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Efficacy of mesenchymal stem cell-based therapies in the treatment of perianal fistulizing Crohn's disease: a systematic review and meta-analysis

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Abstract

Background Perianal lesions of Crohn's disease (CD) are complex and disabling conditions. Mesenchymal stem cell (MSC)-based therapies have emerged as an innovative approach in managing refractory perianal fistulizing CD. We conducted a systematic review and meta-analysis to describe and compare combined remission and clinical outcomes of MSC-based therapies, and then whether one approach stands out from the rest.

Methods We searched in MEDLINE, EMBASE and CENTRAL (up to December 31, 2023) all prospective studies assessing a local injection of MSC-based therapy in perianal fistulas of CD. The primary outcome was achievement of combined remission. MSC-based therapy strategies were compared.

Results Twenty-five studies were included in the meta-analysis, enrolling 596 patients with perianal fistulizing CD. The combined remission rate at 3, 6 and 12 months were 36.2% (95% confidence interval (CI), 24.5–49.7), 57.9% (95% CI 51.3–64.2) and 52% (95% CI 38.8–64.8), respectively. MSC-based therapies demonstrated a significant effect in achieving combined remission compared to placebo at 3 months (relative risk (RR) = 1.6; 95% CI 1.0–2.8) and at 6 months (RR = 1.5; 95% CI 1.1–1.9). At 6 months, the combined remission rate was 57.2% (95% CI 47.2–66.6) for adipose-derived stem cells (ASCs) and 55.7% (95% CI 26.4–81.5) for bone marrow-derived stem cells (BMSCs). In the network meta-analysis, allogeneic ASCs and BMSCs did not demonstrate superiority over each other (RR = 0.74; 95% CI 0.31–1.77).

Conclusion MSC-based therapies are effective for achieving combined remission of refractory and/or complex perianal fistulizing CD. The optimal efficacy effect is reached after 6 months of treatment. No superiority has yet been demonstrated between ASCs and BMSCs therapies

Keywords Crohn's disease, Fistula, Mesenchymal stem cells, Stromal vascular fraction, Meta-analysis

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Background

Crohn's disease (CD) is a chronic and disabling condition that can affect the entire digestive tract [1]. Perianal lesions involve approximately one-third of patients and primarily consist of fistulizing conditions [2]. These manifestations result in significant functional impairment and greatly impact the patients' quality of life [3]. Despite optimal medical and surgical management, around half of the patients do not achieve healing of their perianal lesions [4, 5]. In recent years, cell therapy and regenerative medicine have emerged as an innovative approach in managing refractory perianal fistulas of CD [6]. These innovative therapies mainly lie on mesenchymal stem cell (MSC) which possess trophic, angiogenic, anti-inflammatory, and anti-fibrotic activity [7–9]. MSCs can derived from different sources and were firstly used in an autologous context [7, 8]. Their low immunogenicity also makes administration in an allogeneic setting possible [7, 10]. The ADMIRE trial demonstrated the superiority of allogeneic MSC from adipose tissue over placebo in 212 patients with refractory perianal fistulas of CD [11]. Authors reported combined remission rate (i.e., clinical healing and absence of collections larger than 2 cm on magnetic resonance imaging (MRI)) of 49.5% versus 34.3% at 6 months [12]. However, long-term remission at 104 and 156 weeks is not as conclusive with a reduction of the difference between MSC and placebo to 10% and 7.8%, respectively [12].

Since the ADMIRE trial, allogeneic MSC (i.e., darvadstrocel) are available in clinical practice for managing these complex conditions. In addition, therapies based on allogeneic and autologous stem cell are listed as a therapeutic option by the European consensus of inflammatory bowel disease [13]. Different therapeutic approaches have been evaluated in perianal fistulas of CD based on adipose-derived stem cell (ASC), bone marrow-derived stem cell (BMSC), stromal vascular fraction, and more recently exosomes derived from MSC [6, 14, 15]. The place of regenerative medicine in practice is not yet clear, as there are few available randomized controlled trials (RCT), and the comparative effectiveness of the different strategies is difficult to establish. Meta-analyses have already been conducted on this topic, but they have certain limitations: missing of combined remission analysis, inclusion of patients without CD, inclusion of additional long-term studies from RCTs, no inclusion of non-randomized studies, and no consideration for the chronology in the evaluation of the response. Hence, we conducted a systematic review and meta-analysis of prospective studies assessing efficacy of local injection of MSC-based therapies in perianal fistulizing CD. We aimed to describe combined remission and clinical outcomes of these approaches, and then whether one approach stands out from the rest.

Methods

The protocol for this systematic review and meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024515940, and followed the Cochrane Handbook [16] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [17]. The PRISMA checklist is available in supplementary material.

Selection criteria

We included studies that met the following criteria: (i) Adults or children with perianal fistulizing CD; (ii) Local injection of a mesenchymal stem cell-based therapy for the treatment of fistula; (iii) Assessment of clinical remission and/or radiological remission; (iv) Followed up for at least 3 months; (v) Prospective study (RCT or open-label study); (vi) Study published in English. All editorials, notes, comments, letters, guidelines, case reports, abstracts, reviews articles, or meta-analyses were excluded. Studies that did not exclusively include patients with perianal fistulas of CD were excluded. Studies included only recto-vaginal fistulas of CD were also excluded. When multiple studies reported on the results of the same study (e.g., long-term extension), we used data from the publication that reported on the primary outcome.

Search strategy

We conducted a comprehensive search of MEDLINE, EMBASE and the Cochrane Library (CENTRAL) up to December 31, 2023. The following Medical Subject Heading (MeSH) terms alone or matched with the Boolean operators "AND" or "OR" were used: "mesenchymal stem cells", "stromal vascular fraction", "adipose tissue", "bone marrow", "exosomes", "adipose derived", "stem cell", "crohn disease", and "fistula". A two-step process was applied: title and abstract assessment (step one), followed by full text analysis of relevant articles (step two). Two reviewers (LG and JM) independently scrutinized references for inclusion. Any disagreements between investigators regarding study selection were resolved by consensus. We accurately checked the reference lists of the included studies for any additional relevant work. Finally, additional records were search in regulatory agencies and clinical study reports

(i.e., ClinicalTrial.gov and International Clinical Trials Registry Platform).

Data extraction and quality assessment

Once the eligible studies were selected, two reviewers (LG and JM) extracted data into a standardized form. Data extracted were study characteristics, study design, type of stem cell-based therapy, number of patients, characteristics of patients and fistula, stem cells origin, characteristics and number of injected cells, follow-up, and clinical and radiological response to therapy.

Quality of studies were assessed by two investigators (LG and JM) independently and discrepancies were resolved by consensus. For RCT we used the Cochrane's Risk of Bias tool version 2 (RoB 2) [18]. The RoB 2 tool allows for categorizing studies as "low risk", "some concerns", or "high risk" of bias [18]. Quality of non-randomized trials was measured through the Newcastle–Ottawa Scale (NOS) [19–21]. A NOS score ≥ 6 indicated high quality studies, while studies with NOS values of 1–3 and 4–5 were defined as low and moderate quality studies respectively [19].

Outcomes and strategy for data synthesis

According to ADMIRE study [11], we used the following definition to assess the efficacy to local injection of stem cell-based therapy: (i) Clinical response as a reduction of at least 50% of fistula discharge; (ii) Clinical remission as a closure of all treated external openings without discharge; (iii) Combined remission as a clinical remission, and a radiological healing defined by the absence of collections larger than 2 cm on MRI. Our primary outcome was achievement of combined remission. We extracted this outcome at 3, 6 or 12 months after local injection of stem cell-based therapy. Secondary outcomes were clinical remission and clinical response, also extracted at 3, 6 or 12 months after treatment.

Statistical analysis

Meta-analyses were performed for each of the primary and secondary outcomes (i.e., clinical response, clinical remission, combined remission) and for each period (i.e., 3 months, 6 months, 12 months), combining all therapies. To evaluate different treatment strategies, meta-analyses were carried out separately for the ASCs and BMSCs therapies. Sensitivity analyses were performed according to the methodology of the study to assess if results of clinical outcomes in intervention groups from clinical trials could be analysed with observational studies. Randomized controlled studies were also analysed separately to assess the potential effect of these therapies versus placebo and indirect comparisons were conducted when therapies were compared with the same control treatment.

Random-effects models were used to give a more conservative estimate of the effect, allowing for any heterogeneity among studies [22]. They were estimated by the DerSimonian and Laird method to calculate pooled proportions [23]. To accurately estimate the pooled proportion [24], the logit transformation was applied to observed proportions in order to yield a normal distribution when the observed proportions or the boundaries of the confidence interval are less than 0.2 or greater than 0.8 for more than 20% of the studies [25, 26]. Outcome measures were described as pooled proportions with their corresponding 95% confidence interval (CI). Random-effects models using the inverse variance method were also used to estimate direct and indirect comparisons from randomized trials. Outcome measures were described as relative risk (RR) with their corresponding 95% confidence intervals.

Heterogeneity was quantified by the I^2 parameter [27]. If I^2 was larger than 50%, identification of outlying studies with influence on the overall effect size was performed using three methods: Baujat plot [28], screening for externally studentized residuals [26, 29], and leave-one-out analysis [24]. A study was considered outlier if it was identified by the two out three methods. It was dropped out the meta-analysis if its suppression led to a gain of at least 10 points of heterogeneity for the I^2 parameter. No moderator analysis was performed for these outcomes as not enough studies were available (at least 10 studies) [29].

The Egger's regression test and visual inspection of funnel plots for asymmetry were used to assess publication bias. Statistical tests were performed in a two-sided situation and were considered statistically significant for $p \leq 0.05$. Statistical analyses were performed using RStudio software (v. 4.2.0).

Certainty of evidence

Certainty of evidence for the primary outcome was rated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach according to the Cochrane Handbook [16]. In this approach, direct evidence from studies starts at high quality and can be rated down based on risk of bias in the body of evidence, indirectness, imprecision, and inconsistency to levels of moderate, low, and very low quality [30].

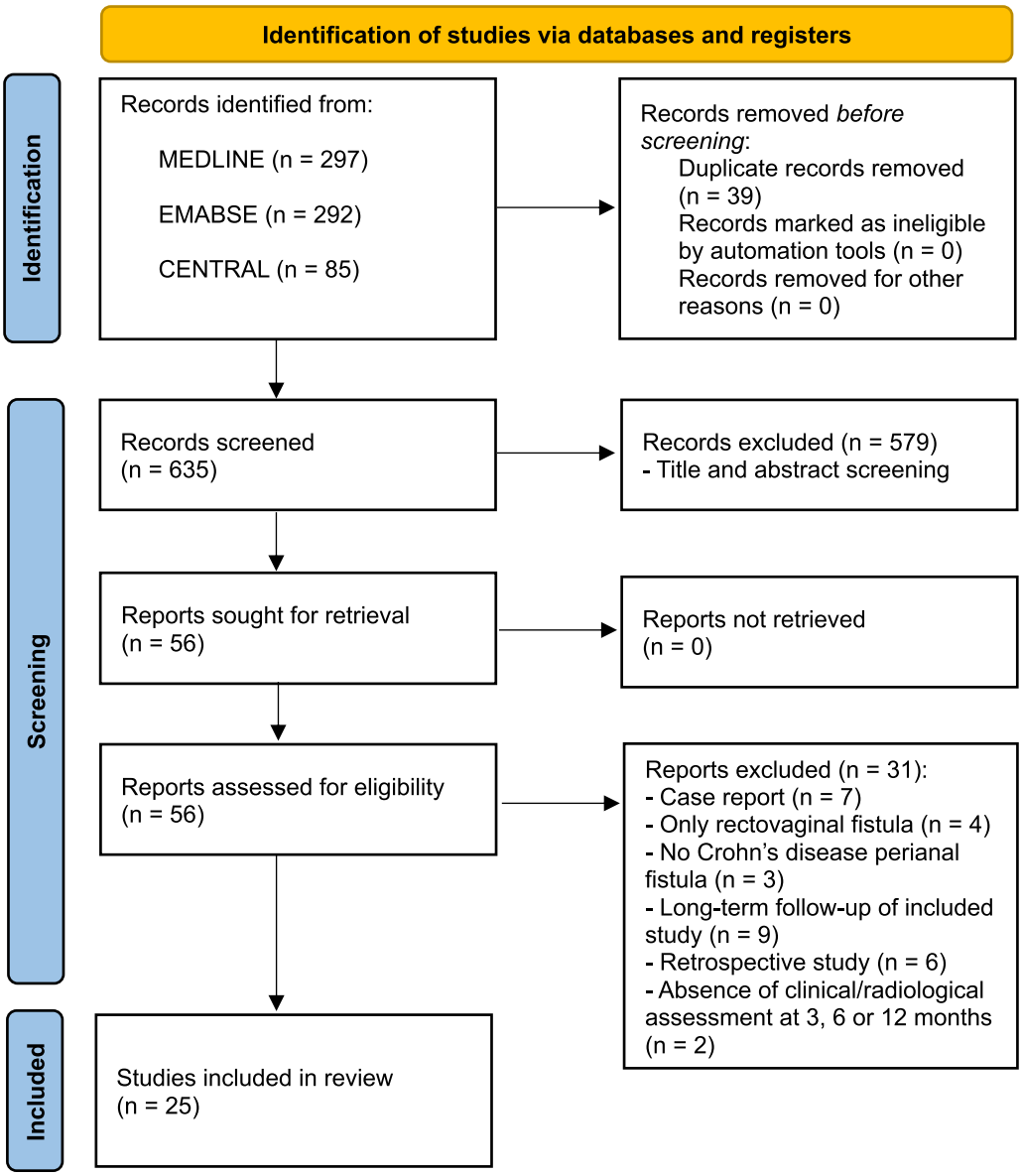

Fig. 1 PRISMA flow diagram

Results

Search results and quality assessment

A total of 635 records were identified through our systematic literature review, of which full texts of 56 articles were reviewed. Of these, 25 studies were included in the systematic review and meta-analysis. No new records were found in reference lists, regulatory agencies or clinical study reports. The study selection flowchart is presented in Fig. 1. The quality of RCT studies included in our analysis is shown in Fig. 2. Two RCT were at low risk [11, 31], whereas two others had some concerns (mainly "Deviations from the intended interventions" and "Measurement of the outcome") [32, 33]. Regarding non-randomized studies, almost all studies were of "high quality" with a NOS score of 6 [34–52], and two studies were of "moderate quality" with a NOS score of 5 (Supplementary Table 1) [53, 54].

Characteristics of included studies and MSC-based therapy process

Table 1 details the characteristics of the included studies. Among the 25 articles, 4 studies were RCT [11, 31–33].

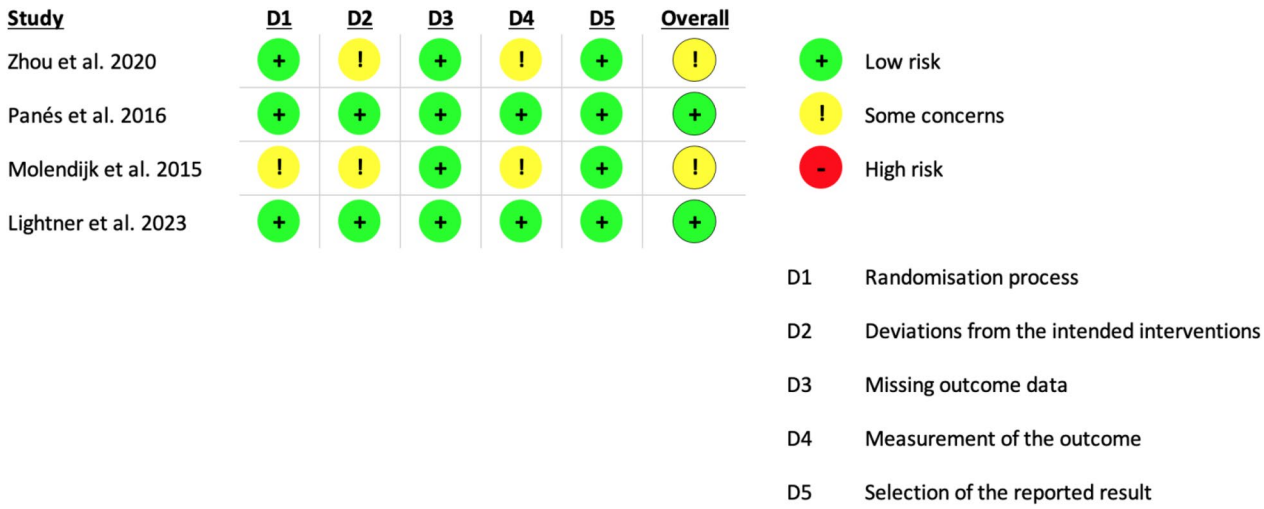

Fig. 2 Risk of bias assessment using the Cochrane risk of bias tool, version 2.0 (RoB 2)

Overall, 596 patients with perianal fistulizing CD were included in the analysis, and the median number of patients per study was 16. Pediatric patients were included in 3 studies, but all patients had ≥ 13 years old [39, 46, 47]. Patients treated all had refractory and/or complex perineal fistula tract. Among the cell-based therapy used, 10 studies investigated ASCs (5 allogeneic and 5 autologous) [11, 33, 39–44, 53, 54], 7 BMSCs (5 allogeneic and 2 autologous) [31, 32, 45–48, 51], 3 stromal vascular fraction [34–36], 2 microfragmented adipose tissue [37, 38], 2 exosomes derived from umbilical cord MSC [49, 52] and 1 allogeneic umbilical cord-derived MSC [50]. A matrix was used in 5 trials and consisted of a fibrin glue [39, 40, 48, 53] or dissolvable plug [41]. Repeated injections were proposed in 9 studies, with up to 4 injections per patient. In 6 trials, repeated injections were performed in case of insufficient response to the treatment [31, 36, 37, 40, 42, 47]. In 3 studies, patients were systematically treated with 2 to 4 injections, with an interval of 4–8 weeks between each injection [46, 48, 52]. The number of cells injected ranged from 20×10^6 to 400×10^6, with an estimated mean of 87.4×10^6 injected cells ($\pm 70.8 \times 10^6$ (standard deviation)).

Primary outcome: combined remission

Combined remission was assessed in 21 studies (84.0%) involving 396 patients perianal fistulizing CD [11, 31–38, 41–52]. The combined remission rate in meta-analyses at 3, 6 and 12 months were 36.2% (95% CI 24.5–49.7), 57.9% (95% CI 51.3–64.2) and 52% (95% CI 38.8–64.8), respectively (Fig. 3). Sensitivity analyses revealed no numerical difference after removing the results of RCTs for combined remission rates (Supplementary Table 2), although these comparisons were not assessed with statistical tests. The Egger's regression test and visual inspection of funnel plots showed that there was no tendency for publication bias (Supplementary Fig. 1).

Meta-analyses for combined remission in the subgroup of RCTs were conducted at 3 and 6 months. These subgroup analyses involved 270 patients [11, 31–33]. MSC-based therapies demonstrated a significant effect in achieving combined remission compared to placebo at 3 months (RR = 1.6; 95% CI 1.0–2.8; $I^2 = 0\%$) and at 6 months (RR = 1.5; 95% CI 1.1–1.9; $I^2 = 0\%$) (Fig. 4).

The body of evidence was rated down for risk of bias and imprecision using the GRADE approach. Consequently, the certainty of the evidence was judged to be very low and low for achieved combined remission with MSC-based therapy for analyses with all studies and subgroup of RCTs, respectively (Supplementary Table 3).

Secondary outcomes: clinical response and clinical remission

Clinical remission was assessed in 19 studies (76.0%) involving 365 patients [11, 31, 35–44, 46–49, 51, 53, 54]. The clinical remission rate in meta-analyses at 3, 6 and 12 months were 32% (95% CI 22.5–43.2), 61.7% (95% CI 49.9–72.3) and 58.3% (95% CI 47.3–68.6), respectively (Supplementary Fig. 2). Clinical response was assessed in 20 studies (80.0%) involving 369 patients 11,31,34–40,42,43,45–53. The clinical response rate in meta-analyses at 3, 6 and 12 months were 70.9% (95% CI 56.7–81.9), 76.1% (95% CI 69.2–81.9) and 77.4% (95% CI 68.8–84.2), respectively (Supplementary Fig. 3). Sensitivity analyses revealed no numerical difference after removing the results of RCTs for clinical response and clinical remission rates (Supplementary Table 2).

Table 1 Characteristics of included studies and cell-based therapy process

Study	RCT	Patients (N)	Fistulas	Cell-based therapy and source	Intervention (number of injected cells/ number of injection)	Follow-up (month)
Arkenbosch et al. [36]	No	25	Refractory and complex CD perianal fistulas	Autologous SFV and PRP	1 ml SVF + 4–5 ml PRP/ injection (number of cells NA) 1 to 4 injections	12
Dozois et al. [41]	No	20	Refractory and complex CD perianal fistulas	Autologous ASCs	20×10^6 per plug (dissolvable plug) 1 injection	12
Furukawa et al. [43]	No	22	Refractory and complex CD perianal fistulas	Allogeneic ASCs	120×10^6 (Darvadstrocel) 1 injection	12
Fathallah et al. [44]	No	27	Refractory and complex CD perianal fistulas	Allogeneic ASCs	120×10^6 (Darvadstrocel) 1 injection	12
Reenaers et al. [45]	No	16	Refractory and complex CD perianal fistulas	Allogeneic BMSCs	30×10^6 1 injection	12
Lightner et al. [31]	Yes	23	Complex CD perianal fistulas	Allogeneic BMSCs	75×10^6 1 or 2 injections	12
Lightner et al. [47]	No	7[†]	Complex CD perianal fistulas	Allogeneic BMSCs	75×10^6 1 or 2 injections	12
Wei et al. [50]	No	10	Refractory and complex CD perianal fistulas	Allogeneic umbilical cord-derived MSC	120×10^6 1 injection	6
Sørensen et al. [35]	No	12	Refractory +/− complex CD perianal fistulas	Autologous SFV and microfat	Mean (95% CI): 37.6×10^6 (29.3–45.8) 1 injection + microfat around around fistula tract	6 to 12
Vosough et al. [48]	No	5	Refractory +/− complex CD perianal fistulas	Autologous BMSCs	40×10^6 per injection (fibrin glue matrix) 4 injections per patient (every 4 weeks)	6
Nazari et al. [49]	No	5	Refractory and complex CD perianal fistulas	Allogeneic exosomes, umbilical cord MSC-derived	5 ml of a 50 µg/ml exosomes solution (0.5×10^{10} particles/ml) 1 injection	6
Cho et al. [53]	No	5[†]	Refractory and complex CD perianal fistulas	Autologous ASCs	Median: 300×10^6 (based on fistula size) 1 injection (fibrin glue matrix)	6
Schwandner [54]	No	12	Refractory and complex CD perianal fistulas	Allogeneic ASCs	120×10^6 (Darvadstrocel) 1 injection	12
Laureti et al. [38]	No	15	Refractory and complex CD perianal fistulas	Microfragmented adipose tissue	20 ml of adipose tissue 1 injection	6
Zhou et al. [33]	Yes	22	Complex CD perianal fistulas	Autologous ASCs	Mean (± SD): 142.3×10^6 (± 45.7) 1 injection	12
Serrero et al. [34]	No	10	Refractory and complex CD perianal fistulas	Autologous SFV and microfat	Median: 22.8×10^6 (IQR: 10.9; 47.8) 1 injection + microfat around around fistula tract	12
Dige et al. [37]	No	21	Refractory and complex CD perianal fistulas	Microfragmented adipose tissue	Median: 46 ml of adipose tissue (range, 18 to 104 ml) 1 to 3 injections	6 (after the last injection)
Panés et al. [11]	Yes	212	Refractory and complex CD perianal fistulas	Allogeneic ASCs	120×10^6 (Darvadstrocel) 1 injection	6
Molendijk et al. [32]	Yes	21	Refractory and complex CD perianal fistulas	Allogeneic BMSCs	Range: 10 to 90×10^6 1 injection	6

Table 1 (continued)

Study	RCT	Patients (N)	Fistulas	Cell-based therapy and source	Intervention (number of injected cells/ number of injection)	Follow-up (month)
Cho et al. [53]	No	9	Complex CD perianal fistulas	Autologous ASCs	Range: 30 to 400×10^6 (based on fistula size) 1 injection (fibrin glue matrix)	8
Lee et al. [40]	No	33	Complex CD perianal fistulas	Autologous ASCs	Mean (± SD): 147×10^6 (± 78) (fibrin glue matrix) 1 or 2 injections (199×10^6 (± 52) for 2nd injection)	12
De la Portilla et al. [42]	No	24	Refractory and complex CD perianal fistulas	Allogeneic ASCs	20×10^6 1 or 2 injections (20×10^6 for 2nd injection)	6
Ciccocioppo et al. [46]	No	10[†]	Refractory and complex CD perianal fistulas	Autologous BMSCs	Median 20×10^6 per injection (range, 15 to 30×10^6) 2 à 4 injections (every 4 weeks)	12
Swaroop et al. [51]	No	10	Refractory and complex CD perianal fistulas	Allogeneic BMSCs	75×10^6 1 injection	24
Hadizadeh et al. [52]	No	20	Refractory and complex CD perianal fistulas	Allogeneic exosomes, umbilical cord MSC-derived	5 ml of a 50 µg/ml exosomes solution (0.5×10^{10} particles/ml) 4 injections per patient (every 8 weeks)	6 (After the last injection)

ASC Adipose-derived stem cell, *BMSC* Bone marrow-derived stem cell, *CD* Crohn's disease, *CI* Confidence interval, *IQR* Interquartile range, *ml* Millilitre, *MSC* Mesenchymal stem cell, *NA* Non available, *PRP* Platelet-rich plasma, *RCT* Randomized controlled trial, *SD* Standard deviation, *SVF* Stromal vascular fraction

[†] Including pediatric patients

Comparison of MSC-based therapy strategies

Meta-analyses for clinical remission and combined remission at 6 months could be conducted for ASCs and BMSCs therapies. Eleven studies were included in these meta-analyses, involving 356 patients (Fig. 5) [11, 31–33, 39, 41, 43, 47, 48, 51, 53]. The clinical remission rate was 56% (95% CI 47.9–63.7) for ASCs and 67.5% (95% CI 24.7–92.9) for BMSCs. The combined remission rate was 57.2% (95% CI 47.2–66.6) for ASCs and 55.7% (95% CI 26.4–81.5) for BMSCs.

Three RCTs were included in the network meta-analysis, 1 evaluating allogeneic ASCs [11] and 2 evaluating allogeneic BMSCs [31, 32]. In direct comparisons, allogeneic ASCs demonstrated a significative effect in achieving combined remission at 6 months (RR = 1.44; 95% CI 1.05–1.99), while allogeneic BMSCs reported a numerically higher but non-significant effect (RR = 1.95; 95% CI 0.87–4.38) (Supplementary Table 4). After indirect comparison, Allogeneic ASCs and BMSCs did not demonstrate superiority over each other (RR = 0.74; 95% CI 0.31–1.77) (Supplementary Table 4).

Discussion

We reported efficacy data of local injection of MSC-based therapies in perianal fistulizing CD through a contemporaneous systematic review and meta-analysis. To our knowledge, this is the first meta-analysis specifically designed to evaluate the combined remission of MSC-based therapies in perianal fistulizing CD. Data from 596 patients across 25 studies were included in the analysis, making this meta-analysis the largest in the literature. Although the analysis includes also non-randomized trials, 84.0% (21/25) of the studies involved patients with refractory perineal disease, highlighting its clinical relevance. Thirdly, strict inclusion criteria were used, and study selection and data extraction were performed through the combined work of two authors who operated independently, reducing the risk of errors. Fourthly, another strength of this work is that our analyses take into account the chronology when evaluating the response to MSC-based therapies. Finally, we proposed a comparison of treatment strategies with MSC.

Our results suggest that MSC-based therapies are effective for the treatment of refractory and/or complex perineal fistulas in CD, with an optimal efficacy achieved after 6 months of treatment. We reported that combined

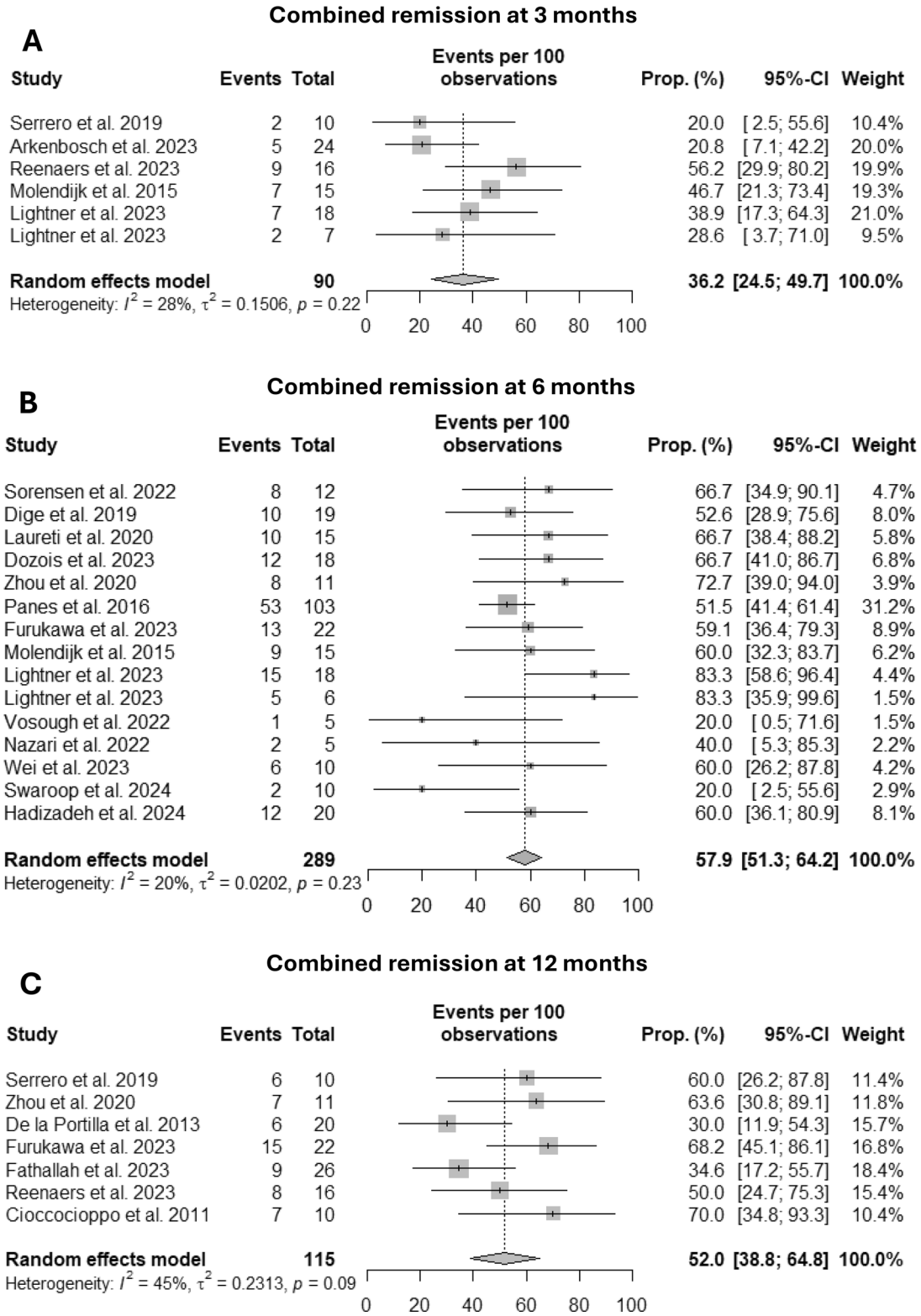

Fig. 3 Forest plot comparing the fistula combined remission rate after treatment with MSC-based therapy. **A** Combined remission at 3 months, **B** Combined remission at 6 months, **C** Combined remission at 12 months

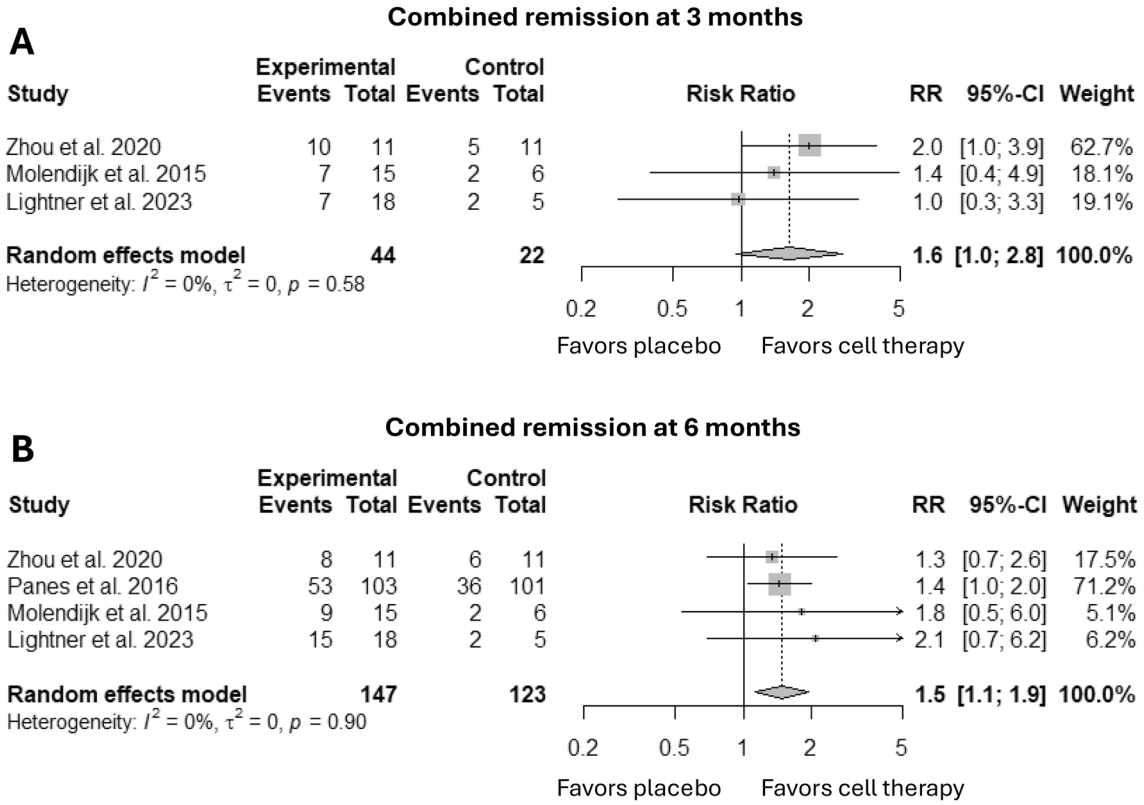

Fig. 4 Forest plot comparing risk ratio for achieving combined remission of fistula after treatment with MSC-based therapy in randomized controlled trials. **A** Combined remission at 3 months, **B** Combined remission at 6 months

remission was achieved in at least 50% of patients at 6 and 12 months (57.9% (95% CI 51.3–64.2) and 52% (95% CI 38.8–64.8), respectively). The meta-analysis of Ciccocioppo et al. showed similar findings with incidence rate of 48% (95% CI 40–57) for combined remission [55]. However, only 3 studies evaluated combined remission and they did not separate the results according to temporal assessment, while our meta-analysis evaluated combined remission of 15 studies at 6 months and 7 studies at 12 months. They also reported a RR of 1.57 (1.07–2.31) for combined remission in RCT, equivalent to our subgroup analysis of RCT conducted at 3 and 6 months that revealed a RR of combined remission compared to placebo of 1.6 (1.0–2.8) and 1.5 (1.1–1.9), respectively. A more recent study described slightly better results with an Odds ratio of 1.77 (1.28–2.45) compared to placebo [56]. However, results of these 2 meta-analyses are limited by the inclusion of fistulas from patients without CD, the additional inclusion of long-term follow-up from RCTs and the lack of consideration for the chronology in the evaluation of the response [55, 56]. Recently, Wang et al. [14] performed a meta-analysis for evaluated MSC in perianal fistula. In subgroup analysis of patients with CD authors reported a RR of 1.43 (1.09–1.8) for combined remission [14]. This meta-analysis included 3 of the 4 RCTs included in our meta-analysis, explaining the similarity of the results. These results will need to be updated with the final results of the phase 3 ADMIRE-CD II study, whose preliminary findings presented at the ECCO congress did not show a significant difference avec le placebo [57].

In our meta-analysis, clinical response was observed in 76.1% (69.2–81.9) and 77.4% (68.8–84.2) at 6 and 12 months respectively, and clinical remission in 61.7% (49.9–72.3) and 58.3% (47.3–68.6) at 6 and 12 months respectively. Ciccocioppo et al. [55] found similar results for clinical response reaching a rate of 80% (95% CI 0.70–0.89). For clinical remission they reported a slightly lower incidence rate of 51% (95% CI 0.40–0.62) [55]. Others meta-analyses have evaluated the efficacy of MSC in perineal fistulas of CD in the literature. However, these studies have not analysed combined remission [15, 58, 59], or included patients without CD or long-term

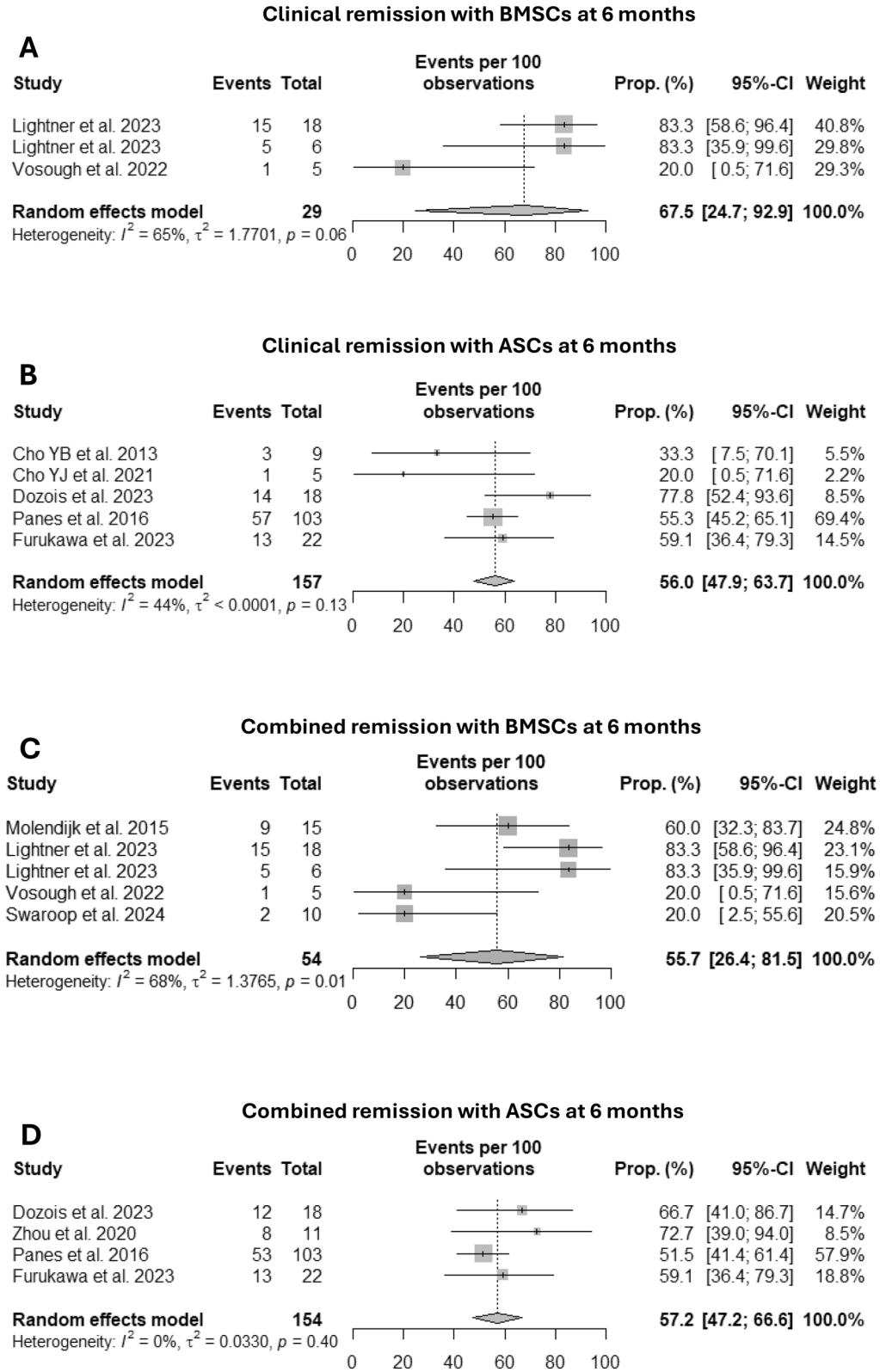

Fig. 5 Forest plot comparing the fistula clinical and combined remission rate after treatment with BMSCs or ASCs. **A** Clinical remission with BMSCs at 6 months, **B** Clinical remission with ASCs at 6 months, **C** Combined remission with BMSCs at 6 months, **D** Combined remission with ASCs at 6 months. *ASC* Adipose-derived stem cell, *BMSC* Bone marrow-derived stem cell

follow-up from RCTs [60–62], which makes it difficult to compare the results with our study.

We aimed to determine which MSC-based therapies strategy was the most effective for perianal fistulas in CD. Meta-analyses could be performed only for BMSCs and ASCs, due to the low number of studies for other therapies. Clinical remission rate was numerically higher with BMSCs than with ASCs, while combined remission rate was similar between both conditions, with the limit that analysis heterogeneity for both outcomes were significantly greater than 50% (65% and 68%, respectively) with wide 95% CI. In addition, 3 RCTs could be included in a network meta-analysis. In indirect comparison, allogeneic ASCs and BMSCs did not demonstrate superiority over each other. In direct comparisons, allogeneic BMSCs reported a numerically higher but non-significant effect than allogeneic ASCs (RR = 1.95 (0.87–4.38) vs 1.44 (1.05–1.99)). It is therefore not possible to determine whether one strategy stands out from the others. Results of these meta-analyses and network meta-analysis should be considered with caution due to their exploratory nature. The number of patients included in studies evaluating BMSCs was limited and ranged from 5 to 23 [31, 32, 47, 48], whereas for ASCs the study of Panés et al. [11] included 212 patients and had a significant weight in the analyses. Additionally, the number of studies included is also small in each group. In a meta-analysis from 2023, authors also tried to determine which therapy is the most effective. They found a RR of 1.35 (1.10–1.67) for ASCs and 1.80 (0.54–6.0) for BMSCs [14]. This result is similar to our analysis but is limited by the fact that only one study represented BMSCs therapies, which theoretically makes it impossible to carry out a meta-analysis. In addition, Cao et al. [58] did not report statistical difference between ASCs and BMSCs regarding healing rates. On the other hand, authors reported a lower recurrence rate with ASCs than BMSCs [58]. In-vitro, preclinical and clinical studies comparing ASCs and BMSCs show that they share many biological characteristics [63]. However, ASCs have demonstrated superior immunomodulatory and inflammation-regulating activity [63–65], proliferation capacity [66] and pro-angiogenic activity [67]. ASCs could therefore represent a more advantageous source in the context of Crohn's disease.

Certain limitations can also be raised with this work. We found significant heterogeneity among the studies regarding the dose of cells injected, the number of injections, the source of cells, and the use of a matrix. These differences could impact the overall results of the meta-analyses. Additionally, among the included studies, only 4 were RCTs, which reduces the certainty of evidence of the results. At last, the number of patients in each study was limited, ranging from 5 to 33, excepted for the study of Panés et al. [11] which included 212 patients. This small number of patients reduce the certainty of evidence of the results.

In conclusion, a wide range of MSC-based therapies are currently under development or already available. These therapies are effective for the treatment of refractory and/or complex perineal fistulas in CD and achieving combined remission. The optimal efficacy effect is reached after 6 months of treatment. No superiority has yet been demonstrated between ASCs and BMSCs therapies. To clarify the role of these innovative therapies in clinical practice, larger-scale RCTs are needed.

Supplementary Information

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Additional file 1.

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The authors declare that they have not use AI-generated work in this manuscript.

Author contributions
LG, FS, and JM participated in the study concept. LG, FS, and JM participated in the study design. LG, FS, and JM participated in the analysis and interpretation of data, along with drafting of the manuscript. RGD performed the statistical analysis of data. All authors participated in the collection of the data and critically reviewed the manuscript for important intellectual content and approved the final version of the manuscript.

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References

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet. 2017;389:1741–55.
2. Panés J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. Nat Rev Gastroenterol Hepatol. 2017;14:652–64.
3. Wewer MD, Zhao M, Nordholm-Carstensen A, Weimers P, et al. The incidence and disease course of perianal Crohn's disease: a Danish nationwide cohort study, 1997–2015. J Crohns Colitis. 2021;15:5–13.
4. Molendijk I, Nuij VJAA, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. Inflamm Bowel Dis. 2014;20:2022–8.
5. Yassin NA, Askari A, Warusavitarne J, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. Aliment Pharmacol Ther. 2014;40:741–9.
6. Nazari H, Naei VY, Tabasi AH, et al. Advanced regenerative medicine strategies for treatment of perianal fistula in Crohn's disease. Inflamm Bowel Dis. 2022;28:133–42.
7. Grégoire C, Lechanteur C, Briquet A, et al. Review article: mesenchymal stromal cell therapy for inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;45:205–21.
8. Ding DC, Shyu WC, Lin SZ. Mesenchymal stem cells. Cell Transplant. 2011;20:5–14.
9. Shi Y, Wang Y, Li Q, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018;14:493–507.
10. Leto Barone AA, Khalifian S, Lee WPA, Brandacher G. Immunomodulatory effects of adipose-derived stem cells: Fact or fiction? BioMed Res Int. 2013;2013:383685.
11. Panés J, García-Olmo D, Van Assche G, et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial. Lancet. 2016;388:1281–90.
12. Panés J, Bouma G, Ferrante M, et al. INSPECT: a retrospective study to evaluate long-term effectiveness and safety of darvadstrocel in patients with perianal fistulizing Crohn's disease treated in the ADMIRE-CD trial. Inflamm Bowel Dis. 2022;28:1737–45.
13. Adamina M, Minozzi S, Warusavitarne J, et al. ECCO guidelines on therapeutics in Crohn's disease: surgical treatment. J Crohns Colitis. 2024;18:1556–82.
14. Wang H, Jiang HY, Zhang YX, Jin HY, et al. Mesenchymal stem cells transplantation for perianal fistulas: a systematic review and meta-analysis of clinical trials. Stem Cell Res Ther. 2023;14:103.
15. Lightner AL, Wang Z, Zubair AC, Dozois EJ. A systematic review and meta-analysis of mesenchymal stem cell injections for the treatment of perianal Crohn's disease: progress made and future directions. Dis Colon Rectum. 2018;61:629–40.
16. Higgins JPT, Thomas J, Chandler J, Cumpston M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
19. Wells G, Shea B, O'Connell D, et al. The Newcastle–Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
20. Hootman JM, Driban JB, Sitler MR, Harris KP, Cattano NM. Reliability and validity of three quality rating instruments for systematic reviews of observational studies. Res Synth Methods. 2011;2:110–8.
21. Zhang Y, Huang L, Wang D, Ren P, et al. The ROBINS-I and the NOS had similar reliability but differed in applicability: a random sampling observational studies of systematic reviews/meta-analysis. J Evid-Based Med. 2021;14:112–22.
22. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2022;7:161–70.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
24. Wang N. How to conduct a meta-analysis of proportions in R: a comprehensive tutorial. 2018. https://doi.org/10.13140/RG.2.2.27199.00161/1.
25. Lipsey MW, Wilson DB. The way in which intervention studies have "personality" and why it is important to meta-analysis. Eval Health Prof. 2001;24:236–54.
26. Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Res Synth Methods. 2010;1:112–25.
27. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
28. Baujat B, Mahé C, Pignon JP, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Stat Med. 2002;21:2641–52.
29. Tabachnick BG, Fidell LS. Using multivariate statistics. 6th ed. Boston: Pearson; 2013.
30. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401–6.
31. Lightner AL, Reese J, Ream J, et al. A phase IB/IIA study of ex vivo expanded allogeneic bone marrow-derived mesenchymal stem cells for the treatment of perianal fistulizing Crohn's disease. Dis Colon Rectum. 2023;66:1359–72.
32. Molendijk I, Bonsing BA, Roelofs H, et al. Allogeneic bone marrow-derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease. Gastroenterology. 2015;149:918-927.e6.
33. Zhou C, Li M, Zhang Y, et al. Autologous adipose-derived stem cells for the treatment of Crohn's fistula-in-ano: an open-label, controlled trial. Stem Cell Res Ther. 2020;11:124.
34. Serrero M, Grimaud F, Philandrianos C, Visée C, et al. Long-term safety and efficacy of local microinjection combining autologous microfat and adipose-derived stromal vascular fraction for the treatment of refractory perianal fistula in Crohn's disease. Gastroenterology. 2019;156:2335-2337.e2.
35. Sørensen KM, Jensen CH, Sheikh SP, Qvist N, Sørensen JA. Treatment of fistulizing perianal Crohn's disease by autologous microfat enriched with adipose-derived regenerative cells. Inflamm Bowel Dis. 2022;28:967–70.
36. Arkenbosch JHC, van Ruler O, Dwarkasing RS, et al. Stromal vascular fraction with platelet-rich plasma injection during surgery is feasible and safe in treatment-refractory perianal fistulising Crohn's disease: a pilot study. Aliment Pharmacol Ther. 2023;57:783–91.
37. Dige A, Hougaard HT, Agnholt J, et al. Efficacy of injection of freshly collected autologous adipose tissue into perianal fistulas in patients with Crohn's disease. Gastroenterology. 2019;156:2208-2216.e1.
38. Laureti S, Gionchetti P, Cappelli A, et al. Refractory complex Crohn's perianal fistulas: a role for autologous microfragmented adipose tissue injection. Inflamm Bowel Dis. 2020;26:321–30.
39. Cho YJ, Kwon H, Kwon YJ, Kim KM, et al. Efficacy and safety of autologous adipose tissue-derived stem cell therapy for children with refractory Crohn's complex fistula: a Phase IV clinical study. Ann Surg Treat Res. 2021;101:58–64.
40. Lee WY, Park KJ, Cho YB, et al. Autologous adipose tissue-derived stem cells treatment demonstrated favorable and sustainable therapeutic effect for Crohn's fistula. Stem Cells. 2013;31:2575–81.
41. Dozois EJ, Lightner AL, Dietz AB, et al. Durable response in patients with refractory fistulizing perianal Crohn's disease using autologous mesenchymal stem cells on a dissolvable matrix: results from the phase I stem cell on matrix plug trial. Dis Colon Rectum. 2023;66:243–52.
42. de la Portilla F, Alba F, García-Olmo D, Herrerías JM, González FX, Galindo A. Expanded allogeneic adipose-derived stem cells (eASCs) for the treatment of complex perianal fistula in Crohn's disease: results from a multicenter phase I/IIa clinical trial. Int J Colorectal Dis. 2013;28:313–23.
43. Furukawa S, Mizushima T, Nakaya R, et al. Darvadstrocel for complex perianal fistulas in Japanese adults with Crohn's disease: a phase 3 study. J Crohns Colitis. 2023;17:369–78.

44. Fathallah N, Akaffou M, Haouari MA, et al. Deep remission improves the quality of life of patients with Crohn's disease and anoperineal fistula treated with darvadstrocel: results of a French pilot study. Tech Coloproctol. 2023;27:1201–10.
45. Reenaers C, Gillard RP, Coimbra C, et al. Clinical and MRI evolution after local injection of bone marrow-derived mesenchymal stem cells in perianal fistulae in Crohn's disease: results from a prospective monocentric study. J Crohns Colitis. 2023;17:728–37.
46. Ciccocioppo R, Bernardo ME, Sgarella A, et al. Autologous bone marrow-derived mesenchymal stromal cells in the treatment of fistulising Crohn's disease. Gut. 2011;60:788–98.
47. Lightner AL, Otero-Pineiro A, Reese J, et al. A phase I study of ex vivo expanded allogeneic bone marrow-derived mesenchymal stem cells for the treatment of pediatric perianal fistulizing Crohn's disease. Inflamm Bowel Dis. 2023;29:1912–9.
48. Vosough M, Nikfam S, Torabi SH, et al. Mesenchymal stromal cell therapy improves refractory perianal fistula in Crohn's disease: case series clinical interventional study. Cell J. 2022;24:62–8.
49. Nazari H, Alborzi F, Heirani-Tabasi A, et al. Evaluating the safety and efficacy of mesenchymal stem cell-derived exosomes for treatment of refractory perianal fistula in IBD patients: clinical trial phase I. Gastroenterol Rep. 2022;10:goac075.
50. Wei J, Zhang Y, Chen C, et al. Efficacy and safety of allogeneic umbilical cord-derived mesenchymal stem cells for the treatment of complex perianal fistula in Crohn's disease: a pilot study. Stem Cell Res Ther. 2023;14:311.
51. Swaroop S, Vuyyuru SK, Kante B, et al. A phase I/II clinical trial of ex-vivo expanded human bone marrow derived allogeneic mesenchymal stromal cells in adult patients with perianal fistulizing Crohn's Disease. Stem Cell Res Ther. 2024;15:140.
52. Hadizadeh A, Akbari-Asbagh R, Heirani-Tabasi A, et al. Localized administration of mesenchymal stem cell-derived exosomes for the treatment of refractory perianal fistula in Crohn's disease patients: a phase II clinical trial. Dis Colon Rectum. Published online September 6, 2024.
53. Cho YB, Lee WY, Park KJ, Kim M, et al. Autologous adipose tissue-derived stem cells for the treatment of Crohn's fistula: a phase I clinical study. Cell Transpl. 2013;22:279–85.
54. Schwandner O. Stem cell injection for complex anal fistula in Crohn's disease: a single-center experience. World J Gastroenterol. 2021;27:3643–53.
55. Ciccocioppo R, Klersy C, Leffler DA, Rogers R, et al. Systematic review with meta-analysis: safety and efficacy of local injections of mesenchymal stem cells in perianal fistulas. JGH Open. 2019;3:249–60.
56. Cheng F, Huang Z, Li Z. Efficacy and safety of mesenchymal stem cells in treatment of complex perianal fistulas: a meta-analysis. Stem Cells Int. 2020;2020:8816737.
57. Serclova Z, Garcia-Olmo D, Chen ST, et al. OP18 efficacy and safety of darvadstrocel treatment in patients with complex perianal fistulas and Crohn's disease: results from the global ADMIRE-CD II phase 3 study. J Crohns Colitis. 2024;18:i34–5.
58. Cao Y, Ding Z, Han C, Shi H, et al. Efficacy of mesenchymal stromal cells for fistula treatment of Crohn's disease: a systematic review and meta-analysis. Dig Dis Sci. 2017;62:851–60.
59. Li A, Liu S, Li L, Yu M. Mesenchymal stem cells versus placebo for perianal fistulizing Crohn's disease: a systemic review and meta-analysis. Surg Innov. 2023;30:398–405.
60. Choi S, Jeon BG, Chae G, Lee SJ. The clinical efficacy of stem cell therapy for complex perianal fistulas: a meta-analysis. Tech Coloproctol. 2019;23:411–27.
61. Cao Y, Su Q, Zhang B, Shen F, Li S. Efficacy of stem cells therapy for Crohn's fistula: a meta-analysis and systematic review. Stem Cell Res Ther. 2021;12:32.
62. Cheng F, Huang Z, Wei W, Li Z. Efficacy and safety of mesenchymal stem cells in the treatment of perianal fistulas in Crohn's disease: a meta-analysis of randomized controlled trials. Rev Esp Enferm Dig Online ahead of print March 10, 2023.
63. Strioga M, Viswanathan S, Darinskas A, Slaby O, Michalek J. Same or not the same? Comparison of adipose tissue-derived versus bone marrow-derived mesenchymal stem and stromal cells. Stem Cells Dev. 2012;21:2724–52.
64. Zhou W, Lin J, Zhao K, et al. Single-cell profiles and clinically useful properties of human mesenchymal stem cells of adipose and bone marrow origin. Am J Sports Med. 2019;47:1722–33.
65. Zaza R, Jamali F, Hassouneh M, Alhattab D, AlAlawi S, Awidi A. Adipose tissue derived mesenchymal stem cells exhibit a superior immune-modulatoery effect on mature dendritic cells compared to bone marrow derived mesenchymal stem cells. Cytotherapy. 2019;21:e11.
66. Li C, Wu X, Tong J, et al. Comparative analysis of human mesenchymal stem cells from bone marrow and adipose tissue under xeno-free conditions for cell therapy. Stem Cell Res Ther. 2015;6:55.
67. El-Badawy A, Amer M, Abdelbaset R, et al. Adipose stem cells display higher regenerative capacities and more adaptable electro-kinetic properties compared to bone marrow-derived mesenchymal stromal cells. Sci Rep. 2016;6:37801.

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