The Outcomes of Biologic Therapies for Fistulizing Crohn's Disease: A Systematic Review

Abstract

Background: Fistulizing Crohn's Disease (FCD) is a distinct and aggressive subset of Crohn's Disease, contributing to substantial morbidity, hospitalizations, and reduced patient well-being. The intricate interplay of factors influencing FCD outcomes warrants an in-depth exploration to refine patient care and therapeutic strategies.The aim of this paper is to conduct a comprehensive systematic reviewto critically evaluate the effectiveness, safety, and cost-effectiveness of biologic therapies and other interventions for FCD

Methods: In line with the PRISMA Statement 2020 guidelines, we conducted a systematic review. We extensively searched databases including PubMed, Embase, and Cochrane Library, with the last search update on November 5, 2023. Studies evaluating FCD patients were examined, emphasizing the disease's clinical burden and influential parameters. Observational studies that underlined treatments and various FCD management strategies correlating with clinical outcomes were primarily considered for inclusion.

Results: Beginning with an initial review of 438 studies, ten met the inclusion criteria and were incorporated into this systematic review. A total of 1122 patients were included. Spanning the years 2014–2022, the incorporated studies delve into diverse FCD treatment modalities. These range from the use of anti-TNF agents, surgical procedures, stem cell therapies, drug amalgamations, to intensifying dosing regimens. The synthesized findings from these studies carve out a progressively evolving treatment milieu for Crohn's disease, emphasizing the indispensability of individualized and empirically supported therapeutic avenues.

Conclusion:FCD presents a formidable challenge in the realm of inflammatory bowel diseases, impacting patient outcomes. This review accentuates the pivotal nature of comprehensive care, early intervention, and addressing intricate disease mechanisms. The collated evidence highlights an imperative for innovative care modalities, targeted therapeutic endeavors, and tailored interventions to manage FCD more effectively and improve patient prognosis.

Keywords: Fistulizing Crohn's Disease; Therapeutic Strategies; Anti-TNF Therapies; Surgical Interventions; Personalized Treatment; Inflammatory Bowel Diseases; Systematic Review

Introduction

Crohn's Disease (CD) is a type of inflammatory bowel disease (IBD) that can affect any segment of the gastrointestinal tract, from the mouth to the anus(1). Its pathogenesis is multifactorial,

involving genetic, environmental, and microbial factors(2). One of the most challenging complications of CD is the formation of fistulas, particularly those affecting the perianal region(3). Fistulizing Crohn's Disease (FCD) has a significant impact on patients' quality of life, often leading to pain, abscess formation, and even social isolation due to its debilitating symptoms(4).

Fistulas in CD are notoriously difficult to treat. While surgical intervention remains a standard approach, it is often reserved for specific cases given its association with potential post-operative complications, including fecal incontinence. Over the past few decades, the emergence of biologic therapies, particularly anti-tumor necrosis factor (anti-TNF) agents, has revolutionized the treatment landscape of FCD(5). These drugs, designed to target specific inflammatory mediators, have shown promise in inducing and maintaining fistula closure. However, there exists variability in their efficacy, with some patients experiencing complete healing and others showing minimal to no response.

Beyond biologic therapies, other medical and surgical interventions have been explored. From laparoscopic ileocecal resection and seton drainage to the innovative use of adipose-derived stem cells, the search for an optimal, comprehensive treatment strategy for FCD remains ongoing(6,7). This is further complicated by the heterogeneity of patient populations, the variety in fistula characteristics, and differences in disease severity and activity.

This systematic review aims to provide a thorough examination of the recent literature on the outcomes of biologic therapies and other interventions for FCD. By analyzing and synthesizing data from various studies, we seek to offer insights into the comparative efficacy, safety, and cost-effectiveness of these treatments. Additionally, this review will elucidate the current gaps in knowledge and potential avenues for future research.

Methods

This systematic review was conducted adhering to PRISMA Statement 2020 guidelines (8).

Eligibility Criteria

Participants: Studies centered on patients diagnosed with Fistulizing Crohn's Disease (FCD).

Intervention: Studies that evaluated various biologic therapies and interventions, including both pharmaceutical and non-pharmaceutical approaches, for FCD management.

Study Design: Consideration was given to interventional studies only.

Outcome Measures: Studies reporting on effectiveness, safety, clinical and radiological healing, fistula closure rates, re-intervention rates, and other pertinent parameters regarding the treatment and management of FCD. The primary focus was on fistula healing and closure rates.

Information Sources

A comprehensive electronic database search was undertaken, spanning PubMed, Embase, and Cochrane Library. For a holistic data collection, manual search techniques were deployed for relevant journals and conferences. Although the search was extensive with no linguistic constraints, it exclusively considered human-based studies. Only studies conducted in the past 10 years were included.

Search Strategy

The search strategy revolved around crucial terms related to FCD management, including "Fistulizing Crohn's Disease", "biologic therapy", "intervention", "anti-TNF", "vedolizumab", "adalimumab", "infliximab", "fistula closure", "treatment outcomes", and "surgical intervention". Both Medical Subject Headings (MeSH) and free-text terms were employed to ensure a comprehensive search. The search remained active until November 5, 2023.

Study Selection

Initially, two autonomous reviewers screened the titles and abstracts from the identified studies. Subsequently, the full content of the shortlisted articles was evaluated against the predefined eligibility criteria. Studies focusing on patients with FCD, assessing varied treatment modalities, and following the mentioned methodologies were selected. Any studies not meeting these requirements were systematically excluded.

Data Extraction and Synthesis

A narrative synthesis approach was chosen. Data from the selected studies were examined to understand the nuances and overall efficacy of different FCD treatment strategies. The results of each study were detailed, accompanied by a thorough critique of the merits and shortcomings observed in each. Data were systematically organized into tables that listed: “author-year, title, study design, sample size, population/setting, intervention, comparator/control, main results.” Crucial findings from the different studies were merged, emphasizing guidelines for clinical practice and future research directions.

Results

Of 438 studies, a total of 411 were assessed for eligibility using titles and abstracts. Of these, 119 were reviewed using full texts. In total, 10 studies were included in the systematic review. The PRISMA flowchart is depicted in **Figure 1**.

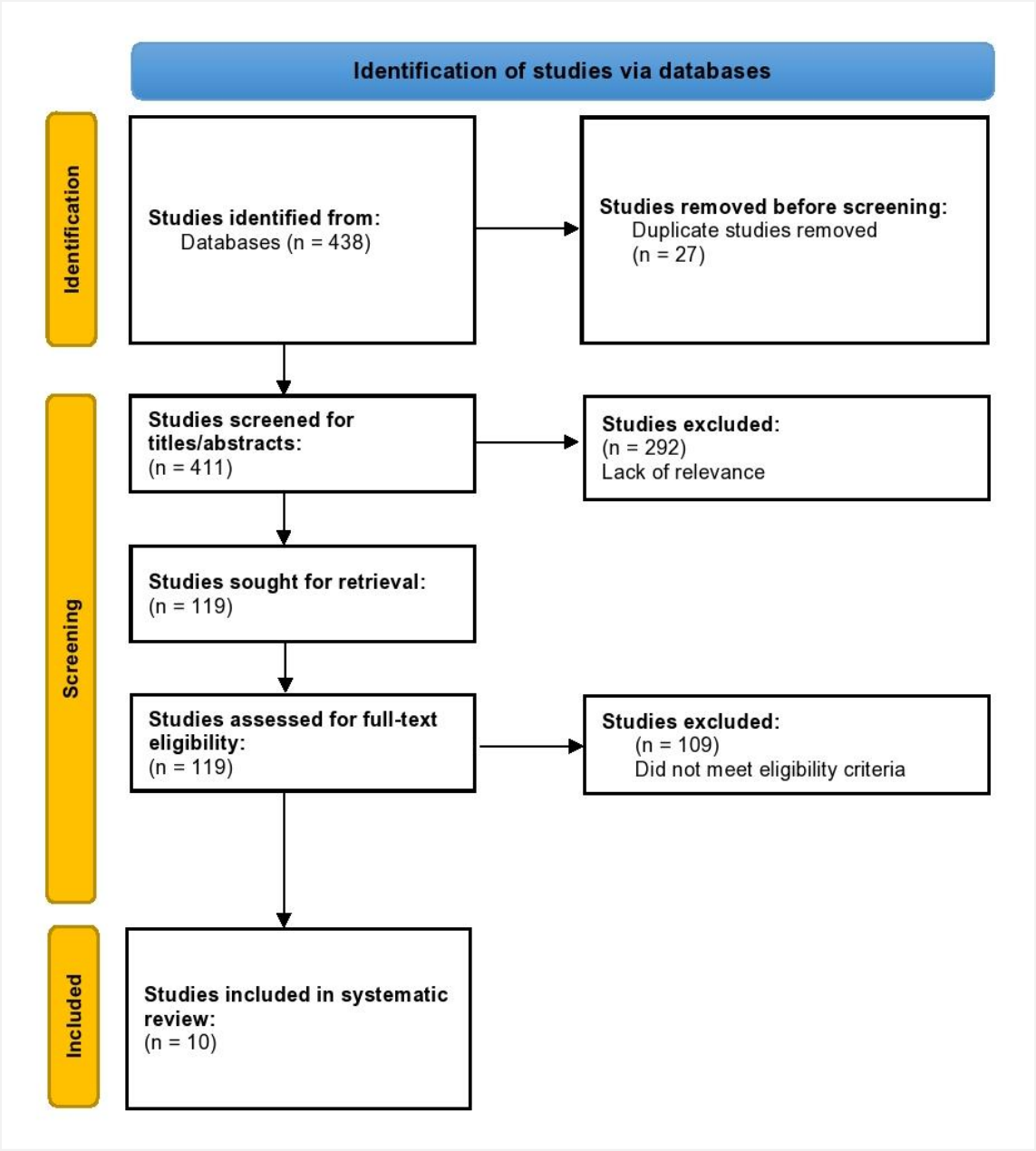

Figure 1. PRISMA Flowchart Depicting the Study Selection Process.

The reviewed studies, spanning from 2014 to 2022, collectively analyze various treatments for Crohn's disease, ranging from anti-TNF therapies, surgical interventions, stem cell applications, drug combinations, and dose intensifications. A total of 1122 patients are collated. Collectively, these studies contribute to the evolving landscape of Crohn's disease treatment, highlighting the importance of personalized, evidence-based therapeutic strategies. An overview of the included studies is presented in **Table 1**.

Table 1. Characteristics of the Included Studies.

Author, Year	Study Design	Sample Size	Population/Setting	Intervention	Comparator/Control	Main Results
Praag, 2022(9)	Multicentre, patient preference study	94	Adults with Crohn's disease and active high perianal fistula with a single internal opening in Netherlands & Italy	4-month anti-TNF therapy and surgical closure	Anti-TNF therapy for 1 year after seton insertion	Radiological healing: 32% in surgical closure group vs 9% in the anti-TNF group (p=0·005). Clinical closure: 68% surgical closure group vs 52% anti-TNF group (p=0·076).
Schwartz, 2022(10)	Randomized, double-blind, phase 4 trial	32	Patients with moderately to severely active CD and 1-3 active perianal fistulae (identified on MRI)	Vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22	Vedolizumab regimen plus an additional dose at week 10	53.6% achieved ≥50% decrease in draining fistulae and 42.9% achieved 100% fistulae closure by week 30.
Wasmann, 2020(11)	Randomized trial	44	Patients with high perianal Crohn's fistulas with a single internal opening across 19 European centers	Chronic seton drainage for 1 year	i) Anti-TNF therapy for 1 year ii) Surgical closure after 2 months under a short course anti-TNF	Highest re-intervention rate in seton treatment: 10/15 vs 6/15 in anti-TNF and 3/14 in surgical closure (p = 0.02).
Hoekman, 2018(12)	Retrospective study	119	Recently diagnosed Crohn's disease patients	Early combined immunosuppression [top-down]	Conventional management [step-up]	Clinical remission rates: 70% in step-up vs 73% in top-down. Relapse rates lower in top-down. 62% of step-up used corticosteroids vs 41% of top-down. 73% of step-up used anti-TNF vs 54% top-down.
Ruemmele, 2018(13)	Clinical trial extension	36	Children/adolescents with Crohn's disease with perianal fistulae	Adalimumab	-	44.4% had fistula closure and 52.8% had improvement at Week 12. Rates sustained to Week 292.
Ponsioen, 2017(14)	Randomized controlled trial	143	Adults with ileocaecal Crohn's disease (non-stricturing)	Laparoscopic ileocaecal resection	Infliximab	Mean IBDQ score at 12 months: 178.1 (resection) vs 172.0 (infliximab); Mean SF-36 total score: 112.1 (resection) vs 106.5 (infliximab); 3.4 days sick leave (resection) vs 1.4 days (infliximab).
Panés, 2016(15)	Randomized, double-blind	212	Adults with Crohn's disease with treatment-refractory complex perianal fistulas	Cx601 (adipose-derived stem cells)	Saline solution (placebo)	50% achieved combined remission in Cx601 group vs 34% in placebo at week 24. 17% in Cx601 group

						experienced treatment-related adverse events vs 29% in placebo.
Regueiro, 2016(16)	Randomized trial	297	Post ileocolonic resection CD patients	Infliximab (5 mg/kg) every 8 weeks for 200 weeks	Placebo	Clinical recurrence: 12.9% (infliximab) vs 20.0% (placebo) at week 76; Endoscopic recurrence: 30.6% (infliximab) vs 60.0% (placebo)
Dewint, 2014(17)	Randomized, double-blind	76	CD patients with active perianal fistulising disease	Adalimumab + ciprofloxacin 500 mg	Adalimumab + placebo	Clinical response at week 12: 71% (combination) vs 47% (adalimumab alone); Remission rate at week 12: 65% (combination) vs 33% (adalimumab alone); No significant difference at week 24.
Steenholdt, 2014(18)	Randomized, controlled, single-blind, multicentre study	69	Patients with secondary IFX failure	Interventions based on serum IFX and IFX antibody levels using the proposed algorithm (n=33).	IFX dose intensification (5 mg/kg every 4 weeks) (n=36)	Intention-to-Treat: Costs: € 6038 (algorithm) vs € 9178 (dose intensification), p<0.001. Response rates: 58% (algorithm) vs 53% (dose intensification), p=0.81. Per-Protocol: Costs: € 4062 (algorithm) vs € 9178 (dose intensification), p<0.001. Response rates: 47% (algorithm) vs 53% (dose intensification), p=0.78.
Abbreviations:CD: Crohn's disease; IBDQ: Inflammatory Bowel Disease Questionnaire; IFX: Infliximab; MRI: Magnetic Resonance Imaging; SF-36: 36-Item Short Form Health Survey; TNF: Tumor Necrosis Factor						

In 2022, Praag led a multicentre study on 94 adults with Crohn's disease across the Netherlands & Italy. They compared a 4-month anti-TNF therapy and surgical closure against anti-TNF therapy for a year post-seton insertion. The results revealed radiological healing of 32% in the surgical closure group versus 9% in the anti-TNF group (p=0·005). Additionally, the surgical closure group exhibited a clinical closure rate of 68% compared to 52% in the anti-TNF group (p=0·076).

Schwartz (2022) undertook a randomized, double-blind trial involving 32 patients with Crohn's Disease. Patients were administered Vedolizumab with schedules differing slightly for the comparator group. Impressively, by week 30, 53.6% of participants achieved ≥50% decrease in draining fistulae, and 42.9% attained complete fistulae closure.

Wasmann's (2020) study recruited 44 European patients diagnosed with high perianal Crohn's fistulas. The randomized trial contrasted chronic seton drainage against anti-TNF therapy and a surgical approach. Notably, the seton treatment exhibited the highest re-intervention rate, a stark difference of 10/15 compared to 6/15 in the anti-TNF group and 3/14 in the surgical group ($p=0.02$).

In 2018, Hoekman analyzed 119 newly diagnosed Crohn's disease patients in a retrospective manner. Patients were divided between early combined immunosuppression and conventional management. The results were comparable, with clinical remission at 70% for step-up versus 73% for top-down. Relapse was lower in top-down, and medication usage varied significantly, indicating the nuanced impacts of treatment strategies.

Ruemmele's 2018 extension of a clinical trial focused on 36 young patients with Crohn's disease and perianal fistulae, all treated with Adalimumab. By week 12, 44.4% achieved fistula closure and 52.8% saw improvement. Remarkably, these results sustained up to week 292, suggesting the long-term efficacy of Adalimumab.

Ponsioen (2017) directed a randomized trial with 143 adults with ileocaecal Crohn's disease. Patients underwent either a laparoscopic ileocaecal resection or were administered Infliximab. After 12 months, there were slight differences in IBDQ and SF-36 scores between groups, but resection patients took more sick leave days: 3.4 days versus 1.4 days in the Infliximab group.

In Panés' 2016 study, 212 adults with complex perianal fistulas were treated with Cx601 stem cells or a saline placebo. The results were promising, with 50% of the Cx601 group achieving combined remission at week 24 versus 34% in the placebo group. Side effects were more prominent in the placebo group, at 29%, compared to 17% in the Cx601 group.

Regueiro (2016) engaged 297 post-operative Crohn's patients in a randomized trial, contrasting Infliximab against a placebo. At week 76, clinical recurrence in the Infliximab group stood at 12.9% versus 20.0% in the placebo. Similarly, endoscopic recurrence was halved: 30.6% with Infliximab compared to 60.0% with placebo.

Dewint (2014) conducted a double-blind study on 76 CD patients, comparing Adalimumab combined with ciprofloxacin against Adalimumab with a placebo. By week 12, the combination group saw 71% clinical response and 65% remission, outperforming the 47% response and 33% remission rates of the Adalimumab-alone group, though differences reduced by week 24.

Lastly, Steenholdt (2014) studied 69 patients with secondary IFX failure. Using an algorithm based on serum IFX and its antibody levels as intervention against IFX dose intensification, results showed cost-effectiveness. The algorithm method resulted in costs of €6038 versus €9178 with dose intensification ($p<0.001$). Response rates were similar at 58% for the algorithm and 53% for the intensification ($p=0.81$).

Discussion

Fistulizing Crohn's Disease, a daunting and often debilitating complication of Crohn's Disease, presents a significant challenge to healthcare professionals and patients alike. This systematic

review analyzed contemporary interventions and therapies targeting FCD to ascertain their efficacy, safety, and cost-effectiveness.

In 1998, a significant advancement in the management of CD was marked by the FDA's endorsement of the inaugural anti-TNF treatment(19). This development facilitated a transformative approach to inflammatory bowel disease care. The principle behind this therapeutic strategy involved the utilization of agents like infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CZP) to mitigate the inflammation in the gut by targeting specific pro-inflammatory markers(20,21). The administration of these treatments varies: IFX is delivered via intravenous infusion, while both ADA and CZP are administered through subcutaneous injections, with each having its own distinct dosing schedule for initiating and sustaining remission(22).

A critical metric in gauging clinical remission in CD is the CDAI score, with scores under 150 indicating remission(23,24). The groundbreaking ACCENT I trial was instrumental in propelling IFX to the forefront of anti-TNF treatments(25). The trial revealed that– patients under IFX maintenance had a twofold likelihood of sustaining remission relative to those on a placebo. Analyzing remission rates brought forth a spectrum: IFX had a range of 33%–72%, ADA stood between 21%–43%, and CZP fell within 22%–29.2%. Notably, a comprehensive analysis accentuated the superior efficacy of anti-TNFs over placebos in ushering remission, with CZP being the outlier, not showcasing any significant remission induction by the 12th week(25).

Addressing fistulas, particularly perianal types, is highlighted in the AGA guidelines for CD(26,27). Among the treatments, only IFX underwent a rigorous clinical trial focused on assessing fistula healing, emerging with promising results within an 8-week window compared to a placebo. Concurrently, the CHARM investigation elucidated ADA's proficiency in securing fistula closures more consistently by the 26th week than placebos(28). This efficacy was further cemented in a subsequent study where the majority of these closures remained intact for over a year. Contrarily, CZP's efficacy in fistula closure remained on par with placebos based on two distinct clinical trials. An integrative strategy for managing fistulas melds the strengths of anti-TNFs and immunomodulators, the infection-controlling capability of antibiotics, and the structural rectifications offered by surgical interventions(29, 30). This holistic approach was validated by the PISA-II study, which highlighted the enhanced outcomes from a surgical and anti-TNF amalgamation over a five-year span compared to just anti-TNF monotherapy(9).

Our systematic review reveals that the therapeutic landscape of FCD has experienced dramatic shifts over recent years. Historically, surgical procedures were the primary approach to managing fistulas in CD, but as demonstrated by the study from Praag et al., combining surgery with biologic therapies such as anti-TNF can lead to more promising outcomes in terms of radiological and clinical closure. This highlights the need to combine modalities to achieve optimal results.The utilization of biologic agents, notably anti-TNF medications, has heralded a transformative phase in FCD treatment(31). Schwartz's phase 4 trial on vedolizumab echoes this sentiment, demonstrating substantial reductions in draining fistulas and complete fistula closure in several patients. The emphasis on precision medicine, wherein therapies are tailored based on the patient's unique genetic and clinical profile, is evident from Hoekman et al.'s study. They

contrasted early combined immunosuppression with conventional management and observed varying remission and relapse rates. This points towards the importance of personalized care strategies in managing FCD.

However, even with these advancements, no single therapeutic modality can be universally deemed the most effective. As elucidated by the studies, individual patient response varies significantly, highlighting the multifaceted nature of FCD. Wasmann et al. highlighted the high re-intervention rates in seton treatment compared to other therapies, hinting at its limitations.An interesting development in the therapeutic realm is the exploration of stem cell therapy. Panés et al. explored the potential of adipose-derived stem cells, yielding promising outcomes in achieving remission. This points towards a broader horizon for regenerative medicine in managing FCD.The cost-effectiveness, a critical consideration in healthcare decision-making, was explicitly tackled by Steenholdt et al. Their analysis underlines that costs can vary dramatically based on the chosen intervention strategy. This brings to the forefront the need for economic evaluations to ensure that treatments are not only clinically effective but also economically viable.

Gaps and Recommendations

Several gaps persist in our understanding of FCD and its optimal management(32,33). The heterogeneity of the included studies, in terms of design, interventions, and patient populations, highlights the need for more harmonized, large-scale trials. Furthermore, long-term outcomes and quality of life assessments post-interventions remain areas requiring more in-depth research.

Based on review of treatment modalities for FCD, we have the following recommendations:

1. **Integrative Treatment Approaches:** Our review highlights the effectiveness of combining surgical interventions with anti-TNF therapy. We recommend further exploration into integrated treatment plans that combine biologic therapies with surgical or other intervention strategies. This could potentially enhance healing rates and reduce the need for re-interventions.

2. **Personalized Medicine:** Given the variability in patient responses to treatments, there is a pressing need for personalized treatment strategies. Genetic and clinical profiling should be utilized to tailor treatment plans to the individual patient's disease characteristics and prognostic factors. This approach may optimize treatment efficacy and patient outcomes.

3. **Cost-Effectiveness Analysis:** Treatment modalities vary significantly in terms of cost. Algorithm-based interventions can be more cost-effective compared to dose intensification strategies. Comprehensive cost-effectiveness analyses should be conducted for all treatment modalities. This will ensure that healthcare resources are utilized efficiently, making treatments accessible and sustainable.

4. **Long-term Efficacy and Safety:** Long-term studies are required to fully understand the efficacy and safety of emerging treatments, such as stem cell therapy. These studies

should not only focus on the immediate clinical outcomes but also evaluate long-term remission rates, quality of life, and any potential adverse effects.

5. **Comparative Effectiveness Research:** There remains a gap in direct comparative effectiveness research among the various treatment modalities for FCD. Future studies should aim to directly compare different biologic therapies, surgical interventions, and emerging treatments in randomized, head-to-head trials to establish a hierarchy of treatment effectiveness.

6. **Healthcare Utilization and Sick Leave:** The impact of different treatments on healthcare utilization and sick leave should be further explored. Understanding these aspects can provide insights into the broader implications of treatment choices on patient life and healthcare systems.

7. **Regenerative Medicine:** The promising results from stem cell therapy trials suggest a potential for regenerative medicine in treating FCD. We recommend increased investment in research into regenerative therapies, including stem cells and novel biologics, to explore their role in healing fistulas and reducing disease recurrence.

8. **Multidisciplinary Care Models:** Given the complex nature of FCD, establishing multidisciplinary care teams comprising gastroenterologists, surgeons, radiologists, and other specialists can enhance patient care. These teams can facilitate integrated treatment plans, ensuring that all aspects of the disease are addressed.

9. **Patient Education and Support:** Enhancing patient understanding of their treatment options, potential outcomes, and the importance of adherence to prescribed therapies is crucial. Additionally, support groups and psychological counseling should be made available to address the mental health aspects of living with FCD.

10. **Innovation in Treatment Delivery:** Exploring innovative delivery mechanisms for existing treatments, such as localized delivery systems for biologic therapies, could improve efficacy and reduce systemic side effects. Research into these areas should be encouraged.

Conclusion

In sum, this systematic review provides a comprehensive analysis of the current therapeutic strategies for Fistulizing Crohn's Disease. While significant advancements have been made, especially with the advent of biologic therapies, a one-size-fits-all approach remains elusive. The future of FCD treatment hinges on precision medicine, further research into novel therapeutic modalities, and a comprehensive understanding of long-term outcomes. As we navigate this complex therapeutic landscape, the ultimate goal remains to enhance the quality of life for individuals afflicted with FCD.

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