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Efficacy and Safety of Stem Cell Therapy in the Treatment of Fistulizing Crohn's Disease and the Role of Autologous Stem Cell Transplantation: A Systematic Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Background: Crohn's Disease (CD), especially its fistulizing form, presents significant treatment challenges. Stem cell transplantation, particularly autologous stem cell transplantation, has emerged as a novel approach for these difficult-to-treat cases. This systematic review concentrates on evaluating the efficacy and safety of stem cell transplantation in treating fistulizing CD.
Methods: We searched PubMed, Embase, and Cochrane Library up to June 2023. Both randomized controlled trials and non-randomized clinical trials involving adult patients (18 years or older) with CD and utilizing various forms of stem cell therapy were included. Primary outcomes were efficacy and safety of stem cell therapy. Data were extracted and synthesized narratively.
Results: The review included nine studies with interventions ranging from mesenchymal stem cell treatment (Darvadstrocel, Cx601), autologous adipose-derived stem cells, to autologous hematopoietic stem cell transplantation (HSCT). Across these studies, significant efficacy was noted in the closure of fistulas and clinical remission with treatments like Darvadstrocel and Cx601. Reductions in Crohn's Disease Activity Index (CDAI) and corticosteroid dosage were observed with treatments like Umbilical Cord Mesenchymal Stem Cells (UC-MSCs). In autologous HSCT, a proportion of patients achieved steroid-free clinical remission and complete endoscopic healing, but with a higher incidence of serious adverse events. Adverse events varied across studies, with some treatments showing manageable profiles while others, notably HSCT, demonstrated significant risks.
Conclusion: Stem cell transplantation, particularly autologous stem cells, demonstrates potential as an effective treatment for fistulizing CD. However, further research with more focused and standardized protocols is essential to validate these findings and establish a clear treatment guideline.

Keywords: Crohn's disease; stem cell therapy; mesenchymal stem cells; hematopoietic stem cells; adipose-derived stem cells.

1. INTRODUCTION

Crohn's Disease (CD) is a chronic, relapsing, and remitting inflammatory condition that predominantly affects the gastrointestinal tract but can involve any part of the digestive system from the mouth to the anus [1]. It is one of the two main forms of Inflammatory Bowel Disease (IBD), the other being Ulcerative Colitis (UC). The exact cause of CD remains unknown, but it is thought to result from a complex interplay of genetic, environmental, and immunological factors leading to an inappropriate inflammatory response to gut microbiota [2].

A distinguishing feature of CD is its transmural inflammation, which can lead to the formation of strictures, fistulas, and abscesses [3]. The disease can present at any age, but onset typically occurs in early adulthood, with patients often experiencing a fluctuating course of active and quiescent disease. This presents a significant disease burden, negatively impacting the quality of life, and posing the risk of various complications [4].

In recent years, stem cell therapy has gained attention as a potential treatment for fistulizing CD [5]. Laboratory studies suggest that stem cells could be effective in treating fistulizing CD due to their ability to modulate the immune system, promote tissue repair, and reduce inflammation [6,7]. Specifically, research indicates that stem cells might help heal fistulas by promoting the regeneration of the damaged tissue and inhibiting the inflammatory process that contributes to fistula development [8].

This clinical challenge has prompted the exploration of novel therapeutic approaches, one of which is stem cell therapy. Stem cells, with their ability to self-renew and differentiate into various cell types, have been proposed as a potential treatment for CD, especially in patients who are refractory to current therapies [9]. Multiple types of stem cells, such as hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and adipose-derived stem cells (ADSCs), have been investigated in this context. The proposed mechanism of action includes the modulation of immune response, promotion of tissue regeneration, and the secretion of anti-inflammatory molecules [10,11].

Stem cell therapy has emerged as a promising approach for fistulizing CD, supported by

laboratory studies showing its potential mechanisms of action. Laboratory research suggests that stem cells could effectively treat fistulizing CD due to their unique properties [6,12]:

1. Immune Modulation: Stem cells have been shown to modulate immune responses, potentially reducing the chronic inflammation characteristic of CD. They can alter the function of various immune cells, including T cells, B cells, and dendritic cells, leading to reduced inflammation and tissue damage.
2. Tissue Regeneration: One of the critical challenges in treating fistulizing CD is the healing of fistulas. Laboratory studies indicate that stem cells can promote the regeneration of damaged tissue. They secrete growth factors and cytokines that stimulate tissue repair and regeneration, which is crucial for healing fistulas.
3. Anti-inflammatory Effects: Stem cells can secrete anti-inflammatory molecules, which help in reducing inflammation locally in the gut. This action can be particularly beneficial in managing the inflammatory processes that contribute to fistula formation.
4. Angiogenesis: Some studies have also highlighted the role of stem cells in promoting angiogenesis, the formation of new blood vessels, which is essential for healing and tissue repair.

Incorporating these insights from laboratory studies, stem cell therapy presents a novel treatment avenue for fistulizing CD. However, this approach is still in the experimental phase, and more research is needed to standardize treatments and fully understand the efficacy and safety profiles of various stem cell therapies.

This systematic review aims to evaluate the current evidence on the use of various forms of stem cell therapy in the treatment of Crohn's Disease. Specifically, we aim to assess the efficacy and safety outcomes reported in both randomized controlled trials and non-randomized clinical trials. The findings of this review will shed light on the potential of stem cell therapy as a therapeutic option for patients with CD and guide future research directions in this rapidly evolving field.

2. METHODS

2.1 Eligibility Criteria

- Participants: Studies involving patients diagnosed with Crohn's Disease were included. Both adult and pediatric populations were considered due to the chronic nature of the disease that can manifest early in life.
- Intervention: Studies investigating various forms of stem cell therapy in the treatment of Crohn's Disease were included.
- Study Design: Both randomized controlled trials (RCTs) and non-randomized clinical trials were considered.
- Outcome Measures: Studies must have reported efficacy and safety outcomes of the stem cell therapies in Crohn's Disease. These could include clinical remission rates, healing rates, changes in disease activity indices, and reported adverse events.

2.2 Exclusion Criteria

- Studies were excluded if they did not focus on Crohn's Disease or did not use stem cell therapy as an intervention.
- Case reports, review articles, and studies with incomplete or insufficient data were also excluded.

2.3 Information Sources

We searched the following databases: PubMed, Embase, and Cochrane Library. Additionally, manual searches were conducted in relevant conference proceedings and in the bibliographies of included studies to identify potential additional eligible studies. The search was limited to studies published in English involving human subjects.

2.4 Search Strategy

The search strategy included a combination of Medical Subject Headings (MeSH) and free-text terms such as "Crohn's Disease", "Stem cell therapy", "Mesenchymal Stem Cells", "Adipose-derived Stem Cells", "Autologous Hematopoietic Stem Cell Transplantation", among others. The search was conducted until June 2023.

2.5 Study Selection

Titles and abstracts of studies retrieved using the search strategy were screened independently by two reviewers for eligibility. Full-text articles of potentially eligible studies were then retrieved and further assessed against the inclusion and exclusion criteria. Disagreements were resolved through consensus or third-party arbitration.

2.6 Data Extraction and Synthesis

Data extraction was conducted by two independent reviewers. The extracted data included study characteristics (author, year of publication, study design), participant demographics, intervention details, outcome measures, and time-point-based findings, findings based on anti-TNF therapy status, and adverse events. Data were synthesized narratively given the heterogeneity of interventions and outcome measures. Findings from the included studies were reported descriptively, highlighting the strengths and weaknesses of each study and emphasizing the implications for clinical practice and future research directions.

3. RESULTS

Of the 313 studies identified, 32 duplicates were removed. The title and abstract screening were conducted for 281 studies. In total, 28 studies were reviewed with full texts, of which 6 were included in this systematic review. The PRISMA flowchart is depicted in Fig. 1. The characteristics of the included trials are presented in Table 1. were reviewed with full texts, of which 6 were included in this systematic review. The PRISMA flowchart.

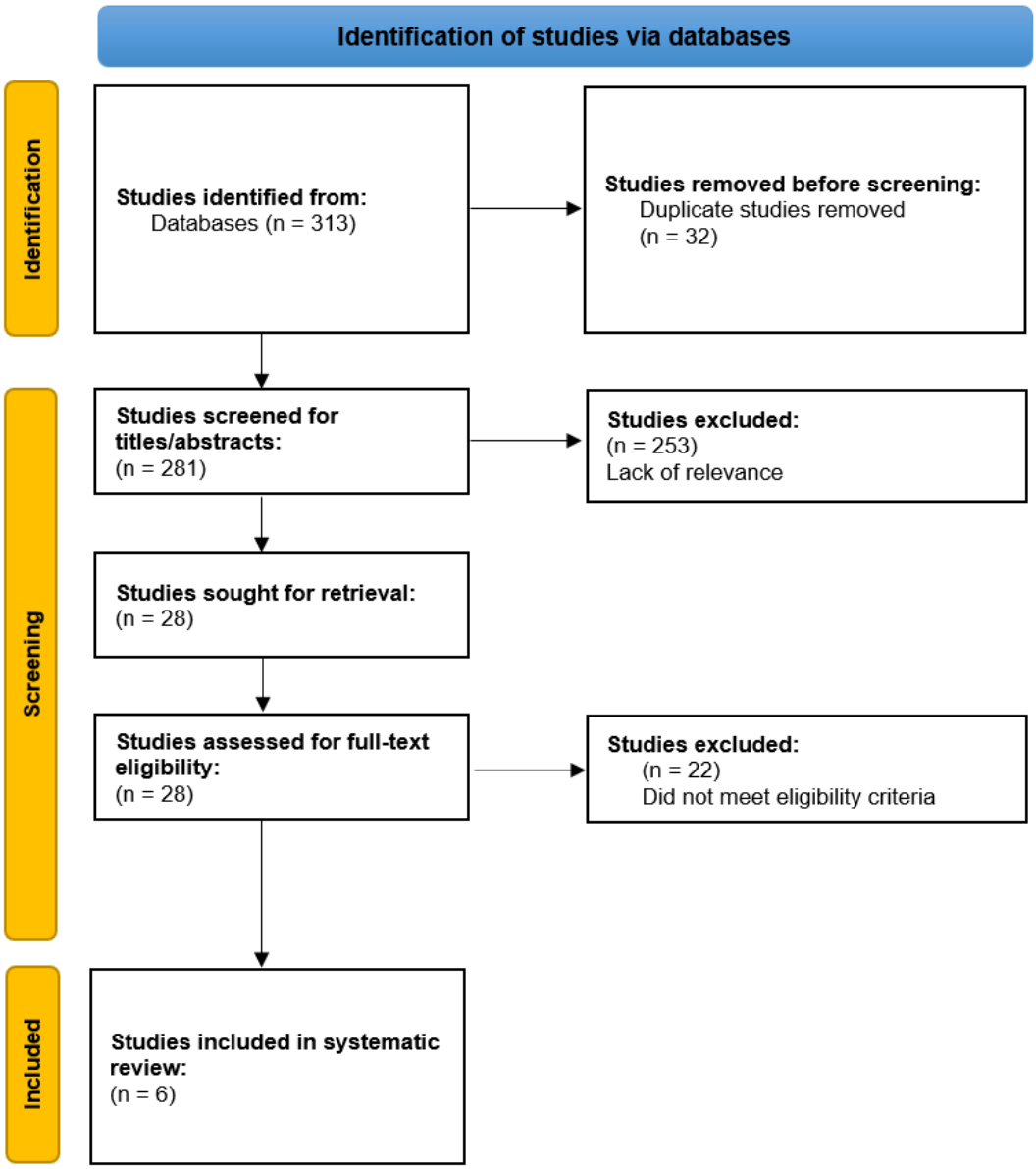

Fig. 1. PRISMA flowchart representing the study selection process

Table 1. Characteristics of the included trials (N=6)

Author, Year	Title	Study Type	Intervention	Inclusion Criteria	Primary Outcomes	N	Time-Point-Based Findings	Findings Based on Anti-TNF Therapy Status	Adverse Events
Garcia-Olmo, 2022 [13]	Follow-up Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel (Mesenchymal Stem Cell Treatment) in Patients With Perianal Fistulizing Crohn's Disease: ADMIRE-CD Phase 3 Randomized Controlled Trial	Phase 3 double-blind randomized controlled study	Darvadstrocel or saline solution (control group)	Patients with Crohn's disease and complex perianal fistulas	Clinical remission at week 104	40	-**Week 24:** Clinical remission was observed in 16 out of 25 patients (64%). -**Week 52:** Clinical remission increased to 20 out of 25 patients (80%). -**Week 104:** Clinical remission was reported in 14 out of 25 patients (56%)	**Patients on Anti-TNF Therapy:** Darvadstrocel Group: 10 out of 17 patients (59%) achieved clinical remission. Control Group: 3 out of 10 patients (30%) achieved clinical remission. **Patients Off Anti-TNF Therapy:** Darvadstrocel Group: 4 out of 8 patients (50%) achieved clinical remission. Control Group: 3 out of 5 patients (60%) achieved clinical remission	7 treatment-emergent serious adverse events were reported through week 104
Panés, 2018 & Panés, 2016; [14,15]	Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease	Randomized placebo-controlled trial	Single local injection of 120 million Cx601 cells or placebo (control)	Patients with Crohn's disease and treatment-refractory, draining, complex perianal fistulas	Combined remission and clinical remission at week 52	212	-**Week 24:** Clinical remission was achieved in 57 out of 103 patients (55.3%) in the Cx601 group, compared to 43 out of 101 patients (42.6%) in the control group. -**Week 52:** Clinical remission was reported in 61 out of 103 patients (59.2%) in the Cx601 group and 42 out of 101 patients (41.6%) in the control group. This reflects a significant treatment difference of 17.6 percentage points (P = .013).	None reported	Adverse events occurred in 76.7% of patients in the Cx601 group and 72.5% of patients in the control group
Zhou, 2020	Autologous adipose-	Clinical trial	Autologous	Patients with	Closure of	22	-**Month 3:** Healing rates	None reported	Adverse

Author, Year	Title	Study Type	Intervention	Inclusion Criteria	Primary Outcomes	N	Time-Point-Based Findings	Findings Based on Anti-TNF Therapy Status	Adverse Events
[16]	derived stem cells for the treatment of Crohn's fistula-in-ano: an open-label, controlled trial		adipose-derived stem cell (ADSC) vs incision-thread-drawing procedure	Crohn's fistula-in-ano	fistulas at months 3, 6, and 12		were 90.9% in the observation group and 45.5% in the control group. -**Month 6:** Healing rates were 72.7% in the observation group and 54.5% in the control group. -**Month 12:** Healing rates were 63.6% in the observation group and 54.5% in the control group.		events occurred in 63.6% of patients in the observation group and 100% patients in the control group. No adverse event associated with ADSC injection
Zhang, 2018 [17]	Umbilical Cord Mesenchymal Stem Cell Treatment for Crohn's Disease: A Randomized Controlled Clinical Trial	Randomized control trial	Peripheral intravenous infusions of 1×106 UC-MSCs/kg, once per week	CD patients who had received steroid maintenance therapy for more than 6 months	CDAI, HBI, corticosteroid dosage	82	-**Week 24:** Clinical remission was reported in 16 out of 25 patients (64%). -**Week 52:** Clinical remission increased to 20 out of 25 patients (80%). -**Week 104:** Clinical remission was reported in 14 out of 25 patients (56%).	**Darvadstrocel Treatment Group:** Patients on Anti-TNF Therapy: Clinical remission in 10 out of 17 patients (59%). Patients not on Anti-TNF Therapy: Clinical remission in 4 out of 8 patients (50%). **Control Group:** Patients on Anti-TNF Therapy: Clinical remission in 3 out of 10 patients (30%). Patients not on Anti-TNF Therapy: Clinical remission in 3 out of 5 patients (60%).	Four patients developed a fever after cell infusion, no serious adverse events
Lindsay, 2017 & Hawkey, 2015 [18,19]	Autologous hematopoetic stem cell transplantation for refractory Crohn disease: a randomized clinical trial	Randomized controlled trial	Mobilisation and autologous HSCT	Patients with treatment-refractory CD	3-month steroid-free clinical remission at 1 year after HSCT,	45	-**Primary Outcome of Steroid-Free Clinical Remission for Three Months:** Occurred in 38.2% (13/34) of patients.	**Reintroduction of Anti-TNF Therapy:** Required in 18% (7 patients) of the HSCT group after a median of 18 weeks. **Response to**	76 serious adverse events occurred in 23 of 40 patients

Author, Year	Title	Study Type	Intervention	Inclusion Criteria	Primary Outcomes	N	Time-Point-Based Findings	Findings Based on Anti-TNF Therapy Status	Adverse Events
					degree of endoscopic healing		-**Remission for 3 Months Off All Medical Therapies:** Achieved by 35.3% (12/34) of patients. -**Steroid-Free Remission at One Year:** Achieved by 43.2% (16/37) of patients. -**Complete and Partial Endoscopic Healing at One Year:** Achieved in 50% (19/38) and 81.6% (31/38) of patients, respectively. -**Free from Evidence of Intestinal Ulceration at One Year:** 47.4% (18/38) of patients.	**Reintroduction of Anti-TNF Therapy:** Significant reduction in mean Crohn's Disease Activity Index (CDAI) from 319 to 174 (p=0.016), with 71.4% (5 patients) experiencing a clinical response (reduction of CDAI > 70 points).	with available data, mostly treatment-related infections
Jauregui-Amezaga, 2016 [20]	Improving safety of autologous haematopoietic stem cell transplantation in patients with Crohn's disease	Prospective study	Autologous HSCT	Patients with refractory CD with impaired quality of life and in whom surgery was not an acceptable option	Toxicity and complications during the procedure and within the first year following transplantation	26	-**Steroid-Free Clinical Remission for Three Months:** Achieved by 38.2% (13/34) of patients. -**Remission for Three Months Off All Medical Therapies:** Reported in 35.3% (12/34) of patients. -**Steroid-Free Remission at One Year:** Attained by 43.2% (16/37) of patients. -**Endoscopic Healing (Complete and Partial) at One Year:** Complete healing in 50% (19/38) and partial healing in 81.6% (31/38) of	None reported	16 patients presented febrile neutropaenia during mobilisation, including one bacteraemia and two septic shocks; one patient died due to systemic cytomegalovirus infection

Author, Year	Title	Study Type	Intervention	Inclusion Criteria	Primary Outcomes	N	Time-Point-Based Findings	Findings Based on Anti-TNF Therapy Status	Adverse Events
							patients. -**Free from Evidence of Intestinal Ulceration at One Year:** Observed in 47.4% (18/38) of patients.		

Abreviations: ADSC: Autologous Adipose-Derived Stem Cell; CD: Crohn's Disease; CDAI: Crohn's Disease Activity Index; HSCT: Hematopoetic Stem Cell Transplantation; HBI: Harvey-Bradshaw Index; UC-MSCs: Umbilical Cord Mesenchymal Stem Cells; TNF: Tumor Necrosis Factor.

The ADMIRE-CD Phase 3 Randomized Controlled Trial by Garcia-Olmo in 2022, involving Darvadstrocel or saline solution for patients with complex perianal fistulas, reported clinical remission at week 104 in 40 patients. At week 24, 64% achieved clinical remission, increasing to 80% at week 52, and 56% at week 104. In the darvadstrocel group, 59% of patients on anti-TNF therapy and 50% off anti-TNF therapy achieved remission, compared to 30% and 60%, respectively, in the control group. Seven serious adverse events emerged during the study.

Panés' [14] and [15] randomized placebo-controlled trials involving 212 patients with treatment-refractory, draining, complex perianal fistulas demonstrated that Cx601, a mesenchymal stem cell treatment, led to clinical remission in 55.3% of patients at week 24 and 59.2% at week 52. The control group saw a lower remission rate of 42.6% and 41.6%, respectively, with adverse events reported in 76.7% of the Cx601 group and 72.5% of the control group.

Zhou's [16] open-label, controlled trial with 22 patients, compared autologous adipose-derived stem cells to the incision-thread-drawing procedure for Crohn's fistula-in-ano. Healing rates at 3, 6, and 12 months were 90.9%, 72.7%, and 63.6% in the observation group, significantly higher than the control group. Adverse events occurred in 63.6% of the observation group, with none directly related to stem cell injection.

Zhang's [17] study on umbilical cord mesenchymal stem cell treatment for 82 Crohn's disease patients, who had received steroid maintenance therapy, reported similar findings to Garcia-Olmo's study regarding clinical remission and anti-TNF therapy status, with four patients developing a fever post-infusion, but no serious adverse events.

Lindsay and Hawkey's [18] and [19] randomized clinical trials on autologous hematopoetic stem cell transplantation for refractory Crohn's disease involved 45 patients. The primary outcome of steroid-free clinical remission for three months was achieved by 38.2% of patients, with 35.3% in remission off all medical therapies, and 43.2% in steroid-free remission at one year. Complete and partial endoscopic healing at one year was observed in 50% and 81.6% of patients, respectively. Reintroduction of anti-TNF therapy was required in 18% of patients post-HSCT. Adverse events were predominantly treatment-related infections, occurring in 76 cases among 40 patients.

Lastly, Jauregui-Amezaga's [20] prospective study on autologous HSCT for 26 patients with refractory Crohn's disease reported similar efficacy outcomes to Lindsay and Hawkey's study. Febrile neutropaenia was a significant issue, occurring in 16 patients, and one patient died due to systemic cytomegalovirus infection.

These studies collectively provide valuable insights into the potential of stem cell therapies for treating fistulizing Crohn's disease, demonstrating varying levels of efficacy, concerns regarding safety and adverse events, and the influence of anti-TNF therapy status on treatment outcomes.

4. DISCUSSION

Our systematic review comprehensively analyzed 6 studies, encompassing a total of 427 participants, all of whom were undergoing various stem cell-based therapies for Crohn's disease.
The series of studies reviewed in the systematic analysis highlight the evolving landscape of stem cell therapy in the treatment of fistulizing CD, particularly focusing on autologous transplantation trials. The discussion of these studies presents a nuanced picture of the current state and future perspectives of this innovative therapeutic approach.

Garcia-Olmo's ADMIRE-CD Phase 3 Trial [13] showcases the efficacy of Darvadstrocel in complex perianal fistulas. Notably, the sustained clinical remission over time, with a peak at week 52, underscores the potential of mesenchymal stem cell therapy. The differentiation in response based on anti-TNF therapy status (59% in patients on anti-TNF vs. 50% in patients off anti-TNF) highlights the need for personalized treatment strategies in CD management. However, the occurrence of serious adverse events signals the necessity for a balanced approach considering safety and efficacy.

Panés' Trials (2018 & 2016) on Cx601 further reinforce the therapeutic promise of mesenchymal stem cells. The clinical remission rates surpassing those of the control group indicate a significant step forward in managing refractory fistulizing CD. The high incidence of adverse events, though, raises concerns about

the tolerability and long-term safety of this intervention.

Zhou's 2020 Trial comparing autologous adipose-derived stem cells with a surgical procedure reveals a substantial healing advantage in the stem cell treatment group. This outcome emphasizes the potential of stem cell therapies in offering less invasive yet effective alternatives to traditional surgical interventions. The lack of adverse events directly related to stem cell injections is encouraging, suggesting a favorable safety profile.

Zhang's 2018 Study on umbilical cord mesenchymal stem cells echoes the findings of Garcia-Olmo's study, providing further evidence for the efficacy of stem cell therapy in CD, albeit with a need for more extensive research on long-term outcomes and safety, as indicated by the fever developed in some patients post-infusion.

Lindsay and Hawkey's Trials [18], along with Jauregui-Amezaga's 2016 Study, focus on autologous hematopoietic stem cell transplantation (HSCT) in refractory CD. These trials collectively highlight the potential of HSCT in inducing clinical remission and endoscopic healing. The need for reintroduction of anti-TNF therapy in a subset of patients post-HSCT indicates that while HSCT can be effective, it may not be a definitive solution for all patients. The occurrence of febrile neutropaenia and other serious adverse events, including a fatality, underscores the risks associated with this approach, necessitating careful patient selection and monitoring.

In general, autologous hematopoietic stem cell transplantation has been used since 1996 for the treatment of severe autoimmune diseases refractory to approved therapies [21]. It is however important to recognize that effectively managing perianal fistulizing Crohn's Disease involves a multidisciplinary approach, where both gastroenterologists and surgeons play critical roles. This includes utilizing therapies based on scientific evidence, alongside necessary surgical evaluations and procedures [22].

Examining our findings in the context of existing literature, we discern an encouraging pattern that supports the efficacy of stem cell therapies in the management of Crohn's disease [23,24]. Amongst the different types of therapies, mesenchymal stem cells and autologous adipose-derived stem cells appear to consistently deliver positive results. However, this optimistic narrative must also be balanced with the recognition of the associated adverse events, emphasizing the need for a carefully tailored and patient-centric application of these therapies.

In contrast, the outcomes related to autologous hematopoietic stem cell transplantation appear more inconsistent. Although there are some indications of potential benefits like steroid-free remission and complete endoscopic healing, the notable number of serious adverse events demand a more careful assessment of the safety and feasibility of this therapeutic strategy [25]. These observations are in harmony with the broader research community, which has also reported mixed results, indicating a need for more in-depth investigation into this treatment modality.

Our analysis also brought attention to the potential benefits of using umbilical cord mesenchymal stem cells, a relatively less explored form of stem cell therapy for Crohn's disease. Though our included study showed promising outcomes, there is a notable scarcity of extensive research on this therapeutic approach compared to others, suggesting the need for further exploration.

Similarly, the role of vedolizumab in the treatment of steroid-refractory intestinal acute graft-versus-host disease, as presented in our included study, did not align completely with the mixed findings reported in the existing literature [26]. The lack of meeting the primary efficacy endpoint in our included study strengthens the call for more comprehensive and systematic research to affirm vedolizumab's role and efficacy in managing this condition.

When considering the broader scope of Crohn's disease management, it is crucial to recognize the highly complex and variable nature of the disease. This heterogeneity demands a multifaceted and comprehensive therapeutic strategy, where stem cell therapies could potentially play a crucial role.

Despite significant advancements in understanding and treating Crohn's disease, it remains a chronic condition requiring life-long management. Hence, it's imperative that therapeutic approaches not only aim for inducing remission but also focus on maintaining remission, improving the patient's quality of life, and minimizing potential treatment-related side effects. Consequently, our evaluation of stem cell

therapies should also take these critical parameters into account.

While stem cell therapies hold promising potential for managing Crohn's disease, our findings also reveal that the effectiveness and safety profiles of different treatment modalities can vary significantly. These differences highlight the need for a tailored and risk-stratified therapeutic strategy that balances the potential benefits of stem cell therapies against their risks, in the context of each patient's unique disease characteristics and prognosis.

The findings of our systematic review also point towards the need for more robust, long-term studies to further clarify the long-term impacts and potential complications associated with stem cell therapies. Furthermore, refining therapeutic protocols and establishing firm criteria for patient selection will also be crucial moving forward. By expanding our knowledge base in this field, we can enhance our understanding of stem cell therapies' potential and create a more effective and safer therapeutic approach to Crohn's disease.

5. CONCLUSION

This systematic review offers an in-depth and comprehensive exploration of the role of stem cell therapies in treating Crohn's disease. Our findings indicate the potential efficacy of several forms of stem cell therapies, including mesenchymal stem cells, autologous adipose-derived stem cells, and umbilical cord mesenchymal stem cells, amongst others. However, the results also underline the complexity and variability associated with these therapies, reflecting the heterogenous nature of Crohn's disease itself. The review further emphasizes the importance of a patient-centric approach, weighing the potential benefits against the associated risks. It also highlights the need for further research, particularly focusing on the long-term effects and safety of these therapies. While stem cell therapies may not be a panacea, they represent a promising avenue for the development of more effective and personalized therapeutic strategies for Crohn's disease. By continuing to expand our understanding in this field, hope to improve the quality of life for patients living with this chronic and often debilitating condition.

6. LIMITATIONS AND STRENGTHS

Our systematic review is subject to certain limitations. Primarily, the included studies varied in terms of their design, intervention methods, and outcome measurements, which may introduce heterogeneity into our findings. Moreover, some studies reported a considerable number of adverse events, indicating the need for more extensive investigations on the safety and tolerability of these therapies. Lastly, most of the included trials had relatively short follow-up periods, limiting the ability to evaluate long-term efficacy and potential late-onset complications.

However, this review also has several strengths that enhance its validity and utility. It includes a comprehensive and systematic assessment of the literature on stem cell therapies for Crohn's disease, incorporating studies with diverse designs and interventions. This broad scope allows for an encompassing overview of the current state of research in this area. Furthermore, the rigorous inclusion criteria and thorough synthesis of data ensure the robustness of our findings. Finally, this review emphasizes the need for patient-centered therapeutic strategies, highlighting the importance of balancing benefits and risks.

7. FUTURE PERSPECTIVES

These studies collectively demonstrate the potential of various stem cell therapies in the management of fistulizing Crohn's Disease. They pave the way for future research, which should focus on optimizing patient selection criteria, determining the long-term safety and efficacy of these therapies, and understanding the mechanisms underlying their therapeutic actions. Personalized medicine approaches, considering individual patient's response to anti-TNF therapies and other medical histories, will be crucial in tailoring stem cell therapies for optimal outcomes. Furthermore, the development of standardized protocols and guidelines will be essential in integrating these novel therapies into clinical practice, ensuring both safety and efficacy for patients with fistulizing Crohn's Disease.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Papadakis KA, Targan SR. Current theories on the causes of inflammatory bowel disease. Gastroenterol Clin North Am. 1999;28(2):283–96.
2. Abautret-Daly Á, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut–brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. Acta Neuropsychiatr. 2018;30(5):275–96.
3. Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis. 2002;8(4):244–50.
4. Pfefferkorn MD, Marshalleck FE, Saeed SA, Splawski JB, Linden BC, Weston BF. NASPGHAN clinical report on the evaluation and treatment of pediatric patients with internal penetrating Crohn disease: intraabdominal abscess with and without fistula. J Pediatr Gastroenterol Nutr. 2013;57(3):394–400.
5. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. Stem Cell Res Ther. 2019;10(1):1–22.
6. Carvello M, Lightner A, Yamamoto T, Kotze PG, Spinelli A. Mesenchymal stem cells for perianal Crohn's disease. Cells. 2019;8(7):764.
7. del Pilar Martínez-Montiel M, Gómez-Gómez GJ, Flores AI. Therapy with stem cells in inflammatory bowel disease. World J Gastroenterol WJG. 2014;20(5):1211.
8. Vosough M, Nikfam S, Torabi S, Sadri B, Amoli HA, Basi A, et al. Mesenchymal stromal cell therapy improves refractory perianal fistula in crohn's disease: case series clinical interventional study. Cell J. 2022;24(2):62.
9. Jasim SA, Yumashev AV, Abdelbasset WK, Margiana R, Markov A, Suksatan W, et al. Shining the light on clinical application of mesenchymal stem cell therapy in autoimmune diseases. Stem Cell Res Ther. 2022;13(1):1–15.
10. Julier Z, Park AJ, Briquez PS, Martino MM. Promoting tissue regeneration by modulating the immune system. Acta Biomater. 2017;53:13–28.
11. Arabpour M, Saghazadeh A, Rezaei N. Anti-inflammatory and M2 macrophage polarization-promoting effect of mesenchymal stem cell-derived exosomes. Int Immunopharmacol. 2021;97:107823.
12. 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(1):1–11.
13. Garcia-Olmo D, Gilaberte I, Binek M, Lindner D, Selvaggi F, Spinelli A, et al. Follow-up study to evaluate the long-term safety and efficacy of darvadstrocel (mesenchymal stem cell treatment) in patients with perianal fistulizing crohn's disease: ADMIRE-CD phase 3 randomized controlled trial. Dis Colon Rectum. 2022;65(5):713.
14. Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, et al. Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. Gastroenterology. 2018;154(5):1334–42.
15. Panés J, García-Olmo D, Van Assche G, Colombel JF, Reinisch W, Baumgart DC, 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(10051):1281–90.
16. Zhou C, Li M, Zhang Y, Ni M, Wang Y, Xu D, 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(1):1–13.
17. Zhang J, Lv S, Liu X, Song B, Shi L. Umbilical cord mesenchymal stem cell treatment for Crohn's disease: a randomized controlled clinical trial. Gut Liver. 2018;12(1):73.
18. Lindsay JO, Allez M, Clark M, Labopin M, Ricart E, Rogler G, et al. Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial. Lancet Gastroenterol Hepatol. 2017;2(6):399–406.
19. Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, et al. Autologous hematopoetic stem cell transplantation for refractory Crohn disease: a randomized clinical trial. Jama. 2015;314(23):2524–34.
20. Jauregui-Amezaga A, Rovira M, Marín P, Salas A, Pinó-Donnay S, Feu F, et al. Improving safety of autologous haematopoietic stem cell transplantation in patients with Crohn's disease. Gut. 2016;65(9):1456–62.

21. Farge D, Labopin M, Tyndall A, Fassas A, Mancardi GL, Van Laar J, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. Haematologica. 2010;95(2):284.
22. Steinhart AH, Panaccione R, Targownik L, Bressler B, Khanna R, Marshall JK, et al. Clinical practice guideline for the medical management of perianal fistulizing Crohn's disease: the Toronto consensus. Inflamm Bowel Dis. 2019;25(1):1–13.
23. Lightner AL, Faubion WA. Mesenchymal stem cell injections for the treatment of perianal Crohn's disease: What we have accomplished and what we still need to do. J Crohn's Colitis. 2017;11(10):1267–76.
24. 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(5):629–40.
25. Benitez J-M, Meuwis M-A, Reenaers C, Van Kemseke C, Meunier P, Louis E. Role of endoscopy, cross-sectional imaging and biomarkers in Crohn's disease monitoring. Gut. 2013;62(12):1806–16.
26. Coltoff A, Lancman G, Kim S, Steinberg A. Vedolizumab for treatment of steroid-refractory lower gastrointestinal acute graft-versus-host disease. Bone Marrow Transplant. 2018;53(7):900–4.

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