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World J Gastroenterol 2021 June 28; 27(24): 3429-3692



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The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for WJG as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2019 is 7.1 and Scopus CiteScore rank 2019: Gastroenterology is 17/137.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Li-Li Wang*; Production Department Director: *Yun-Jie Ma*; Editorial Office Director: *Ze-Mao Gong*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

June 28, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Stem cell injection for complex anal fistula in Crohn's disease: A single-center experience

Oliver Schwandner

ORCID number: Oliver Schwandner
0000-0001-9119-1479.**Author contributions:** Schwandner O performed the research and wrote the paper.**Institutional review board****statement:** According to the Ethics Committee of the Bavarian State Chamber of Physicians retrospective reviews of anonymized patient data do not require ethical approval, No. 2021-1022.**Informed consent statement:**

Patients were not required to give informed consent to the study because the retrospective analysis used anonymized clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The author had honoraria from Takeda and Medtronic for invited presentations during advisory board meetings and satellite symposia. Neither funding nor financial support was administered for the current study.**Data sharing statement:** No additional data are available.**Open-Access:** This article is an open-access article that was**Oliver Schwandner**, Department of Proctology, Krankenhaus Barmherzige Brueder, Regensburg 93049, Germany**Corresponding author:** Oliver Schwandner, FASCRS, MD, Professor, Department of Proctology, Krankenhaus Barmherzige Brueder, Pruefeninger Str 86, Regensburg 93049, Germany. oliver.schwandner@barmherzige-regensburg.de**Abstract****BACKGROUND**

Despite tremendous progress in medical therapy and optimization of surgical strategies, considerable failure rates after surgery for complex anal fistula in Crohn's disease have been reported. Therefore, stem cell therapy for the treatment of complex perianal fistula can be an innovative option with potential long-term healing.

AIM

To evaluate the results of local administration of allogenic, adipose-derived mesenchymal stem cells (darvadstrocel) for complex anal Crohn's fistula.

METHODS

All patients with complex anal fistulas associated with Crohn's disease who were amenable for definite fistula closure within a defined observation period were potential candidates for stem cell injection (darvadstrocel) if at least one conventional or surgical attempt to close the fistula had failed. Darvadstrocel was only indicated in patients without active Crohn's disease and without presence of anorectal abscess. Local injection of darvadstrocel was performed as a standardized procedure under general anesthesia including single-shot antibiotic prophylaxis, removal of seton drainage, fistula curettage, closure of the internal openings and local stem cell injection. Data collection focusing on healing rates, occurrence of abscess and follow-up was performed on a regular basis of quality control and patient care. Data were retrospectively analyzed.

RESULTS

Between July 2018 and January 2021, 12 patients (6 females, 6 males) with a mean age of 42.5 (range: 26-61) years underwent stem cell therapy. All patients had a minimum of one complex fistula, including patients with two complex fistulas in 58.3% (7/12). Two of the 12 patients had horse-shoe fistula and 3 had one complex fistula. According to Parks classification, the majority of fistulas were trans-

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Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: January 9, 2021

Peer-review started: January 9, 2021

First decision: January 23, 2021

Revised: March 10, 2021

Accepted: June 4, 2021

Article in press: June 4, 2021

Published online: June 28, 2021

P-Reviewer: Pelletier AL, Yuksel I, Zhao L

S-Editor: Fan JR

L-Editor: A

P-Editor: Ma YJ



sphincteric (76%) or suprasphincteric (14%). All patients underwent removal of seton, fistula curettage, transanal closure of internal opening by suture (11/12) or mucosal flap (1/12) and stem cell injection. At a mean follow-up of 14.3 (range: 3-30) mo, a healing rate was documented in 66.7% (8/12); mean duration to achieve healing was 12 (range: 6-30) wk. Within follow-up, 4 patients required reoperation due to perianal abscess (33.3%). Focusing on patients with a minimum follow-up of 12 mo (6/12) or 24 mo (4/12), long-term healing rates were 66.7% (4/6) and 50.0% (2/4), respectively.

CONCLUSION

Data of this single-center experience are promising but limited due to the small number of patients and the retrospective analysis.

Key Words: Complex anal fistula; Crohn's disease; Stem cell therapy; Mesenchymal stem cells; Darvadstrocel; Treatment; Surgery; Outcomes

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Core Tip: This is a retrospective single-center study on the application of allogenic, adipose-derived mesenchymal stem cells (darvadstrocel) for complex perianal fistula associated with Crohn's disease, providing structured inclusion and exclusion criteria for 12 patients. The current data demonstrate that the management by local stem cell therapy is safe and effective. However, based on the small patient sample size and the retrospective analysis of routine clinical data, a general conclusion remains limited. Therefore, further prospective controlled studies are mandatory to assess the definite role of adipose-derived mesenchymal stem cells for complex anal fistula in Crohn's disease.

Citation: Schwandner O. Stem cell injection for complex anal fistula in Crohn's disease: A single-center experience. *World J Gastroenterol* 2021; 27(24): 3643-3653

URL: <https://www.wjgnet.com/1007-9327/full/v27/i24/3643.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v27.i24.3643>

INTRODUCTION

Both medical and surgical options for complex perianal fistulas associated with Crohn's disease remain difficult and challenging[1-5]. Despite recent progress in medical treatment including biologicals and actual trends in sphincter-preserving surgical techniques, considerable recurrence rates after definite surgery for Crohn's anal fistula have been documented[2,3,5]. As an interdisciplinary treatment regimen is the prerequisite for disease control and potential long-term remission of perianal fistulizing Crohn's disease, therapeutic goals include symptom improvement (e.g., reduction of secretion, absence of pain), prevention of recurrent perianal abscess requiring further surgery, preservation of continence, improvement of quality of life and, finally, healing of the fistula.

Focusing on surgical procedures for complex anal fistulas, conventional procedures such as advancement flap repair have shown considerable failure rates for Crohn's fistulas, whereas innovative surgical options such as ligation of the intersphincteric fistula tract (LIFT), biomaterials (e.g., plug) or video-assisted anal fistula treatment seem to have a 50% healing rate after 12 mo without significant impairment of continence[6]. Recently, several reports and randomized studies have demonstrated that stem cell therapy for Crohn's complex anal fistula has raised the healing rates after 12 mo[2,7,8].

Impressed by the encouraging healing rates reported from the ADMIRE trial[7,8], it was the aim of this retrospective single-center study to evaluate the current results of stem cell therapy for complex anal fistulas in Crohn's disease with special focus on indication, patient selection and long-term outcome.

MATERIALS AND METHODS

Clinical setting

Stem cell injection was performed by administration of human, allogenic, expanded adipose-derived mesenchymal stem cells (darvadstrocel) for complex anal fistulas associated with Crohn's disease in adult patients. For the current study, Alofisel® (5 million cells/mL) was used (Takeda GmbH, Konstanz, Germany). Upon authorization of the European Medicines Agency (initial authorization on December 14, 2017), Alofisel® is indicated in patients with non-active or mildly active Crohn's disease when fistulas show an inadequate response (failure either due to persistence or recurrence) to at least one conventional, biological or surgical therapy. Darvadstrocel was only administered if the fistulas had conditioning by curettage or seton drainage. All potential candidates for stem cell injection had fully informed consent of the innovative method and underwent a selection process by multidisciplinary evaluation and discussion (gastroenterology and proctology); finally, the center was trained by an educational and hands-on workshop for the use of darvadstrocel in complex fistulas in Crohn's disease to ensure that only specialist physicians perform the procedure. Moreover, intrainstitutional education was conducted for darvadstrocel administration (*e.g.*, pharmacy, surgical team).

Study population

All patients with complex anorectal fistulas associated with Crohn's disease who were amenable for definite fistula closure were potential candidates for darvadstrocel administration if at least one conventional or surgical attempt to close the fistula had failed. All patients suffered from complex fistula according to American Gastroenterological Association and Parks classification[9,10]. All patients had a minimum of one complex fistula, including patients with two complex fistulas in 58.3% (7/12). According to Parks classification, 76% of the fistulas were transsphincteric and 14% were suprasphincteric. Darvadstrocel was only indicated in patients without active Crohn's disease, ruled out by ileocolonoscopy, and without the presence of anorectal abscess assessed by clinical examination and/or pelvic magnetic resonance imaging (MRI). Additionally, all patients had interdisciplinary discussion prior to surgical treatment. Specific inclusion and exclusion criteria are outlined in [Table 1](#).

Study design and outcome evaluation

To evaluate the outcome of patients who underwent local stem cell injection by the application of darvadstrocel, a retrospective analysis of existing routine clinical data was performed. In detail, regular clinical data of patient care and quality control (including patients' characteristics, type of therapy, outcome evaluation during routine clinical follow-up) were retrospectively analyzed in an anonymized fashion. Patients underwent darvadstrocel administration not for primary study purpose but for quality assurance and patient care. To assess outcome, criteria of healing included that both internal and external openings were closed, no abscess or fluid collection was present and if the patient was free of symptoms (*e.g.*, pain, secretion). Healing was assessed by clinical examination and proctoscopy. Strict criteria and definitions of persistence and recurrence are outlined in [Table 2](#).

Special consideration for coronavirus disease 2019 pandemic

Due to the coronavirus disease pandemic in the beginning of 2020, the coronavirus disease 2019 (COVID-19) outbreak had direct implications for patients with perianal fistulizing Crohn's disease regarding their schedule for definite surgery. As a result of the primary outbreak in March 2020, no patients had elective surgery for Crohn's associated complex anal fistulas at our institution between March 2020 and July 2020 according to governmental restrictions (German Ministry of Health). Moreover, according to a second restriction period for elective procedures at our institution starting in November 2020, potential procedures were postponed to 2021. Finally, a relevant number of patients with fistulizing perianal Crohn's disease under immunosuppression and/or maintenance therapy (*e.g.*, biologicals) postponed their surgery to 2021.

Preoperative assessment

All patients amenable for stem cell injection were seen in the proctological office 2-4 wk prior to darvadstrocel treatment. Informed consent was given, including for efficacy from the ADMIRE study, innovation of the current technique, and monitoring of side effects or adverse events, surgical technique and follow-up observation. Procto-

Table 1 Inclusion and exclusion criteria for administration of darvadstrocel

Inclusion	Exclusion
Complex anal fistulas associated with Crohn's disease (including horse-shoe fistula)	Simple fistulas associated with Crohn's disease, rectovaginal fistula
At least one conventional, biological or surgical therapy prior to stem cell injection	No medical, biological or surgical therapy prior to stem cell injection
No active Crohn's disease confirmed by ileocolonoscopy	Active Crohn's disease confirmed by ileocolonoscopy
No perianal abscess or sepsis confirmed by clinical exam, endoanal ultrasound and/or pelvic MRI	Perianal abscess or significant inflammation in the pelvis or anorectal region confirmed by MRI
Interdisciplinary recommendation	No recommendation by multidisciplinary team
Patient compliant for medical consultation, follow-up examination and interdisciplinary monitoring of disease	Non-compliance of patient
Pretreatment of fistulas by seton drainage ("conditioning")	Fistulas without seton drainage or conditioning by curettage
Maximum of two fistulas with two internal and two external openings (each)	More than two complex fistulas
No anorectal stenosis	Presence of anorectal stenosis
Fully informed consent possible	No informed consent possible

MRI: Magnetic resonance imaging.

Table 2 Definitions of outcome

Parameter	Definition	Supplementary definition
Healing	Complete healing of internal and external opening; no abscess, no symptoms	Assessment by clinical examination including proctoscopy
Persistence	No complete healing with persistence of fistula (external opening) and/or symptoms	Defined postoperative observation period
Recurrence	Recurrence of fistula after period with complete healing and interval without symptoms	With or without occurrence of abscess

logical examination included clinical examination and proctorectoscopy to rule out abscess or proctitis in the immediate preoperative phase. No antibiotic treatment was administered; setons were controlled to be correct in place. No routine curettage of fistulas drained by setons was performed in the preoperative period, and no specific change for medical treatment was performed.

Surgical technique

All surgical procedures were performed under general anesthesia. The patient was placed in lithotomy position. A single-shot antibiotic prophylaxis was routinely administered (cefuroxime/metronidazole). Initially, a careful examination under anesthesia was performed to ensure that there was no presence of abscess or proctitis; moreover, assessment of fistula length, anatomy and topography according to Parks classification[10] was performed. After removal of setons, a vigorous curettage of the fistula tracts was performed by using a metallic curette. Additionally, injection of a sodium chloride solution (0.9%) was administered after curettage. No excision of the fistula tracts were conducted; however, the external openings were sparingly excised. Afterwards, the internal openings were closed by either direct suturing (absorbable suture, Vicryl 3/0; Ethicon EndoSurgery, Norderstedt, Germany) or by mucosal flap (absorbable suture, Vicryl 3/0) if necessary.

After preparing and resuspension of the stem cells and gentle aspiration by using a syringe and injection needles (22-G), darvadstrocel was injected according to the manufacturer's recommendations: Two vials were injected around the internal openings (transanal approach), and the other two vials were injected along the fistula tracts creating small deposits of the cell suspension along the fistulas from external openings (perianal approach). After injection, a soft massage along the fistula region was performed; finally, a sterile bandage was placed around the anal region.

Postoperatively, no specific restrictions related to feeding and mobility were present; after wound control on the first postoperative day, the patient was discharged from hospital. No specific wound management was proposed (only clear water twice a day). Maintenance therapy was given as planned prior to surgery. Neither intravenous nor oral antibiotic therapy was given in the postoperative period.

Follow-up

Regular follow-up examination was performed 2, 4 and 6 wk after surgery in the proctological office, to obtain clinical data related to quality assurance and patient care. Moreover, follow-up examination was advised at 6, 12 and 24 mo after stem cell injection. Additionally, gastroenterological monitoring was advised to provide regular monitoring of Crohn's disease. As clinical follow-up was primarily indicated for routine quality control and was not indicated for study purpose, regular follow-up did not include postoperative MRI as routine examination.

RESULTS

Study population and patient characteristics

Between July 2018 and January 2021, a total of 12 patients (6 females, 6 males) with a mean age of 42.5 (range: 26-61) years underwent stem cell therapy for complex anal fistula associated with Crohn's disease. All patients had medical therapy (infliximab, adalimumab, vedolizumab or azathioprine), and complex fistulas did not respond to either medical or surgical treatment prior to stem cell therapy. Mean duration of Crohn's disease was 19.3 years (range: 7-36 years), and median duration of perianal fistulizing Crohn's disease was 8.7 years (range: 1-16 years). All fistulas had at least one conventional surgical approach to close the fistula (except seton drainage) prior to stem cell therapy; mean number of surgical attempts to close the fistula was 2.0 (range: 1-4). Details on study population and patients' characteristics are detailed in [Table 3](#).

Fistula characterization

All patients underwent fistula conditioning by seton drainage for a mean duration of 31.5 (range: 6-72) wk, and 4 patients had undergone fecal diversion due to severe perianal sepsis. All patients had a minimum of one complex fistula, including patients with two complex fistulas in 58.3% (7/12). Two of 12 patients had horse-shoe fistula, and 3 of 12 had one complex fistula. In total, 21 fistula tracts were documented in 12 patients. According to Parks classification, the majority of fistulas were trans-sphincteric (76%) or suprasphincteric (14%).

Surgery

All patients underwent removal of seton, fistula curettage, transanal closure of internal opening by suture (11/12) or mucosal flap (1/12) and stem cell injection. No intraoperative complications or side effects were noted. Postoperative morbidity included 1 patient with fever (without signs of perianal sepsis) on the second postoperative day. No serious adverse events were documented.

Outcome

Details on efficacy evaluation and outcome are outlined in [Table 4](#). At a mean follow-up of 14.3 mo (range: 3-30 mo), a healing rate was documented in 66.7% (8/12); mean duration to achieve healing was 12 wk (range: 6-30 wk). Four patients had either fistula persistence ($n = 2$, 16.7%) or fistula recurrence ($n = 2$; 16.7%). Within follow-up, 4 patients developed perianal abscess (33.3%) and required reoperation. From 4 patients with ileostomy, one stoma reversal was performed 2 years after fistula healing.

Focusing on patients with a minimum follow-up of 12 mo (6/12) or 24 mo (4/12), long-term healing rates were 66.7% (4/6) and 50.0% (2/4), respectively.

DISCUSSION

Despite significant progress in medical treatment, including biologicals and cell-based therapies, development of sphincter-saving surgical techniques and interdisciplinary co-working, failure rates after definite surgery for perianal fistulizing Crohn's disease are still high[3,11-13]. Moreover, in patients with severe and refractory perianal

Table 3 Patient population

	1	2	3	4	5	6	7	8	9	10	11	12
Age	26 yr	31 yr	52 yr	49 yr	39 yr	35 yr	61 yr	26 yr	54 yr	44 yr	45 yr	48 yr
Sex	Male	Female	Female	Female	Male	Female	Male	Female	Male	Male	Male	Female
CPF Parks classification (number of fistulas)	Transsphincteric (2)	Transsphincteric (2)	Suprasphincteric (1)	Transsphincteric (2)	Transsphincteric (1) Intersphincteric (1)	Transsphincteric (2)	Transsphincteric (2)	Transsphincteric (1)	Suprasphincteric (1) Transsphincteric (1)	Transsphincteric horse-shoe-fistula (2)	Transsphincteric horse-shoe-fistula (2)	Suprasphincteric (1)
Number of internal/external openings	2/2	2/2	1/1	2/2	2/2	1/2	2/2	1/1	2/2	1/2	1/2	1/1
Length of fistula tract	3 cm each	3 cm each	4 cm	2 cm; 5 cm	10 cm; 1.5 cm	12 cm; 1.5 cm	3 cm; 7 cm	3 cm	6.5 cm; 2.5 cm	2.5 cm; 2.5 cm	3.0 cm; 3.0 cm	3.0 cm
Previous medical treatment	Azathioprin	Azathioprin Infliximab	Azathioprin	Azathioprin	Azathioprin	Azathioprin	Azathioprin Infliximab	Azathioprin	Adalimumab	Azathioprin Adalimumab	Infliximab	Azathioprin Antibiotics
Actual medical treatment	Adalimumab	Ustekinumab	Azathioprin	None	Ustekinumab	Vedolizumab	Ustekinumab	Infliximab	Infliximab	Infliximab	Adalimumab	None
Previous surgical treatment for abscess and fistula	Multiple abscess excisions, previous fistula surgery (1)	Multiple abscess excisions, previous fistula surgery (1)	Multiple abscess excisions, previous fistula surgery (3)	Multiple abscess excisions, previous fistula surgery (2)	Multiple abscess excisions, previous fistula surgery (3)	Multiple abscess excisions, previous fistula surgery (2)	Multiple abscess and fistula surgeries (11)	Multiple abscess and fistula surgery (4)	Multiple abscess and fistula surgery (4)	Multiple abscess and fistula surgery (4)	Multiple abscess and fistula surgery (3)	Multiple abscess and fistula surgery (9)
Previous treatment (stoma)	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	No
Seton drainage prior to Darvadstrocel (duration)	Yes (6 wk)	Yes (4 mo)	Yes (10 mo)	Yes (18 mo)	Yes (8 wk)	Yes (12 wk)	Yes (9 mo)	Yes (60 wk)	Yes (36 wk)	Yes (48 wk)	Yes (24 wk)	Yes (12 wk)
Method of closure of internal opening	Suture (1), mucosal flap (1)	Suture (2)	Suture (1)	Suture (2)	Suture (2)	Suture (1)	Suture (2)	Suture (1)	Suture (2)	Suture (1)	Suture (1)	Suture (1)
Intraoperative adverse events	No	No	No	No	No	No	No	No	No	No	No	No
Postoperative adverse events	No	No	No	No	No	No	No	No	No	No	Fewer (day 2)	No

CD: Crohn's disease; CPF: Crohn's perianal fistula.

Table 4 Efficacy evaluation and outcomes

	1	2	3	4	5	6	7	8	9	10	11	12
Length of follow-up (mo)	27	30	8	24	26	16	12	6	8	6	6	3
Efficacy evaluation (clinical)	Complete healing	Complete healing	Complete healing	Recurrence	Persistence	Complete healing	Complete healing	Complete healing	Persistence	Complete healing	Recurrence	Complete healing
Efficacy evaluation (MRI)	Not performed	Complete healing	Not performed	Recurrence	Persistence	Not performed	Not performed	Not performed	Not performed	Persistence	Recurrence	Not performed
Time to fistula closure	6 wk	12 wk	9 wk	---	---	12 wk	30 wk	9 wk	--	9 wk	---	10 wk
Incidence of abscess during follow-up	Yes	No	No	No	Yes	No	No	No	Yes	No	Yes	No
Further surgery during follow-up	Yes; Abscess excision (twice)	No	No	Seton drainage	Yes; Abscess excision	No	No	No	Yes; Abscess excision	No	Yes; Abscess excision	No
Maintenance therapy	Adalimumab	Ustekinumab	Azathioprin	Infliximab	Ustekinumab	Vedolizumab	Ustekinumab	Ceased	Infliximab	Infliximab	Infliximab	None
Stoma reversal (if present)	No stoma	Stoma reversal	No stoma	No	No stoma	No stoma	No stoma	No stoma	No stoma	No	No	No stoma

MRI: Magnetic resonance imaging.

disease, the decision to perform fecal diversion or even proctectomy has a tremendous impact on quality of life, particularly in younger patients. Impressed by the preliminary results of limited single-center studies and the encouraging data of the ADMIRE study[7,8], this was a retrospective single-center study analyzing routine clinical data on the application of allogenic, adipose-derived mesenchymal stem cells (darvadstrocel) for complex perianal fistula associated with Crohn's disease, providing structured inclusion and exclusion criteria in 12 patients.

In general, the optimal surgical treatment of complex anal fistulas in patients with Crohn's disease remains challenging. As the majority of patients need surgery for perianal fistulizing Crohn's disease and a high proportion of patients need further surgery due to abscess and recurrent fistula, the integrity of the anal sphincter is essential for preservation of continence[3]. Therefore, the risk of deterioration of continence status increases with the number of surgical procedures and the invasiveness of procedures performed. For complex anal fistulas according to

American Gastroenterological Association and Parks classification[9,10], transrectal flap procedures (advancement or mucosal flap repair) and the LIFT procedure can be considered as effective surgical options in stable disease and absence of proctitis and/or anorectal stenosis with acceptable healing rates[11-18]; however, fecal incontinence and soiling is reported in approximately 10% of patients after endorectal flap procedures[6,11,18]. Focusing on the LIFT procedure, the risk of incontinence is low, but about half of the patients need additional surgery due to recurrence[14-16]. The main "disadvantage" or limitation of both procedures are high complex fistulas with suprasphincteric course or multi-tract fistulas with two internal and external openings ("multiple branching tracts"). In these patients, long-term seton drainage is the favored option; alternatively, proctectomy can be considered. Based on this "surgical dilemma", the novel therapeutic approach of local stem cell therapy seems to be an alternative for highly selected patients with multi-tract, complex fistulas.

In the meantime, a variety of limited studies demonstrated that local injection of mesenchymal stem cells can induce long-term fistula healing without the risk of incontinence and without serious adverse events related to the mesenchymal stem cells themselves[19-22]. Following the results of the multicenter, phase III randomized control trial (ADMIRE), the application of allogenic, adipose-derived, mesenchymal stem cells combined with transanal closure of the internal opening and fistula curettage, a 50% healing rate of stem cell therapy compared with a 34% success in the placebo group was documented after 24 wk, and healing rates were sustained to 52 wk [7,8].

Impressed by these results and personally searching for the "best option" in patients with multi-branching or two-tract complex fistula, it was the aim of the current single-center experience to evaluate the outcome of local injection of darvadstrocel in a highly selected group of patients. Following the current single-center experience with stem cell therapy, strict inclusion and exclusion criteria were defined. In accordance with the inclusion criteria of the ADMIRE study[7,8], only patients with complex fistulas associated with Crohn's disease—in the majority two complex fistula, suprasphincteric fistula and horse-shoe-fistula, without active luminal Crohn's disease (stable disease under medical treatment) and no evidence of perianal sepsis were included. In contrast, simple fistulas or rectovaginal fistulas were excluded for stem cell therapy. Moreover, in the current study, patients with single-tract intersphincteric or transsphincteric fistulas as well as relatively short single-tract fistulas (fistula length less than 3 cm) were not candidates for stem cell therapy; in these patients, advancement flap repair, mucosal flap repair or LIFT procedure was the preferred option. Within the observation period, a total of 28 patients underwent flap or LIFT procedure for complex fistula associated with Crohn's disease (data not shown).

All patients had drainage of fistulas by seton for a minimum of 6 wk. In contrast to the ADMIRE study[7,8], 4 patients who underwent fecal diversion due to perianal sepsis related to complex fistulas years before admission to our center were included in the current study after interdisciplinary discussion, as the only alternative surgical treatment would have been a proctectomy in these patients, and patients refused this option. Finally, all 12 patients had at least one attempt to surgically close the fistula with no success; thus, all fistulas treated with stem cell therapy were recurrent complex fistula.

Focusing on surgical technique and administration of darvadstrocel, no difficulties or intraoperative morbidity were documented. One patient had fever on the second postoperative day without any signs of perianal sepsis. No serious adverse events in the immediate postoperative course were noted.

After a mean follow-up of 14.3 mo (range: 3-30 mo), healing rate was 66.7% (8 of 12 patients). Healing was based on strict criteria and was assessed by clinical examination and proctoscopy in the follow-up period. In terms of postoperative MRI (5/12 patients), 1 female patient with clinical evidence of fistula healing also had radiological healing as documented by MRI, whereas 3 patients had radiological recurrence (2) or persistence (1). One patient with clinical healing had radiologic persistence of fistula without signs of contrast enhancement. Focusing on patients with a minimum follow-up of 12 mo (6/12) or 24 mo (4/12), long-term healing rates were 66.7% (4/6) and 50.0% (2/4), respectively.

The occurrence of perianal abscess during follow-up was relatively frequent in the current collective. Four patients (33.3%) developed perianal abscess in the postoperative course, and surgery (abscess excision) was required (1 patient had abscess formation twice). Interestingly, the occurrence of perianal abscess was late (3, 4, 7, 9 and 22 mo after darvadstrocel administration), and abscess localization was near to one former external opening. The incidence of abscess was related to recurrence in 1 patient (supralelevatoric abscess with proctosigmoiditis), occurred with exacerbation of

systemic disease (subcutaneous abscess with active inflammation of ileocolic region and proctitis), and was associated with fistula persistence in 2 patients. As a consequence of the relatively high incidence of perianal abscess following stem cell therapy in the current series, a more wide or radical excision of the external opening should be recommended in future procedures to prevent perianal abscess. Moreover, patients with the occurrence of abscess could not be defined "in remission"; however, there was no change in medical treatment. Therefore, the differentiation of abscess as a local problem following fistula surgery or as a problem of systemic disease with direct implications for medical treatment should be more in focus between gastroenterologists and surgeons.

Analyzing the further course of patients with long-term healing in terms of medical therapy, 1 patient had ceased maintenance therapy after recommendation of the gastroenterologist. Focusing on patients who had fecal diversion in the past, one female patient underwent stoma reversal 2 years after stem cell injection. In the other 3 patients, follow-up is still too short, as stoma reversal should be advised not prior to a minimum period of 6 mo after definite fistula surgery (1 patient), and the other two patients had recurrence.

Specifically addressing the observation period related to the COVID-19 pandemic, stem cell therapy was not performed within March 2020 and July 2020 and within a second period starting in November 2020 due to general restrictions concerning elective operations in Germany. Based on governmental restrictions and in-hospital limitations (*e.g.*, reduced capacity in the surgical theater) as well as logistic reasons (*e.g.*, transportation of stem cells under specific conditions) patients with stable disease and without signs of active perianal disease were postponed. This was in accordance with other European and United States experiences related to the management of patients with inflammatory bowel disease[23,24].

The current results clearly demonstrate that an innovative sphincter-sparing surgical approach including fistula curettage, transanal closure of internal openings and local injection of darvadstrocel leads to promising long-term healing rates in patients with no "effective" alternative, such as flap repair or LIFT procedure. However, fundamental limitations of this single-center experience are the small number of patients, the retrospective design, and the absence of a control group. Therefore, the definite role of local application of mesenchymal stem cells has to be discussed within multidisciplinary round tables or consensus conferences to have clear position statements[25-28]. Actually, we are still in the episode of a "learning curve" in terms of patient selection, ideal surgical technique, interdisciplinary treatment discussion, role of maintenance therapy and evaluation of outcomes, among others. Therefore, generally accepted indications and pathways of stem cell therapy for complex fistulas in Crohn's disease cannot be derived; however, the current results should be a plea for further standardization and interdisciplinary consensus.

CONCLUSION

These single-center data demonstrate that local injection of adipose-derived mesenchymal stem cells (darvadstrocel) is safe and effective in patients suffering from perianal fistulizing Crohn's disease. Providing long-term healing in 66.7% of patients, stem cell therapy seems to be an innovative and promising surgical therapy for complex anal fistula associated with Crohn's disease. However, this single-center experience is limited due to the small number of patients and the retrospective assessment of routine clinical data related to quality control. As a technical consequence of a high incidence of perianal abscess during follow-up, a wide excision of the external opening should be recommended for future procedures. Finally, further interdisciplinary efforts including controlled studies are necessary to evaluate the definite role of stem cell therapy for complex anal fistula in Crohn's disease.

ARTICLE HIGHLIGHTS

Research background

Despite significant progress in medical therapy and surgical options, definite surgery for complex anal fistula in Crohn's disease remains challenging.

Research motivation

At present, failure rates after surgery for complex anal fistula associated with Crohn's disease are still high, and surgical options in patients with recurrent and/or multi-tract fistula are limited.

Research objectives

The primary objective was to assess whether local stem cell injection is associated with acceptable healing rates in a routine clinical setting.

Research methods

Providing strict inclusion and exclusion criteria, 12 patients with complex anal fistulas associated with Crohn's disease underwent local application of allogenic, adipose-derived mesenchymal stem cells (darvadstrocel). Darvadstrocel was only indicated in patients without active Crohn's disease confirmed by ileocolonoscopy and without presence of anorectal abscess. Study design was retrospective and routine clinical data were analyzed.

Research results

Twelve patients (6 females, 6 males) with complex anal fistula associated with Crohn's disease underwent fistula curettage, transanal closure of internal openings and local darvadstrocel administration. Fifty-eight percent of patients had two complex fistulas, and seventy-six percent of the fistulas were transsphincteric. After a mean follow-up of 14.3 mo, a healing rate of 66.7% (8/12) was documented. Perianal abscess occurred in 33.3% of patients during follow-up.

Research conclusions

This single-center experience demonstrates that local stem cell injection for complex perianal fistulizing disease is safe and provides acceptable healing rates. However, conclusions are limited due to the small number of patients and the retrospective study design.

Research perspectives

Based on the current results, local stem cell injection could be a new "puzzle piece" for effective treatment of complex anal fistulas associated with Crohn's disease.

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