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Effectiveness and safety of darvadstrocel in patients with complex perianal fistulizing Crohn's disease: a systematic review

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Abstract

Background Managing complex perianal fistulizing Crohn's disease (CD) remains challenging, despite current medical and surgical treatment approaches. Darvadstrocel, a therapy utilizing adipose-derived stem cells, shows promise in promoting tissue regeneration and healing, offering a novel and effective treatment for fistula management.

Method A systematic literature search was conducted on PubMed and Scopus to identify studies involving patients with complex perianal fistulizing CD treated with darvadstrocel.

Results In total, 2 randomized controlled trials (RCT), 5 observational studies with retrospective data collection and 2 observational studies with prospective design were included in the final review. Data from the European ADMIRE-CD RCT demonstrated that darvadstrocel is superior to placebo in terms of clinical and imaging improvement over both the short and long term. These findings align with the prospective studies analyzed in this systematic review. The rate of treatment-emergent adverse events in the ADMIRE-CD trial's RCTs was similar in both the darvadstrocel and control groups, with perianal abscess being the most common adverse event up to 52 weeks after drug administration. Retrospective studies indicated no side-effects beyond 52 weeks.

Conclusions Darvadstrocel appears to be a new, potentially effective and safe treatment option for the management of complex perianal fistulas. However, more randomized clinical trials are needed to evaluate the efficacy and safety profile of the drug.

Keywords Fistulizing Crohn's disease, darvadstrocel, adipose-derived stem-cells, treatment

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Introduction

Crohn's disease (CD) is a chronic inflammatory condition affecting the gastrointestinal tract; it may be complicated by the formation of fistulas. A fistula (Latin for pipe) is defined as a chronic tract of granulation tissue between 2 epithelial lined surfaces [1]. Perianal fistulas in patients with CD may originate from infected anal glands at the dentate line and/or penetration of fissures or ulcers into the anorectal wall [2]. The localization of CD is strongly associated with the development of perianal fistulas, with up to 92% of patients with perianal fistulas also having colonic and rectal involvement of the disease [3]. According to population-based studies, the incidence of perianal fistulas in CD ranges from 20-35%, and these fistulas can cause severe pain, fecal incontinence and purulent drainage, leading to a significant reduction in patients' quality of life [4,5].

The diagnosis of perianal fistulas is based on clinical examination and imaging studies. Pelvic magnetic resonance imaging (MRI) and endoanal ultrasound are the preferred

imaging modalities for determining the location and extent of the disease, and ruling out septic complications. Several fistula classifications have been proposed. Park's classification describes 5 different anatomical types of fistula: superficial, intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric [6]. The American Gastroenterology Association has proposed the distinction of fistulas into simple and complex. A simple fistula is low, including superficial, low intersphincteric or low transsphincteric below the dentate line, has a single external opening, and there is no evidence of perianal complications, such as abscess or rectovaginal fistula. On the other hand, complex fistulas are high, above the dentate line (intersphincteric or transsphincteric or extrasphincteric or suprasphincteric origin of the fistula tract), may have multiple external openings, and may be associated with perianal abscess, connections with the vagina or bladder, anorectal stricture, and/or proctitis [1,7].

In the context of perianal fistulizing CD, a recent consensus has classified it into 4 classes. Class 1 includes patients with minimal CD, while Class 2 comprises patients with chronic symptoms requiring intervention for the fistula. Class 3 refers to patients who require proctectomy, and Class 4 includes patients with persistent symptoms after proctectomy [8].

Despite the wide range of medical and surgical treatment approaches, managing complex perianal fistulizing CD remains challenging, with many patients experiencing poor life quality and frequent relapses. The use of antibiotics, anti-tumor necrosis factor (TNF) agents and immunomodulators, in combination with seton placement, has demonstrated efficacy in treating complex perianal fistulas. Currently, evidence suggests that anti-TNF agents, alone or in combination with thiopurines, are effective for inducing and maintaining remission in complex perianal fistulizing CD [9]. Seton draining is used as a bridge to other more definite therapy [10]; however, seton draining is often an acceptable long-term option in patients with complex fistulas [11,12]. Furthermore, a systematic review demonstrated that combination therapy with (temporary) seton drainage, immunomodulators and anti-TNF may be more beneficial in achieving perianal fistula closure than anti-TNF alone [13]. The recent PISA trial demonstrated that short-term anti-TNF treatment combined with surgical closure is more effective than anti-TNF therapy alone in inducing long-term MRI healing in patients with CD perianal fistulas [14]. Other surgical treatment options include use of fibrin glue [15], mucosal advancement flap (AF) surgery [16], ligation of the intersphincteric fistula tract (LIFT) [17], and fistula laser closure [18]. AF surgery is the most extensively studied definitive treatment for perianal CD, with overall success rates ranging from 45-75%. However, it carries a risk of incontinence in approximately 8-10% of patients. LIFT is a promising technique, although most data are based on sporadic fistula patients, and data specific to CD patients are limited. However, the risk of incontinence with LIFT appears to be very low, less than 2%. Plugs and glues are considered safe techniques with low incontinence rates, but their long-term efficacy is limited. Laser techniques, such as FiLaC (Fistula-tract Laser Closure) and VAAFT (Video-assisted Anal Fistula Treatment), are not currently considered conventional methods [19]. In addition, these options are generally ineffective in providing long-term healing, with high rates of failure and relapse [20]. Consequently, new and effective treatment options are needed for patients with complex fistulizing CD, particularly those who are refractory to anti-TNF agents.

Stem-cell therapies appear to be an attractive approach for complex fistulizing CD, because of their immunomodulatory properties, anti-apoptotic and angiogenic effects via the release of cytokines and growth factors [21]. Specifically, mesenchymal stem cells (MSCs) generate paracrine activity, involving secretion of peptides and hormones, such as vascular endothelial growth factor, platelet-derived growth factor, interleukin (IL)-11 and insulin-like growth factor 1. In addition, MSCs may upregulate the anti-inflammatory cytokine IL-10, while reducing the secretion of proinflammatory TNFα and IL-12. This in turn may be accompanied by the differentiation of naïve T cells to an immunoregulatory regulatory T cell (Treg) phenotype [22,23]. There is considerable evidence that Treg cells play a key role in inflammatory bowel disease (IBD) pathogenesis, and patients with IBD have been found to harbor significantly reduced numbers of peripheral Treg cells [24]. Adipose-derived stem cells (ASCs) are MSCs and can differentiate to multiple cell types. Experimental *in vitro* and *in vivo* studies have suggested that ASCs may promote angiogenesis and increase cell proliferation, thus stimulating wound healing [25]. Furthermore, ASCs appear to have a higher level of secretion of cytokines that have been implicated in the immunomodulatory modes of action of multipotent stromal cells, such as IL-6 and transforming growth factor-β1; having a higher immunomodulatory capacity than their bone marrow-derived counterparts, they are more potent suppressors of dendritic cells [26,27]. In contrast to bone marrow-derived MSCs, ASCs can be easily isolated from subcutaneous adipose tissue of the abdomen, thigh and arm. Furthermore, ASCs can potentially be isolated in large numbers, given the abundant adipose tissue in the human body [28].

Darvadstrocel (DVS) (Cx601, Alofisel; TiGenix S.A.U., Madrid, Spain) is an expanded allogeneic ASC therapy for the treatment of complex perianal fistulas in patients with CD. It appears to promote tissue regeneration and healing, ultimately leading to closure of the fistula. The European Medicines Agency has approved darvadstrocel for the treatment of complex perianal fistulas in adult patients with non-active or mildly active luminal CD, when fistulas have shown an inadequate response to at least one conventional or biologic therapy [29]. The purpose of this literature review is to summarize the current evidence about the effectiveness of darvadstrocel in cases of complex fistulizing CD.

Materials and Methods

Literature search

We performed an in-depth review of the literature in PubMed and Scopus up to April 2023 in order to identify studies

reporting on the efficacy of darvadstrocel, using the following search string: ("darvadstrocel" OR "alofisel"). In addition, the reference lists of all relevant articles were evaluated further for additional studies.

Inclusion/exclusion criteria

To be included in this literature review, studies had to meet the following criteria: (i) observational design (prospective or retrospective cohort) or interventional design (randomized or non-randomized study); (ii) patients diagnosed with perianal complex fistulizing CD based on imaging modalities; and (iii) patients treated with the standard dose of darvadstrocel (120×10^6 cells total), alone or with conventional therapy. Data extraction and evaluation of study eligibility were independently carried out by 2 investigators (FSF and KM).

Outcomes of interests

The main outcome of interest was the reporting of the rates of imaging and clinical response after the administration of the drug. In addition, highlighting both the main side-effects of the drug and the percentage of patients who experienced adverse effects after darvadstrocel administration was an additional objective of this study.

Results

Search results

Searching the Scopus and PubMed databases yielded 100 results. Of these, 29 were excluded because they were duplicates. From the remaining 71 articles, after a detailed review of the title and abstract, 52 articles were extracted. Finally, 9 articles were included in the final review (Fig. 1).

Characteristics of included studies

The characteristics of the included studies are described in Table 1 [30-39]; they included 2 phase 3 randomized controlled trials (RCT), 5 observational studies with retrospective data collection, and 2 observational studies with prospective design.

Four studies were derived from the data of the ADMIRE CD trial [31,32,38,39], in which double-blind randomization was performed among 212 patients with CD and treatment-refractory, draining, complex perianal fistulas at 49 hospitals in Europe and Israel. The primary endpoint was combined remission, both clinical and by imaging. Clinical remission was defined as closure of all treated external openings that were draining at baseline, and imaging remission as absence

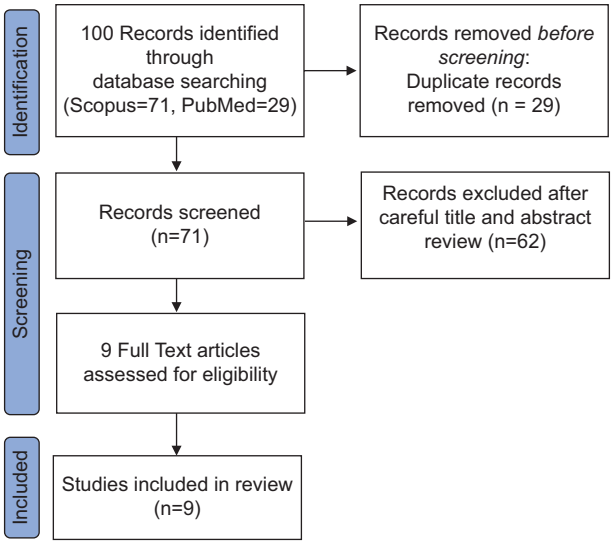

Figure 1 Flow diagram showing the selection process for the studies evaluated

of collections >2 cm of the treated perianal fistulas confirmed by MRI. Assessment was performed at week 24 [39] and week 52 [38], and safety was documented. Limitations of this trial were the exclusion of younger patients and those with more than 2 internal and 3 external openings, as well as those with other types of treatment-refractory fistulas (e.g., rectovaginal or abdominal) and those with previous surgery other than drainage and seton placement [39]. Furthermore, limitations of the follow up to week 52 are that approximately 35-40% of patients in each treatment group withdrew before the end of the study [38].

Two other studies described the long-term effectiveness of darvadstrocel in the ADMIRE-CD trial. The INSPECT study was conducted in 7 countries across 35 centers, and carried out a retrospective collection of data from patients enrolled in the ADMIRE-CD trial over a period of 104 weeks. The objective of the INSPECT study was to evaluate the clinical remission rate among patients treated with darvadstrocel and a control group. Clinical remission was defined as closed fistulas (those no longer draining despite gentle finger compression), or fistulas that were no longer spontaneously draining, or in the absence of this level of detail, fistulas that were no longer draining [32]. Similarly, Garcia-Olmo *et al* accessed the long-term safety and effectiveness of darvadstrocel at 2 years post-treatment in patients with CD during an extended 104-week follow up. The patients were still participating in the ADMIRE-CD study, including 25 patients treated with darvadstrocel and 15 patients from the control group [31].

In addition, 3 retrospective case-series studies were found, with samples of from 3 to 11 patients treated with darvadstrocel [33,35,37]. In one of these, all patients had rectovaginal fistula [37].

Two other current prospective observational studies were included in this literature review: a multicenter phase 3, open-label, single-arm study from Japan with 22 patients [34],

Table 1 Characteristics of included studies regarding the efficacy and safety of darvadstrocel in perianal complex fistulizing Crohn's disease

Study design	Number of patients	Concomitant treatments	Follow-up period	Evaluation criteria	Time point	Outcomes	Related adverse events	Study (year) [ref.]
Double-blind RCT-ADMIRE CD Trial-Phase 3	212 Pts of whom 107 Darvadstrocel 105 control Pts	N/A	52 weeks	Clinical evaluation + MRI	24 weeks 52 weeks	Combined remission 51.5% (53/103) vs. 35.6% (39/101) (97.5%CI 0.5-31.2) P=0.021 56.3% (58/103) vs. 38.6% (39/101) (95%CI 4.2-31.2) P=0.010	20.4 (21/103)% vs. 26.5% (27/102)	Panes *et al* (2016), (2018) [37,38]
Retrospective	12 Pts	3 Pts: Infliximab 3 Pts: Ustekinumab 2 Pts: Adalimumab 1 Pts: Azathioprine 1 Pts: Vedolizumab 1 Pts: None	14.3 month (3-30)	Clinical evaluation +/- MRI	12 weeks (6-30)	Healing rate: 66% (8/12)	Perianal abscess 33% (4/12)	Schwander *et al* (2021) [29]
Retrospective	11 Pts	5 Pts: Infliximab 3 Pts: Adalimumab 2 Pts: Vedolizumab 1 Pts: Tacrolimus	41.5 weeks (12-81)	Clinical evaluation	41.5 weeks	72.7% (8/11): complete closure of fistula 27.3% (3/11): No response	1 Pts: cytomegalovirus viremia Perianal abscess 36.4% (4/11)	Cabalzar-Wondberg *et al* (2021) [34]
Retrospective	4 Pts with rectovaginal fistula	1 Pts: Infliximab and azathioprine 1 Pts: Azathioprine 1 Pts: Adalimumab	6 months	Clinical evaluation	6 months	25% (1/4) Clinical healing	None	Nikolic *et al* (2021) [36]
RCT- Phase 3 ADMIRE-CD Trial	40 Pts of whom 25 Darvadstrocel 15 Control Pts	17 /25 (anti-TNF/ immunosuppressants / combination) 12 /15 (anti-TNF/ immunosuppressants / combination)	104 weeks	Clinical evaluation	24 weeks 52 weeks 104 weeks	Clinical remission 64% (16/25) vs. 47% (7/15) 80% (20/25) vs. 47% (7/15) 56% (14/25) vs. 40% (6/15)	None	Garcia-Olmo *et al* (2022) [30]
Retrospective-INSPECT Long-term follow up ADMIRE-CD Trial	89 Pts of whom 43 Pts Darvadstrocel 46 Control Pts	anti-TNF agents or immunosuppressants or combination	208 weeks	Clinical evaluation	52 weeks 104 weeks 156 weeks	Clinical remission 67.4% (29/43) vs. 52.2% (24/46) 53.5% (23/43) vs. 43.5% (20/46) 53.5% (23/43) vs. 45.7% (21/46)	None	Panes *et al* (2022) [31]
Retrospective	3 Pts	Vedolizumab / ustekinumab /anti-TNF	6 months	Clinical evaluation+ MRI/TP-US	6 months	Persistence of all fistula tracts, no collections 100% (3/3)	Perianal abscess 33% (1/3)	Colombo *et al* (2022) [32]

(Contd...)

Table 1 *(Continued)*

Study design	Number of patients	Concomitant treatments	Follow-up period	Evaluation criteria	Time point	Outcomes	Related adverse events	Study (year) [ref.]
Prospective, open-label, single-arm study-Phase 3	22 Pts	40.1% Biologic agent only 9.1 % Azathioprine only 31.8% Biologics + azathioprine 18.2% No biologics or immunosuppressants	52 weeks	Clinical evaluation+MRI	24 weeks 52 weeks	Clinical remission and absence of collection >2 cm 59.1% (95%CI 38.5-79.6%) 68.2% [95%CI 48.7-87.6%]	1 Pt: exacerbation of luminal Crohn's disease 1 Pt: Blood bilirubin increase	Furukawa *et al* (2023) [33]
Prospective	27 Pts	19 Pts: Infliximab 5 Pts: Adalimumab 15 Pts: Azathioprine 2 Pts: Methotrexate 3 Pts: Mercaptopurine	12 months	Clinical evaluation+MRI	12 months	Complete clinical response: 51.9% Complete radiological response: 50% Combined clinical and radiological response: 34.6% Decreased perianal activity index from 6.4 to 1.6 (P<0.001)	None	Fathallah *et al* (2023) [35]

CI, confidence interval; MRI, magnetic resonance imaging; TNF, tumor necrosis factor; Pts, patients; RCT, randomized controlled trial; TP-US, transperineal ultrasound

and a single center study from France with 27 patients that additionally assessed the life quality of patients and possible predictive factors [36].

Efficacy of darvadstrocel

Overall, 186 patients with complex perianal fistulizing CD were treated with darvadstrocel. Data from the European ADMIRE-CD trial showed that darvadstrocel is superior to placebo in both the short and long term. A significantly higher proportion of patients treated with darvadstrocel achieved both clinical and imaging remission compared to the control group at 24 weeks (51.5% vs. 35.6%, 97.5% confidence interval [CI] 0.5-31.2; P=0.021] [39] and at 52 weeks (56.3% vs. 38.6%, 95%CI 4.2-31.2; P=0.010) [38]. In addition, a higher rate of clinical remission was demonstrated at week 104 (53.5% vs. 43.5%; difference 15.3%, 95%CI 4.9-35.4%) and at week 156 (53.5% vs. 45.7%; difference: 7.8%, 95%CI −12.9% to 28.6%) [32], showing that darvadstrocel may lead to sustained fistula healing in patients with complex perianal fistulizing CD. However, it should be mentioned that clinical remission rates failed to reach statistical significance compared to the control group.

These findings are consistent with current prospective studies that have demonstrated significant healing rates. In a multicenter single-arm study from Japan, 59.1% of patients receiving darvadstrocel achieved combined remission at week 24 (95%CI 38.5-79.6%). This effect was additionally maintained at week 52 (68.2%, 95%CI 48.7-87.6%) [34]. Another prospective study found 51.9% and 50% complete clinical and radiological response rates, respectively, at 12 months. The combined clinical and radiological response rate was 34.6%. Furthermore, patients with a combined response had Crohn's anal fistula-quality of life scale grades significantly lower compared to those without a complete clinical+radiological response (15.0 vs. 32.8, P=0.01) [36].

In a retrospective study, a high rate of complete clinical closure of fistula (72.7%, 8/11) was observed after an average follow-up time of 41.5 weeks. Additionally, complete fistula healing was observed in half of the patients 4-6 weeks after the operation [35]. In a separate retrospective study, a similar healing rate (66%, 8/12) was demonstrated at 12 months [30]. In another retrospective study, involving only 4 patients with CD-related rectovaginal fistula who had failed biological therapy, only 1 patient (25%) achieved healing of the fistula, with re-epithelialization of both the vaginal and rectal opening and the absence of clinical symptoms [37].

Safety

Safety data arising from the ADMIRE-CD trial's RCTs demonstrated a favorable safety and tolerability profile of darvadstrocel up to 24 and 52 weeks after infusion. The rate of patients experiencing treatment emergent adverse events

was similar in both the darvadstrocel and control groups, with a slightly higher percentage of patients in the control group experiencing treatment emergent adverse events, considered to be treatment-related. Proctalgia (15%) and abscess/fistula (33%) were the most common treatment-related adverse events in both groups, up to week 52 [38,39]. Both retrospective studies investigating the long-term effectiveness of darvadstrocel after 52 weeks reported no adverse events related to treatment [31,32]. In the other retrospective studies, perianal abscess formation was the most common adverse event, occurring in approximately 1 in 3 patients, while 1 case of cytomegalovirus viremia was reported [30,35]. The safety profile of darvadstrocel was favorable in both prospective studies, with only 1 case of exacerbation of CD and 1 case of increased blood bilirubin being recorded [34,36].

Discussion

The management of complex perianal fistulizing CD remains a challenge. It is difficult to treat with biological and conventional therapy, often requiring surgical intervention, and is associated with a poor quality of life. According to the above evidence, darvadstrocel appears to be an effective and safe treatment option for the therapy of complex perianal fistulizing CD. The pivotal phase 3 ADMIRE-CD trial demonstrated a higher combined remission rate in patients treated with darvadstrocel compared to placebo after 1 year, while similar healing rates were subsequently demonstrated from other prospective studies. However, it should be mentioned that ADMIRE-CD had several limitations, as luminal activity of CD was an exclusion criterion, and active luminal CD is common in patients with perianal complications [40]. Moreover, data on the efficacy of darvadstrocel in cases of rectovaginal fistulas are scarce, and the available data come from a case series with only a small sample [37], as no RCTs exist on this topic. In addition, the safety and efficacy of darvadstrocel in pediatric and adolescent populations has not yet been established, although a clinical study on this population is ongoing [41]. It should be mentioned that, given the limited sample size of patients combined with the diverse study designs and varying outcomes, conducting a meta-analysis on the effectiveness and safety of darvadstrocel may not be feasible.

MSCs have been shown to be safe and well-tolerated by the host patient, because of the absence of human leukocyte antigen (HLA) class II antigen and low HLA I, which provides protection from the innate and adaptive immune response [42,43]. In the ADMIRE-CD trial, there was no significant difference in the rate of adverse events between the darvadstrocel group and the control group, and the most common treatment-related adverse events were local reactions. Additionally, a recent meta-analysis investigating MSC injections for perianal CD treatment, including darvadstrocel, showed no increase in adverse or serious adverse events compared to control subjects [44]. While animal models have suggested that MSCs may have a tumorigenic role by promoting angiogenesis and neoplasm growth [45,46], to date there have been no reported cases of neoplasms after darvadstrocel injection. Moreover, no specific dose adjustments are necessary for elderly patients or those with renal or hepatic impairment [47].

An interesting safety concern of darvadstrocel is the use of ASCs in pregnant women with perianal CD. A retrospective study investigated the influence of intralesional injection of autologous ASCs on fertility and fetal development; it involved 5 women who achieved remission after stem cell treatment and decided to become pregnant. The miscarriage rate was similar to that of the general population, all patients succeeded in becoming pregnant and all deliveries were carried out by elective cesarean section to protect the perianal area. Furthermore, no treatment-related malformations were observed in the neonates [48]. However, larger studies are warranted. Furthermore, data on the safety of darvadstrocel for breastfeeding mothers is lacking.

In conclusion, based on the current evidence, darvadstrocel therapy may be considered a standard of care in the management of patients with perianal fistulizing CD who have not responded to conventional medical and surgical therapies. The studies conducted so far have shown that darvadstrocel has a short-term efficacy that can be sustained in the long run for most patients. However, the long-term efficacy of darvadstrocel has not yet been proven to be significantly superior to placebo, although there is a trend favoring darvadstrocel. Therefore, more real-world data, such as that from the INSPIRE registry, and head-to-head comparative studies with other surgical options, such as AF surgery, are needed to better understand the long-term results. The INSPIRE registry is a European study that evaluates the safety and effectiveness of darvadstrocel treatment in patients with complex perianal fistulas over 36 months. In a recent interim analysis after 6 months, 205 patients who received darvadstrocel treatment were evaluated. The results showed that 73% of all treated patients (AT) and 74% of patients treated per protocol of patients (PP) had a clinical response, and 65% (AT and PP) achieved clinical remission. There were minimal changes in CD activity. Adverse events were reported in 20% (AT), with 9.3% experiencing serious events. No ectopic tissue formation or deaths were reported. These findings are consistent with the pivotal ADMIRE-CD study in terms of effectiveness and safety [49]. It is important to note that this analysis was presented in abstract form, which means there may be some limitations regarding the availability of complete data and a detailed analysis.

It is important to note that a major limitation of darvadstrocel therapy may be its cost; currently, no data on absolute costs or cost-effectiveness have been provided. Additionally, further studies and randomized controlled trials are necessary to directly compare the efficacy and safety of darvadstrocel therapy with other types of MSCs, such as allogeneic or autologous bone marrow-derived MSCs, in the treatment of perianal fistulizing CD [50,51].

Summary Box

What is already known:

- Managing complex perianal fistulizing Crohn's disease remains challenging, with many patients experiencing poor life quality and frequent relapses
- The use of antibiotics, anti-tumor necrosis factor agents, and immunomodulators, in combination with seton placement, has demonstrated efficacy in treating complex perianal fistulas
- Mesenchymal stem cells have immunomodulatory properties

What the new findings are:

- Darvadstrocel may be considered a standard of care in the management of patients with perianal fistulizing Crohn's disease who have not responded to conventional medical and surgical therapies
- The safety profile of darvadstrocel is favorable

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