

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Stem Cell Therapy for Perianal Fistulas in Crohn's Disease



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G&H How common are perianal fistulas in Crohn's disease, and how effective is standard medical therapy?

JP Perianal fistulas affect up to 40% of patients diagnosed with Crohn's disease at some point in the course of their disease. These manifestations are associated with Crohn's disease and do not occur in ulcerative colitis.

There are 3 main lines of standard medical therapy for perianal fistulas. Antibiotics may offer transient relief, but in the majority of patients (>90%), symptoms recur upon drug discontinuation, even if patients had a partial response. The next line of therapy consists of immunosuppressants (mostly thiopurines, azathioprine, or mercaptopurine). There is a lack of robust data on the effectiveness of immunosuppressants for perianal fistulas, even though these drugs are used relatively frequently in this setting in clinical practice (although more often in Europe than in the United States). Based on subgroup analysis of studies of patients with luminal Crohn's disease who have active perianal fistulas, approximately one-fourth of patients with perianal fistulas achieve clinical remission in response to treatment with immunosuppressants. The last resort for standard medical therapy in this setting consists of anti-tumor necrosis factor (TNF) drugs. There is robust evidence for the efficacy of infliximab (Remicade, Janssen) from a trial that specifically evaluated this drug in perianal Crohn's disease. Approximately half of the patients (48%) achieved remission at week 14, and their response was sustained over a period of 54 weeks in 58% of patients. There are

no other trials on this condition. Thus, there is still a need for other treatment options for perianal fistulas.

G&H What is the rationale for using stem cells to treat perianal fistulas?

JP The stem cells that have been used for the treatment of perianal fistulas are mesenchymal stem cells. This type of cell is used because of its immunomodulatory action. These cells dampen the inflammatory response for various mechanisms; mainly, they reduce the activation of CD4 T lymphocytes and promote the formation of regulatory T cells. They also dampen the proinflammatory action of dendritic cells and have an anti-inflammatory action on B cells, which reduces the activation and production of antibodies, as well as reduces the toxicity of natural killer cells. Thus, mesenchymal stem cells produce a variety of immunomodulatory actions to dampen inflammatory response, including the intestinal inflammation and consequences associated with perianal fistulas.

In addition, these cells have a regenerative capability. For example, they can transform into fibroblasts to help form a scar in the tract of a fistula.

G&H What sources and methods of delivery have been used for stem cells in this setting?

JP For the treatment of perianal fistulas, 2 sources of mesenchymal stem cells have been used: bone marrow and adipose tissue. A phase 3 trial of adipose-derived mesenchymal stem cells showed efficacy similar to that

found in previous phase 2 trials using bone marrow–derived mesenchymal stem cells, suggesting that the origin of the cells does not affect their efficacy for the treatment of perianal fistulas. All trials have delivered the cells, regardless of origin, via local injection along the walls of the fistula tract.

G&H What is the ideal dose of cells?

JP Various doses have been used. In a study by Molendijk and colleagues, the results of which were published in *Gastroenterology* in 2015, patients with perianal fistulas were randomized to treatment with a single injection of 1 of 3 doses: 1×10^7 cells, 3×10^7 cells, or 9×10^7 cells. The 2 doses with the highest efficacy were 1×10^7 cells and 3×10^7 cells. In a trial of bone marrow–derived stem cells by Ciccocioppo and colleagues, the results of which were published in *Gut* in 2011, repeat injections of 2×10^7 cells were administered, with a median number of injections of 3.

In a large phase 3 trial, the results of which were recently released online ahead of print publication in *Lancet*, my colleagues and I used a fixed number of adipose-derived stem cells (12×10^7). In some patients, all of these cells were injected into a single fistula tract, whereas in other patients, the cells were split between 2 fistula tracts (ie, between 6×10^7 cells and 12×10^7 cells per fistula tract). There was no difference in response between patients with a single tract and those with 2 tracts. Thus, a number within that range was sufficient to obtain closure of the tracts.

G&H Are repeat injections always needed?

JP In the previously mentioned trial by Ciccocioppo and colleagues, repeat injections (up to 6) of mesenchymal stem cells were used only if the fistulas did not close. The number of patients who achieved closure of their fistula tracts increased with the number of injections. Thus, there may be an advantage to repeating an injection if closure is not achieved with the first injection.

However, there have been several studies in which only a single injection is administered. For example, in the aforementioned trial by my colleagues and I, only a single injection was used.

G&H Could you discuss findings from key studies on stem cell therapy for perianal fistulas?

JP The first important study was a phase 2 trial by Garcia-Olmo and colleagues, the results of which were published in *Diseases of the Colon & Rectum* in 2009. In this randomized controlled trial, all of the patients had

perianal fistulas, although some had fistulas in the context of Crohn's disease and others had cryptoglandular fistulas. This trial showed significant benefits with injecting adipose-derived mesenchymal stem cells. Complete fistula closure was observed in 71% of patients treated with these stem cells and only in 16% of the control (placebo) population. The proportions of closure were similar in patients who had Crohn's disease–related fistulas and patients who had cryptoglandular fistulas. However, this trial used autologous cells, meaning that the researchers obtained adipose tissue from the patient, extracted the mesenchymal stem cells, expanded these cells, and then injected them into the same patient. The entire process—from obtaining the adipose tissue to the product being ready for injection—took approximately 4 months. This is a significant delay for a patient who has a perianal fistula.

In the previously mentioned trial by Ciccocioppo and colleagues, repeat injections of mesenchymal stem cells were administered to 10 patients, and complete closure was observed in 7 of those patients. The cells were also autologous and derived from bone marrow.

The aforementioned trial conducted by Molendijk and colleagues, which tested 3 doses of mesenchymal stem cells, was the first to use allogeneic stem cells rather than autologous stem cells. Using allogeneic stem cells is advantageous because there is no need to wait a long time for the product to be expanded; allogeneic stem cells are expanded, frozen, and ready to use as soon as they are thawed.

Allogeneic stem cells were also used in the recent study by my colleagues and I. The endpoint in this study was very stringent; it combined clinical remission (complete absence of drainage) and absence of collections with a diameter greater than 2 cm. The latter was a coprimary efficacy endpoint because persistence of abscesses is associated with a high rate of relapse.

G&H How long do the effects of stem cell therapy last?

JP The aforementioned trial of my colleagues and I has the longest follow-up period (52 weeks), but only the initial 24-week follow-up data have been published thus far. However, according to a recent press release, among patients who achieved closure, most did so between weeks 6 and 12 and the majority sustained that closure over time (up to 52 weeks). These findings were somewhat surprising because initially we did not know how long these cells live after being injected; we thought that the cells might have a relatively short life span and that some patients might relapse. It turned out that the proportion of patients with sustained response is very high among patients who achieved closure in the first weeks.

G&H Has there been any research on combining the stem cells with glue or other agents?

JP Some of the initial trials combined stem cells with glue. However, the addition of glue did not offer an advantage, and it was later observed that glue compromised the viability of the cells. Therefore, in more recent trials, stem cells have been injected only in a suspension with media.

G&H Is this therapy associated with any significant adverse events?

JP One of the benefits of this therapy is that it has a local effect; none of the trials conducted thus far with local injection of mesenchymal stem cells have reported any systemic complications, including infections. The most frequent adverse event is pain at the site of injection, which occurs regardless of whether active treatment or placebo is used and affects approximately 12% to 15% of patients. This adverse event is mainly related to the surgical manipulation of this sensitive zone.

The second most frequent adverse event is the appearance of perianal abscesses. As with pain at the site of injection, perianal abscesses occur at the same frequency in patients who receive stem cells as those who receive placebo. Stem cell therapy requires the manipulation of a highly contaminated tract, as the fistula tract is contaminated with bacteria. Even if the surgeon tries to remove as much of the infectious component from the fistula tract as possible, it is not feasible for the tract to be completely sterile; therefore, abscesses are a complication of this procedure.

G&H Should this treatment be avoided in any patients?

JP The main exclusion criterion is the presence of an infectious complication. In the recent study that my colleagues and I performed, patients with abscesses that could not be adequately drained were excluded. The main reason for this exclusion was that the pH in an abscess is very low, which could kill the stem cells; likewise, a high level of bacteria might compromise the viability of the cells.

Other exclusion criteria are mainly related to the safety of the patient. For example, in our recent trial, we excluded patients with significant luminal disease because we were only using a locally administered therapy and would not allow other types of therapy during the trial. We did not want to leave patients with luminal disease untreated. However, in clinical practice, if I had a patient with a persistent fistula who also had luminal disease

that responded to an anti-TNF agent, I would treat this patient with stem cells.

G&H Where in the treatment algorithm does stem cell therapy fit?

JP I believe that there are 2 potential situations in which stem cell therapy could be used in perianal disease. One is in the patient who has failed the 3 lines of therapy discussed earlier. Some of these patients would otherwise be sent for surgery, which may be aggressive, such as an ostomy (or at least a temporal ostomy). Thus, for patients who have an inadequate response to the current medical treatment choices, stem cell therapy is a clear option. In the recent study by my colleagues and I, 80% of patients belonged to this difficult-to-treat population (patients who had failed immunosuppressants and/or anti-TNF agents).

However, stem cell therapy should not be positioned only as the last resort before surgery. There are some patients who have not yet used immunosuppressants or anti-TNF agents in whom perianal fistulizing disease is the main or only manifestation of Crohn's disease. Usually, these patients would be treated with a therapy that has systemic immunosuppression, such as an anti-TNF agent. However, the patient could avoid the risks of systemic immunosuppression by undergoing stem cell therapy, which is a local therapy and does not compromise the immune response systemically. However, because stem cells do not treat Crohn's disease in other sites, this therapy cannot be used as the sole therapy in patients with manifestations other than perianal fistulas.

G&H What are the next steps in research in this area?

JP Several issues still need to be studied. There has been research on only up to 2 fistula tracts with 12×10^7 cells; studies thus far have not included patients with very complicated perianal fistulizing disease who may have more fistula tracts. Studies should determine whether stem cell therapy is effective for these patients. All fistula tracts likely have the same or similar pathogenesis, so I would expect that this therapy is effective in this setting as well, but it has to be specifically tested. As mentioned before, an area that should be explored further is whether patients who have not achieved complete closure with 1 injection would benefit from an additional injection. Another area that needs to be explored is rectovaginal fistulas, which have been excluded in previous studies. Rectovaginal fistulas cause pain and deterioration in all aspects of life, and the surgical options for these fistulas have very poor outcomes and a very high relapse rate. Observational data

have suggested that stem cell therapy is highly effective for these fistulas, but a properly designed and executed study is needed for confirmation.

Dr Panes has received consulting fees from TiGenix.

Suggested Reading

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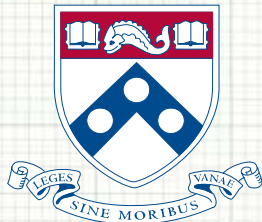
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TiGenix announces positive 52-week phase III results of Cx601 in complex perianal fistulas in Crohn's disease patients [press release]. TiGenix; March 7, 2016.

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