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Allogenic adipose derived stem cells present a potential novel approach for treating refractory fistulizing Crohn's disease

Panés J, García-Olmo D, Van Assche G, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet 2016 Jul 28. pii: S0140-6736(16)31203-X. doi: 10.1016/S0140-6736(16)31203-X. [Epub ahead of print]

Crohn's disease is a common inflammatory bowel disorder with potentially debilitating complications. Perianal fistulas are a common complication, with population studies demonstrating prevalence of fistulizing disease in anywhere from one third to around half of patients with Crohn's, appearing to increase in likelihood with rectal & sigmoid colon involvement (1-4). Many of these perianal fistulas present a challenge for the clinician as they fail to respond to medical therapy or fail to sustain this response after withdrawing seemingly successful therapy (4-6). Smaller trials have demonstrated some success, however, with refractory fistulizing disease utilizing stem cell therapy. A 2010 study, noting promising results utilizing mesenchymal stromal cells (MSCs) in graft versus host disease involving gut tissue, utilized MSCs aspirated from the bone marrow of 10 adult patients with refractory Crohn's disease (7). Colonoscopy was performed at week 0 and week 6, demonstrating improved disease severity in 3 of the 9 patients having undergone MSC infusion, the 10th patient being pulled from the study due to an allergic reaction during infusion. A subsequent 2011 study utilized intrafistular MSC injections in 10 patients with refractory fistulizing disease every 4 weeks (8). These patients were monitored for 12 months afterward via surgical, radiologic, & endoscopic evaluation. Seven patients demonstrated complete closure and 3 with incomplete closure; mucosal healing was noted in in all 10 patients. Later, a 2015 study involving 15 patients with refractory perianal fistulizing Crohn's disease received varying concentrations of intrafistular MSC treatments; with physical examination 6, 12, and 24 weeks later (9). About half of individual fistulas healed using this therapy, as opposed to about a third in the placebo group. Collectively, these studies suggest MSCs do appear to promote healing of perianal fistulas. These studies utilized small sample sizes, however, and a larger study is indicated to assess the effect on a larger population.

A recently published study in 2016 (10) aims to accomplish this, being the first large scale randomized, placebo controlled clinical trial utilizing MSCs to treat refractory perianal fistulizing Crohn's disease. This study used an adipose-derived mesenchymal stem cell line (Cx601) as potentially therapeutic MSCs. 212 patients from 49 hospitals in 7 European countries and Israel were recruited to participate. Inclusion criteria included patients 18 years of age or older with non-active to mildly active luminal disease - defined by a Crohn's Disease Activity Index (CDAI) of 220 or less with complex perianal fistulas. This was defined as one or more of the following: high intersphincteric, high trans-sphincteric, extra-sphincteric, or suprasphincteric origin; at least two external openings, or associated collection or abscess less than 2 cm. Further criteria included a maximum of three external and 2 internal openings. The fistulas were required to have been draining for at least 6 weeks before inclusions. The patients also had to have failed therapy with at least one of the following: antibiotics (ciprofloxacin or metronidazole with lack of response after one month of treatment), immunomodulators, or induction or maintenance therapy with anti-TNF therapy. Patients refractory only to antibiotics represented less than 25% of the study population. Excluded from the trial were patients with a history of rectovaginal fistulas, rectal or anal stenosis, active severe proctitis, patients with diverting stomas, abscess or collection >2 cm, or having received corticosteroid therapy in the previous 4 weeks.

After risk stratification based upon previously received therapy (immunomodulators, anti-TNF therapy, both, or neither), patients were randomized into either a placebo or experimental arm. Both groups underwent pelvic MRIs 2 weeks before treatment to identify abscesses. Also 2 weeks out, both groups also underwent examination under anesthesia with curettage and, as clinically indicated, seton placement of fistulas before intrafistular MSC injection. Setons were removed immediately

before MSC injection. Fistula was then clinically assessed at weeks 6, 12, 18, and 24; assessing for spontaneous drainage after gentle finger compression was applied to treat external openings. Disease was monitored radiologically via pelvic MRI at week 24, compared to baseline read. The primary outcome measured was rate of combined remission (both clinical and radiologic improvement). Secondary outcomes included rate of clinical remission, time to remission, and analyzed amongst the subgroups after risk stratification as noted above.

Regarding the primary outcome, a significantly greater number of patients achieved combined remission at week 24 in the MSC group; 50% vs. 34%. When evaluating subgroups, the effect was greater than placebo in all four groups, however, the greatest difference was noted neither (difference of 33.1% compared to placebo) or both anti-TNF and immunomodulator therapy (difference of 20.0% compared to placebo). Of interest, while median time to clinical remission was significantly shorter in the MSC arm compared to placebo (~7 weeks vs. ~14 weeks); there was ultimately no significant difference noted between these two groups in achieving clinical remission alone (53% vs. 41%). Overall, more adverse events were noted during the study in the placebo group (29%) than the experimental group (17%). The most common adverse events noted were proctalgia and anal abscesses. An equal number of patients in each group had a serious treatment related adverse event of anal abscess, however, no deaths occurred during the study.

These results suggest a viable therapeutic option for refractory perianal fistulizing Crohn's disease. There is a clear benefit imparted upon group members receiving Cx601 injections, though the long-term effects of this therapy are unclear at his point. A prospective study monitoring the rates of sustained remission after MSC therapy for a longer period of time would be helpful in establishing any long term benefit of this therapy added to a patient's existing regimen may be necessary to justify the cost of obtaining and injecting this MSC line. A study in a pediatric population, earlier in disease onset, would also be of interest to evaluate for any differences in therapeutic response between age groups and length of disease state. Furthermore, one wonders if patients who were refractory only to previous antibiotic therapy but responded to MSC injections may have benefited from more aggressive medical therapy just as well as the Cx601 infusion. Of course, as the authors noted, immunomodulators and anti-TNF therapy comes with its own risks that are arguably more severe than those of Cx601 infusion noted during this study. To be certain, further studies are indicated to assess the longer-term effects of Cx601 and its relative effects on different age groups, on different types of fistulizing disease, and against various therapies. Also certain, however, is that this potential therapeutic avenue seems likely to offer many patients an opportunity to avoid escalation of medical therapy which carry significant risks as well as debilitating surgical interventions. Expanding future studies to include the aforementioned groups may demonstrate additional populations what benefit from this promising intervention (11). The apparent relative safety of this intervention compared to conventional medical therapy may justify its current cost, and in fact, may begin to bring it down if this therapy can be demonstrated to be integrated earlier in treatment of fistulizing disease and avoid higher risk medication and surgical interventions.

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