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MINIREVIEWS

Review of stem cells as promising therapy for perianal disease in inflammatory bowel disease

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Abstract

Those patients with perianal Crohn's disease or ulcerative colitis experience a difficult to treat disease process with a delayed state and often inability to heal despite current therapies. The approaches currently used to treat these patients with corticosteroids, antibiotics, immunomodulators, anti-tumor necrosis factor-α drug, and surgical repair are limited in their healing ability. This review presents all current literature since emergence in the early 2000s of stem cell therapy for patients with perianal inflammatory bowel disease and analyzes the efficacy, outcomes and safety within these studies.

Key words: Crohn's disease; Stem cells; Mesenchymal; Perianal disease; Fistula; Inflammatory bowel disease

Core tip: Allogeneic and autologous mesenchymal stem cells (MSCs) are being researched for use in patients with refractory perianal Crohn's disease. Studies from 2003 until now demonstrate efficacy and safety of MSC therapy in this patient population. Up until now, there are no large multi-center, randomized double-blind, placebo-controlled studies examining this.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract that can disturb anywhere from the mouth to the anus. One of the most common manifestations of CD includes perianal disease, specifically including fistulas, abscesses, fissures, and stenosis. These complications frequently result in a significant burden for the patient due to abscess formation, perianal leakage, pain, and an overall decreased quality of life. Treatment options for perianal CD have traditionally included symptomatic management, antibiotics, and medications including immunomodulators and anti-tumor necrosis factor α agents, or surgery in cases with persistent refractory disease. However, surgical options are often limited and come with their own risks, which include incontinence and recurrence of disease. Recently, however, mesenchymal stem cells (MSCs) have been studied in perianal CD and results have been quite promising. This paper provides an up-to-date review on the use of MSC for perianal CD.

MSC therapy has been demonstrated to be a potentially effective treatment for perianal CD in a variety of ways. These stem cells are non-hematopoietic multipotent cells that can depress immune activation and encourage healing of inflamed tissue. MSCs have been found to hinder dendritic cell formation from monocytes, restrict naïve and memory CD4+ cells, stop T cell activation via inhibitory effects on mature dendritic cells, and encourage proliferation of regulatory T cells[1-6]. In addition, MSCs can travel to the site of inflammation and there contribute to local healing[7]. Over the last several years, multiple studies have evaluated autologous and allogeneic MSCs, to determine the safety and efficacy of treating perianal CD. The results are promising demonstrating significantly increased rates of healing for perianal disease refractory to conventional therapy alone. Here we will present studies involving autologous adipose, then autologous bone marrow studies, and then allogeneic adipose and bone marrow studies.

AUTOLOGOUS ADIPOSE STEM CELL STUDIES

The first report describing MSCs for perianal CD was a case report by García-Olmo *et al*[8] in 2003. Here, a rectovaginal fistula in CD was successfully healed seven days after the injection of adipose-derived MSCs. This same author then executed a phase Ⅰ clinical trial involving four individuals suffering from refractory complex Crohn's fistulas, again injecting the fistula tracts with autologous adipose-derived MSCs. Tissue repair was reported in three of four of patients at eight weeks, without adverse events during the one and two year follow up visits[9].

García-Olmo *et al*[10] then led a third study, a phase IIb trial, involving 49 patients with complex perianal cryptoglandular and CD fistulas comparing fibrin glue therapy to fibrin glue plus adipose-derived MSCs. Individuals in this latter group received a second dose of MSC if fistula healing did not appear after two months. In those with CD, fistula healing at twelve months occurred in five of seven (71%) in those given fibrin glue plus MSC as opposed to one of seven (14%) in those given fibrin glue alone[10]. Quality of life was also found to be better in the combined treatment group[10]. These early positive findings for MSCs treating perianal CD laid the groundwork for further work. In a dose-escalation phase Ⅰ trial led by Cho *et al*[11], ten individuals affected by perianal CD fistulas were given autologous adipose-derived MSCs. Following two months of treatment, fistula healing marked by epithelization was detected in three in ten (30%), with continued results at the eight month visit.

Lee *et al*[12] performed a follow-up phase Ⅱ study, including 33 treated subjects given injections of fibrin glue and adipose-derived MSCs with doses proportionate to fistula sizes, followed by repeat injections of increased doses if fistula closure did not complete by two months. Fistula healing was found in twenty-seven of thirty-three (82%) individuals by two months, with continued healing to twelve months in twenty-three of twenty-six (88%)[12]. The other six subjects of the original group developed an incomplete closure, five of which had a > 50% closure and decreased drainage[12].

Cho *et al*[13] did a further follow up study from their 2013 phase Ⅰ trial. Here adipose-derived MSC in fistulizing CD analyzed forty-one of forty-three patients for 12 mo and 24 mo weeks showing complete healing in 80.8% (21 of 26) patients in the complete healing pool and 75% (27 of 36) patients in the modified intention to treat pool[13]. The modified intention to treat pool included those patients who had efficacy data at one year in the phase Ⅱ study. Interestingly, regarding maintenance of complete closure, 27 patients achieved this at eight weeks, twenty-three of 26 (88.5%) at twelve months, twenty of 24 (83.3%) at twenty-four months[13]. Recurrence was seen in 11.5% at one year and 16.7% at two years. For the modified intention to treat group nine patients (25%) demonstrated an incomplete response at two years. Thus, the authors concluded that the use of MSC is safe and efficacious in perianal fistulizing disease.

For the Cho *et al*[13] study, one of the most unique aspects is the analysis of patients with MSC therapy and anti-TNF therapy. Of the twenty-four month group of twenty-seven patients showing complete healing, four patients receiving infliximab were documented. This was used due to enteric CD exacerbation, with 75% of these patients having complete closure prior to treatment with infliximab and having continued resolution of their fistula after infusion.

More recently, Dietz *et al*[14] led a phase Ⅰ clinical trial over a six month period assessing the safety and feasibility of autologous stem cell therapy for persistent,

Table 1 Summary of studies utilizing stem cell therapy in perianal Crohn's disease

Ref.	Study year	Stem cell therapy type	Type of study	Type of perianal disease	Method and amount of administration	Concurrent therapies	Outcome
[8]	2003	Autologous Adipose Stem Cell Studies	Case Report	Complex recurrent rectovaginal CD fistula	Local injection of 9 × 106 MSCs	Olsalazine (previously failed immunomodulators and biologics)	Healed 7 d after injection; no serious adverse events from MSC therapy were observed
[9]	2005	Autologous Adipose Stem Cell Studies	Phase Ⅰ Clinical Trial	Complex refractory CD fistulas, refractory to medical therapy and failing surgical therapy at least twice	Local injection of 3 × 106 MSCs	Immunosuppression without infliximab	Tissue repair in 75% (3 of 4) patients at 8 wk, no AE at 1 and 2 yr follow up; no serious adverse events from MSC therapy were observed
[10]	2009	Autologous Adipose Stem Cell Studies	Phase IIb Clinical Trial	Complex perianal cryptoglandular and CD fistulas, refractory to medical and surgical therapy (including at least one induction with anti-TNF)	Local injection of 2 × 106 MSCs plus fibrin glue vs fibrin glue alone; second local injection of 4 × 106 MSCs if no healing seen at 8 wk	Immunosuppression without infliximab, cyclosporine, or tacrolimus	71% (5 of 7) with fistula healing at 12 mo *vs* 14% healing in control group; higher quality of life in those with stem cell treatment; 1 serious adverse event from therapy (anal abscess)
[11]	2013	Autologous Adipose Stem Cell Studies	Dose-escalation Phase Ⅰ Clinical Trial	Perianal CD fistula, with CD confirmed by biopsy; 5 patients with previously unsuccessful surgical therapy	Local injection of 1 × 107, 2 × 107, 4 × 107 MSC, based on fistula size (total of 3-40 × 107 MSC)	Immunosuppression including infliximab	30% (3 of 10) patients with complete healing at two months and then continued eight month follow up; no serious adverse events from MSC therapy were observed
[12]	2013	Autologous Adipose Stem Cell Studies	Dose-proportional Phase Ⅱ Clinical Trial	Perianal CD fistula, less than 2cm in length	Local injection of 3 × 107 or 6 × 107 MSC, per 1 cm of fistula length; average 15.8 × 107 MSC, followed by second injection of 1.5 × previous (average 19 × 107 MSC) if incomplete closure at 8 wk	Immunosuppression including infliximab, but no infliximab within three months prior to MSC therapy	82% (27 of 33) patients with healing at 2 mo and continued healing of 88% these individuals (23 of 26) at 12 mo; of the 6/33 patients with incomplete closure, 5 had > 50% closure; no serious adverse events from MSC therapy were observed
[13]	2015	Autologous Adipose Stem Cell Studies	Phase Ⅱ Clinical Trial	Perianal CD fistulas	Local injection of 3 × 107 MSC, per 1 cm of fistula length; if second dose needed, 1.5 × previous dose administered	Immunosuppression including biologics	80.8% (21 of 26) patients with complete healing at 12 and 24 mo; recurrence in 11.5% at 12 mo and 16.7% at 24 mo; no serious adverse events from MSC therapy were observed
[14]	2017	Autologous Adipose Stem Cell Studies	Phase Ⅰ Clinical Trial	Refractory Perianal Fistulas in CD	Intra-operative placement of fistula plug, consisting of 20 × 106 MSC per plug attached to a bioabsorbable matrix	Biologic therapies (patients had failure to immunomodulators)	Healing in 83% (10 of 12) of patients at 6 mo; no serious adverse events from MSC therapy were observed
[15]	2011	Autologous Bone Marrow Stem Cell Studies	Phase Ⅱ Clinical Trial	Active complex perianal CD fistulas, refractory to medical and surgical therapies (including biologics)	Local injection of 1.5-3 × 107 MSC every 3 wk until improvement or until no longer available (2-5 injections total)	All patients took mesalamine and azathioprine, except for 2 taking prednisone with mesalamine and 2 on mesalamine monotherapy	Complete closure 67% (6 of 9) patients at 2 mo with continued closure at 12 mo; no serious adverse events from MSC therapy were observed

[16]	2017	Allogeneic Adipose Stem Cell Studies	Phase Ⅲ Randomized Clinical Trial	Refractory complex perianal CD fistulas; maximum of 2 internal and 3 external openings; draining for at least 6 wk	Local injection of 120 million C × 601 MSC or placebo; second injection of	Biologic therapies, immunomodulators, antibiotics	Closure at 24 wk in 50% (53 of 107) patients compared to placebo 34% (36 of 105) patients; shorter time to remission in treatment group *vs* placebo: 6.7 wk *vs* 14.6 wk; serious adverse events occurred in 6.8% of treatment subjects (7 of 103) and 6.9% of placebo subjects (7 of 102)-in both groups, the most common serious events were anal abscess/fistula and proctalgia
[17]	2015	Allogeneic Bone Marrow Stem Cell Studies	Phase IIa Randomized Clinical Trial	Refractory perianal CD fistulas to medical and surgical therapies, including all patients refractory to anti-TNF therapy	Local injections of 1 × 107 MSC for 5 patients; 3 × 107 MSC for 5 patients; 9 × 107 MSC for 5 patients; placebo for 6 patients	Stable doses of concurrent therapies, including mesalamine and steroids > 4 wk, immunomodulators > 8 wk, and anti-TNF > 8 wk	Healing in 47% (7 of 15) patients with MSC therapy vs 33% (2 of 6) with placebo at 12 wk; no serious adverse events from MSC therapy were observed

AE: Adverse events; MSC: Mesenchymal stem cell; CD: Crohn's disease; TNF: Tumor necrosis factor.

refractory perianal CD. This trial, dubbed Stem Cells on Matrix Plugs (STOMP), delivered concentrated, adipose-derived MSC attached to a bioabsorbable matrix to 12 patients. By three months, 9 of 12 patients (75%) achieved complete healing through clinical and radiographic determination; by six months, 10 of 12 of patients (83%) achieved this. There were no serious adverse events due to MSC therapy nor plug placement, and the study authors found these matrix plugs to be safe and effective for refractory perianal CD[14].

AUTOLOGOUS BONE MARROW STEM CELL STUDIES

There is much less data available regarding autologous bone marrow MSC treatment, compared to adipose-derived MSC treatment, in CD. A study led by Ciccocioppo utilized nine subjects with actively draining complex perianal fistulas who received intrafistular injections of bone marrow-derived MSC once monthly until healing was achieved or until they were no longer accessible. In all subjects, MSC expansion was successful. The fistulas were wholly closed in six of nine (67%) subjects at two months, with continued results at twelve months; in the other three cases incomplete closure was achieved[15].

ALLOGENEIC ADIPOSE STEM CELL STUDIES

A longer-term study evaluating allogeneic adipose-derived MSC for perianal CD was recently published with encouraging results. Led by Panes, this phase Ⅲ randomized clinical trial included 212 patients across 49 hospitals in Israel and Europe; 107 were given one injection of MSCs and 105 were given placebo with a saline injection. These participants had complex, medically refractory perianal fistulas draining for at least 6 wk, with a maximum of 2 internal and 3 external openings. The patients were kept on concurrent therapy during this study with biologics or immunomodulators or antibiotics. Twenty-four weeks after one local injection, those given MSC had significant clinical improvement delineated by closure of the external fistula tract and no fluid collections > 2 cm on magnetic resonance imaging (MRI). The authors found 53 of 107 subjects (50%) treated with MSC healed as opposed to 36 of 105 subjects (34%) given placebo (n = 36). Additionally, those given MSC experienced a much shorter time to remission of their disease: 6.7 wk as opposed to 14.6 wk. Explanations for why those in the placebo group experienced such high rates of fistula closure and remission include the fact that all patients received fistula curettage, internal orifice closure, and surgical drainage. While this study did not address the potential benefits of repeat injections of MSCs or dosage of injections based on size of fistula tract, it did provide large-scale, sustained positive results of MSCs for perianal CD. An expansion of this project has been developed in the United States, which is also a phase Ⅲ multicenter, randomized clinical trial evaluating allogeneic adipose-derived MSC for perianal CD[16].

ALLOGENEIC BONE MARROW STEM CELL STUDIES

Finally, Molendijk *et al*[17] studied allogeneic MSCs derived from bone marrow in a phase IIa randomized clinical trial in the Netherlands. There were twenty-one patients with refractory perianal fertilizing CD included; five were given a single shot of 1 × 107 MSCs, five were given 3 × 107 MSCs, five were given 9 × 107 MSCs, and six were given placebo. These injections were placed around the internal openings of fistula walls. Fistula healing was determined to be cessation of drainage and absence of fluid collections > 2 cm on MRI, and was observed in

seven of 15 (47%) of those administered MSCs and two of 6 (33%) of those given placebo. These encouraging results were found not only at the study's primary endpoint, week twelve, but also endured through week twenty-four. Amongst the range of dosages of MSCs given, the best effects were observed in those given 3 × 107. Notably, none of the treatment regimens were associated with an increase in adverse events (Table 1)[17].

CONCLUSION

Perianal CD is quite challenging for both patients and providers with delayed and difficult healing, despite current standard therapy including antibiotics, immunomodulators, anti-TNF treatment, and surgical repair. Need for novel treatment options to improve outcomes in these patients is obvious. Here, the promising results of recent and ongoing studies utilizing stem cell therapy-either allogeneic or autologous-for treatment of this patient population are presented. Given this data, the authors conclude that future randomized double-blind, placebo-controlled multi-center studies on the efficacy and safety of stem cell therapy for perianal disease in CD are warranted.

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