Allogeneic mesenchymal stem cells for Crohn's disease-associated complex perianal fistulas

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 111
ISSN online: 1998-0469

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Vienna, March 2018

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This report should be referenced as follows:

Wolf, S., Stanak, M. Allogeneic mesenchymal stem cells for Crohn's Disease-associated complex perianal fistulas. Decision Support Document No. 111; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
http://hta.lbg.ac.at/page/imprint

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at"

Decision Support Document No.: 111

ISSN-online: 1998-0469

Content

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List of abbreviations

AdHopHTA ..... European Project on Hospital-Based Health Technology Assessment
AGA ..... American Gastroenterological Association
ASCs ..... Adipose-tissue-derived stem cells
BE ..... Belgium
BM-MSCs ..... Bone-marrow-derived mesenchymal stem cells
CD ..... Crohn's disease
CDAI ..... Crohn's Disease Activity Index
CHMP ..... Committee for Medicinal Products for Human Use
CRD ..... Centre for Review and Dissemination
CT ..... Computer Tomography
ECCO ..... European Crohn's and Colitis Organisation
ECM ..... Extracellular cell matrix
EMA ..... European Medicine Agency
EMT ..... Epithelial-to-mesenchymal transition
EUA ..... Examination under anaesthesia
EUS ..... Endoanal ultrasound
FDA ..... Food and Drug Administration
GRADE ..... Grading of Recommendations Assessment, Development and Evaluation
IBDQ ..... Inflammatory Bowel Disease Questionnaire

IEC ..... Intestinal epithelial cells
IFX ..... Infliximab
IG ..... Interventional group
IHE ..... Institute of Health Economics
LIFT ..... Ligation of the inter-sphincteric fistula tract
NW ..... Nebenwirkungen
MAF ..... Mucosal advancement flap
MMP ..... Matrix metalloproteinase
MRI ..... Magnetic resonance imaging
MSCs ..... Mesenchymal stem/stromal cells
NK ..... Natural killer
PDAI ..... Perianal Disease Activity Index
PDAI ..... Perianal Disease Assessment Index
PoP ..... Planned and Ongoing Projects
QoL ..... Quality of life
RCT ..... Randomised controlled trial
RoB ..... Risk of bias
SF-36 ..... Short-form-36
TC ..... Transitional cells
TNF ..... Tumour necrosis factor
TPUS ..... Transcutaneous perineal ultrasound
US ..... United States
USA ..... United States of America

Executive Summary

Introduction

Health Problem

The scope of this review includes complex perianal fistulas caused by Crohn's disease (CD) that are refractory to conventional and/or biologic agents, or in patients intolerant to such treatments. CD is a chronic inflammatory condition characterised by transmural inflammation and skip lesions. It can lead to fibrosis and strictures or results in sinus tracts giving rise to micro perforations and fistulas [2]. Fistulas usually occur when a fissure penetrates the gut wall, surrounded by granulation tissue with acute and chronic inflammation [3]. The main symptoms of perianal fistulas are anal pain with defecation and associated swelling, perianal itching, bleeding, and/or discharge of pus or stool from cutaneous fistula openings [3-5]. According to the American Gastroenterological Association (AGA), fistulas can be categorised into simple and complex ones [1, 4].

complex perianal fistulas caused by Crohn's disease (CD) can lead to anal pain with defecation/perianal swelling or itching, bleeding, incontinence

fistula classification by AGA into simple and complex ones

The highest number of CD patients is reported in the USA, Canada, and Europe, with prevalence rates of above 300 per 100,000 inhabitants [2]. In Austria, incidence rates of 11.5 per 100,000 inhabitants were estimated, with 9.5 and 14.6 in the rural and urban areas, respectively [6]. There is a slight predominance of CD developing in females and in a population of ages 20-29 years [3, 7]. Around 17% of the patients with CD develop perianal fistulas 10 years after diagnosis with the highest risk for patients with rectal involvement [8].

estimated incidence rate in Austria: 11.5 per 100,000 inhabitants

Description of Technology

The current report focuses on allogenic mesenchymal stem cells (MSCs) in patients with complex perianal fistulas caused by CD. Current standard treatments are associated with high recurrence rates [9]. During the actual process, via a fine long needle, allogeneic MSCs are injected locally and distributed into the patient's tissue adjacent to all fistula tracts and internal openings [10]. Allogeneic MSCs are assumed to prevent repeating surgeries, which can lead to high morbidity (i.e. incontinence), and subsequently to a loss of quality of life (QoL). Additionally, due to their less invasive character, especially for the anal sphincter apparatus, they may prevent the need for a permanent stoma [2, 5].

mesenchymal stem cells (MSCs) deemed to prevent repeated surgeries and the need for permanent stoma

Currently, there is one product "Darvadstrocel/Cx601" available. Cx601 has not yet received marketing authorisation. On December 15, 2017, it received a positive opinion from the Committee for Medicinal Products for Human Use by the European Medicines Agency (EMA).

no marketing authorisation for Cx601

Methods

The aim of this assessment was to investigate if adult human MSCs of allogeneic origin are more effective to increase remission rates and the QoL of CD-patients with complex perianal fistulas. Additionally, it was investigated if MSCs are safer concerning adverse events in comparison to placebo, fibrin glue or fistula plugs.

aim: efficacy and safety of allogeneic MSCs compared to placebo, fibrin glue or fistula plugs

systematic literature search in 4 databases, 590 citations after deduplication, 3 studies included, additional search in clinical trials for ongoing studies

A systematic literature search was conducted in four databases (Cochrane, CRD, Embase, Medline). The systematic search was limited to the years 2007 to 2017, English or German language, randomized controlled trials (RCTs) and prospective non-RCTs for efficacy and additionally, to interventional single-arm studies for safety. After deduplication, overall 590 citations were identified, of which three studies were included for data extraction and further analysis. A search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted in order to identify ongoing and unpublished studies, resulting in 45 potential hits.

Results

Included studies

evidence comparing MSCs to placebo

Effectiveness outcomes were addressed by two RCTs [11, 12] comparing allogeneic MSCs to placebo. For the safety outcomes, one further single-arm study [13] was included.

2 RCTs + 1 single-arm study (n=231 + 24 pts)

age range: 37-41 years

CDAI-scores at study start: range ≤200 to ≤250

The two RCTs included a total of 231 patients. The single-arm study included 24 patients. All studies included European patients. The mean age of all included patients was within a range of 37-41 years. The studies included patients based on different Crohn's Disease Activity Index (CDAI)-scores ranging from ≤200 to ≤250, indicating differences in the severity of the disease at study start. In two studies, the classification of complex perianal fistulas deviated from the definition of complex perianal fistulas of the AGA, which was used as an inclusion criteria in the PICO.

across 3 studies: two different stem cell types and varying dosages

Two studies [11, 13] administered adipose-tissue-derived MSCs, while one study [12] assessed bone-marrow-derived stem cells. The dosages of the studies ranged from 10 million to 120 million cells. In one study [13], a second dose of cells was administered in case of lacking response to the first dose.

sponsoring and conflict of interests

Two studies [11, 13] were sponsored by the manufacturer TiGenix and one study [12] was funded by the DigestScience Foundation, which has possible ties to the manufacturer (Takeda).

Clinical effectiveness

very low quality of evidence: significant improvement in combined remission (2 RCTs) and improvement in response (1 RCT) – not significant, inconclusive QoL-results across IBDQ, SF-36, PDAI and CDAI-scores, indicating no QoL improvement through MSC-therapy

Both RCTs [11, 12] reported improvements in combined remission in the interventional group compared to the placebo group. Only one RCT [11] reported on response, however, this results were not statistically significant ($p = 0.054$). None of the two RCTs reported on fistula-relapse-free-survival. The two RCTs used similar scores to evaluate the QoL/severity of disease of the patients: With regard to the Irritable Bowel Disease Questionnaire (IBDQ), the RCTs reported controversial results about the effect of the MSCs on QoL. QoL measured with the Short-form 36 questionnaire (SF-36) was reported by one RCT [12] and resulted in inconclusive results. With reference to the Perianal Disease Activity Index (PDAI), one study showed improved severity of the disease from baseline to week 12, but a deterioration at week 24, while the second RCT showed contrasting results for both, week 12 and week 24 compared to baseline. The RCTs reported different CDAI-scores and showed that the disease was more severe in patients of one study and less severe in patients of the other study. Overall, the results across the different scores were very inconclusive, indicating that MSC-therapy is not deemed to improve QoL or reduce severity of the disease of the patients. The overall quality of evidence for the effectiveness endpoints was very low.

Safety

None of the included studies reported any cases of peri-interventional mortality. Several sever adverse events were reported in the included studies with anal abscesses reported the most. Across all studies severe anal abscesses occurred more commonly in the MSC-groups than in the control groups. In contrast, severe cases of proctalgia, anal inflammation and liver abscesses were only reported in the control groups. The single-arm study [13] reported one case of pyrexia out of 24 patients and in one RCT [12] one patient of the first MSC-group (10 million cell dose) developed an adenocarcinoma. However, the correlation between the administration of the MSC-therapy and the occurrence of the adenocarcinoma remained unclear. The overall level of evidence for safety endpoints was low.

low strength of evidence: no cases of mortality reported, severe adverse events: anal abscesses most common, 1 RCT: 1 case of adenocarcinoma

Upcoming evidence

There are three ongoing RCTs of allogeneic MSCs compared to placebo. Two of these will provide long-term follow-up effectiveness and safety data for the weeks 52 and 104. Thus, these RCTs will fill the current evidence gap of effectiveness and safety data beyond 24 weeks. The two RCTs are currently scheduled for study completion by July 2021. The third RCT will investigate the intravenous administration of allogeneic MSCs in patients with treatment-resistant moderate-to-severe CD. Study completion date is expected for July 2018. In addition to the ongoing RCTs, there is one small, single-arm, phase I study that will investigate allogeneic MSCs in complex or multiple perianal as well as rectovaginal fistulas. Study completion date is expected for March 2025.

2 ongoing RCTs: long-term follow-up weeks 52 and 104 (2021), 1 ongoing RCT: intravenous allogeneic MSC (2018), 1 ongoing single-arm study: allogeneic MSCs in rectovaginal fistulas (2025)

Reimbursement

Currently, the administration of allogeneic MSCs (product: Cx601) is not included in the Austrian benefit catalogue and therefore, it is not reimbursed by the Austrian healthcare system. Furthermore, no list price of Cx601 is available yet.

Cx601 not reimbursed in Austria, no list price available

Discussion and Recommendation

The available RCTs of allogeneic MSC-therapy compared to placebo reported similarly positive results for combined remission and contrasting results for QoL and severity of the disease of the patients. RCTs comparing MSC-therapy with therapies established in the clinical practice, such as fibrin glue or fistula plugs, are lacking. Information about the grading system for the evaluation of the severity of adverse events was also not present. Differences in the classification of complex perianal fistulas and different stem cell dosages (range: 10-120 million cells) of the included studies might make generalizability of the results more difficult. However, the study population was generalizable with regard to patients' demographics and origin. Long-term effectiveness and safety data beyond 24 weeks were missing. Special concerns exist about the missing long-term outcomes for safety, as the correlation of allogeneic MSCs with the development of malignancies remains unanswered in existing clinical trials.

inconclusive results for QoL, missing comparator other than placebo, lacking grading system for severity of adverse events, different fistula classification + dosage → generalizability more complex, missing long-term evidence (malignancies)

Compared to existing systematic reviews, the present systematic review focused solely on the effect of allogeneic MSCs on complex perianal fistulas caused by CD.

focus on allogeneic MSCs and complex fistulas

societal impact of MSCs: opportunity costs

current evidence *not* sufficient to prove effectiveness and safety of MSCs compared to placebo
re-evaluation suggested for 2022

An effective and safe allogeneic MSC-therapy would have a societal impact because the patients concerned are in the productive stage of their lives. However, the current evidence is *not* sufficient to prove that allogeneic MSCs in patients with complex perianal fistulas caused by CD, who are refractory to standard medical therapy, are more effective compared to placebo therapy. Additionally, it remains *uncertain* if MSCs are safer than placebo procedures. New study results will potentially influence the effectiveness and safety estimate considerably. The re-evaluation is recommended in 2022 when further ongoing studies will be finished and thereby, will bring additional evidence for long-term effectiveness and safety beyond 24 weeks.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

komplexe, perianale Fisteln, verursacht durch Morbus Crohn (CD), können zu Analschmerzen mit Defäkation/perianaler Schwellung oder Juckreiz, Blutungen, Inkontinenz führen

Der Fokus der vorliegenden Übersichtsarbeit liegt auf Morbus Crohn (MC)-bedingte komplexe, perianale Fisteln bei PatientInnen, die gegenüber konventionellen und/oder biologischen Wirkstoffen refraktär oder intolerant sind. MC ist eine chronisch-entzündliche Darmerkrankung, die durch eine transmurale Entzündung und durch einen diskontinuierlichen, segmentalen Befall der Darmschleimhaut (sog. skip lesions) gekennzeichnet ist. Damit einhergehend können Fibrosen, Strikturen oder ein Sinus-Track entstehen, welche folglich zu Mikroperforationen und Fisteln führen können [2]. Fisteln treten gewöhnlich dann auf, wenn eine Fissur umgeben von Granulationsgewebe mit akuten und chronischen Entzündungen die Darmwand durchdringt [3]. Die Hauptsymptome perianaler Fisteln sind Analschmerzen mit Defäkation und damit verbundenen Schwellungen, perianaler Juckreiz, Blutung und/oder Ausfluss von Eiter oder Stuhl aus kutanen Fistelöffnungen [3-5]. Laut der American Gastroenterological Association (AGA) werden Fisteln als einfach und komplex kategorisiert [1, 4].

Fisteleinteilung gemäß AGA Definition in einfache und komplexe Fisteln

geschätzte Inzidenzrate in Österreich: 11,5 pro 100.000 EinwohnerInnen, höheres Risiko für Frauen und PatientInnen im Alter von 20-29 Jahren

Die höchste Anzahl von MC-PatientInnen wird für die USA, Kanada und Europa mit Prävalenzraten von über 300 pro 100.000 EinwohnerInnen berichtet [2]. In Österreich wird die durchschnittliche Inzidenzrate auf 11,5 pro 100.000 EinwohnInnen geschätzt (städtische Gebiete: 14,6 und ländliche Gebiete: 9,5) [6]. Frauen und PatientInnen im Alter von 20-29 Jahren haben ein höheres Risiko an MC zu erkranken [3, 7]. Etwa 17 % der PatientInnen mit MC, im Speziellen PatientInnen mit rektaler Krankheitslokation, entwickeln perianale Fisteln 10 Jahre nach Diagnosestellung [8].

Beschreibung der Technologie

mesenchymale Stammzellen (MSCs): nicht-hämatopoetische multipotente Zellen mit entzündungshemmenden, immun-modulatorischen Heilungseigenschaften lokal injiziert, Vermeidung von wiederholten Operationen und der Notwendigkeit eines permanenten Stomas

MSCs sind nicht-hämatopoetische, multipotente Zellen, die entzündungshemmende, immunmodulatorische und fibroblast-ähnliche potentiell heilende Eigenschaften aufweisen. Während des eigentlichen Prozesses werden die allogenen MSCs über eine Nadel lokal injiziert und in das Gewebe des/der PatientIn entlang aller Fistelgänge und inneren Öffnungen verteilt. Anschließend werden die Zellen entlang der Fistelgänge durch die äußeren Öffnungen verteilt. Die optimale Dosierung von MSCs ist bisher unklar. Wiederholte Injektionen können für PatientInnen erforderlich sein, wenn nach der ersten Injektion keine Wirkung – in Form von Schließung der Fisteln – zu erkennen ist [10]. Derzeitige (medikamentöse und chirurgische) Standardbehandlungen sind mit hohen Rezidivraten verbunden [9]. Durch eine zusätzliche Therapie mit allogenen MSCs könnten wiederholte Operationen, die zu einer hohen Morbidität (z. B. Inkontinenz) und folglich zu einem Verlust an Lebensqualität führen können, verhindert werden. Darüber hinaus kann durch die Therapie mit allogenen MSCs aufgrund des weniger invasiven Eingriffs, insbesondere für den Schließmuskelapparat, die Notwendigkeit eines permanenten Stomas verhindert werden [2, 5].

bisher keine Marktzulassung für Cx601 in Europa

Derzeit gibt es ein Produkt „Darvadstrocel/Cx601“, dass noch nicht am Markt zugelassen ist. Am 15. Dezember 2017 erhielt Cx601 jedoch eine positive Stellungnahme des Ausschusses für Humanarzneimittel der Europäischen Arzneimittel-Agentur (EMA).

Methoden

Ziel: Wirksamkeit und Sicherheit von allogenen MSCs im Vergleich zu Placebo, Fibrinkleber oder Fistel Plugs

Ziel des vorliegenden Berichts war es, die Effektivität von erwachsenen, humanen MSCs allogener Herkunft mit Bezug auf die Remissionsraten, die Reaktion und die Lebensqualität von MC-PatientInnen mit komplexen, perianalen Fisteln zu untersuchen. Darüber hinaus wurde Evidenz zur Sicherheit von MSCs im Hinblick auf unerwünschte Nebenwirkungen im Vergleich zu Placebo, Fibrinkleber oder Fistel Plugs zusammengefasst.

systematische Literatursuche in 4 Datenbanken, 590 Zitate nach Dedublizierung, 3 Studien eingeschlossen, zusätzliche Suche nach laufenden Studien in klinischen Studienregistern

Eine systematische Literaturrecherche wurde in vier Datenbanken (Cochrane, CRD, Embase, Medline) durchgeführt. Die systematische Suche beschränkte sich auf die Jahre 2007 bis 2017, auf randomisierte kontrollierte Studien (RCTs) und prospektive nicht-RCTs für die Effektivität und zusätzlich auf interventionelle einarmige Studien für die Sicherheit in deutscher und englischer Sprache. Nach Dedublizierung wurden insgesamt 590 Zitate identifiziert, wovon drei Studien zur Datenextraktion und weiteren Analyse einbezogen wurden. Zusätzlich wurde eine Suche in drei klinischen Studienregistern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) durchgeführt, um laufende und unveröffentlichte Studien zu identifizieren. Die Suche resultierte in 45 Treffern, wovon lediglich vier Studien als potentiell relevant eingeschätzt wurden.

Ergebnisse

Verfügbare Evidenz

Evidenz zu MSCs im Vergleich zu Placebo

Für die Evidenz zur Effektivität wurden zwei RCTs [11, 12] herangezogen, die allogene MSCs mit Placebo verglichen. Für die Evidenz zur Sicherheit von MSCs wurde zusätzlich eine einarmige Studie [13] eingeschlossen.

2 RCTs + 1 single-arm Studie (n=231 + 24 pts)

Alter zwischen 37-41 Jahren

CDAI-Punkte beim Studienstart zwischen ≤200 und ≤250

Die beiden RCTs umfassten insgesamt 231 PatientInnen. Die einarmige Studie umfasste 24 PatientInnen. Alle Studien schlossen europäische PatientInnen mit ein. Das durchschnittliche Alter aller eingeschlossenen PatientInnen lag zwischen 37-41 Jahren. In den Studien wurden PatientInnen mit Crohn's Disease Activity Index (CDAI)-Punkten zwischen ≤200 und ≤250 inkludiert, was auf Unterschiede in der Schwere der Erkrankung zu Beginn der Studie hinweist. In zwei Studien wich die Klassifikation komplexer, perianaler Fisteln von der Definition komplexer, perianaler Fisteln der AGA ab, die als Einschlusskriterium für die PICO verwendet wurde.

zwei unterschiedliche Stammzellentypen und unterschiedliche Dosierungen in den 3 Studien

In zwei Studien [11, 13] wurde die Therapie mit MSCs aus dem Fettgewebe untersucht, während sich eine Studie [12] mit der Therapie mit MSCs aus dem Knochenmark befasste. Die MSC-Dosierungen der Studien lagen zwischen 10 Millionen und 120 Millionen Zellen. In einer Studie [13] wurde eine zweite Dosierung von Zellen – bei fehlender Wirkung der ersten Dosierung – verabreicht.

Sponsoring und Interessenskonflikt

Zwei Studien [11, 13] wurden vom Hersteller TiGenix gesponsert und eine Studie [12] von der DigestScience Foundation, die möglicherweise Verbindungen zum Hersteller (Takeda) aufweist, finanziert.

Klinische Wirksamkeit

In beiden RCTs [11, 12] kam es zu einer Verbesserung der kombinierten Remission in der MSC-Gruppe gegenüber der Placebo-Gruppe. Nur ein RCT [11] lieferte Ergebnisse zur Reaktion und zeigte eine Verbesserung der Reaktion in der Interventionsgruppe. Die Ergebnisse waren jedoch nicht statistisch signifikant (p=0,054). Keines der beiden RCTs berichtete über das Fistel-rezidiv-freie Überleben. In den RCTs wurden dieselben Fragebögen/Indizes zur Messung der Lebensqualität (QoL) bzw. des Schweregrades der Krankheit angewendet: Mit Bezug auf den Irritable Bowel Disease Fragebogen (IBDQ) zeigten die RCTs umstrittene Ergebnisse bezüglich des MSC-Therapieeffekts auf die Lebensqualität. Die mit dem Short-form 36-Fragebogen (SF-36) gemessene Lebensqualität wurde in einem RCT [12] ermittelt, wonach MSC-Therapien zu keiner eindeutigen Verbesserung der Lebensqualität führten. Mit Bezug auf den Perianal Disease Activity Index (PDAI) wies eine Studie einen geringeren Schweregrad der Erkrankung in Woche 12 verglichen zu Woche 0 auf, jedoch wiederum eine Verschlechterung der Erkrankung in Woche 24. Im Vergleich dazu, zeigte das zweite RCT, kontroverse Ergebnisse sowohl für Woche 12 als auch für Woche 24. Die RCTs präsentierten verschiedene Crohn's Disease Activity Index (CDAI)-Punkte, wodurch aufgezeigt wurde, dass sich die Schweregrade der Erkrankung in den beiden Studien gemäß des CDAI-Indexes unterschieden. Insgesamt waren die Ergebnisse der Fragebögen/Indizes sehr unschlüssig, was darauf hindeutet, dass eine Verbesserung der Lebensqualität bzw. eine Verringerung des Schweregrades der Erkrankung durch die MSC-Therapie nicht bestätigt werden kann. Die Gesamtqualität der Evidenz für die Wirksamkeitsendpunkte war sehr niedrig.

sehr niedrige Qualität der Evidenz: signifikante Verbesserung der kombinierten Remission (2 RCTs) und Verbesserung der Reaktion (1 RCT) – nicht signifikant, nicht aussagekräftige QoL-Ergebnisse gemäß IBDQ-, SF-36-, PDAI- und CDAI, Verbesserung der Lebensqualität durch MSC-Therapie nicht sicher

Sicherheit

Keine der eingeschlossenen Studien berichtete von peri-interventionellen Mortalitätsfällen. In den eingeschlossenen Studien wurden mehrere schwerwiegende, unerwünschte Nebenwirkungen aufgelistet, wovon Analabszesse am häufigsten auftraten. Über alle Studien hinweg kamen schwerwiegende Analabszesse in den MSC-Gruppen häufiger vor als in den Placebo-Gruppen. Im Gegensatz dazu wurden schwerwiegende Fälle von Proktalgie, analen Entzündungen und Leberabszessen nur in den Kontrollgruppen berichtet. Die einarmige Studie [13] berichtete, dass Pyrexie in einem von 24 PatientInnen auftrat und in einem RCT [12] entwickelte ein Patient der ersten MSC-Gruppe (10 Millionen Zellen) ein Adenokarzinom. Die Korrelation zwischen der MSC-Therapie und dem Auftreten des Adenokarzinoms bleibt jedoch unklar. Die Evidenz für die Sicherheitsendpunkte war insgesamt niedrig.

niedrige Qualität der Evidenz: keine Mortalitätsfälle aufgezeigt, schwere, unerwünschte Nebenwirkungen: Analabszesse am häufigsten, 1 RCT: 1 Patient mit Adenokarzinom

Laufende Studien

Zurzeit gibt es drei laufende RCTs zu allogenen MSCs im Vergleich zu Placebo. Zwei davon werden langfristige Effektivitäts- und Sicherheitsdaten für einen Nachbeobachtungszeitraum von 52 und 104 Wochen liefern. Somit könnte die aktuelle Evidenzlücke zu Wirksamkeits- und Sicherheitsdaten über einen Nachbeobachtungszeitraum von 24 Wochen gefüllt werden. Der Abschluss beider RCTs ist derzeit für Juli 2021 angesetzt. In einem weiteren RCT wird die intravenöse Verabreichung allogener MSCs bei PatientInnen mit behandlungsresistentem, mittelschwerem bis schwerem MC untersucht. Der Abschluss der Studie wird für Juli 2018 erwartet. Zusätzlich zu den laufenden RCTs gibt es eine kleine, einarmige Phase-I-Studie, die allogene MSCs bei PatientInnen mit komplexen oder multiplen perianalen, sowie rektovaginalen Fisteln untersucht. Studienabschluss wird für März 2025 erwartet.

2 laufende RCTs: Langzeit-Follow-up: 52 und 104 Wochen (2021), 1 laufendes RCT: allogene MSCs intravenös (2018), 1 laufende, einarmige Studie: allogene MSCs in rektovaginalen Fisteln (2025)

Kostenerstattung

momentan wird Cx601 in Österreich nicht erstattet, kein Listenpreis verfügbar

Aktuell ist die Behandlung mit allogenen MSCs (Produkt: Cx601) nicht im österreichischen Leistungskatalog enthalten und wird daher vom österreichischen Gesundheitssystem nicht erstattet. Zudem ist noch kein Listenpreis von Cx601 verfügbar.

Diskussion

keine eindeutigen Ergebnisse bezüglich Lebensqualität, Fehlen eines Komparators anders als Placebo, fehlendes Bewertungssystem für Schweregrad unerwünschter Nebenwirkungen, unterschiedliche Fistel-klassifizierung & Dosierung → Generalisierbarkeit komplexer, fehlende Langzeitevidenz (Malignität)

Die verfügbaren RCTs zur allogenen MSC-Therapie im Vergleich zu Placebo zeigten ähnlich positive Ergebnisse für kombinierte Remission und kontroverse Ergebnisse bezüglich der Lebensqualität und des Schweregrades der Erkrankung. RCTs, die MSC-Therapien mit in der klinischen Praxis etablierten Therapien, z. B. Fibrinkleber oder Fistel Plugs, verglichen, fehlen. Informationen zur Bewertung der Schwere unerwünschter Nebenwirkungen lagen ebenfalls nicht vor. Die Generalisierbarkeit der Studienergebnisse könnte durch die unterschiedlichen Klassifizierungen komplexer, perianaler Fisteln und aufgrund der unterschiedlichen Stammzelldosierungen (zwischen 10-120 Millionen Zellen) mit Schwierigkeiten verbunden sein. Jedoch bezüglich der Demographie und Herkunft der PatientInnen war die Studienpopulation generalisierbar. Evidenz zu langfristigen Wirksamkeits- und Sicherheitsdaten, über 24 Wochen, fehlten. Besondere Bedenken bestehen vor allem hinsichtlich der fehlenden Langzeitergebnisse für die Sicherheit von MSC-Therapien, da die Korrelation allogener MSCs mit der Entwicklung maligner Erkrankungen in bestehenden klinischen Studien unbeantwortet bleibt.

Fokus auf allogene MSCs bei komplexen Fisteln

Im Vergleich zu bestehenden systematischen Übersichtsarbeiten konzentriert sich der vorliegende Bericht ausschließlich auf die klinische Wirksamkeit und Sicherheit von allogenen MSCs bei komplexen, perianalen Fisteln, die durch MC verursacht wurden.

Empfehlung

Opportunitätskosten durch MSCs-Therapien

aktuelle Evidenz unzureichend, um die Wirksamkeit und Sicherheit von MSCs im Vergleich zu Placebo zu belegen

erneute Bewertung für 2022 empfohlen

Eine effektive und sichere MSC-Therapie allogener Herkunft würde zusätzlich gesellschaftliche Auswirkungen mit sich bringen, insbesondere da die meisten, betroffenen PatientInnen im berufsfähigen Alter sind. Aktuelle Evidenz reicht jedoch *nicht* aus, um zu belegen, dass allogene MSCs bei PatientInnen mit MC-assoziierten komplexen, perianalen Fisteln wirksamer sind als Placebo. Zudem bleibt *unklar*, ob eine MSC-Therapie sicherer als eine Placebo-Prozedur ist. Neue Studienergebnisse werden möglicherweise die Effektivitäts- und Sicherheitseinschätzungen erheblich beeinflussen. Die erneute Bewertung wird im Jahr 2022 empfohlen, wenn weitere laufende Studien abgeschlossen sind und dadurch zusätzliche Evidenz für langfristige Daten zur Wirksamkeit und Sicherheit über 24 Wochen hinaus erbracht werden können.

1 Scope

1.1 PICO question

PIKO-Frage

Are adult human mesenchymal stem cells (MSCs) of allogeneic origin in comparison to placebo, fibrin glue or fistula plugs in patients with complex perianal fistulas without abscesses caused by non-active or mildly active luminal Crohn's disease (CD) more effective to increase the quality of life (QoL) and remission rates and safer concerning adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Second-line or add-on therapy for adult (≥18 years old) patients with complex perianal fistulas without abscesses caused by non-active or mildly active luminal Crohn's disease. The presented fistulas are refractory to conventional and/or biologic agents for Crohn's disease, or in patients intolerant to such treatments. Classification of the fistulas by the definition of complex fistulas of the American Gastroenterological Association (AGA). International classification of disease (ICD)-10-CM code: K50.1, Crohn's disease of the colon, K60.3 anal fistulas, K60.4 rectal fistulas, K60.5 anorectal fistulas Contraindications/exclusions: concomitant rectovaginal or abdominal fistulas MeSH Terms: Ileitis terminals, Enterocolitis regionalis, Enteritis regionalis colon/rectum, Morbus Crohn (MC), sklerosierende chronische Enteritis
Intervention	Adult human mesenchymal stem cells of allogeneic origin administered by a single local (intralesional) injection. Currently, there is one agent available in Europe: • Alofisel® (TiGenix, Living Medicines, BE) MeSH Term: Mesenchymal stem cell, MSC, Cx601, Cx-601, darvadstrocel
Control	Placebo/ Sham Filling materials for the fistula tracts, i.e. fibrin glue, fistula plugs
Outcomes	

Efficacy	• **QoL**
	  • Inflammatory Bowel Disease Questionnaire (IBDQ)
	  • Short-form 36 questionnaire (SF-36)
	  • Perianal Disease Activity Index (PDAI)
	  • Crohn's Disease Activity Index (CDAI)
	• **Fistula relapse-free survival** *(decisive benefit for patients after three month/13 weeks of fistula relapse-free survival)*
	• **Combined remission** *(closure of all treated external openings that were draining at baseline despite gentle finger compression and absence of collections larger than 2cm of the treated perianal fistulas)*
	• **Response** *(closure of at least 50% of all external openings that were draining at baseline)*

Safety	• Treatment-emerged adverse events • Severe treatment-emerged adverse events • Treatment-related adverse events • Severe treatment-related adverse events

Study design	Time duration: 2007-2017
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Uncontrolled before-after study

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What are the mesenchymal stem cells and what is/are its comparator(s)?
B0002	What is the claimed benefit of allogeneic mesenchymal stem cells in relation to the comparators?
B0004	Who administers allogeneic mesenchymal stem cell transplantation and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use allogeneic mesenchymal stem cells?
B0009	What supplies are needed to use allogeneic mesenchymal stem cells?
B0003	What is the phase of development and implementation of allogeneic mesenchymal stem cells?
A0020	For which indications have allogeneic mesenchymal stem cells received marketing authorisation?
A0021	What is the reimbursement status of allogeneic mesenchymal stem cells?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes are allogeneic mesenchymal stem cells used?
A0002	What are Crohn's disease-associated complex perianal fistulas in the scope of this assessment?
A0003	What are the known risk factors for Crohn's disease-associated complex perianal fistulas?
A0004	What is the natural course of Crohn's disease-associated complex perianal fistulas?
A0005	What is the burden of disease for patients with Crohn's disease-associated complex perianal fistulas?
A0006	What are the consequences of Crohn's disease-associated perianal fistulas for the society?
A0024	How are Crohn's disease-associated complex perianal fistulas currently diagnosed according to published guidelines and in practice?
A0025	How are Crohn's disease-associated complex perianal fistulas currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are allogeneic mesenchymal stem cells utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of allogeneic mesenchymal stem cells on mortality?
D0003	What is the effect of allogeneic mesenchymal stem cells on the mortality due to causes other than Crohn's disease-associated complex perianal fistulas?
D0005	How do allogeneic mesenchymal stem cells affect symptoms and findings (severity, frequency) of Crohn's disease-associated complex perianal fistulas?
D0006	How do allogeneic mesenchymal stem cells affect progression (or recurrence) of Crohn's disease-associated complex perianal fistulas?
D0012	What is the effect of allogeneic mesenchymal stem cells on generic health-related quality of life?
D0013	What is the effect of allogeneic mesenchymal stem cells on disease-specific quality of life?
D0011	What is the effect of allogeneic mesenchymal stem cells on patients' body functions?
D0016	How does the use of allogeneic mesenchymal stem cells affect activities of daily living?
D0017	Was the use of allogeneic mesenchymal stem cells worthwhile?

Safety	
Element ID	Research question
C0008	How safe are allogeneic mesenchymal stem cells in comparison to placebo?
C0002	Are the harms related to dosage or frequency of applying allogeneic mesenchymal stem cells?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of allogeneic mesenchymal stem cells?
C0007	Are allogeneic mesenchymal stem cells associated with user-dependent harms?

2.2 Sources

Description of the technology

Quellen: Beschreibung der Technologie

- Hand search in the POP, AdHopHTA, and CRD databases for Health Technology Assessments.
- Background publications identified in database search: see Section 2.3 and in an additional hand search via Google Scholar.
- Documentation provided by the manufacturer.
- Questionnaire completed by the submitting hospital.

Health problem and current Use

Quellen: Beschreibung des Gesundheitsproblems

- Hand search in the POP, AdHopHTA, and CRD databases for Health Technology Assessments.
- Background publications identified in database search: see Section 2.3 and in an additional hand search via Google Scholar.
- Documentation provided by the manufacturer.
- Questionnaire completed by the submitting hospital.

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 21st and 28th December 2017 in the following databases:

- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)
- Embase
- Medline via Ovid

Einschränkungen: 2007-2017, Studiendesign, Englisch und Deutsch, 590 Zitate nach Deduplizierung

The systematic search was limited to the years 2007 to 2017. It was further limited to randomized controlled trials (RCTs) and prospective non-RCTs for efficacy and interventional single-arm studies for safety. Moreover, the search was restricted to articles published in English or German. After deduplication, overall 590 citations were included. The specific search strategy employed can be found in the Appendix.

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 8th January 2018 resulting in 45potential hits, of which three RCTs and one single-arm, phase I study might be relevant for the topic of this assessment.

Suche nach laufenden Studien

The manufacturer of the most common product (Darvastrocel/Cx601) submitted one publication which had already been identified in the systematic literature search.

Einreichung von Hersteller

By hand-search, no additional publications were identified. In total 3 studies were included for data extraction and further analysis.

insgesamt 3 Publikationen identifiziert

2.4 Flowchart of study selection

Overall, 590 hits were identified, and 3 publications selected for analysis. The references were screened by two independent researchers and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

Literaturauswahlprozess

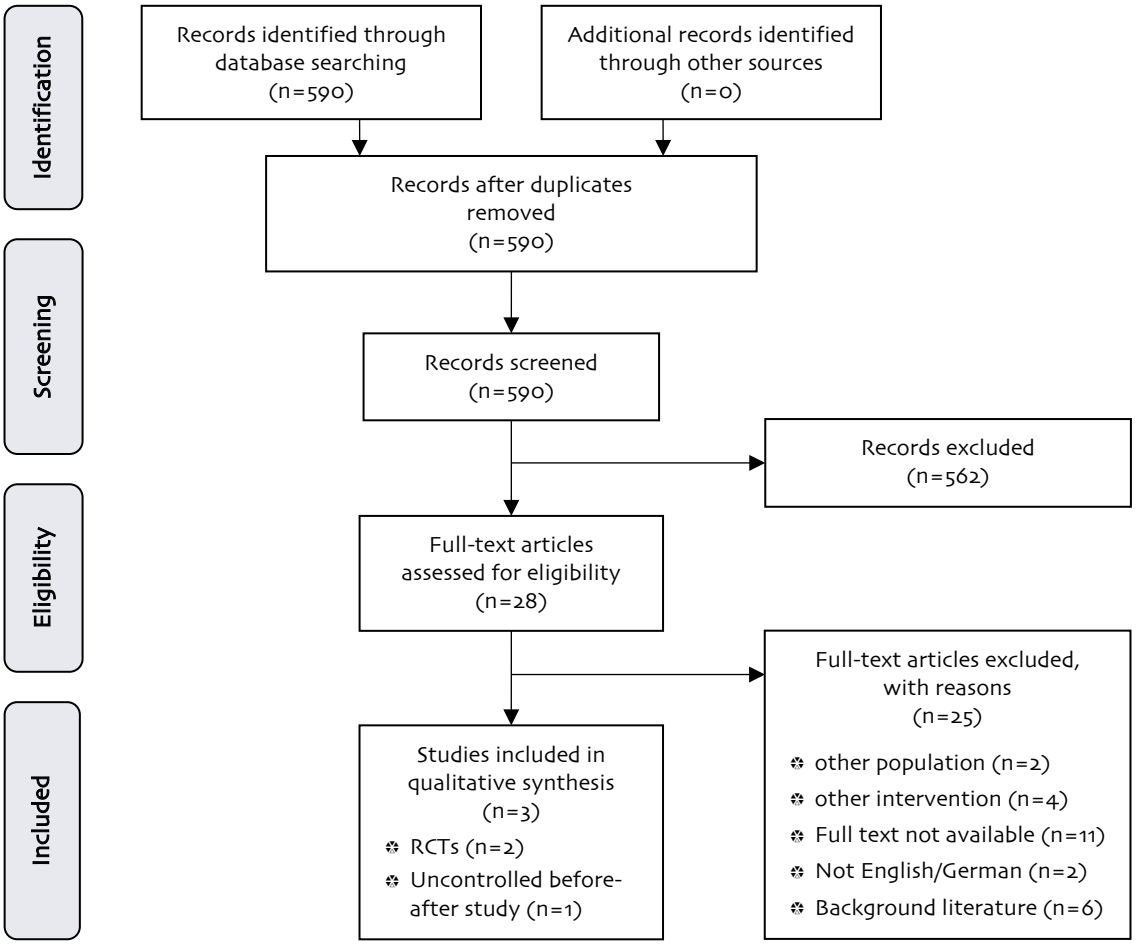

Figure 2-1: Flowchart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion von 1 Autorin, Kontrolle von 1 Autor

Data from the included studies were systematically extracted into data extraction tables based on study design and the research question (See Appendix Table A-1 and Table A-4). The data were extracted by one researcher (SW) and validated for accuracy by another researcher (MS).

Qualitätsbeurteilung: RCT: Cochrane Risk of Bias Single-arm: IHE checklist

Two independent researchers conducted quality appraisal; differences were settled via consensus. Quality appraisal was conducted with different tools, depending on the study design. Randomised studies were evaluated using the Cochrane Risk of Bias tool [14]. Single-arm case series were evaluated using the Institute of Health Economics (IHE) checklist [15] (see Appendix Table A-3 and Table A-4).

2.6 Synthesis

Zusammenfassung der Evidenz: GRADE

The research questions were answered in plain text format, with reference to Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence tables included in Table 7-1 and Table A-5 and the data-extraction tables in the Appendices (see Table A-1 and Table A-2) [16]. No quantitative analysis of outcomes was performed, due to limited number and consistency of RCTs (n=2).

quantitative Analyse nicht möglich

3 Description and technical characteristics of the technology

3.1 Features of the technology and comparators

B0001 – What are mesenchymal stem cells and what is/are its comparator(s)?

mesenchymale Stammzellen (MSCs): anhämopoetische Zellen mit möglicher entzündungshemmender Wirkung, Regulierung des Immunsystems, Zunahme der lokalen Zellen für die Heilungsphase

MSCs are non-hematopoietic multipotent cells that can generate osteogenic, adipogenic, and chondrogenic cells and come with potential anti-inflammatory, immunomodulatory and fibroblast-like healing properties [4, 17]. In detail, MSCs claim to regulate the adaptive and innate immune systems by suppression of T-cells and maturation of dendritic cells. They aim to reduce B-cell activation and proliferation as well as inhibit proliferation and cytotoxicity of natural killer (NK) cells. Additionally, MSCs aim to promote the generation of regulatory T-cells via soluble factors or cell-to-cell contact mechanisms, reduce T-cell proliferation, suppress the inflammatory infiltrates and cytokines, and express anti-inflammatory cytokines [9, 18]. Overall, MSCs attempt to provide a way of increasing the number of cells locally, in the critical phase of healing [5].

unterschiedliche MSC-Typen: allogene vs. autologe MSC, MSC aus Fettgewebe vs. aus Rückenmark

When analysing MSCs, two distinctions need to be made. First, there is a difference between allogeneic and autologous MSCs. Autologous cells seem to have a lower rate of rejection and better tolerability in patients. However, they require additional preparation steps including a fat pad or BM harvest, expansion, and occasional thawing to be ready-to use in patients. The advantage of allogeneic stem cells is that they are ready-to-use, as these extra steps are not needed. Thus, greater numbers of patients can be treated and delays in treatment can be impeded. However, allogeneic cells are more likely to be rejected or cause a rejecting antibody response than autologous MSCs. Currently, there are no relative safety and efficacy studies comparing autologous with allogeneic cells [9, 19, 20]. Secondly, MSCs can be derived from either adipose-tissue or bone-marrow (BM). Adipose-tissue-derived MSCs provide the advantage that they can be harvested in large quantities with minimal adverse effects through liposuction [5, 9]. Currently, there is a debate about which ones are preferably used in treating perianal CD [18].

bisher Placebo als Komparator, Füllungsmaterial für Fisteln zukünftig auch mögliche Komparatoren

So far, placebo has been used as the comparator to MSC-based therapy. The placebo group receives the equal doses of i.e. saline solution instead of MSCs [5]. Additionally, fistula closing materials, i.e. fibrin glue or fistula plugs, are suggested as comparator intervention, however, they may be associated with a high recurrence rates [information provided by submitting hospital].

B0002 – What is the claimed benefit of allogeneic mesenchymal stem cells?

weniger invasive Therapie für Sphinkterapparat: möglicherweise Vermeidung von Inkontinenz, rezidiven Fisteln, Beeinträchtigungen durch wiederholende Operationen

With the current standard medical and surgical treatments, durable remission rates of complex perianal fistula remain as low as 37% [9]. The MSC-therapy claims to reduce the risk of repeated surgery and thus lead to lower morbidity (i.e. incontinence) and increased QoL [2, 5]. In addition, MSC-therapy claims to reduce the risk of removal of part of the colon and/or the need for a permanent stoma. Proctectomy is required in 10-20% of patients with perianal fistulising disease [21]. MSCs aim to be a less invasive therapy especially for the sphincter-based fistulas, avoiding anal incontinence, recurrence of new fistulas, and reducing impairment caused by surgical standard treatment [information provided by submitting hospital]. Another potential benefit of the therapy with MSCs is its local mode of action, meaning that the local injection of MSCs might lead to fewer systemic complications, including infections as compared to systemic therapies [2].

3.2 Administration, investments, personnel and tools required to use mesenchymal stem cells

B0004 – Who administers allogeneic mesenchymal stem cell transplantation and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use allogeneic mesenchymal stem cells?

B0009 – What supplies are needed to use allogeneic mesenchymal stem cells?

MSC-Administration in multidisziplinärem Setting, Vorbereitung: MRI, EUA, Seton, Eingriff unter Allgemeinanästhesie, Operationssäle in spezialisierten Krankenhäusern nötig

MSCs are administered in a multi-disciplinary setting consisting of a specialised surgeon, a proctologist, a gastroenterologist, and a radiologist [1, 2, 5, 22]. In advance of the interventional process, a pelvic magnetic resonance imaging (MRI) scan is required in order to guide the surgical process and to assess the presence of abscesses. In addition, patients have to undergo a fistula preparation visit that includes an examination under general anaesthesia (EUA), fistula curettage, and seton placement – if necessary, at least two weeks before the investigational administration of the MSCs. The actual interventional process is conducted under general anaesthesia. For the preparations as well as for the actual intervention, an operating room in a specialised hospital is needed [information provided by submitting hospital].

lokale Injektion der MSC in die Fistelgänge und inneren Öffnungen mittels einer Nadel, Evidenz für optimale Dosierung fehlt

During the interventional process, MSCs are injected locally and distributed into the patient's tissue adjacent to all fistula tracts and internal openings. Subsequently, the cells are distributed along the fistula tracks through external openings and openings of the fistula walls [10]. Therefore, a fine long needle is required. The optimal dose of MSCs administered remains unclear. Repeated injections may be required for patients who did not achieve closure of their fistula tracts after the first administration [2].

3.3 Regulatory & reimbursement status

B0003 – What is the phase of development and implementation of allogeneic mesenchymal stem cells?

MSC-therapy is an emerging therapy in the field of autoimmune diseases, such as graft versus host disease, multiple sclerosis, systemic lupus erythematosus, systemic sclerosis, and Crohn's disease (CD). The first trial in human patients with CD was in 2003 [23]. By 2017, there were approximately 16 trials available, of which eight trials investigated MSC-therapy in fistulising CD, including both autologous and allogeneic stem cells [20, 24]. We could not identify information in which countries MSCs are marketed or available.

MSC-Therapie bei Autoimmunkrankheiten, 2003 erste Studie mit Morbus Crohn (MC) PatientInnen, 16 Studien bis 2017

A0020 – For which indications have allogeneic mesenchymal stem cells received marketing authorisation?

To date, MSCs can only be used under two regulatory statuses in Europe: approved clinical trial or compassionate use (refer to Regulation [EC] No. 1394/2007 and Directive 2001/83/EC) regulated by the European Medicines Agency (EMA). The MSC-therapies in the United States (US) are regulated by the Centre for Biologic Evaluations and Research, a division of the US Food and Drug Administration (FDA) [5].

Verwendung von MSCs in Europa als zugelassene, medizinische Studie oder in Spezialfällen

Currently, there is one product "Darvadstrocel/Cx601" available. Cx601 has no marketing authorisation. However, on December 15, 2017, it received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the EMA. It is the first allogeneic stem cell therapy in Europe that received a positive CHMP opinion. The company expects marketing approval of Cx601 for February 2018 [information provided by the manufacturer].

keine Markzulassung für Darvadstrocel/Cx601, Hersteller erwarten Markzulassung für Februar 2018

A0021 – What is the reimbursement status of allogeneic mesenchymal stem cells?

The administration of allogeneic MSCs (Cx601) is not included in the Austrian benefit catalogue, therefore, it is not reimbursed by the Austrian health care system. Furthermore, no list price of Cx601 is available.

keine Finanzierung von Cx601 in Österreich, kein Listenpreis verfügbar

4 Health Problem and Current Use

4.1 Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes are allogeneic mesenchymal stem cells used?

A0002 – What is the disease and health condition in the scope of this assessment?

The scope of this assessment includes complex perianal fistulas caused by CD that are refractory to conventional medication and/or biologic agents, or in patients intolerant to such treatments [11].

refraktäre, komplexe perianale Fisteln verursacht durch MC

CD is a chronic inflammatory condition characterised by transmural inflammation and skip lesions. CD may lead to fibrosis and strictures or result in sinus tracts giving rise to micro perforations and fistulas [2]. Fistulas usually occur when a fissure penetrates the gut wall surrounded by granulation tissue with acute and chronic inflammation [3].

MC: chronisch-entzündliche Darmkrankheit, Fisteln: Fissur dringt in Granulationsgewebe mit akuter, chronischer Entzündung ein

Perianal fistulas can be classified with the Park's classification of fistulas. It distinguishes between the following fistula tracts [4]:

Klassifizierung perianaler Fisteln mit Park's Klassifizierung:

- **Inter-sphincteric:** The fistula tract travels along the inter-sphincteric plane to the perianal skin [7, 25]. It occurs in 20-45% of the cases [9].

inter-Sphinkter

- **Trans-sphincteric:** The fistula tract encompasses a portion of the internal and external sphincter or the puborectal muscle and terminates on the skin overlying the buttocks [7, 25]. It accounts for 30-60% of the cases [9].

trans-Sphinkter

- **Supra-sphincteric:** The fistula tract runs upwards in the inter-sphincteric space, then downwards crossing the levator ani muscle, subsequently, reaching the perianal skin [25]. It occurs in 20% of the cases [9].

supra-Sphinkter

- **Extra-sphincteric:** The fistula tract extends from an internal opening in the bowel proximal to the anus, encompasses the entire sphincter apparatus, and opens onto the skin overlying the buttocks [7]. It accounts for 2-5% of the cases [9].

extra-Sphinkter

- **Superficial:** The fistula tract does not involve the sphincter complex [25].

oberflächlich

According to the American Gastroenterological Association (AGA), perianal fistulas are distinguished into simple and complex ones [1, 4]:

AGA Klassifizierung von Fisteln: einfache und komplexe Fisteln

- Simple perianal fistulas are characterised as low fistulas that include inter-sphincteric and trans-sphincteric fistulas with the internal opening at or below the dentate line. They have a single external opening, and are not associated with proctitis, rectovaginal fistulas or anorectal strictures.
- Complex perianal fistulas include the following characteristics:
  - High fistulas involve at least one-third of the external anal sphincter. They include inter-sphincteric fistulas with high secondary extensions, trans-sphincteric fistulas with the internal opening above the dentate line, supra-sphincteric and extra-sphincteric fistulas.
  - Possible multiple external openings.
  - Possibly associated with present perianal abscesses, rectovaginal fistulas, anorectal strictures, or active rectal disease at endoscopy.

A0003 – What are the known risk factors for Crohn's disease-associated complex perianal fistulas?

MC Risikofaktoren:

The risk factors of the underlying disease, CD, and thus, the cause of perianal fistulas include:

geringe weibliche Prädominanz

- **Gender**: There is a slight female predominance, meaning that hormonal factors might play a role [7].

genetisch

- **Genetic**: CD is more common in those of Ashkenazi Jewish ethnicity than in non-Jews. However, ethnic and racial differences may be related to environmental and lifestyle factors in addition to underlying genetic differences. Hereditary predisposition can be emphasised as approximately 10-25% of individuals with CD have a first degree relative with the disease [7]. Most strongly CD-associated genes include CARD15, IBD5 locus, autophagy genes like ATG16L1 and IRGM, and interleukin (IL)-23 receptor [26].

Rauchen

- **Smoking**: Nicotine and/or smoking by-products may directly affect mucosal immune responses, smooth muscle tone, gut permeability, and microvasculature. Current and past smoking is associated with increased risk of CD as well as with the recurrence of CD [7].

„Western-style" Diät

- **"Western" style diet**: Fried and sugary foods are associated with increased risk of developing CD [7].

Antibiotikaeinnahme

- **Antibiotic exposure**, particularly tetracyclines, are associated with an increased risk of CD [information provided by the external reviewer].

psychosoziale Faktoren

- **Psycho-social factors**: Stress may have a role in exacerbating the symptoms in patients with CD, possibly through activation of the enteric nervous system and the elaboration of pro-inflammatory cytokines [7].

Risikofaktoren für MC-assoziierte perianale Fisteln: Herkunft, Diagnosealter <40 Jahre, Krankheitsort: rektal, Abszesse, Darmstrikturen

Risk factors for developing perianal fistulas caused by CD involve:

- **Race**: Non-Caucasians and those of Sephardic Jewish ethnicity with CD have a higher risk of perianal disease [7].
- **Age at diagnosis:** CD patients who are younger than 40 years of age have a greater risk of perianal disease [3, 7].
- **Disease location**: Patients with colonic (41%) [rectal (91%)] or ileocolonic CD have a higher risk of perianal disease [3, 7, 25].
- Presence of abscesses and intestinal strictures [3].

A0004 – What is the natural course of Crohn's disease-associated complex perianal fistulas?

hohe Rezidivraten, häufigstes Diagnosealter zwischen 20 und 29 Jahren, 17 % entwickeln Fisteln 10 Jahre nach Diagnose, keine Auswirkungen auf Mortalität aber Morbidität (Inkontinenz)

The natural course of CD is deemed to be both, relapsing and remitting. CD is most commonly diagnosed in a population of 20-29 years of age. Approximately 17% of patients with CD develop perianal fistulas 10 years after diagnosis, especially in patients with rectal involvement. A recent study investigated the mortality and causes of death in CD and reported that there was no significant difference in overall mortality as well as cause-specific mortality (gastrointestinal cancer, cancer and heart disease) between CD patients and healthy patients [8]. However, CD leads to high morbidity (i.e. pain and incontinence) and thus, reduces the QoL of the patients. Due to the high recurrence rates of current standard medical and surgical treatments, additional therapies are needed, especially for high refractory patients.

4.2 Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with Crohn's disease-associated complex perianal fistulas?

wesentliche Beeinträchtigung der Lebensqualität, zusätzliche Probleme möglich: sekundäre Infektionen, Abszessbildung, steigende Invaliditätsraten

The presence of complex perianal fistulas negatively impacts the QoL of the patients, particularly, due to anal pain with defecation and associated swelling, perianal itching, bleeding and/or discharge of pus or stool from cutaneous fistula openings, as well as in some cases due to faecal incontinence [3-5]. Besides, additional problems induced by perianal fistulas such as secondary infections, abscess formations, organ system function impairment, and high disability rates can occur [18]. About one-third of the patients with CD-associated perianal fistulas are non-responders to standard medical treatments, what makes the treatment of perianal fistulas more complicated [5].

A0006 – What are the consequences of Crohn's disease-associated perianal fistulas for the society?

Diagnosealter am häufigsten zwischen 20 und 29 Jahren → berufstätiges Alter → Berufsunfähigkeit + steigende Inzidenzraten → zusätzliche soziale Kosten

In general, CD incidence rates are higher in more developed countries [12]. In particular, younger age is associated with higher incidence of CD. The highest number of incidents of CD was described in the population of young adults, between 20 and 29 years of age, with 16.6 cases per 100,000 person-years [7]. When it comes to CD-associated perianal fistulas, the cumulative incidence is 12% after one year and this doubles 20 years after diagnosis [25]. CD has a negative impact on patients' work, social, and sexual lives. Consequently, this and the fact of increasing incidence rates of perianal fistulas in CD patients leads to additional societal costs [information provided by submitting hospital].

4.3 Current clinical management of the disease or health condition

A0024 – How are Crohn's disease-associated complex perianal fistulas currently diagnosed according to published guidelines and in practice?

Diagnosestellung von MC-assoziierten perianalen Fisteln:

Guidelines recommend the combination of different diagnostic modalities [25]:

- **Examination under anaesthesia** (EUA) is considered as the gold standard to diagnose and classify perianal fistulas in CD patients. It should be always performed by a colorectal surgeon. An EUA allows immediate intervention, such as seton placement preferably before starting anti-tumour-necrosis-factor (TNF) treatment [3, 25, 27].

Untersuchung unter Narkose (EUA)

- **MRI** is considered as the gold standard imaging technique for the perianal CD [3, 25]. It is meant to be a highly accurate non-invasive modality for the diagnosis and classification of perianal fistulas and may identify clinically "silent" abscesses and luminal inflammation. Additionally, it can achieve an optimal picture of the exact route of fistulas, the presence of abscesses, relation with sphincteric structures, and muscular layers as well as differences between active granulation and fibrotic tissues.

Magnetresonanz-tomographie (MRI)

endoanaler Ultraschall (EUS)

- **Endoanal ultrasound** (EUS) is a useful alternative to MRI conducted by a coloproctologist. However, its accuracy can be limited by the restricted view. Using hydrogen peroxide may enhance fistula tracts, thereby improving their identification and image definition [3, 25].

zusätzliche Methoden zur Diagnosestellung von MC-assoziierten perianalen Fisteln:

Endoskopie

Transkutaner perinealer Ultraschall (TPUS)

Fistulographie

In addition, the following diagnostic can be used:

- **Endoscopy** is used for the assessment of the rectum to determine the most appropriate surgical management strategy [25].
- **Transcutaneous perineal ultrasound** (TPUS) is another simple and accurate diagnostic method for the classification of perianal fistulas in CD, for the preliminary assessment as well as for the follow-up of the perianal CD. However, TPUS is limited by its narrow view in identifying deep abscesses [3].
- **Fistulography** is an internal diagnostic imaging technique performed by an interventional radiologist to determine the characteristics of a fistula. It results in poor accuracy, however, it can provide additional information in some exceptionally complex fistulas. Fistulography is limited by the exposure to radiation during the intervention [25].

Kennzeichen von Fisteln verursacht durch MC: Lokation abseits der Mittellinie, rezidive Fisteln, etc.

In case that perianal disease is the initial presentation of CD, it can be difficult to distinguish it from haemorrhoids, fissures, and fistulas seen in patients who do not have CD. Features, such as the location other than the posterior midline, the presence of multiple, recurrent, or non-healing fissures, fissures that are asymptomatic suggest CD-associated fistulas [7].

A0025 – How are Crohn's disease-associated complex perianal fistulas currently managed according to published guidelines and in practice?

nach Diagnosestellung sofortige Maßnahmen zur Schadenskontrolle: Antibiotika, Seton-Platzierung

In the first step, the diagnosis of CD-associated perianal fistulas should be followed by immediate damage control policies including treatment of local infection, usually by use of antibiotics (combination of ciprofloxacin and metronidazole). In addition, perianal abscesses should be drained with non-cutting seton placements in order to control infections, as setons allow a continuous draining of the fistula tract [1, 4]. The choice of medical treatments depends on the location of the disease, its severity, and the response to earlier therapies [28]. Generally, the standard medical therapy consists of a first-line anti-TNF-therapy in combination with further antibiotics and/or immunosuppressants, which are explained in more detail below:

Erstlinien-Standardtherapie: anti-TNF-Therapie + Antibiotika + möglicherweise Immunosuppresiva

- **Anti-TNF-therapy** is recommended by European Crohn's and Colitis Organisation (ECCO) guidelines as first-line medical therapy for induction and maintenance therapy in a patient with complex perianal fistulas caused by CD. Infliximab (IFX) presents the only anti-TNF-agent claimed to be effective in closing complex perianal fistulas [4]. Another anti-TNF agent, adalimumab, is also moderately effective for the induction and maintenance of fistula closure [1, 9, 25, 28].
- **Antibiotics** should be added to medical and surgical treatments to avoid local sepsis and to maintain clinical response. In fact, antibiotics in association with anti-TNF-agents or immunosuppressants are meant to enhance the effect of these medications [4]. Therefore, antibiotics are part of the first-line management with anti-TNF-agents [1].
- **Immunosuppressants**, such as thiopurines or thalidomide, are used for the treatment of active fistulas. However, long-term use of immunomodulators is limited due to their toxicity [3, 25].

keine klinische Reaktion: neues anti-TNF-Medikament, chirurgische Optionen, lokale Therapie, z. B. MSCs

If there is no clinical response to medical treatments, there are three further options available (see Figure 4-1) [1, 2, 5]:

1. Consider a change of the biologic such as a new anti-TNF-agent.
2. Reassess and consider surgical options (further detail below).
3. Consider local therapy such as MSC-therapy.

chirurgische Optionen:

Surgical treatments are administered after imaging techniques and endoscopy had outlined the anatomy of fistulas [4]. The following surgical interventions are available:

Mukosallappen-verschiebung (MAF)

- **Mucosal advancement flap** (MAF) presents a surgical treatment option for the closure of internal fistula openings [25]. It involves the mobilisation of a rectal mucosal flap of tissue (mucosa, submucosa or circular muscle) to cover the internal opening of the fistula tract, leaving the anal sphincter complex untouched [21].

Ligatur des inter-Sphinkter-Fistelganges (LIFT)

- **Ligation of the inter-sphincteric fistula tract** (LIFT) is a surgical option in the management of trans-sphincteric fistulas. The procedure is based on ligation of the fistula tract in the inter-sphincteric space, thereby, severing communication between the fistula and the anal canal lumen, and excision of the presumed source of the fistula, the inter-sphincteric anal gland. Within the inter-sphincteric space, one suture is used to ligate the fistula tract at the level of the internal anal sphincter. Once the fistula tract passing through the external anal sphincter and the buttock are debrided of granulation tissue, another suture is used to ligate the fistula at the level of the external anal sphincter [information provided by the external reviewer].

Fistelplug

- **Fistula plugs** are cone-shaped plugs synthesized from lyophilized porcine small intestine mucosa that are threaded through the fistulous tract and fixed in place with a suture. As a result, the fistula tracts are filled by leaving the sphincter apparatus untouched [29].

Fibrinkleber

- **Fibrin glue** consists of fibrinogen and thrombin with which a fibrin clot is formed to stimulate wound healing by inducing angiogenesis and fibroblast growth [21, 25, 29].

temporäres Stoma

- **Diverting temporary stoma** is an artificial bowel outlet, also called ostomy. It presents an option for patients with severe perianal sepsis with insufficient response to a seton placement, or as a temporary measure to improve the condition of the patient until complete induction of medical therapy or proctectomy [21].

Proktektomie

- **Proctectomy** (with a permanent stoma) is a surgery to remove all or part of the rectum and often the last resort in severe, therapy-refractory fistulising disease, especially in CD patients with complex fistulas associated with uncontrollable and debilitating abscesses, recurrent sepsis, colonic or perianal disease, refractory proctitis, or anal stenosis [3, 25].

MSC empfohlen als Zusatztherapie zu Standardmedikamenten in refraktären PatientInnen oder in PatientInnen ohne vorheriger medikamentöser Therapie oder mit Fisteln als erstes Anzeichen für MC

All surgical interventions have high recurrence rates in common and an increased risk of a permanent stoma. The boundaries of current therapies suggest MSC-therapy as an ultima-ratio add-on therapy to standard medical therapies in patients who are refractory to either anti-TNF-agents (i.e. infliximab) as first-line therapy alone or in combination with antibiotics and/or immunomodulators [26]. Biologics and/or immunomodulators are given to control luminal disease and perianal inflammation, while MSCs are meant to close any residual fistulas [5]. In addition, MSC-therapy can also be administered to patients who have not yet used anti-TNF-agents and immunomodulators or in whom the perianal fistulising disease is the main or only manifestation of the CD. Thereby, the patients could avoid the risk of systemic immunosuppression by undergoing stem cell therapy [2].

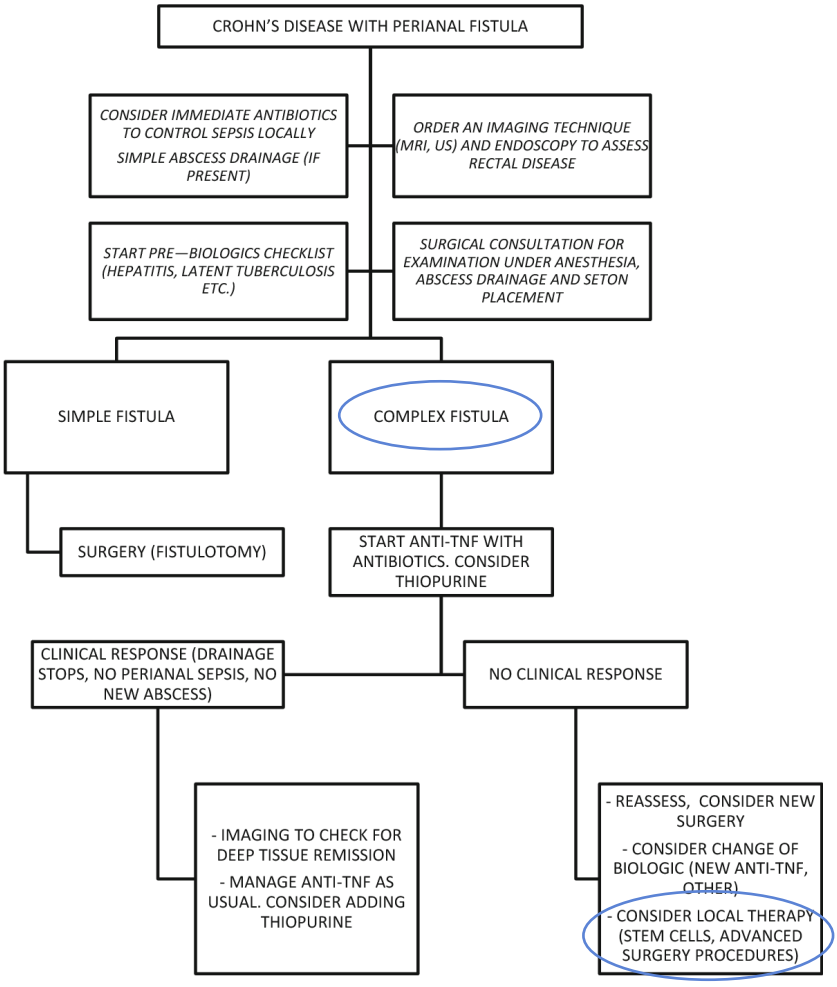

Figure 4-1: Clinical management algorithm for the treatment of perianal fistulas caused by Crohn's disease (Source: [1])

4.4 Target population

A0007 – What is the target population in this assessment?

In this assessment, the target population includes patients with perianal complex fistulas caused by non-active or mildly active luminal CD that are refractory to standard medical treatments involving anti-TNF-agents alone or in combination with antibiotics and/or immunomodulators, or in patients intolerant to such treatments. Patients with simple perianal or rectovaginal fistulas were excluded from this assessment.

PatientInnen mit komplexen, perianalen Fisteln als Ursache von MC, refraktär zu Standardmedikamenten

A0023 – How many people belong to the target population?

In the USA, Canada, and Europe the highest prevalence rates have been reported with above 300 per 100,000 people [2]. In Austria, incidence rates of 11.5 per 100,000 inhabitants were estimated, with 9.5 and 14.6 in the rural and urban areas, respectively [6]. In general, approximately, 17% and 24% of patients with CD develop perianal fistulas at 10 and 20 years after diagnosis, respectively. In particular, patients with rectal involvement (92%) develop perianal fistulas. Approximately 45% of the patients diagnosed with perianal disease, develop the fistulas before being diagnosed with CD and about 70-80% of the patients suffer from complex perianal fistulas [2, 7]. The majority of the patients (60-70%) are refractory to conventional medical treatments [2].

Inzidenzraten Österreich: 9,5 von 100.000 Einwohnern (ländliches Gebiet), 14,6 von 100.000 Einwohnern (städtisches Gebiet), 24 % mit perianalen Fisteln 20 Jahre nach MC-Diagnose, 60-70% refraktäre PatientInnen

A0011 – How much are allogeneic mesenchymal stem cells utilised?

The previous administrations of MSCs in patients with CD-associated complex perianal fistulas have been within the scope of approval studies. Therefore, an estimate on the number of current and potential/expected utilisation of MSCs in complex perianal fistulas is not yet available for Austria.

Schätzung für die Verwendung von MSCs für Österreich schwierig

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *critical* to derive a recommendation:

kritische Outcomes: Lebensqualität, kombinierte Remission, Reaktion

- Quality of life (QoL) measured with:
  - Inflammatory Bowel Disease Questionnaire
  - Short-form-36 score
  - Perianal Disease Activity Index
  - Crohn's Disease Activity Index
- Combined remission
- Response

IBDQ: Fragebogen mit 4 Kategorien, nicht speziell für perianale Krankheit, höhere Punkte assoziiert mit besserer Lebensqualität

The **Inflammatory Bowel Disease Questionnaire** (IBDQ) is a 32-item questionnaire filled in by patients including four categories: bowel function, emotional status, systemic symptoms, and social functioning. It does not include a special category for perianal CD. The total score on this index ranges from 32 to 224, with higher scores indicating better QoL. The score of patients in remission is between 170 and 190 [30].

SF-36: Fragebogen mit 8 Gesundheitszuständen, nicht speziell für MC, höhere Punkte assoziiert mit besserer Lebensqualität

The **Short-form-36** (SF-36) score is a multi-item generic health survey filled in by patients including eight health domains: physical functioning, role physical functioning, bodily pain, general health, vitality, social functioning, emotional role, and mental health. The questionnaires are not specially formed for CD. The response scales for the SF-36 items vary across and within the scales with the number of response options ranging from 3 (for physical functioning) to 6 (for vitality and mental health). The scores are calculated by summing the responses across scale items and then transforming these raw scores to a 0–100 scale, with higher scores indicating better QoL [31].

PDAI: Fragebogen mit 5 Kategorien, speziell für perianale Krankheit, niedrigere Punkte assoziiert mit weniger schwerwiegender Krankheit

The **Perianal Disease Activity Index** (PDAI) is a scoring system for clinicians to evaluate the severity of perianal CD, with lower scores indicating more severe disease. The score includes five items: discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration. Thus, it includes a special category for fistulising disease. Each item is graded on a 5-point Likert scale ranging from score 0 (no symptoms) to score 4 (severe symptoms) [30].

CDAI: Fragebogen mit 8 Kategorien, nicht speziell für perianale Krankheit, niedrigere Punkte assoziiert mit weniger schwerwiegender Krankheit

The **Crohn's Disease Activity Index** (CDAI) is a scoring system for clinicians to evaluate the severity of the disease, involving eight categories: the number of liquid stools, abdominal pain, general well-being, extraintestinal complications, antidiarrheal drugs, abdominal mass, and haematocrit body weight. A special category for the fistulising disease is not included. The score ranges from 0 to 600, with lower scores indicating less experienced severe disease. The limit between active and very severe disease was defined as a cut-off value of 450 points. CDAI scores of 220–450 were labelled as moderately active disease and scores of 150–219 as a mildly active disease [30].

kombinierte Remission: Verschluss von allen nässelnden, behandelten Fisteln, keine Kollektionen >2 cm

Combined remission is characterised as the closure of all treated external openings that were draining at baseline despite gentle finger compression, the absence of discharge in all individual fistulas, and/or the absence of collections larger than 2cm determined by MRI. In the literature, the combination of the last two criteria is also referred to as fistula healing of all individual fistulas [11, 12].

Reaktion: Verschluss von zumindest 50 % der behandelten Fisteln

Response is characterised as the closure of at least 50% of all treated external openings that were draining at baseline [11, 12]. The definition of response was chosen from the biggest RCT available with 200 patients.

wichtiger Endpunkt: Fistel-rezidiv-freies-Überleben: ausschlaggebender Nutzen ab 13 Wochen

Fistula relapse-free survival, defined as the length of time patients survive without any signs or symptoms of returning and/or new fistulas after primary stem cell treatment for CD-associated perianal fistulas. According to expert opinions, a decisive benefit for patients results as of 13 weeks of fistula relapse-free survival [information provided by submitting hospital]. This endpoint was deemed *important*, but not crucial to derive a recommendation.

5.2 Included studies

MSCs vs. Placebo: 2 RCT inkludiert

To evaluate the effectiveness of allogeneic MSCs, we included two randomised controlled trials (RCTs) [11, 12] comparing allogeneic MSCs with placebo.

Study characteristics

1 multinationales RCT, 1 RCT aus den Niederlanden, Nachuntersuchungen bis 24. Woche

The two RCTs were conducted in Spain, Belgium, Austria, Canada, Germany, France, Italy, Israel [11] and in the Netherlands [12]. The studies were sponsored by the manufacturer TiGenix and by the Digest Science Foundation, respectively. In both studies, the length of follow-up was 24 weeks. Long-term comparative data beyond 24 weeks is currently not available.

1 RCT: 120 Millionen MSCs aus Fettgewebe, 1 RCT: 3 verschiedene MSC-Dosierungen aus Knochenmark

The two RCTs investigated different types of MSCs, namely ASCs [11] and BM-MSCs [12]. In Panés et al. [11], 120 million cells were administered in the interventional group for a maximum of three fistula tracts and 24 mL saline solution (placebo) in the control group. In comparison, the study of Molendijk et al. [12] investigated three different doses of BM-MSCs: (1) 10 million, (2) 30 million and (3) 90 million cells compared to placebo, defined as 0.9% NaCI/5% human albumin solution.

Patient characteristics

1 RCT: 212 pts, 41 davon vollendeten 24 Wochen nicht, 1 RCT: 21 pts, 5 pts pro Therapiegruppe, 6 pts in Kontrollgruppe

Panés et al. included 212 patients, of which 107 belonged to the interventional group and 105 to the control group. Of the 212 patients, 41 (19.3%) were lost to follow-up. Molendijk et al. included 21 patients in their study. Five patients in each of the three interventional groups and six patients in the control group. No patients were lost to follow-up.

durschnittliches Alter beider RCTs: 38 Jahre

The mean age of the patients was around 38 years in both RCTs ranging from 33.4 to 40.8 years across the different treatment groups.

Both RCTs had the same inclusion criteria except the CDAI-score and the categorisation of the fistula tracts. In Panés et al., the patients included had a CDAI score ≤220, indicating non-active or mildly active luminal CD, and complex perianal fistulas, defined by the AGA guidelines. In comparison, Molendijk et al. included patients with a CDAI score ≤250 and with actively draining perianal fistulas with one to two internal openings and one to three fistula tracts. The definition for complex perianal fistulas applied by Molendijk et al. did not correspond to the AGA guidelines. Non-complex fistulas were also included in their study, although described as complex. There was homogeneity with regard to exclusion criteria, except for pregnancy and breastfeeding, renal or hepatic failure, change in concomitant medication, documented human immunodeficiency virus infection, active hepatitis B, C, or tuberculosis, malignancy within the past five years and a history of lymphoproliferative disease, which were only considered in Molendijk et al.

Unterschiede in Einschlusskriterien: CDAI-Punkte, Fistelklassifizierungen abweichend von AGA-Definition

1 RCT: zusätzliche Ausschlusskriterien, z. B. Schwangerschaft, Hepatitis C, Malignität in den letzten 5 Jahren, etc.

Detailed patient and study characteristics of included studies are displayed in Table A-1.

5.3 Results

Treatment effect on mortality

D0001 – What is the expected beneficial effect of allogeneic mesenchymal stem cells on mortality?

D0003 – What is the effect of allogeneic mesenchymal stem cells on the mortality due to causes other than Crohn's disease-associated complex perianal fistulas?

No evidence was found to answer the research question. None of the included studies reported cases of overall or disease-specific mortality, neither in the treatment group nor the placebo arm.

keine Evidenz zur Gesamt- und krankheitsspezifischen Mortalität

Treatment effect on morbidity

D0005 – How do allogeneic mesenchymal stem cells affect symptoms and findings (severity, frequency) of Crohn's disease-associated complex perianal fistulas?

This research question was answered in the section "Health-related quality of life".

Referenz zu "Health-related quality of life"

D0006 – How do allogeneic mesenchymal stem cells affect progression (or recurrence) of Crohn's disease-associated complex perianal fistulas?

Combined remission

Both RCTs reported a significant improvement in combined remission in the interventional group compared to the placebo arm: Panés et al. [11] reported 50% (n=107) versus 34% of the patients (n=105) achieving combined remission after 24 weeks (mean difference 15.2%, CI 0.2-30.3, p=0.024). For the second interventional group (30 million cell dose), Molendijk et al. [12] reported the highest percentage (80%) of the patients (n=5) achieving combined remission compared to 33.3% of the patients (n=6) in the control arm after 12 weeks (p=0.06). The percentages of patients with combined remission in the other interventional groups were lower (IG1: 40%, n=5, and IG3: 20%, n=5).

1 RCT: signifikant verbesserte kombinierte Remission,
1 RCT: signifikant verbesserte kombinierte Remission in 1/3 der MSC-Gruppen

Response

1 RCT: höhere Reaktionsrate in MSC-Gruppe als in Kontrollgruppe, nicht signifikant

Panés et al. [11] reported that 66% of the 107 patients receiving stem cells responded to the treatment[1], compared to 53% of the 105 patients who received placebo. However, this effect was not statistically significant (p=0.054). The RCT of Molendijk et al. did not report response rates.

Relapse-free survival

Fistel-rezidiv-freies-Überleben wurde in keinem der RCTs berichtet

With regard to the outcome fistula relapse-free survival, none of the two included RCTs [16, 19] reported the percentage of patients who were relapse-free 13 weeks after the intervention.

Health-related quality of life

D0012 – What is the effect of allogeneic mesenchymal stem cells on generic health-related quality of life?

D0013 – What is the effect of allogeneic mesenchymal stem cells on disease-specific quality of life?

unterschiedliche Indizes zur Messung der Lebensqualität

Different QoL scores, namely the (s)IBDQ, the SF-36, the PDAI, and the CDAI, were reported to evaluate this research question.

(s)IBDQ

IBDQ: 1 RCT: ähnliche Lebensqualitäts-verbesserungen zwischen Gruppen, 1 RCT: stärkere Verbesserungen in der Kontrollgruppe, MSCs kein beweiskräftiger Effekt auf Lebensqualität

The RCTs used different versions of the IBDQ questionnaire: Panés el al. [11] used the IBDQ and reported similar improvements in QoL-scores from baseline to week 24 in the treatment group and control group. In comparison, Molendijk et al. [12] used the short-form IBDQ and reported the best QoL-improvement in the control group, while there was worsening QoL in the first and third interventional group (10 and 90 million cell dose), and only a slight improvement in interventional group 2 (30 million cell dose) from baseline to week 24.

SF-36

SF-36: 1 RCT: kontroverse Ergebnisse: z. B. Lebensqualität-verbesserung bezüglich physischen Funktionen vs. Lebensqualität-verschlechterung bezüglich allgemeinen Gesundheits-wahrnehmungen

Solely Molendijk et al. [12] reported SF-36 scores for week 0 and 24 in their RCT, which yielded very inconclusive results. For physical functioning, improvements were reported in all groups, with the highest improvement in the second interventional group (30 million cell dose), while for physical role functioning worsening QoL in all interventional groups and a slight improvement in QoL in the control group was reported. With regard to bodily pain, worsening QoL was shown for the first and second interventional group (10 and 30 million cell doses), while QoL improvements were shown for the third interventional (90 million cell dose) and the control group. For general health perceptions all groups led to worsening QoL and for vitality, only the second interventional group (30 million cell dose) reported a slight improvement in QoL. For social functioning, emotional role functioning and mental health the results were very heterogeneous.

[1] Defined as a closure of at least 50% of all treated external openings, after 24 weeks.

PDAI

Panés et al. [11] showed that the disease of the patients was less severe in week 12 compared to baseline, with better improvements in the interventional group, but a worsening disease at week 24. In comparison, Molendijk et al. [12] showed that the severity of the disease of the patients of the interventional group was lower at week 12, but not in patients of the control group. Inconclusive effects on the severity of the disease were reported at week 24.

PDAI: 1 RCT: schwerwiegendere Krankheit nach 24 Wochen, 1 RCT: keine beweiskräftigen Ergebnisse in MSC-Gruppen in 24. Woche

CDAI

Both RCTs also reported CDAI scores: Panés et al. [11] showed a worse severe disease of the patients at week 24 compared to baseline for both groups, however, a less worsening for the control group. In detail, this holds true for the categories general wellbeing and abdominal pain, while there was a slight reduction in the number of liquid stools in the interventional group. In comparison, Molendijk et al. [12] reported less severe disease at week 24 compared to baseline in all groups, but the third interventional group (90 million cell dose), with the highest improvement in the second interventional group (30 million cells dose).

CDAI: 1 RCT: Verschlechterung des Krankheitsschweregrades in 24. Woche, 1. RCT: Verbesserung des Schweregrades nach 24 Wochen → größte Verbesserung in MSC-Gruppe 2

In total, across the different scores, results were very inconclusive in both studies [11, 12]. Therefore, MSCs are not deemed to improve QoL of the patients.

Verbesserung der Lebensqualität durch MSCs nicht sicher

Non of the two RCTs reported significance levels for the QoL-scores. Specific improvements or deteriorations in the scores are listed in the GRADE Table 7-1. An overview of all results of the RCTs are displayed in Table A-1.

keine Signifikanzniveaus für Lebensqualitätdaten

Function

D0011 – What is the effect of allogeneic mesenchymal stem cells on patients' body functions?

D0016 – How does the use of allogeneic mesenchymal stem cells affect activities of daily living?

The effect of MSC-therapies on patients' body functions was illustrated with different QoL scores. Overall, both studies [11, 12] reported very inconclusive results across the different scores. Consequently, MSC-therapy is not deemed to improve QoL of the patients. However, it seemed that there might be small improvements in physical functioning (i.e. number of liquid stools), social functioning and mental health.

keine beweiskräftigen Ergebnisse, jedoch mögliche Verbesserungen in physischen und sozialen Funktionen und in psychischer Gesundheit

Patient satisfaction

D0017 – Was the use of allogeneic mesenchymal stem cells worthwhile?

Based on the improved remission data, MSC-therapy might be worthwhile for patients. However, if remission has no impact on patients QoL and based on the reported, very inconclusive QoL-data, the question, if MSC-therapy is worthwhile for patients, remains unclear.

unklar ob MSCs für PatientInnen lohnenswert sind

6 Safety

6.1 Outcomes

The following outcome was defined as *critical* to derive a recommendation:

- Severe treatment-related adverse event

kritischer Endpunkt: schwerwiegende behandlungsbedingte Nebenwirkungen (NW)

Severe treatment-emerged adverse events and treatment-related adverse events were deemed *important*, but not crucial to derive a recommendation.

In accordance with the EUnetHTA guidelines on safety outcomes, adverse events are defined as "any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device" [32]. Adverse events, including (severe) treatment-emerged adverse events and (severe) treatment-related adverse events, which may occur during or shortly after the intervention or during follow-up, are the most common safety issues associated with the MSC-administration and the comparator interventions. The most frequently reported adverse events have been described.

NW definiert gemäß den EUnetHTA Leitlinien

6.2 Included Studies

For the safety evaluation of the MSC-administration, two RCTs and one prospective interventional single-arm study were included. The two RCTs [11, 12] have already been described in the previous section (Clinical Effectiveness, 5.2.). De la Portilla et al. [13] investigated the administration of allogeneic ASCs in 24 patients with complex perianal fistulas caused by CD.

Sicherheit: 2 RCTs & 1 zusätzliche einarmige Studie (n=24 pts)

Study characteristics

The single-arm study [13] was conducted in Spain and sponsored by the manufacturer TiGenix. The study did not report any competing interests. The length of the reported follow-up was 24 weeks.

einarmige Studie aus Spanien, 24 Wochen Nachuntersuchungen

De la Portilla et al. [13] assessed the safety and efficacy of allogeneic ASCs in patients with CD-associated complex perianal fistulas. During the first administration, 20 million cells were injected in one draining fistula tract. If fistula closure was not complete at week 12, the second administration of 40 million cells was performed.

Effektivität und Sicherheit von MSCs aus Fettgewebe

With regard to safety outcomes, treatment-emerged adverse events and (severe) treatment-related adverse events were reported. However, information about the grading system for the evaluation of the severity of adverse events was lacking.

keine Informationen zur Evaluierung der Schweregrade der NW

Patient characteristics

16/24 pts vollendeten 24 Wochen, Durchschnittsalter: 36 Jahre, CDAI-Score: ≤200 zu Studienbeginn

The study of de la Portilla et al. [13] included 24 patients (full analysis) with complex perianal fistulas caused by CD that underwent the administration of ASCs. Of the 24 patients, eight patients prematurely withdrew from the study, thus, 16 patients completed the study period of 24 weeks. The mean age of the 24 patients was 36 years. Unlike to the RCTs that included patients with a CDAI-score of ≤220 [11] and ≤250 [12], the single-arm study [13] included patients with non-active luminal CD defined by a CDAI ≤200.

nicht alle berichteten Fisteln komplex gemäß der AGA Definition von komplexen, perianalen Fisteln

With regard to the classification of the fistulas, de la Portilla et al. [13] reported the effect of ASCs on complex perianal fistulas. However, the majority of the treated fistulas had solely one track (62.5%), one external opening (75.0%) and pictured trans-sphincteric tracks (70.8). These characteristics of the fistula tracks do not match the AGA definition of complex perianal fistulas[2].

Detailed patient and study characteristics of included studies are displayed in Table A-1 and Table A-2.

6.3 Results

Patient safety

C0008 – How safe are allogeneic mesenchymal stem cells in comparison to placebo?

keine Gesamt- oder krankheitsbedingten Mortalitätsfälle

None of the included studies [11-13] reported cases of peri-interventional mortality neither in the MSC-group nor in the placebo group.

schwerwiegende anale Abszesse: 1 RCT: 5 Fälle in MSC-Gruppe + 5 Fälle in Kontrollgruppe, einarmige Studie: 1 Fall

Out of 204 patients, Panés et al. [11] reported 25 cases of anal abscesses. Out of those nine cases (MSC-group, n=103) and seven cases (control group, n=101) were reported as severe treatment-emerged adverse events, of which five cases in each group were assessed as severe treatment-related adverse events. In comparison, in Molendijk et al. [12] four out of 21 patients developed anal abscesses, of which non were reported as severe. De la Portilla et al. [13] reported four cases of anal abscesses out of 24 patients, with one case referred to as severe.

schwerwiegende Proktalgia: 1 RCT: 1 Fall in Kontrollgruppe

Proctalgia (cramps in the anal area) was reported in 24 out of 204 patients in Panés et al. [11], of which one case in the control group (n=101) was assessed as severe. In comparison, in de la Portilla et al. [13] two out of 24 patients developed proctalgia, however, no case was rated as severe.

schwerwiegende anale Entzündung: 1 RCT: 1 Fall in Kontrollgruppe

Panés et al. [11] also reported one case of anal inflammation in the control group (n=101), which was reported as severe treatment-related adverse event. In de la Portilla et al. [13] two out of 24 patients developed anal inflammations, non of them were severe.

[2] Defined as high fistulas involving more than two thirds of the external sphincter, of high inter-sphincteric, high trans-sphincteric, extra-sphincteric or supra-sphincteric origin and with possible multiple external openings.

One severe case of liver abscess was reported in the control group (n=101) of Panés et al. [11]. In Molendijk et al. [12] one case of adenocarcinoma was reported in the first MSC-group (10 million cell dose).

schwerwiegendes Leberabszess: 1 RCT: 1 Fall in Kontrollgruppe, Adenokarzinom: 1 RCT: 1 Fall in MSC-Gruppe 1

Pyrexia (fever) was reported in one out of five patients in the first MSC-group (10 million cells dose) in Molendijk et al. [12], however, it was not severe. In contrast, one pyrexia case out of four cases was assessed as severe in de la Portilla et al. (n=24) [13].

schwerwiegende Pyrexie: einarmige Studie: 1 Fall

By calculating the chance of developing a severe treatment-related adverse event, overall, out of 1,000 patients, 23 fewer patients of the MSC-group will develop a severe treatment-related adverse event compared to the control group, meaning that severe treatment-related adverse events occur more often in the control group (see Figure 6-1).

PatientInnen ohne MSC-Therapie höhere Chancen schwerwiegende, behandlungsbezogene, NW zu entwickeln

All (severe) treatment-emerged and treatment-related adverse events are listed in more detail in Table A-1 and Table A-2 of the Appendix.

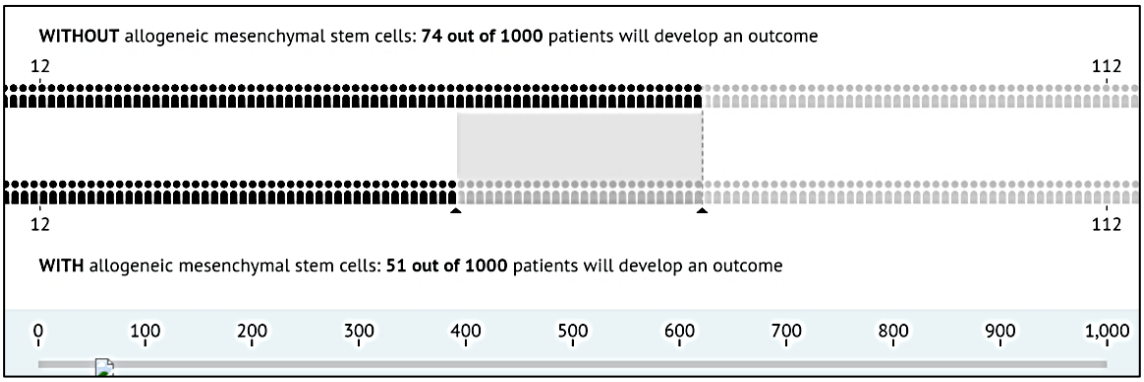

*Figure 6-1: Chance of developing severe treatment-related adverse event. 74 out of 1,000 patients, who do not receive MSC-therapy, will develop a severe adverse event, in comparison with 51 out of 1,000 patients, who do receive the intervention. In total, **23 fewer** patients of the MSC-group will develop a severe treatment-related adverse event compared to the placebo group; Reference: GRADEpro/GDT*

C0002 – Are the harms related to dosage or frequency of applying allogeneic mesenchymal stem cells?

In the RCT of Molendijk et al. [12], three different doses were compared to one placebo group. In the first treatment group (MSC dose of 10 million cells, n=5) 17 adverse events occurred in five patients, whereas in the second treatment group (MSC dose of 30 million cells, n=5), nine adverse events and in the third treatment group (MSC dose of 90 million cells, n=5) ten adverse events appeared in five patients. In comparison, 14 adverse events occurred in six patients of the control group (n=6). Thus, the lowest dose of MSCs resulted, in more adverse events than the highest MSC-dose and, in more adverse events than in the control group. Thereby, the authors pointed out that a lower dose of MSC is associated with increased adverse events. In fact, the middle dose of MSCs resulted in the lowest number of adverse events.

häufigste unerwünschte NW in der MSC-Gruppe 1, die wenigsten unerwünschten NW in der MSC-Gruppe 2

C0004 – How does the frequency or severity of harms change over time or in different settings?

keine Evidenz

No evidence was found to answer this research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of allogeneic mesenchymal stem cells?

Effekt unklar bei PatientInnen mit Komorbiditäten

No direct evidence was found to answer this research question.

However, there are possible issues with MSC-therapies administered in patients with other comorbidities. As CD is an autoimmune disease, MSCs are aiming in suppressing the patient's immune system. Therefore, patients might be more susceptible to other infections.

C0007 – Are allogeneic mesenchymal stem cells associated with user-dependent harms?

MSC-Dosierung und Injektionsmethode möglichen Effekt auf Effektivität und Sicherheit

No direct evidence was found to answer this research question. However, the dosage of MSCs may have an impact on effectiveness and safety outcomes. Moreover, the way MSCs are injected may influence its effectiveness and safety. However, currently, no direct comparisons between different modalities, i.e. intravenous vs. local injection, are available.

7 Quality of evidence

RoB für RCTs: Cochrane Collaboration's Tool: 1 RCT moderater RoB, 1 RCT hoher RoB

RoB für einarmige Studie: IHE-Checkliste: einarmige Studie: hoher RoB

The risk of bias (RoB) for individual studies was assessed with the Cochrane Collaboration's tool for randomised trials [33] as well as with the Institute of Health Economics (IHE) checklist for single-arm studies [15]. Both assessments are presented in Table A-3 and Table A-4 in the Appendix. One RCT [11] was rated with a moderate RoB, whereas the second RCT [12] was rated with a high RoB. In both RCTs, the blinding of the patients and the treating physician was unclear due to lacking information. Additionally, there is a RoB due to treatment effects of concomitant therapies in both RCTs and due to the small sample size in the RCT of Molendijk et al. [12]. The observational study [13] was rated with a high RoB. The most severe biases occurred due to the unclear study design and study population, the lack of information about co-interventions, as well as, the missing comparison of effects before and after the intervention. Furthermore, the conclusions were not supported by the results as the intervention was marked as safe, even though, two patients left the study because of severe adverse events.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE scheme [16] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [16].

Unterscheidung zwischen hoher, moderater, niedriger oder sehr niedriger Qualität der Evidenz

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion;

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table Table 7-1 and in the evidence profile in Table A-5.

Stärke der Evidenz zur Effektivität sehr niedrig, und niedrig für Sicherheit

Overall, the strength of evidence for the effectiveness of allogeneic MSCs in comparison to placebo was very low. The strength of evidence for the safety of allogeneic MSCs in comparison to placebo was low. For the comparison of the stem cells to fistula plugs or fibrin glue, no evidence is available.

Table 7-1: Summary of findings table of allogeneic mesenchymal stem cells

Outcomes	Anticipated absolute effects* (97.5% CI)		Relative effect (97.5% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with allogeneic mesenchymal stem cells				
Quality of life (QoL) assessed with: IBDQ	Panés (n=204): IG vs. CG: improvement +4.8 vs. +5.3 points; Molendijk (n=21): IG vs. CG: deterioration -0.1 (based on self-calculated mean of 3 IGs) +4.0 points			225 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	Patient-reported outcome
Quality of life (QoL) assessed with: SF-36	Molendijk (n=21): IG vs. CG: deterioration -1.14 vs. improvement +0.8 points (self-calculated means across 8 health states)			21 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,e,f]	Patient-reported outcome
Quality of life (QoL) assessed with: PDAI	Panés (n=204): IG vs. CG: improvement -2.3 vs -1.4 points; Molendijk (n=21): IG vs. CG: improvement -1.9 (based on self-calculated mean of 3 IGs) vs. -1.3 points			225 (2 RCTs)	⨁⨁⨁◯ MODERATE [a,d]	Clinical assessment of severity of the disease
Quality of life (QoL) assessed with: CDAI	Panés (n=204): IG vs. CG: deterioration +4,7 vs. +0.8 points; Molendijk (n=21): IG vs. CG: improvement -8.0 (based on self-calculated mean of 3 IGs) vs. -17.8 points			225 (2 RCTs)	⨁⨁◯◯ LOW [a,c,d]	Clinical assessment of severity of the disease
Combined remission: 120 million adipose-tissue-derived MSCs assessed with: clinical and MRI assessment, follow up: mean 24 weeks	The mean combined remission: 120 million adipose-tissue-derived MSCs was 0 %	The mean combined remission: 120 million adipose-tissue-derived MSCs in the intervention group was 15 % more (0,2 more to 30,2 more)		212 (1 RCT)	⨁⨁⨁◯ MODERATE [e,g,h]	Significant difference, but wide confidence intervals
Combined remission: different dosages bone-marrow-derived MSCs assessed with: clinical and MRI assessment, follow up: mean 12 weeks	Molendijk (n=21): IG1 (10 million cells): 2/5 pts (40%), IG2 (30 million cells): 4/5 pts (80%), IG3 (90 million cells): 1/5 pts (20%), CG: 2/6 pts (33.3%); significant difference IG2 vs. CG: p=0.06			21 (1 RCT)	⨁◯◯◯ VERY LOW [a,c,f,i]	
Response to 120 million adipose-tissue-derived MSCs assessed with: closure of at least 50% of all treated external openings, follow up: mean 24 weeks	The mean response to 120 million adipose-tissue-derived MSCs was 0 %	The mean response to 120 million adipose-tissue-derived MSCs in the intervention group was 13 % more (0,1 fewer to 26,1 more)		212 (1 RCT)	⨁⨁⨁◯ MODERATE [e,g,h]	Wide confidence intervals, not statistically significant (p=0.054)
Severe treatment-related adverse events (STRAE), follow up: mean 24 weeks	74 per 1,000	51 per 1,000	RR 0.69	226 (2 RCTs)	⨁⨁◯◯ LOW [a,f]	RR self-calculated

* *The risk in the intervention group (and its 97.5% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 97.5% CI).*

Abbreviations: *CDAI = Crohn's Disease Activity Index, CG = Control group, CI = Confidence interval, IBDQ = Irritable Bowel Disease Questionnaire, IG = Interventional group, PDAI = Perianal Disease Activity Index, pts = Patients, RCT = Randomised controlled trial, RR = Risk ratio, SF-36 = Short-form 36, STRAE = Severe treatment-related adverse event*

Explanations

[a] *Study with high risk of bias included*
[b] *Subjective outcome measure*
[c] *Heterogeneity of results*
[d] *Clinical assessment*
[e] *Not applicable (one study)*
[f] *Small sample size*
[g] *Study with moderate risk of bias*
[h] *Wide confidence intervals*
[i] *Differences in inclusion criteria (definition of complex fistula + CDAI score)*

8 Discussion

MSC-therapy presents a possible therapy method treating draining perianal fistulas with the aim of fistula closure. Currently, no product received marketing authorisation. However, marketing approval of Cx601 is expected by the manufacturer in February 2018.

MSC-Therapieziel: Schließung der Fisteln, bisher keine Marktzulassung

With regard to effectiveness of MSC-therapy, both RCTs reported a slight improvement in combined remission in the interventional group compared to the placebo group: Panés et al. [11] reported 50% (n=107) versus 34% of the patients (n=105) achieving combined remission after 24 weeks (mean difference 15.2%, CI 0.2-30.3, p=0.024). However, it remains questionable, why dichotomous outcomes were changed into percentages in order to calculate the mean difference. In Molendijk et al. [2] the highest percentage (80%) of the five patients of the second MSC-group achieving combined remission compared to 33.3% of the six patients in the control group after 12 weeks (p= 0.06). Response rates were only reported by Panés et al. [11]. Higher rates were reported in the MSC-group, however, this was not statistical significant (p=0.054). Based on the results of the QoL-assessment via different scores, MSCs were not deemed to improve QoL of the patients. Non of the two RCTs reported significance levels for the QoL-scores.

Verbesserung in kombinierter Remission und Wirkung in der MSC-Gruppe, jedoch keine nachweißbare Verbesserung in Lebensqualität

Several sever adverse events were reported in the included studies with anal abscesses reported the most. Across all studies severe anal abscesses occurred more commonly in the MSC-groups than in the control groups. In contrast, severe cases of proctalgia, anal inflammation and liver abscesses were only reported in the control groups. De la Portilla et al. [13] reported one case of pyrexia out of 24 patients and in Molendijk et al. [12] one patient of the first MSC-group (10 million cell dose) developed an adenocarcinoma. Figure 6-1 showed that the chance of developing severe treatment-related adverse events is higher for the placebo group than for the treatment group, thus, the development of severe treatment-related adverse events, except immunity-related adverse events, such as common colds, might be triggered mostly by the interventional process itself than by the effect of the MSC-treatment. However, this effect was based on low quality evidence.

Sicherheit: anale Abszesse häufigste schwerwiegende NW, 1 RCT: 1 Fall von Adenokarzinom

Interpretation of the findings

Study quality, validity of endpoints and overall level of evidence

The RCTs [11, 12] that investigated allogeneic MSCs compared to placebo had a moderate and high RoB, respectively, due to the unclear blinding of the patients and the treating physician as well as due to the possible treatment effects of concomitant therapies. The small sample size of one RCT [12] additionally caused a high RoB. The RCTs reported inconclusive results for QoL across different scores, which could be partly explained by the subjectiveness of reported QoL data by means of the IBDQ and SF-36, as well as, by the varying dosages across the RCTs. The overall level of evidence for the effectiveness endpoints was very low.

moderates/hohes Verzerrungspotential, 1 RCT kleine pts-Anzahl, Subjektivität QoL-Daten, Gesamtqualität der Evidenz für Effektivität sehr niedrig

fehlende Informationen zur Evaluation des Schweregrades der NW, Gesamtqualität der Evidenz für Sicherheit niedrig

The remaining observational study [13] had a high risk of bias due to the unclear study design and study population, the lack of information about co-interventions, as well as due to the missing before-and-after comparison of the interventional effects. With regard to safety, the varying presentation of the adverse events across the three included studies, made it difficult to show, which adverse events are more likely to occur in which treatment group. Information about the evaluation of the severity of adverse events was lacking. The overall level of evidence for the safety endpoints was low.

Relevance of the outcomes assessed in clinical trials for patient-relevant benefits

Subjektivität der Daten zur Lebensqualität, Messung von Remission und Reaktion vertrauenswürdig, jedoch insgesamt keine beweiskräftige Effektivität der MSCs

Effectiveness outcomes included in this review directly (QoL and severity of the disease) and indirectly (combined remission, response) measured the impact on patients QoL. All outcomes were reported in a consistent way. However, QoL data via the IBDQ and SF-36 questionnaires involve a level of subjectiveness, as data are assessed through questionnaires handed out to patients. Combined remission and response were reliable and valid tools in order to indirectly measure changes in the severity of perianal fistulas, as both endpoints were investigated via clinical and/or MRI assessment. Possible improvements in remission rates but lacking improvement in QoL makes the findings/evidence inconclusive.

Factors that may influence the external validity

mögliche PatientInnenselektion in den 3 Studien

The three included studies were not consistent about the severity of disease of the participants at study start: The CDAI-scores, used as inclusion criteria, ranged from ≤200 to ≤250. In addition, the definitions of complex perianal fistulas varied across the studies. Both might indicate selective patient selection in the studies.

unterschiedliche Dosierungen und Zelltypen

Furthermore, different allogeneic stem cell types and stem cell dosages were used in the included studies. One study [12] showed that dosage differences can impact effectiveness and safety outcomes. However, there is no direct evidence available whether cell type or dosage affect different stages of the disease and long-term results.

bisher Placebo einzige Vergleichstherapie

In both RCTs [11, 12], placebo was used as the comparator. Based on clinical practice, fistula track filling material, such as fistula plugs, may be used as another comparator. Currently, no evidence is available that investigate allogeneic MSCs compared to treatments other than placebo.

Evidence gaps, ongoing studies and related questions

keine Langzeitevidenz über 24 Wochen: Beunruhigung bezüglich Entwicklungen von Malignität

Currently, no long-term evidence of allogeneic MSCs beyond 24 weeks is available. Thus, it is currently questionable if there is a sustainable effect – long-term fistula closure – of the MSCs as well as if long-term severe treatment-related adverse events are likely to occur after 24 weeks, which is crucial to point out in the light of the worsening in the QoL-scores in Panés et al. from week 12 to week 24. In this regard, the concern of developing malignancies after MSC-administration has to be emphasized. In Molendijk et al. [12], one case of adenocarcinoma occurred in the second interventional group, which presents, in fact, one out of five patients. The authors argued that this might be due to genetic reasons, as the father of this patient had died of same cancer at young age. However, the "not-correlation" between the occurrence

of the adenocarcinoma and the MSC-administration could not be proved. In fact, latest evidence reported that there can be unwarranted differentiation of the transplanted MSCs with the potential to suppress anti-tumour immune-response and generate new blood vessels, which consequently can promote tumour growth and metastasis development [34, 35].

zusätzliche MSC-Therapie: PatientInnen möglicherweise empfänglicher für Infektionen

Indeed, the effect of MSCs on the immune system is not sufficiently addressed in current evidence. As CD patients often already receive immune suppressive treatments, an additional MSC-therapy may lead to patients being more receptive to infections. Therefore, further research is crucial, particularly, if the therapy leads to severe, life-threatening conditions for the patients after 24 weeks.

fortlaufende Studien: 2 RCTs mit Langzeitevidenz über 24 Wochen

Several ongoing studies (Table A-7 and Table A-8) will provide further data on effectiveness and safety of MSCs compared to placebo. Two studies will provide long-term follow-up data for week 52 and week 104, respectively, and thus might fill the gap in the existing evidence. However, both studies are sponsored by the manufacturer TiGenix. The study (NCT01541579) assessing follow-up data until week 104 reported an expected study completion date of May 2017. However, by February 2018 the results are still pending.

weitere Forschung notwendig:

Moreover, the following questions still remain unanswered, thus, further research is needed in these areas:

- direkter Vergleich der Zelltypen: Direct comparisons of the different cell types, i.e. autologous versus allogeneic as well as adipose-tissue-derived versus bone-marrow-derived allogeneic MSCs [9, 19, 20].
- Evidenz für optimale Stammzelldosierung: The optimal stem cell dose for allogeneic MSC-transplantation also with relation to stages of the disease remains unclear [9, 17].
- Evidenz für optimale Verabreichung der Stammzellen: Optimal modalities (oral, intravenous, arteriovenous, local injection) for allogeneic MSC-administration [20]. A randomized controlled, phase III study (NCT00482092) will investigate the effect of intravenous MSC-administration on draining fistulas (Table A-7).
- Evidenz für Therapiekombinationen: Evidence if combinations of medical and surgical treatment approaches are superior to either single treatment alone [27].
- direkte Vergleiche von MSC-Therapie zu z. B. chirurgischen Eingriffen: Direct comparisons of allogeneic MSC-therapy to other treatments than placebo, i.e. biologic therapy or alternative surgical treatment options, such as fibrin glue [10].
- Evidenz zu MSCs bei PatientInnen mit rektovaginalen Fisteln: Effectiveness and safety of allogeneic MSCs in rectovaginal fistulas in CD [9]. A small, single-arm, phase I study (NCT02677350) will also include CD patients with rectovaginal patients (Table A-8).
- Evidenz zu MSCs bei schwangeren und/oder stillenden Frauen: In female patients of child-bearing age with established CD, the cumulative probability of developing perianal fistulas following delivery is lower as in the general CD population [27]. Nevertheless, evidence for effectiveness and safety of MSC-treatments in pregnant women is needed.

Conclusion

MC gesellschaftliche Kosten, MSC als Zusatztherapie bei refraktären pts?

CD-associated complex perianal fistulas are associated with high recurrence rates. In combination with the productive age of the patients, the disease leads to additional societal costs. Therefore, MSC-therapy was suggested as an add-on therapy in patients, refractory to current standard treatments.

bisherige Evidenz: 2 RCTs (231 pts), größere Chance für kombinierte Remission, keine beweiskräftigen Lebensqualität-verbesserungen

The current evidence of allogeneic MSC-therapy versus placebo includes two RCTs with a total number of 231 patients. Patients receiving MSCs are more likely to achieve combined remission, while inconclusive results of QoL of the patients, indicating no QoL improvements through MSC-therapies, were reported. No evidence is available comparing allogeneic MSC-therapy to other treatments than placebo.

keine Langzeitdaten über 24 Wochen, problematisch in Bezug auf Malignität

There are concerns about the lacking long-term outcomes beyond 24 weeks, especially for safety with regard to the correlation of allogeneic MSC-therapies and the development of malignancies [34, 35]. This concern is not sufficiently addressed in existing clinical trials.

im Vergleich zu vorhandenen Reviews: Fokus auf allogenen MSCs bei komplexen perianalen Fisteln

The present systematic review focused solely on the effect of allogeneic MSCs on complex perianal fistulas caused by CD. In comparison, Cao et al. [18] reported the effect of MSCs on fistulising CD for both, autologous and allogeneic stem cells. Garcia-Olmo et al. [5] investigated the effect of autologous and allogeneic MSCs on perianal fistulas, including different treatment modalities. In Ye et al. [36] the efficacy and safety of autologous and allogeneic MSCs in refractory CD, without focusing on perianal disease, were investigated. In Grégoire et al. [20] the effect of autologous and allogeneic MSCs on irritable bowel diseases, not solely on CD, was reported. Overall, non of the present systematic reviews focused explicitly on complex perianal CD-associated fistulas.

insgesamt schwache Evidenz: MSCs zurzeit nicht als Zusatztherapie empfohlen

Existing evidence concludes that QoL is not improved, while remission is. This is very inconclusive. Hence, based on this data, currently, one cannot recommend the intervention as an add-on treatment to existing treatment options for complex perianal fistulas caused by CD.

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according to choice is highlighted.

Table 9-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is *not* sufficient to prove that allogeneic MSCs in patients with complex perianal fistulas caused by CD who are refractory or intolerant to standard medical therapy are …

unsichere Evidenz, dass MSCs effektiver und sicherer sind als Placebo-Therapien

> … more effective, because despite the slight improvement in combined remission, the data do not indicate improvement of QoL. Hence, the effectiveness of MSC-therapy in comparison to placebo remains uncertain.
>
> … safer as placebo, because the occurrence of adverse events, except immunity-related adverse events, were similar in the treatment and the control group. Thus, MSC-therapy is meant to be as safe as, but not safer as the placebo-procedure.

No evidence was available for comparing MSC-therapy to treatments other than placebo, i.e. fibrin glue or fistula plugs.

Placebo bisher einziger untersuchter Komparator

New study results will potentially influence the effect and safety estimate considerably. The re-evaluation is recommended in 2022 when further ongoing studies will be finished and thereby will bring additional evidence for long-term effectiveness and safety beyond 24 weeks.

Re-evaluation für 2022 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Allogeneic expanded mesenchymal stem cells: Results from randomised controlled trials

Author, year	Panés et al., 2016 [11]	Molendijk et al., 2015 [12]
Country	Spain, Belgium, Austria, Canada, Germany, France, Italy, Israel	The Netherlands
Sponsor	TiGenix	DigestScience Foundation
Intervention/Product	Allogeneic expanded adipose-derived MSCs (Davardstrocel, Cx601) **IG:** 120 million cells for a maximum of 3 fistulas (n=107)	Allogeneic expanded bone-marrow-derived MSCs **IG1**: 1 x 10^7 (10 million cells) (n=5) **IG2**: 3 x 10^7 (30 million cells) ((n=5) **IG3**: 9 x 10^7 (90 million cells) (n=5)
Comparator	Placebo, namely 24 mL saline solution (n=105)	Placebo, namely 0.9% NaCl/5% human albumin solution with no cells (n=6)
Study design	Randomised, double-blind, parallel-group, placebo-controlled study (NCT01541579)	Randomised, double-blind, placebo-controlled study (NCT01144962)
Number of patients	212[3]	21
Inclusion criteria	✿ ≥18 years of age ✿ CDAI score of ≤220: non-active or mildly active luminal disease ✿ Complex perianal fistulas ✿ Refractory to at least one of the treatments: antibiotics ciprofloxacin or metronidazole, immunomodulators azathioprine, 6-mercaptopurine, or methotrexate or induction or maintenance of anti-TNF agents	✿ ≥18 years of age ✿ CDAI score of <250 at screening and baseline ✿ Actively draining perianal fistulas ✿ Refractory to conventional therapies, namely anti-TNF agents, antibiotics, steroids, thiopurines, methotrexate, surgery or a combination thereof ✿ 1-2 internal openings and 1-3 fistula tracts ✿ Diagnosis of CD at least 3 months before enrollment ✿ Stable dose of current drugs (mesalamine and steroids ≥4 weeks; immunosuppressive drugs ≥8 weeks; anti-TNF agents ≥8 weeks)
Exclusion criteria	✿ Rectovaginal fistulas ✿ Active severe proctitis ✿ Rectal or anal stenosis ✿ Abscess ✿ Previous fistula surgery other than drainage or seton placement ✿ Diverting stomas ✿ Collections >2 cm if not properly drained during preparation visit ✿ No previous treatment for perianal fistulizing CD, including antibiotics ✿ Treatment with corticosteroids within 4 weeks before study start	✿ Rectovaginal fistulas ✿ Active luminal disease ✿ Anal or rectal stricture ✿ Acute perianal infection ✿ Need for immediate surgery ✿ Complex perianal fistulas with >2 internal openings ✿ Opportunistic infection within 6 months before screening or serious infection in previous 3 months ✿ Infection and need for antibiotic treatment ✿ Use of antibiotics after trial inclusion ✿ Use of any investigational drug within 1 month before screening or within 5 half-lives of the investigational agent ✿ Change in concomitant medication ✿ Not able or willing to undergo MRI ✿ Renal or hepatic failure ✿ Documented human immunodeficiency virus infection, active hepatitis B, C, or tuberculosis ✿ Malignancy within past 5 years ✿ History of lymphoproliferative disease ✿ Pregnancy, breastfeeding or no adequate contraception

[3] The number of patients was not clearly defined. In clinicaltrials.gov the number of patients included was 278. In the study 289 patients were assessed for eligibility and 212 patients were randomly assigned.

Author, year	Panés et al., 2016 [11]	Molendijk et al., 2015 [12]
The mean age of patients (years):	**IG**: 39.0; **CG**: 37.60	**IG1**: 40.4; **IG2**: 40.8; **IG3**: 33.4; **CG**: 37.3
Follow-up (weeks)[4]	After intervention: ❁ 12 weeks ❁ 24 weeks	After intervention: ❁ 12 weeks ❁ 24 weeks
Loss to follow-up, n (%)	**IG**: 19 (17.8); **CG:** 22 (21)	0 (0)
Outcomes		
Efficacy		
QoL: **(1) (s)IBDQ** (high is better) **(2) SF-36** (high is better) **(3) PDAI** (low is better) **(4) CDAI** (lower is better)	**(1) IBDQ scores (week 0 to 24)[5]:** *Total:* **IG**: 173.5 to 178.3; **CG**: 169.4 to 174.7 *Bowel function:* **IG**: 57.1 to 57.2; **CG**: 56.8 to 56.4 *Emotional status:* **IG**: 63.2 to 64.7; **CG**: 61.5 to 63.9 *Systemic symptoms:* **IG**: 25.9 to 26.2; **CG**: 25.0 to 25.6 *Social function:* **IG**: 27.7 to 29.5; **CG:** 26.5 to 28.4 **(2) SF-36 scores: NA** **(3) PDAI scores:** Week 0 to 12: **IG**: 6.7 to 3.9; **CG**: 6.5 to 4.9 Week 0 to 24: **IG**: 6.7 to 4.4; **CG**: 6.5 to 5.1 **(4) CDAI scores (week 0 to 24):** *Total:* **IG**: 87.8 to 92.5; **CG**: 93.3 to 94.1 *Number of liquid stools:* **IG**: 9.8 to 9.5; **CG**: 9.3 to 10.0 *Abdominal pain:* **IG**: 1.6 to 2.7; **CG**: 2.0 to 3.0 *General well being:* **IG**: 2.7 to 3.1; **CG**: 3.2 to 3.3	**(1) sIBDQ scores (week 0 to 24):** **IG1**: 61.0 to 60.0; **IG2**: 48.8 to 51.7; **IG3**: 52.8 to 50.5; **CG**: 55.3 to 59.3 **(2) SF-36 scores (week 0 to 24):** *Physical functioning:* **IG1**: 96.0 to 97.0; **IG2**: 75.0 to 87.5; **IG3**: 92.0 to 92.0; **CG**: 85.0 to 86.7 *Physical role functioning:* **IG1**: 80.0 to 73.8; **IG2**: 53.8 to 51.6; **IG3**: 75.0 to 71.3; **CG**: 69.8 to 70.8 *Bodily pain:* **IG1**: 91.6 to 81.3; ; **IG2**: 71.6 to 67.5; **IG3**: 74.6 to 77.8; **CG**: 62.2 to 74.2 *General health perceptions:* **IG1**: 68.0 to 61.6; **IG2**: 33.4 to 30.5; **IG3**: 64.6 to 60.2; **CG**: 58.2 to 51.8 *Vitality:* **IG1**: 73.8 to 70.0; **IG2**: 38.8 to 39.1; **IG3**: 62.5 to 50.0; **CG**: 64.0 to 63.5 *Social functioning:* **IG1**: 90.0 to 82.5; **IG2**: 57.5 to 62.5; **IG3**: 77.5 to 80.0; **CG**: 87.5 to 87.5 *Emotional role functioning:* **IG1**: 85.0 to 80.0; **IG2**: 51.7 to 62.5; **IG3**: 68.3 to 71.7; **CG**: 80.6 to 79.2 *Mental health:* **IG1**: 81.0 to 85.0; **IG2**: 51.0 to 53.8; **IG3**: 70.0 to 66.0; **CG**: 79.2 to 80.0 **(3) PDAI scores (estimation based on graphical representation[6]):** week 0 to 12: **IG1**: 4.4 to 3.2; **IG2**: 3.8 to 1.0; **IG3**: 5.0 to 3.9; **CG**: 5.2 to 5.3 Week 0 to 24: **IG1**: 4.4 to 1.8; **IG2**: 3.8 to 1.5 (significant, p=0.03); **IG3**: 5.0 to 4.3; **CG**: 5.2 to 3.9 **(4) CDAI scores (week 0 to 24):** **IG1**: 80.2 to 64.8; **IG2**: 203.3 to 171.3; **IG3**: 57.3 to 80.8; **CG**: 75.8 to 58.0
Fistula relapse-free survival	NA	NA

[4] In week 12 efficacy data were assessed. In week 24 both, efficacy and safety data were assessed.

[5] All QoL scores in Panés et al. were reported for the modified intention-to-treat population (204 pts not the total intention-to-treat population of 212).

[6] Figure 3 of Molendijk et al. [2].

Author, year	Panés et al., 2016 [11]	Molendijk et al., 2015 [12]
Combined remission, n (%)	Week 24[7]: **IG**: 53 (50); **CG**: 36 (34) (significant difference 15.2%, 97.5% CI 0.2-30.3; p=0.024)	Week 12[8]: **IG1**: 2 (40); **IG2**: 4 (80); **IG3**: 1 (20); **CG**: 2 (33.3) (significant difference IG2 vs. CG: p=0.06)
Response, n (%)	Week 24[9]: **IG**: 71 (66); **CG**: 56 (53) (difference 13.0%, 97.5% CI -0.1-26.1; p=0.054)	NA
Safety		
TEAE, n (%)	Total number of adverse events per treatment group[10]: **IG**: 49 (48); **CG**: 44 (43) Anal abscess: **IG**: 12 (12); **CG**: 13 (13) Diarrhoea: **IG:** 7 (7); **CG**: 3 (3) Abdominal pain: **IG**: 4 (4); **CG**: 6 (6) Proctalgia (cramps in the anal region): **IG**: 13 (13); **CG**: 11 (11) Nasopharyngitis (common cold): **IG**: 10 (10); **CG**: 5 (5) Fistula: **IG**: 3 (3); **CG**: 6 (6)	Total number of adverse events per treatment group[11]: **IG1**: 17 (340); **IG2**: 9 (180); **IG3:** 10 (200); **CG:** 14 (233) Anal abscess: **IG1**: 1 (20); **IG2**: 1 (20); **IG3**: 1 (20); **CG**: 1 (16.7) Diarrhea: **IG1**: 1 (20); **CG**: 1 (16.7) Abdominal pain: **IG1**: 1 (20); **IG2**: 1 (20); **IG3**: 3 (60) Painful perianal swelling: **IG1**: 1 (20); **CG**: 3 (50) Not painful perianal swelling: **IG1**: 1 (20); **CG**: 1 (16.7) Nasopharyngitis (common cold): **IG1**: 5 (100); **IG2**: 2 (40); **IG3**: 1 (20); **CG**: 2 (33.3) Pyrexia (fever (29.7°C)): **IG2**: 1 (20) Blood from fistula: **IG1**: 1 (20) Painful anal sphincters: Fissura ani: **IG1:** 1 (20) Anal blood: **CG:** 1 (16.7) Anal pus: **IG2**: 1 (20) Thrombosed haemorrhoid: **CG**: 1 (16.7) Pimples buttocks: **IG3**: 1 (20); **CG**: 1 (16.7) Pimples abdomen: **CG:** 1 (16.7) Mild activity CD: **IG1**: 1 (20); **CG**: 1 (16.7) Exacerbated activity CD: **IG1**: 1 (20) Flatulence: **CG**: 1 (16.7) Nausea: **IG3**: 1 (20) Vomiting: **IG3**: 1 (20) Lack of appetite: **IG1**: 1 (20) Pneumonia: **IG2**: 1 (20) Otitis: **IG2**: 1 (20) Headache: **IG2**: 2 (40) Back pain: **IG3**: 1 (20) Rosacea: **IG1**: 1 (20) Cold sore: **IG1**: 1 (20) Postoperative anal pain and pus and/or bloody discharge from the fistula or anus: 21 (100)

[7] n presents the number of patients who achieved closure of all treated external openings and had an absence of collections ≥2 cm; Percentages present the proportion of patients with combined remission of the total number of patients per treatment group.

[8] MRI assessment was done only at week 12, thus, combined remission could only be measured in accordance with the definition with 12 weeks of follow-up; n presents the number of all individual fistulas demonstrate the absence of discharge and of collections ≥2 cm; percentages present the proportion of completely healed fistulas of the total number of all individual fistulas.

[9] n presents the number of patients who achieved closure of at least 50% of all treated external openings; percentages present the proportion of patients with a respond of the total patients per treatment group.

[10] Presented are TEAEs that have occurred in ≥5% of patients of all treatment groups up to 24 weeks of follow-up.

[11] If a treatment group is not mentioned for a specific AE, this AE did not occur in any patient of that treatment group.

Author, year	Panés et al., 2016 [11]	Molendijk et al., 2015 [12]
TRAE, n (%)	Anal abscess[12]: **IG**: 6 (6); **CG**: 9 (9) Proctalgia (cramps in the anal region): **IG**: 5 (5); **CG** 9 (9) Procedural pain: **IG**: 1 (1); **CG**: 2 (2) Fistula discharge: **IG**: 1 (1); **CG**: 2 (2) Induration: **IG**: 0; **CG**: 2 (2)	NA
STEAE, n (%)	Anal abscess: **IG**: 9 (9); **CG**: 7 (7)	NA
STRAE, n (%)	Anal abscess[13]: **IG**: 5 (5); **CG**: 5 (5) Proctalgia (cramps in the anal region): **IG**: 0; **CG**: 1 (1) Anal inflammation: **IG**: 0; **CG**: 1 (1) Liver abscess: **IG**: 0; **CG**: 1 (1)	Adenocarcinoma[14]: **IG1**: 1 (20)

Abbreviations: *CD = Crohn's disease, CDAI = Crohn's Disease Activity Index, TNF = tumour necrosis factor, IG = interventional group, CG = control group, PDAI = Perianal Disease Activity Index, CI = confidence interval, SD = standard deviation, (s)IBDQ = (short-form) Irritable Bowel Disease Questionnaire, NA = not available, p = p-value, pts = patients, QoL = quality of life, TEAE = treatment-emerged adverse event, TRAE = treatment-related adverse event, STEAE = severe treatment-emerged adverse event, STRAE = severe treatment-related adverse event, n = number, MSC = mesenchymal stem cells*

Table A-2: Allogeneic expanded mesenchymal stem cells: Results from an observational study

Author, year	de la Portilla et al., 2013 [13]
Country	Spain
Sponsor	TiGenix
Intervention/Product	Allogeneic expanded adipose-derived MSCs: 20 million cells/draining fistula tract additional 40 million cells/draining fistula tract if fistula closer was incomplete at week 12
Comparator	None
Study design	Prospective interventional single-arm study (NCT01372969)
Number of pts	24
Inclusion criteria	✿ ≥18 years of age ✿ CDAI score ≤200: non-active luminal CD ✿ Diagnosis of CD at least 12 months before enrolment ✿ Presence of persistent and active complex perianal fistula with <3 fistulous tracts and/or external openings ✿ Good general state of health
Exclusion criteria	✿ Rectovaginal, anal, or non-perianal enterocutaneous fistulas ✿ Any abscess before start of treatment ✿ Presence of setons unless removed prior to treatment ✿ Rectal and/or anal stenosis ✿ Severe proctitis or dominant active luminal disease requiring immediate therapy ✿ Treatment with anti-TNF agent in previous 8 weeks or tacrolimus or cyclosporine in previous 4 weeks ✿ Congenital or acquired immunodeficiency and allergy to anaesthetics or MRI contrast
Age of patients (yrs)	36.0

[12] Presented are TRAEs and STEAEs that have occurred in ≥2% of patients of all treatment groups up to 24 weeks of follow-up.

[13] All STRAEs are reported that occurred up to week 24 of follow-up.

[14] One patient treated with 10 million MSCs developed an adenocarcinoma of the cecum with peritoneal carcinomatosis. The correlation between the intervention and the occurrence of an adenocarcinoma was unclear.

Author, year	de la Portilla et al., 2013 [13]
Follow-up (weeks)	After intervention: • 12 weeks • 24 weeks
Loss to follow-up, n (%)	8[15]
Outcomes	
Efficacy (n=22)	
QoL: (1) (s)IBDQ (high is better) (2) SF-36 (high is better) (3) PDAI (low is better) (4) CDAI (lower is better)	(1) (s)IBDQ: NA (2) SF-36 scores: NA (3) PDAI scores (estimations[16]): Week 0: 6.2; Week 12: 5.2; Week 24: 3.9 (significantly decreased at week 24 of more than 37% compared to baseline mean value; p=0.0076) (4) CDAI scores (estimations): Week 0: 80; Week 12:91; Week 24:80
Fistula-relapse free survival	NA
Combined remission[17], n (%)	Week 12: 6 (30) of 24 of 20 patients Week 24: NA
Response, n (%)	NA
Safety (n=24)	
TEAE, n (%)[18]	• Proctalgia (cramps in the anal region): 2 (8.3) • Pyrexia (fever): 4 (16.7) • Anal abscess: 4 (16.7) • Anal fistula infection: 2 (8.3) • Increase in C reactive protein: 3 (12.5) • Musculoskeletal and connective tissue disorders: 3 (12.5) • Anxiety: 3 (12.5)
TRAE, n (%)	• Anal abscess: 3 (12.5) • Pyrexia (fever): 1 (4.2) • Uerine leiomyoma: 1 (4.2)
STEAE, n (%)	NA
STRAE, n (%)	• Pyrexia (fever): 1 (4.2) • Perianal abscess: 1 (4.2)

Abbreviations: *CD = Crohn's disease, CDAI = Crohn's Disease Activity Index, TNF = Tumour necrosis factor, MRI = Magnetic Resonance Imaging, MSS = Magnetic Resonance Imaging Score of Severity, p = p-value, pts = patients, TEAE = treatment-emerged adverse event, TRAE = treatment-related adverse event, STEAE = severe treatment-emerged adverse event, STRAE = severe treatment-related adverse event, PDAI = Perianal Disease Activity Index, NA = not available, MSC = mesenchymal stem cells*

[15] Of 24 treated patients, 16 patients completed the study period and 8 were prematurely withdrawn for various reasons: 2 dropped out due to protocol deviations (1 patient received antibiotic treatment for more than 4 weeks; 1 patient did not perform the screening pregnancy test at screening or visit). Other premature withdrawal reasons were presence of adverse event (perianal abscess) in 2 patients and outbreak of the underlying Crohn's disease in 4 cases.

[16] Data of PDAI- and CDAI-scores were estimated from Figure 2 of de la Portilla et al. [3].

[17] Combined remission was defined as the fistula closure assessed via clinical and MRI assessment.

[18] Presented are TEAEs and TRAEs that have been occurred in >1 patient of the full analysis population (24 patients).

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [37] and in the Guideline of EUnetHTA [14].

Table A-3: Risk of bias – study level (randomised studies), see [33]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
ADMIRE I, [11]	yes	yes	unclear[19]	unclear[20]	yes	no[21]	moderate
NCT01144962, [12]	unclear[22]	unclear[23]	unclear[24]	Unclear[25]	no[25]	no[26]	high

[19] No information about the blinding of the patients was reported.

[20] The surgeon was unmasked, while the clinicians assessing the efficacy were blinded.

[21] Possible bias due to treatment effects of concomitant therapies.

[22] No information about the adequate generation of the randomisation was reported.

[23] No information about the adequate allocation concealment was given.

[24] No information about the blinding was reported.

[25] No serious adverse events have been reported.

[26] Possible bias due to small sample size and treatment effects of concomitant therapies.

Table A-4: Risk of bias – study level (case series), see [3]

Study reference/ID	De la Portilla, 2013, [13]
Study objective	
1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section?	yes
Study design	
2. Was the study conducted prospectively?	unclear
3. Were the cases collected in more than one centre?	yes
4. Were participants recruited consecutively?	unclear
Study population	
5. Were the characteristics of the participants included in the study described?	partial[27]
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	yes
7. Did participants enter the study at a similar point in the disease?	unclear
Intervention and co-intervention	
8. Was the intervention clearly described in the study?	yes
9. Were additional interventions (co-interventions) clearly described?	partial[28]
Outcome measures	
10. Were relevant outcome measures established a priori?	yes
11. Were outcome assessors blinded to the intervention that patients received?	yes
12. Were the relevant outcomes appropriate objective/subjective methods?	no
13. Were the relevant outcome measures made before and after the intervention?	no[29]
Statistical analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	yes
Results and conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	yes
16. Were losses to follow-up reported?	no
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	partial
18. Were the adverse events reported?	yes
19. Were the conclusions of the study supported by the results?	no[30]
Competing interests and sources of support	
20. Were both competing interest and source of support for the study reported?	yes
Overall Risk of bias	high

[27] Not all relevant patient characteristics were reported.

[28] It can be assumed that there might be concomitant therapies like in other bigger studies.

[29] Outcome measures were made 12 and 24 weeks after the interventional process.

[30] The intervention was reported as safe, even if two patients left the study, due two severe adverse events (i.e. anal abscess and pyrexia).

Table A-5: Evidence profile: efficacy and safety of allogeneic mesenchymal stem cells in Crohn's disease patients with complex perianal fistulas [4]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allogeneic mesenchymal stem cells	Placebo	Relative (97.5% CI)	Absolute (97.5% CI)		
Quality of life (assessed with: IBDQ)												
2	randomised trials	very serious [a,b]	serious [c]	not serious	not serious	none	Panés (n=204): IG vs. CG: improvement + 4.8 vs. + 5.3 points; Molendijk (n=21): IG vs. CG: deterioration -0.1 (based on self-calculated mean of 3 IGs) + 4.0 points				⨁◯◯◯ VERY LOW	CRITICAL
Quality of life (assessed with: PDAI)												
2	randomised trials	serious [a,d]	not serious	not serious	not serious	none	Panés (n=204): IG vs. CG: improvement -2.3 vs -1.4 points; Molendijk (n=21): IG vs. CG: improvement -1.9 (based on self-calculated mean of 3 IGs) vs. -1.3 points				⨁⨁⨁◯ MODERATE	CRITICAL
Quality of life (assessed with: CDAI)												
2	randomise d trials	serious [a,d]	serious [c]	not serious	not serious	none	Panés (n=204): IG vs. CG: deterioration + 4,7 vs. +0.8 points; Molendijk (n=21): IG vs. CG: improvement -8.0 (based on self-calculated mean of 3 IGs) vs. -17.8 points				⨁⨁◯◯ LOW	CRITICAL
Quality of life (assessed with: SF-36)												
1	randomised trials	very serious [a,b]	not serious [e]	not serious	serious [f]	none	Molendijk (n=21): IG vs. CG: deterioration -1.14 vs. improvement +0.8 points (self-calculated means across 8 health states)				⨁◯◯◯ VERY LOW	CRITICAL
Combined remission: 120 million adipose-tissue-derived MSCs (follow up: mean 24 weeks; assessed with: clinical and MRI assessment)												
1	randomised trials	not serious [g]	not serious [e]	not serious	serious [h]	none	107	105	-	mean 15% more (0.2 more to 30.2 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Combined remission: different dosages bone-marrow-derived MSCs (follow up: mean 12 weeks; assessed with: clinical and MRI assessment)												
1	randomised trials	serious [a]	serious [c]	serious [i]	serious [f]	none	Molendijk (n=21): IG1 (10 million cells): 2/5 pts (40%), IG2 (30 million cells): 4/5 pts (80%), IG3 (90 million cells): 1/5 pts (20%), CG: 2/6 pts (33.3%); significant difference IG2 vs. CG: p=0.06				⨁◯◯◯ VERY LOW	CRITICAL
Response to 120 million adipose-tissue-derived MSCs (follow up: mean 24 weeks; assessed with: closure of at least 50% of all treated external openings)												
1	randomised trials	not serious [g]	not serious [e]	not serious	serious [h]	none	107	105	-	mean 13% more (0.1 fewer to 26.1 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Severe treatment-related adverse events (follow up: mean 24 weeks)												
2	randomised trials	serious [a]	not serious	not serious	serious [f]	none	6/118 (5.1%)	8/108 (7.4%)	RR 0.69	23 fewer per 1,000	⨁⨁◯◯ LOW	CRITICAL

Abbreviations: *CDAI = Crohn's Disease Activity Index, CG = Control group, CI = Confidence interval, IBDQ = Irritable Bowel Disease Questionnaire, IG = Interventional group, N = Number, PDAI = Perianal Disease Activity Index, pts = Patients, RCT = Randomised controlled trial, RR = Risk ratio, SF-36 = Short-form 36, STRAE = Severe treatment-related adverse event*

Explanations

[a] *Study with high risk of bias included*
[b] *Subjective outcome measure*
[c] *Heterogeneity of results*
[d] *Clinical assessment*
[e] *Not applicable (one study)*
[f] *Small sample size*
[g] *Study with moderate risk of bias*
[h] *Wide confidence intervals*
[i] *Differences in inclusion criteria (definition of complex fistula + CDAI score)*

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Applicability table

Table A-6: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The study population of the included studies differed with regard to the CDAI score. In the three studies, the CDAI scores for inclusion in the study ranged from ≤200 to ≤250, indicating different severity of the disease at study start. In addition, the definition of complex perianal fistulas differed from the definition of the American Gastroenterological Association in two studies. Thus, the complexity of the fistula tracks might not be the same for every study, even though the studies explicitly stated that they include patients with complex perianal fistulas. The mean age of participants was consistent across the studies (range: 37-41 years) and was reflective for the usual time of diagnosing perianal fistulas. All studies delivered evidence from European populations.
Intervention	The interventions differed in allogeneic stem cell type and dosage. Two studies administered adipose-derived mesenchymal stem cells, while the third study assessed bone-marrow-derived stem cells. Currently, there are no direct comparisons of these two cell types. The dosages of the studies ranged from 10 million to 120 million cells (for a maximum of three fistula tracks). In one study the second dose of cells was administered in case of lacking response to the first dose. Based on the dose-escalating study [12], a higher dosage is not necessarily associated with better effects on patients outcomes. However, further research is needed for the long-term follow-up (>24 weeks).
Comparators	In both RCTs, placebo was used as the comparator. In one study, placebo was defined as saline solution, while in the second RCT, it was defined as human albumin solution. There are suggestions that fistula track filling material, such as fistula plug could be used as a comparator treatment. However, there is no evidence of MSC-therapy compared to other treatments than placebo.
Outcomes	Not all critical efficacy endpoints were reported by all included studies. With regard to combined remission, Panés et al. reported it for 24 weeks, while the other two studies assessed it for 12 weeks. Furthermore, response to treatment was only reported by Panés et al. There were difference in the reported safety outcomes, and measurements were not clearly described. Severe treatment-related adverse events were only assessed in two studies.
Setting	One RCT was conducted in various hospitals in Spain, Belgium, Austria, Germany, France, Italy, Canada, and Israel. The other RCT was conducted at the Leiden University Medical Center in the Netherlands. The single-arm study was conducted in the Virgen del Rocio University Hospital in Spain. Two out of the three studies were sponsored by the manufacturer TiGenix. The Dutch study was funded by the DigestScience Foundation, which is also sponsored by one manufacturer (Takeda).

List of ongoing randomised controlled trials

Table A-7: List of ongoing randomised controlled trials of adult human allogeneic mesenchymal stem cells

Identifier/Trial name	Patient population	Estimated enrolement	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03279081 Adult phase-III randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess efficacy and safety of Cx601, allogeneic expanded adipose-derived stem cells for complex perianal fistula(s) in Crohn's disease. ADMIRE-CD-II	Complex perianal fistula(s) associated with Crohn's disease	326	Adult allogeneic expanded adipose-derived stem cells (eASC), Cx601	Placebo	Combined Remission of complex perianal fistula(s) at week 24	October 1, 2021	TiGenix S.A.U.
NCT01541579 A phase III, randomized, double-blind, parallel group, placebo-controlled, multicentre study to assess efficacy and safety of eASCs for the treatment of perianal fistulising Crohn's disease over a period of 24 weeks and an extended follow-up period up to 104 weeks.	Complex anal fistulas associated with Crohn's disease	278	Allogeneic eASCs 5 million cells/mL, Cx601	Placebo	Combine remission of perianal fistulising Crohn's: clinical assessment of closure of all treated external openings that were draining at baseline despite gentle finger compression at week 24, and absence of collections > 2 cm of the treated perianal fistulas confirmed by centrally blinded MRI assessment by week 24	May 2017	TiGenix S.A.U.
NCT00482092 A phase III, multicenter, placebo-controlled, randomized, double-blind study to evaluate the safety and efficacy of PROCHYMAL® (ex vivo cultured adult human mesenchymal stem cells) intravenous infusion for the induction of remission in subjects experiencing treatment-refractory moderate-to-severe Crohn's disease	Treatment-resistant Moderate-to-severe Crohn's Disease	330	PROCHYMAL® adult human mesenchymal stem cells Intravenous infusion of suspension of adult human mesenchymal stem cells, a total of 1200 million (high dose) or 600 million (low dose) cells infused in four visits over two weeks.	Placebo	Disease remission (CDAI at or below 150) [Time Frame: 28 days] Reduction in number of draining fistulas [Time Frame: 28 days]	July 2018	Mesoblast International Sàrl

Table A-8: List of ongoing observational trials of adult human allogeneic mesenchymal stem cells

Identifier/Trial name	Patient population	Estimated enrolement	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT02677350 A phase I, pilot trial to evaluate the safety and efficacy of injection of allogeneic mesenchymal bone-marrow-derived human stem cells in patients with fistulising Crohn's disease. GALENE	Complex or multiple perianal or rectovaginal fistulas	20	Allogeneic bone marrow-derived human mesenchymal stem cells (hMSCs), 2 x 10^7 hMSCs at week 4 intervals for a maximum of 4 treatment sessions	None	Until 16 months: treatment-emergent adverse event rates, infections, hospitalizations or surgical intervention; physical examination; vital signs; laboratory tests (biochemistry, haematology, urinalysis)	March 2025	Joshua M Hare, University of Miami

Literature search strategies

Search strategy for Cochrane

Search Name: Mesenchymal Stem Cells for Crohn's Fistula	
Search Date:13.12.2017	
ID	Search
#1	MeSH descriptor: [Rectal Fistula] explode all trees
#2	(anal or anus or ano* or peri*an* or rect*) near fistul* (Word variations have been searched)
#3	MeSH descriptor: [Crohn Disease] explode all trees
#4	Crohn* (Word variations have been searched)
#5	Crohn* near fistula* (Word variations have been searched)
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Mesenchymal Stromal Cells] explode all trees
#8	MeSH descriptor: [Mesenchymal Stem Cell Transplantation] explode all trees
#9	(mesenchymal or stroma*) near cell* (Word variations have been searched
#10	MSC:ti,ab,kw
#11	#7 or #8 or #9 or #10
#12	#6 and #11
#13	stem cell* near ((anal or anus or ano* or peri?an* or rect*) near (fistul* or Crohn*)) (Word variations have been searched)
#14	Alofisel (Word variations have been searched)
#15	TiGenix (Word variations have been searched)
#16	"Living Medicines" (Word variations have been searched)
#17	Cx*601 (Word variations have been searched)
#18	#12 or #13 or #14 or #15 or #16 or #17
Total: 18 Hits	

Search strategy for CRD

Search Name: Stem Cell Therapy for Crohns Fistula	
Search Date:13.12.2017	
ID	Search
#1	MeSH DESCRIPTOR Rectal Fistula EXPLODE ALL TREES
#2	((anal OR anus OR ano* OR peri*an* OR rect*) NEAR fistul*)
#3	MeSH DESCRIPTOR Crohn Disease EXPLODE ALL TREES
#4	(Crohn*)
#5	(Crohn* NEAR Fistul*)
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	MeSH DESCRIPTOR Mesenchymal Stromal Cells EXPLODE ALL TREES
#8	MeSH DESCRIPTOR Mesenchymal Stem Cell Transplantation EXPLODE ALL TREES
#9	((mesenchymal OR stroma*) NEAR cell*)
#10	#7 OR #8 OR #9
#11	#6 AND #10
#12	(stem cell* NEAR (fistul* OR Crohn*))
#13	(Alofisel)
#14	(cx601)
#15	(cx-601)
#16	(TiGenix)
#17	(Living Medicines)
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
Total: 18 Hits	

Search strategy for Embase

Search Date:13.12.2017		
No.	Query Results	Results
#18	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	524
#17	'living medicines'	4
#16	tigenix:df,dn,mn,tn	35
#15	'cx 601'	1
#14	cx601	8
#13	alofisel	1
#12	('stem cell*' NEAR/5 (anal OR anus OR ano* OR peri*an* OR rect*) NEAR/5 (fistul* OR crohn*)):ti,ab	30
#11	#6 AND #10	467
#10	#7 OR #8 OR #9	134,498
#9	((mesenchymal OR stroma*) NEAR/5 cell*):ti,ab	133,999
#8	'mesenchymal stem cell transplantation'/mj/exp	5,642
#7	'mesenchymal stroma cell'/mj/exp	4,673
#6	#1 OR #2 OR #3 OR #4 OR #5	83,321
#5	'crohn* fistula'	16
#4	crohn*:ti,ab	64,666
#3	'crohn disease'/mj/exp	42,469
#2	((anal OR anus OR ano* OR peri*an* OR rect*) NEAR/5 fistul*):ti,ab	14,527
#1	'anus fistula'/mj/exp	2,419

Search strategy for Ovid Medline

Search Date:13.12.2017		
No.	Query Results	Results
1	exp Rectal Fistula/	5,927
2	((anal or anus or ano* or peri?an* or rect*) adj5 fistul*).mp.	1,0217
3	exp Crohn Disease/	38,879
4	Crohn*.mp.	54,313
5	Crohn$2 fistula*.mp.	96
6	1 or 2 or 3 or 4 or 5	62,897
7	exp Mesenchymal Stromal Cells/	30,630
8	exp Mesenchymal Stem Cell Transplantation/	9,983
9	((mesenchymal or stroma*) adj5 cell*).mp.	117,488
10	7 or 8 or 9	117,488
11	6 and 10	333
12	(stem cell* adj5 ((anal or anus or ano or peri?an* or rect*) adj5 (fistul* or Crohn*))).mp.	21
13	Alofisel.ti,ab.	0
14	Cx?601.ti,ab.	14
15	TiGenix.ti,ab.	3
16	Living Medicines.ti,ab.	0
17	11 or 12 or 13 or 14 or 15 or 16	346
18	remove duplicates from 17	299

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