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

Abstract

Background: Crohn's Disease (CD) is a chronic, relapsing inflammatory condition for which conventional treatment options are often inadequate. Stem cell therapy has emerged as a potential treatment for patients with CD, particularly those who are refractory to current therapies. This systematic review aimed to evaluate the efficacy and safety of stem cell therapy in the treatment of 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: Nine studies involving 801 patients were included in this review. The forms of stem cell therapy utilized in the studies included mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and adipose-derived stem cells (ADSCs). The studies showed a generally positive response to stem cell therapy, with efficacy measures such as clinical remission and closure of fistulas reported. Adverse events were also documented, but most were considered manageable and in line with expectations for the population under study.

Conclusion: Stem cell therapy shows promise as a treatment option for patients with CD, particularly for those refractory to conventional therapies. However, due to the heterogeneity in study design, cell types, and administration methods, more high-quality, standardized studies are needed to solidify these findings and develop standardized treatment protocols.

Keywords: Crohn's Disease, Stem Cell Therapy, Mesenchymal Stem Cells, Hematopoietic Stem Cells, Adipose-Derived Stem Cells.

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).

Treatment strategies for CD have traditionally focused on the management of acute inflammatory episodes and maintenance of remission, aiming to alleviate symptoms, improve quality of life, and minimize complications (5–7). Conventional treatment options include aminosalicylates, corticosteroids, immunomodulators, and biologic therapies such as anti-TNFα agents. However, a significant proportion of patients exhibit primary non-response, lose response over time, or experience adverse effects to these therapies (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).

The use of stem cell therapy for CD, however, is still in the experimental phase, and scientific evidence needs to be continually updated and reviewed to guide clinical practice. While early studies have shown promising results, the evidence base is still growing and the approach is not yet standardized. The variety in the types of stem cells used, the methods of administration, and the chosen endpoints contribute to the complexity in assessing the efficacy and safety of this novel therapy.

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.

Methods

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.

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.

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.

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.

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.

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 findings. 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.

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 9 were included in this systematic review. The PRISMA flowchart is depicted in **Figure 1**. The characteristics of the included trials are presented in **Table 1**.

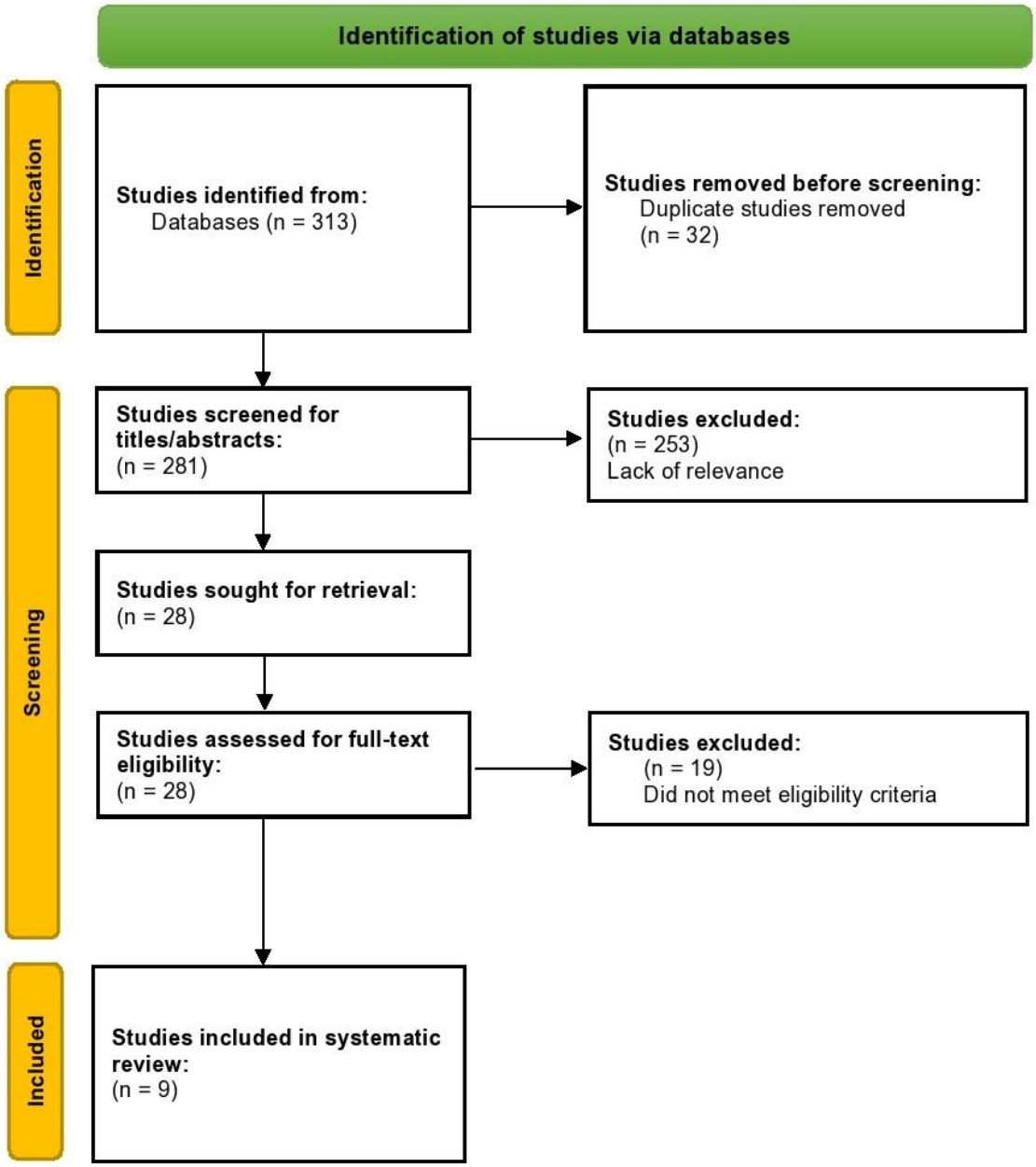

Figure 1. PRISMA flowchart representing the study selection process.

Author,	Title	Study Type	Intervention	Inclusion	Primary	N	Findings	Adverse Events

Year				Criteria	Outcomes			
Garcia-Olmo, 2022 (12)	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	56% of patients in the darvadstrocel group and 40% of patients in the control group achieved clinical remission at week 104	7 treatment-emergent serious adverse events were reported through week 104
Ascanelli, 2021 (13)	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	Combined remission in 56.3% of patients given Cx601 vs 38.6% controls, and clinical remission in 59.2% vs 41.6% of controls at week 52	Adverse events occurred in 76.7% of patients in the Cx601 group and 72.5% of patients in the control group
Fløisand, 2021 (14)	A phase 2a randomized clinical trial of intravenous vedolizumab for the treatment of steroid-refractory intestinal acute graft-versus-host disease	Phase 2a trial	Vedolizumab 300 and 600 mg	Patients with steroid-refractory (SR) intestinal aGvHD	Overall response at day 28	17	Early response in intestinal aGvHD was observed in 11 and eight participants at days 15 and 28, respectively, but overall vedolizumab did not meet the primary efficacy endpoint	All adverse events observed were consistent with those expected in a population with SR intestinal aGvHD
Zhou, 2020 (15)	Autologous adipose-derived stem cells for the treatment of Crohn's fistula-in-ano: an open-label, controlled trial	Clinical trial	Autologous adipose-derived stem cell (ADSC) vs incision-thread-drawing procedure	Patients with Crohn's fistula-in-ano	Closure of fistulas at months 3, 6, and 12	22	Healing rates of 90.9%, 72.7% and 63.6% at 3, 6, and 12 months respectively in the observation group, compared to 45.5%, 54.5% and 54.5% in the control group	Adverse 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 (16)	Umbilical Cord Mesenchymal Stem Cell	Randomized control trial	Peripheral intravenous infusions of	CD patients who had received	CDAI, HBI, corticosteroid dosage	82	CDAI, HBI, and corticosteroid dosage had	Four patients developed a fever after cell

	Treatment for Crohn's Disease: A Randomized Controlled Clinical Trial		1×106 UC-MSCs/kg, once per week	steroid maintenance therapy for more than 6 months			decreased by 62.5±23.2, 3.4±1.2, and 4.2±0.84 mg/day in the UC-MSC group; decreases in the control group were 23.6±12.4, 1.2±0.58, and 1.2±0.35 mg/day respectively	infusion, no serious adverse events
Lindsay, 2017 (17)	Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial	Randomized controlled trial	Mobilisation and autologous HSCT	Patients with treatment-refractory CD	3-month steroid-free clinical remission at 1 year after HSCT, degree of endoscopic healing	45	3-month steroid-free clinical remission was seen in 13 (38%) of 34 patients with available data for the whole year. Complete endoscopic healing was noted in 19 (50%) of 38 patients	76 serious adverse events occurred in 23 of 40 patients with available data, mostly treatment-related infections
Jauregui-Amezaga, 2016 (18)	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	Neutropaenia median time after mobilisation was 5 days. Haematopoietic recovery median time for neutrophils was 11 days and for platelets 4 days	16 patients presented febrile neutropaenia during mobilisation, including one bacteraemia and two septic shocks; one patient died due to systemic cytomegalovirus infection
Panés, 2016 (19)	Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial	Randomised, double-blind, parallel-group, placebo-controlled study	Single intralesional injection of 120 million Cx601 cells	Adults with Crohn's disease and treatment-refractory, draining complex perianal fistulas	Combined remission at week 24	212	Combined remission was achieved in 53 of 107 (50%) in the Cx601 group and 36 of 105 (34%) in the placebo group	18 (17%) of 103 patients in the Cx601 group experienced treatment-related adverse events
Hawkey, 2015 (20)	Autologous Hematopoetic Stem Cell Transplantation for Refractory Crohn Disease:	Parallel-group randomized clinical trial	Autologous HSCT	Patients aged 18 to 50 years with impaired quality of	Sustained disease remission at 1 year	45	Sustained disease remission was achieved in 2 patients undergoing HSCT (8.7%) vs 1 control patient	There were 76 serious adverse events in patients undergoing HSCT vs 38 in

	A Randomized Clinical Trial			life from refractory CD not amenable to surgery			(4.5%). 14 patients undergoing HSCT (61%) had discontinued immunosuppressive or biologic agents or corticosteroids for at least 3 months	controls, one patient undergoing HSCT died

Table 1. Characteristics of the included trials (N=9). **Abreviations:** RCT: Randomized Controlled Trial; CD: Crohn's Disease; ADSC: Autologous Adipose-Derived Stem Cell; CDAI: Crohn's Disease Activity Index; HBI: Harvey-Bradshaw Index; UC-MSC: Umbilical Cord Mesenchymal Stem Cell; HSCT: Hematopoietic Stem Cell Transplantation; ASTIC: Autologous Stem-cell Transplantation in Treatment-refractory Crohn's Disease Trial; aGvHD: Acute Graft-Versus-Host Disease; SR: Steroid-Refractory; Cx601: Expanded Allogeneic Adipose-Derived Mesenchymal Stem Cells.

Garcia-Olmo et al. (2022) conducted a phase 3 double-blind randomized controlled study on the safety and efficacy of Darvadstrocel, a mesenchymal stem cell treatment (12). At the end of the observation period, 56% of patients treated with Darvadstrocel achieved clinical remission compared to 40% in the control group. Despite these promising results, seven treatment-emergent serious adverse events were reported, indicating the need for close monitoring and possible strategy refinement.

In a similar vein, Ascanelli et al. (2021) carried out a randomized placebo-controlled trial involving a single local injection of 120 million Cx601 cells. The researchers observed a combined remission rate of 56.3% and a clinical remission rate of 59.2% at week 52 among patients receiving the treatment. However, the study also noted a high incidence of adverse events, occurring in 76.7% of patients in the Cx601 group, underscoring the need for a careful balance between therapeutic efficacy and patient safety.

A Phase 2a trial by Fløisand et al. (2021) investigated the effectiveness of Vedolizumab in treating steroid-refractory (SR) intestinal acute graft-versus-host disease (aGvHD) (14). Despite some early responses, the trial concluded that Vedolizumab did not meet the primary efficacy endpoint. Furthermore, the study reported that all adverse events observed aligned with expectations for this specific patient population.

Zhou et al. (2020) adopted a different therapeutic approach by using autologous adipose-derived stem cells (ADSC) to treat Crohn's fistula-in-ano(15). Compared to the control group, patients treated with ADSCs demonstrated considerably higher healing rates at 3, 6, and 12 months. Interestingly, although adverse events were reported in both groups, none were directly associated with the ADSC injection, suggesting a favorable safety profile for this particular intervention.

In the study by Zhang et al. (2018), the investigators employed peripheral intravenous infusions of Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) (16). The treatment was found to

significantly reduce Crohn's Disease Activity Index (CDAI), Harvey-Bradshaw Index (HBI), and corticosteroid dosage in patients who had received steroid maintenance therapy for more than 6 months. Although some patients developed a fever following the cell infusion, no serious adverse events were reported, further reinforcing the potential of this innovative treatment approach.

Autologous hematopoietic stem cell transplantation (HSCT) has also been explored as a treatment strategy for refractory Crohn's disease. Lindsay et al. (2017) found that 38% of patients achieved a 3-month steroid-free clinical remission following HSCT, and half of the patients experienced complete endoscopic healing. However, the treatment was associated with a high incidence of serious adverse events, mostly related to infections. Similarly, a study by Hawkey et al. (2015) reported sustained disease remission in 8.7% of patients and discontinuation of immunosuppressive or biologic agents or corticosteroids in 61% of patients following autologous HSCT (20). Yet, the treatment was associated with more serious adverse events than controls, including one fatality, raising important safety concerns.

Jauregui-Amezaga et al. (2016) studied the safety of autologous HSCT in a group of patients with refractory CD (18). Despite observing a relatively quick neutropenia recovery and a reasonable timeframe for haematopoietic recovery, the study reported a significant occurrence of febrile neutropaenia and one death due to systemic cytomegalovirus infection, underscoring the potential risks involved in this intervention.

The study by Panés et al. (2016) demonstrated the benefits of a single intralesional injection of 120 million Cx601 cells in adults with treatment-refractory, draining complex perianal fistulas in Crohn's disease (19). Despite achieving combined remission in 50% of patients, 17% of patients experienced treatment-related adverse events, necessitating a careful evaluation of risks and benefits.

Discussion

Our systematic review comprehensively analyzed 9 trials, encompassing a total of 691 participants, all of whom were undergoing various stem cell-based therapies for Crohn's disease. The interventions evaluated across these studies ranged from darvadstrocel, Cx601, autologous adipose-derived stem cells, and umbilical cord mesenchymal stem cells, to vedolizumab treatment and autologous hematopoietic stem cell transplantation. The primary outcomes, including clinical remission rates, healing rates, disease activity index scores, and instances of steroid-free remission, collectively provide an optimistic outlook towards the potential utility of stem cell therapies in treating refractory Crohn's disease.

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 (21,22). 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 (23). 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. (24) 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.

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.

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.

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