cryopreserved in the Human Cell Therapy Laboratory. Upon scheduling of plug placement, MSCs were thawed and returned to culture in the presence of a Gore Bio-A Fistula Plug (MATRIX; W. L. Gore, Flagstaff, AZ) in a polypropylene bioreactor for 3−6 days. The mean dose was approximately $20 \times 10^6$ cells per plug. Patients underwent intraoperative placement of the stem cell−loaded plug (MSC-MATRIX) 6 weeks after the MSC harvest by the same surgeon (EJD).

The primary end point of this study was to determine the safety and feasibility of using autologous MSC-MATRIX for treatment of refractory CD fistulas. The secondary end point of efficacy was defined both clinically and 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 on physical examination at the week-24 (6-month) visit. Radiographic response was defined by decreases 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 of the treated fistula, and without increase in the Van Assche magnetic resonance imaging 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 to study treatment. This serious event was debridement of granulation tissue in the fistula tract unrelated to the placement of

*Abbreviations used in this paper:* CD, Crohn's disease; MATRIX, Gore Bio-A Fistula Plug; MSC, mesenchymal stem cell.

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**EDITOR'S NOTES**

BACKGROUND AND CONTEXT

Perianal fistulizing Crohn's disease is a debilitating condition, and the majority of patients respond incompletely to standard medical and surgical therapy. More effective therapy is required.

NEW FINDINGS

A novel combination product of matrix loaded with autologous mesenchymal stem cells (MSC) was safe and highly effective in complete closure of perianal fistulas in 10 of 12 patients.

LIMITATIONS

This study is a small, phase I trial and requires rigorous testing in a randomized, controlled phase II trial.

IMPACT

The novel combination product of matrix loaded with autologous MSC may provide a highly effective and safe therapy for the treatment of refractory perianal fistulas.

MSC-MATRIX and did not result in study withdrawal. There were 2 nonserious adverse events related to seromas at the site of fat collection. In addition, there were 11 nonserious adverse events, of which 4 were related to underlying CD and 5 were unrelated to underlying CD or to 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, 1 developed an abscess at 3 months that required 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.

Magnetic resonance imaging was used to define the characteristics of the treated fistula tracts at baseline and 6 months (Figure 1*A* and *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 in length and diameter of fistula tract were decreases of 23.5 mm and 5.0 mm, respectively, in responding patients, and increases of 0.2 mm and 10 mm, respectively, in the treatment failures. There was a significant decrease in the length of

**Table 1.** Patient Demographics

| Patient no. | Age, y[a] | Sex | Disease duration, y[b] | Previous management | Previous surgical management | Prior EUA, n | Clinic findings at EUA | Clinical response | Drainage | Incontinence |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 21 | Female | 13 | IFX, ADA, 6-MP, steroids | Seton; fistulotomy | 9 since 2011 | Transsphincteric with puborectalis/ levator plate extensions | Yes | No | No |
| 2 | 58 | Male | 4 | IFX, ADA; AZA | Seton; fistulotomy | 8 since 2012 | Suprasphincteric | No | Yes | No |
| 3 | 40 | Female | 2 | IFX; ADA | Seton | 7 since 2012 | Intersphincteric fistula | Yes | No | No |
| 5 | 18 | Male | 6 | IFX; ADA | Seton | 12 since 2011 | Intersphincteric fistula | Yes | No | No |
| 7 | 24 | Male | 4 | 6-MP; ADA | Seton; diversion | 7 since 2012 | Transsphincteric with puborectalis/ levator extension | Yes | No | No |
| 8 | 25 | Female | 7 | IFX; Cimzia; steroids | Seton | 4 since 2008 | Transsphincteric | Yes | No | No |
| 9 | 33 | Female | 2 | IFX; ADA; AZA; steroids | Seton | 5 since 2013 | Transsphincteric | Yes | No | No |
| 12 | 51 | Female | 6 | IFX+6MP | Seton | 1 since 2009 | Transsphincteric | No | Yes | No |
| 13 | 31 | Male | 17 | ADA; AZA | I&D | 5 since 1998 | Transsphincteric | Yes | No | No |
| 14 | 56 | Male | 10 | IFX; AZA; steroids | None | None | Intersphincteric | Yes | No | No |
| 17 | 21 | Female | 3 | IFX; MTX; ADA; | Seton | 5 since 2014 | Transsphincteric | Yes | No | No |
| 18 | 42 | Male | 4 | ADA | Seton; I&D; fistulotomy | 3 since 2013 | Transsphincteric | Yes | No | No |

ADA, adalimumab; AZA, azathioprine; EUA, examination under anesthesia; I&D, incision and drainage; IFX, infliximab; 6-MP, 6-mercaptopurine; MXT, methotrexate.
[a]Mean age, 35 y; median age, 32 y.
[b]Mean disease duration, 6.5 y; median disease duration, 5 y.