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Refractory Crohn's Disease: Perspectives, Unmet Needs and Innovations

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Abstract: Crohn's disease (CD) is a complex, chronic inflammatory bowel disease characterized by unpredictable flare-ups and periods of remission. Despite advances in treatment, CD remains a significant health burden, leading to substantial direct healthcare costs and out-of-pocket expenses for patients, especially in the first-year post-diagnosis. The impact of CD on patients' quality of life is profound, with significant reductions in physical, emotional, and social well-being. Despite advancements in therapeutic options, including biologics, immunomodulators, and small molecules, many patients struggle to achieve or maintain remission, leading to a considerable therapeutic ceiling. This has led to an increased focus on novel and emerging treatments. This context underscores the importance of exploring advanced and innovative treatment options for managing refractory CD. By examining the latest approaches, including immunomodulators, combination therapies, stem cell therapies, and emerging treatments like fecal microbiota transplantation and dietary interventions, there is an opportunity to gain a comprehensive understanding of how best to address and manage refractory cases of CD.

Keywords: refractory Crohn's disease, mesenchymal stem cell therapy, medical therapy, combination therapy, fecal microbiota transplantation, biologic drugs, perianal Crohn's disease, small molecules, hyperbaric oxygen therapy

Introduction

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease (IBD) affecting individuals across all age groups. Nonetheless, most diagnoses occur in young adults, with an observed increase in diagnoses aged between 20 and 60.[1–3] The reported prevalence of CD varies, with the highest rates observed in Germany, where it reaches 322 cases per 100.000 people.[4] However, CD incidence has increased in Asia, Africa, and Latin America due to industrialization and adopting Westernized diets and lifestyles.[5,6]

Around 1 in 5 patients with CD develop perianal disease within 10 years of their diagnosis, with 11.5% presenting with it at the time of diagnosis.[7] Complications such as strictures, fistulas, and abscesses occur in approximately 50% of patients with CD.[8] An IBD diagnosis leads to more than triple the direct healthcare costs compared to non-IBD patients, along with significantly higher out-of-pocket expenses and productivity losses, particularly in the first year after diagnosis.[9] To understand the impact of this disease, a systematic review published in 2013, calculated the total annual economic burden of CD in Europe and the USA which was estimated to be nearly €30 billion, with indirect costs (such as lost productivity and absenteeism) comprising more than half of these costs.[10] The primary drivers of CD-related costs include disease severity, hospitalizations, surgeries, and the use of biologic therapies. Moreover, CD significantly impairs HRQoL, with patients reporting lower physical, emotional, and social well-being compared to the general population. HRQoL declines are more pronounced during active disease phases and improve during remission, but rarely reach levels comparable to the general population.[10] The impact of this condition on quality of life and bowel disability remains high despite the progress in therapeutic management.[11–13]

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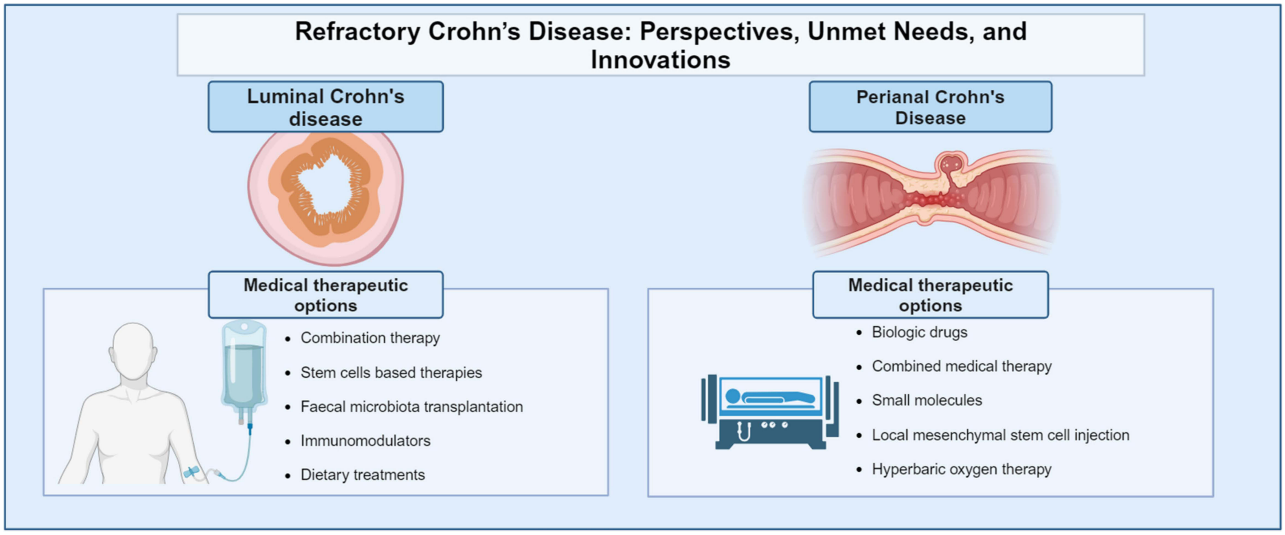
Graphical Abstract



The therapeutic armamentarium of CD evolved from early 20th-century dietary changes to the introduction of corticosteroids in the 1940s. Immunomodulators emerged in the 1970s-80s. The late 1990s saw a breakthrough with biologics, and recent years have brought small molecule drugs.[14–17] However, despite the numerous therapies available to treat the disease, disease remission is not always reached or maintained with these therapies, shaping the concept of a "therapeutic ceiling".[18] About 50% of patients experience secondary loss of response, and 30% experience primary non-response after biologic treatment.[19,20] The main goal of the available therapies is to target chronic inflammation, primarily driven by an imbalance between pro-inflammatory and anti-inflammatory cytokines, as well as dysregulated immune cells. However, in refractory cases, where the disease does not respond to standard treatments, the underlying mechanisms may involve more complex immune dysregulation, microbial imbalances, or genetic factors, necessitating more advanced or personalized therapeutic approaches.

In this context, efforts to define refractory IBD have been made. Refractory IBD has been described as a disease that does not respond or loses response to all classes of licensed immunosuppressive and biologic agents or a disease not amenable to surgery by the 2021 European Crohn's and Colitis Organization (ECCO) topical review consensus.[21] This evolving definition encompasses newer therapeutic agents introduced into the landscape of CD treatment. However, it currently excludes small molecules, including those that target specific Janus kinases or modulators of the sphingosine-1 phosphate receptor (S1PR). Refractory perianal fistulizing CD was defined by the same consensus as a failure of at least one surgical intervention and anti-tumor necrosis factor therapy (anti-TNF).[21] However, the size of the problem has not yet been defined since the global prevalence of refractory CD is unknown.[22] Classically, risk factors for severe disease include early onset disease, perianal disease, ileocolic and upper GI tract location. However, lack of treatment optimization, non-adherence to therapy, delayed diagnosis, and disparities in care can also negatively affect prognoses of these patients.[23]

Despite numerous studies defining risk factors for aggressive disease, there remains a scarcity of predictors or biomarkers indicating refractory disease behavior or a scoring system incorporating these variables. This shortfall may be attributed to the heterogeneous nature and course variability of the disease. From a molecular perspective, a recent study has explored the underlying mechanisms of refractory disease in IBD, observing increased mucosal transcription of IL-17 and IL-23 in patients with non-response to biologic therapy.[23] The diagnosis and treatment of refractory CD continue to be areas of active debate. This review aims to explore optimal management strategies and available therapies, with the goal of guiding future research and improving clinical practice.

Diagnosis and Challenges of Refractory CD

Diagnosing refractory CD involves ruling out other potential causes of symptoms, evaluating disease activity, assessing the adherence of patients to treatment and, in some cases, using therapeutic drug monitoring (TDM). Therefore, its diagnosis requires accuracy and attention.

The complexity of the scenario is also enhanced by the fact that clinical symptoms may be present even though the disease is in remission, with clinical scores like the Harvard-Bradshaw Index (HBI) correlating poorly with endoscopic activity.[24] For this reason, treatment targets have evolved from symptomatic improvement to clinical remission and endoscopic healing, normalization of biomarkers, absence of disability, restoration of quality of life, as defined by STRIDE-II consensus.[25] The disease activity assessment should therefore include using serum or fecal biomarkers, conducting endoscopy. Clinical response was defined as a reduction of at least 50% in patient-reported outcomes related to abdominal pain and stool frequency, while clinical remission for CD was defined by either score of abdominal pain at ≤1 and stool frequency ≤3, or a HBI score of less than 5. Endoscopic healing was defined as a Simple Endoscopic Score for Crohn's Disease (SES-CD) of less than 3 points or the absence of ulcerations, with SES-CD ulceration subscores of 0. Although endoscopic healing is a treatment goal, patients still favor non-invasive monitoring methods, as intestinal ultrasound.[26] The presence of clinical symptoms despite treatment optimization necessitates the exclusion of another potential that could mimic active IBD symptoms. Disorders of Gut-Brain Interaction (DGBI) are more common among individuals with IBD compared to the general population, with approximately 40% experiencing symptoms compatible with irritable bowel syndrome (IBS).[27] Organic conditions that may contribute to the differential diagnosis are bacterial infections (including Clostridium difficile, Salmonella, Yersinia, and Campylobacter), viral infections (such as CMV), sexually transmitted infections (like Chlamydia trachomatis and syphilis), bowel enteropathy linked to medication use (such as NSAIDs, mycophenolate, or cocaine). Additionally, exposure to cell cycle checkpoint inhibitors, radiotherapy, and ischemic changes due to vascular insufficiency or vasculitis should be considered. Other potential causes include sarcoidosis, coeliac disease, intestinal lymphoma, bile acid malabsorption, and small bowel overgrowth.[21]

Adherence to treatment poses a frequent challenge in chronic conditions, potentially worsening disease severity and increasing the risk of relapse, reduced effectiveness of anti-TNFs and heightened morbidity.[28] It is estimated that between 53% to 75% of individuals with IBD fail to adhere to prescribed medication regimens as directed.[28,29] Jackson et al in their systematic review noted significant associations between demographic, clinical, and psychosocial factors and non-adherence in IBD.[30] However, they found inconsistencies due to heterogeneity of inclusion criteria across studies. Notably, younger age, employment status, unmarried status, and shorter disease duration were linked to non-adherence to oral medication. Moreover, prescription of concomitant medications was associated with lower adherence. Psychological distress and doctor-patient discordance were also cited as contributors to non-adherence, although findings regarding depression and anxiety varied across studies. There are two main approaches for assessing adherence: direct methods, such as biochemical analysis, and indirect methods, like pill counts, pharmacy refills, self-reporting, or electronic monitoring devices.[28]

Therapeutic drug monitoring entails assessing drug concentrations and detecting the emergence of antidrug antibodies (ADA).[31] It proves particularly valuable in patients receiving therapy with anti-TNFs or thiopurines. It may also be considered for those undergoing treatment with vedolizumab or ustekinumab.[32] TDM serves two primary purposes: addressing the loss of response (reactive TDM) or optimizing treatment during remission (proactive TDM), offering potential benefits under specific circumstances. A proactive TDM approach facilitates the identification of poor adherence, which becomes increasingly relevant with subcutaneous infliximab and vedolizumab formulations.[33] However, challenges persist in TDM implementation. Inter-assay variability challenges translating findings to clinical practice.[34] The turnaround time for results may lead to delays in dose adjustments.[35] Various patient-related and disease-related factors, such as inflammatory burden or disease phenotype, influence pharmacokinetics, and in this context, fistulizing disease may necessitate a tailored TDM approach.[36]

Optimizing Current Medical Treatments for Refractory Luminal CD

Biologic medications are fundamental in managing moderate-to-severe CD. The available agents include anti-TNFs (such as infliximab, adalimumab, and certolizumab pegol), antibodies targeting the p40 subunit of interleukins (IL)-12

and −23 (ustekinumab), and α4β7 integrins on leukocytes (vedolizumab).[37–39] Recently, the FDA has approved a specific interleukin-23 inhibitor (risankizumab) and an oral selective Janus kinase (upadacitinib) for adults with moderate-to-severe CD who have had an inadequate response to one or more TNF blockers.[40] Further strategies have been explored in refractory patients with CD, such as altering drug sequencing (ascending/descending ladder) and employing switching and sequential therapy, all geared towards improving treatment outcomes in IBD in clinical settings. Nevertheless, the long-term response rate remains inadequate.[41] A significant proportion of patients, up to one-third, may experience a primary non-response. For these patients, switching to a biologic with a different mechanism of action is often more effective. In clinical practice, when patients exhibit reduced responsiveness to medications, healthcare providers often consider TDM. Other strategies include reinduction, increasing dose frequency or drug dosage. However, there is no clear evidence on the best strategy for optimizing anti-TNF therapies, though options include either doubling the dose or shortening the intervals between doses.[42]

Regarding ustekinumab, a multicenter study led by Fumery et al enrolled 100 patients with active CD who needed to escalate their ustekinumab dosage to 90 mg every four weeks due to either a loss of response or an incomplete response to the standard dose of 90 mg every eight weeks. The study discovered that two-thirds of the patients achieved a clinical response after the treatment was intensified to 90 mg every four weeks.[43] A systematic review evaluating the effectiveness of reinduction and/or shortening the dose interval of ustekinumab found that shortening the interval to every 4 to 6 weeks was the most common escalation strategy, leading to endoscopic response in patients with CD with inadequate response or loss of response to induction or maintenance therapy.[44]

Recent studies have also demonstrated that increasing the dosing frequency of vedolizumab to every four weeks is associated with improved endoscopic outcomes.[45,46]

Currently, there is minimal to no data available to guide the optimization of risankizumab and upadacitinib beyond the approved doses to enhance clinical outcomes.[47]

In cases where drug optimization fails to yield results, medical therapeutic approaches may involve combining two drugs with distinct mechanisms, considering bowel bone marrow autotransplantation, hematopoietic stem cell therapy, fecal microbiota transplantation or immunomodulators. Dietary treatments may represent an adjunctive measure in these patients.

Combination Therapy

Combination therapies encompass two scenarios: 1) pairing a biologic or small molecule with an immunosuppressor such as thiopurine, methotrexate, or calcineurin inhibitor, and 2) dual-targeted therapy (DTT), which involves using two biologic agents and/or small molecules concurrently. These approaches may be considered for patients with concurrent IBD and extraintestinal manifestations or those with medically refractory IBD lacking viable alternatives. However, cost, logistics, and safety concerns have hindered research progress.

The seminal study in this area was the SONIC trial (*Study Of Biologic and Immunomodulator Naive Patients In Crohn's Disease*), published in 2010, where Colombel et al conducted a randomized controlled trial (RCT) in patients with CD, revealing that the combination of infliximab and azathioprine was more effective than either treatment alone.[48] Patients who underwent combination therapy experienced notably greater rates of achieving corticosteroid-free clinical remission and mucosal healing at week 26 and lower instances of immunogenicity. At week 30, antibodies to infliximab were identified in only 0.9% patients undergoing combination therapy, compared to 14.6% receiving infliximab alone. Interestingly, the combination therapy group was also determined to be the safest course of action. The investigation into the enhanced efficacy of combination therapy was extended through a subsequent post hoc analysis of SONIC. This analysis revealed that the elevated efficacy rates were attributed to increased drug levels rather than solely to the utilization of combination therapy.[49] The results of the COMMIT trial, unveiled in 2014, investigated the efficacy of combining infliximab with parenteral methotrexate in contrast to infliximab alone. Although it showed that patients receiving the combination had higher levels of infliximab and lower occurrences of anti-drug antibodies compared to those on monotherapy, no clear benefit was evident in clinical outcomes.[50]

The more recent PROFILE (PRedicting Outcomes For CD using a moLecular biomarker) study recently validated this finding. Indeed, it demonstrated that initiating treatment with a combination of infliximab and an immunomodulator in

patients with newly diagnosed active CD led to significantly superior outcomes at one year compared to the accelerated step-up approach.[51] Colombel et al also published the EXPLORER trial in 2023, a Phase IV, single-arm, open-label study evaluating triple combination therapy with vedolizumab, adalimumab, and methotrexate in biologic-naïve patients with newly diagnosed CD.[52] This combination therapy led to endoscopic and clinical remission at week 26 in 34.5% and 54.5% of patients, respectively, without any safety concerns related to the treatment regimen.

Apart from RCTs, much of the data on combination drugs in IBD stems from lower-quality sources such as cohort studies, case series, and reports. Recent meta-analyses and comprehensive reviews have explored the efficacy and safety of this treatment approach.[53,54] Ribaldone et al in their systematic review focused on dual biologic therapy with anti-TNFs, vedolizumab, or ustekinumab, included seven studies involving 18 patients (56% with CD). Patients received a combination of anti-TNFs and vedolizumab or vedolizumab and ustekinumab, resulting in clinical improvement in 100% and 93% of patients, respectively.[53] Another recent meta-analysis of 30 studies, including 279 patients receiving dual biologic therapy in combination or with tofacitinib (79% patients with CD), found that pooled clinical and endoscopic remission rates were 59% and 34%, respectively.[54] Surgical intervention was required in 12% of cases, with 31% experiencing adverse effects, including 7% categorized as life-threatening, over a median follow-up of 32 weeks. A retrospective multicenter European observational study of 98 IBD patients undergoing combination therapy with biologics and small molecules, along with accompanying extraintestinal manifestations or other immune-mediated inflammatory diseases, found that the most common combination was anti-TNFs and vedolizumab, with 80% of patients being treatment-naïve to the second drug.[55] Dual therapy with ustekinumab and vedolizumab led to an endoscopic response in 11 out of 13 patients with CD after an 11-month follow-up.[55] Moreover, in a recent systematic review with meta-analysis conducted by Alayo et al, comprising 13 studies and 273 patients, the safety and efficacy of biologics and small molecules in IBD were analyzed. The review revealed that 77.9% of patients treated with anti-TNFs and vedolizumab achieved clinical response, while 55.1% attained clinical remission.[56] The pooled rates of clinical remission and response among patients on vedolizumab plus ustekinumab were 47.0% and 83.9%, respectively. However, the combination of vedolizumab and tofacitinib was associated with lower rates of clinical response (59.9%) and clinical remission (55.1%). Regarding adverse events, a study examining DTT in IBD patients revealed varying rates, ranging from 13% to 30%, with infections being the most prevalent adverse effect.[57] Research into combination therapy involving ustekinumab and vedolizumab typically indicated minimal adverse effects.[58–61] At the same time, slightly higher rates were observed with anti-TNFs and vedolizumab, ranging from 15% to 37.5%, primarily due to an increased risk of infections.[41,56,61] Conversely, limited data on patients receiving anti-TNFs and ustekinumab showed clinical response without adverse effects.[59–63] Further studies comparing the efficacy and safety of combination therapies are warranted due to the limited data on infection risk and long-term effects.

For a comprehensive overview of the studies examining combined therapy for refractory luminal CD, please refer to Tables 1 and 2.

Dual therapy could be an attractive opportunity for refractory patients with CD. In the future, identifying the most effective and safest combinations and exploring combinations with non-immunosuppressive treatments, such as those targeting environmental factors like diet or the microbiome, will be essential.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is widely used in benign and malignant hematological diseases.[104] Stem cells are retrievable from peripheral blood, bone marrow, or umbilical cord units. Hematopoietic stem-cell transplantation can take two forms: autologous, where the stem cells originate from the recipient, or allogeneic, where they are sourced from another individual or one or more umbilical cord blood units. During the last decade, mainly autologous HSCT gained increasing attention in treating refractory autoimmune diseases. Indeed, HSCT aims to regenerate the immune system and establish immune tolerance, offering a viable treatment option for refractory CD by addressing the immune dysregulation that is thought to be a key factor in IBD pathophysiology.

Autologous HSCT was used in patients with CD affected by malignant hematological disease during the 1990s. An improvement or a disease remission was reported after HSCT.[105–107] In 2003, a retrospective analysis that included 7 patients with CD and 4 with UC diagnosis treated with allogeneic HSCT for acute/chronic myeloid leukemia or

Table 1 Description of Selected Studies for Combined Therapy of Refractory Luminal Crohn's Disease

Study	Publication Year	Country	Number of Patients with CD Included	Biologic/ Small Molecule	Immunosuppressant	Main Findings	Study Design	Level of Evidence
Sandborn et al[64]	2013	International (multicenter)	368	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A
Sands et al[65]	2014	International (multicenter)	315	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A
Sands et al[66]	2014	International (multicenter)	209	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A
Shelton et al[67]	2016	USA (multicenter)	107	VDZ	Thiopurines or methotrexate	Despite one-third of patients being on combination immunomodulator therapy, this study did not demonstrate a larger benefit for those on combination therapy, though our sample size may be too small to detect a difference	Prospective cohort	B
Dulai et al[67]	2016	USA (multicenter)	212	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective	C
Baumgart et al[68]	2016	Germany (Multicenter)	97	VDZ	azathioprine, mercaptopurine, methotrexate, tacrolimus and cyclosporin	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Stallmach et al[69]	2016	Germany (Multicenter)	67	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Szántó et al[70]	2017	Hungary (single)	4	VDZ	CyA	Combination therapy was effective as induction in all cases and cyclosporine was discontinued after a mean of 130 days. Colonoscopy after VDZ induction showed mucosal healing in one patient, significant regression in one patient and moderate regression of mucosal inflammation in three patients.	Retrospective	C
Eriksson et al[71]	2017	Sweden (multicenter)	147	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Kopylov et al[71]	2017	Israeli (multicenter)	130	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B

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Samaan et al[72]	2017	United Kingdom (multicenter)	27	VDZ	Thiopurines or methotrexate	Dividing patients by those receiving vedolizumab monotherapy or in combination with an immunomodulator, the response rates were 13/21 (62%) and 9/16 (56%), respectively.	Retrospective cohort	C
Allegretti et al[73]	2017	USA (multicenter)	96	VDZ	Thiopurines or methotrexate	The addition of an immunomodulator after induction enhanced the likelihood of achieving a clinical response at 52 weeks, functioning as salvage therapy.	Retrospective cohort	C
Lenti et al[74]	2018	United Kingdom (multicenter)	135	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Shmidt et al[75]	2018	USA (multicenter)	264	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Macaluso et al[76]	2018	Italy (multicenter)	84	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Kotze et al[77]	2018	Canada (single)	122	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Chaparro et al[78]	2018	Spain (multicenter)	521	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Christensen et al[79]	2019	Usa (single)	9	VDZ	5 Tac, 4 CyA	By week 14 of treatment, 44% of patients with CD achieved steroid-free clinical remission. After 52 weeks of treatment, 33% of patients with CD were in steroid-free clinical remission.	Prospective cohort	B
Meserve et al[80]	2019	USA (multicenter)	650	VDZ	Thiopurines or methotrexate	Number of concomitant immunosuppressive agents (corticosteroids or immunomodulators; OR, 1.72 per agent) used were independently associated with infections.	Retrospective cohort	C
Biemans et al[81]	2019	Netherlands (multicenter)	192	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Amiot et al[82]	2019	France (multicenter)	173	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Verstock et al[83]	2019	Belgium (single)	179	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Watanabe et al[84]	2020	Japan (multicenter)	79	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A

(*Continued*)

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Table 1 (Continued).

Study	Publication Year	Country	Number of Patients with CD Included	Biologic/ Small Molecule	Immunosuppressant	Main Findings	Study Design	Level of Evidence
Visuri et al[85]	2020	Sweden (multicenter)	68	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Eriksson et al[86]	2021	Sweden (multicenter)	169	VDZ	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Vermeire et al[87]	2022	International (multicenter)	275	VDZ	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A
Sandborn et al[88]	2012	International (multicenter)	131	UST	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A
Kopylov et al[89]	2014	Canada (single)	40	UST	Azathioprine or Methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Khorrami et al[89]	2016	Spain (multicenter)	116	UST	NR	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Wils et al[90]	2016	France and Switzerland (multicenter)	122	UST	Thiopurines or methotrexate	In multivariate analysis, concomitant immunosuppressant at inclusion was the only predictive factor of a clinical benefit to ustekinumab at 3 months (OR, 5.43; 95% confidence interval, 1.14–25.77; P = 0.03). No difference was observed in patients receiving thiopurines or methotrexate.	Retrospective cohort	C
Feagan et al[91]	2016	International (multicenter)	494	UST	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	RCT	A
Battat et al[92]	2017	Canada (multicenter)	62	UST	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Ma et al[93]	2017	Canada (multicenter)	104	UST	NR	The combination therapy had a lower risk of response loss to ustekinumab during maintenance than monotherapy did (hazard ratio, 0.39)	Retrospective cohort	C
Greenup et al[94]	2017	Canada (single)	69	UST	Azathioprine or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C

Iborra et al[94]	2019	Spain (multicenter)	305	UST	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Liefferinckx et al[95]	2019	Belgium (multicenter)	152	UST	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Miyazaki et al[96]	2020	Japan (single)	47	UST	Thiopurine	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Retrospective cohort	C
Biemans et al[97]	2020	Netherland (multicenter)	221	UST	Thiopurines or methotrexate	No observed statistically significant correlation between the use of concomitant immunosuppressants and therapeutic response.	Prospective cohort	B
Hanauer et al[98]	2020	International (multicenter)	397	UST	Thiopurines or methotrexate	No association of concomitant immunosuppressants with response. Rates of antibody formation were similar between patients not receiving concomitant immunosuppressives compared with those on immunosuppressives at Week 44	RCT	A

Notes: The studies were graded based on the study design in A: Randomized Controlled Trials (RCTs) or Meta-analysis of RCTs; B: Prospective Studies, C: Retrospective Studies, D: Case Series.
Abbreviations: CD, Crohn's Disease; CyA, Cyclosporine; NR, Not Reported; OR, Odds Ratio; RCT, Randomized Controlled Trial; Tac, Tacrolimus; UST, Ustekinumab; VDZ, Vedolizumab.

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Table 2 Description of Selected Studies for Double Target Therapy of Refractory Luminal Crohn's Disease

Study	Publication Year	Country	Study Indication	Number of Patients with CD Included	Therapeutic option	No. of Therapeutic Trials Discontinued DT, *n*/*N* (%)	Median Duration of Follow-Up (weeks)	Main Findings	Safety	Study Design	Level of Evidence
Buer et al[99]	2018	Norway (multicenter)	Uncontrolled IBD	4	Anti-TNF + VDZ	2/10 (20.0%)	68	100% clinical remission 50% endoscopic remission 25% endoscopic improvement	No adverse events in patients with CD	Case series	D
Mao et al[58]	2018	United States (single)	Uncontrolled IBD	3	VDZ + UST/ GOL	0/3 (0%)	NA	3/3 clinical remission	4 infections (2 C. difficile, 1 hand-foot mouth disease, 1 influenza)	Case series	D
Yang et al[61]	2020	United States/ Canada (multicenter)	Uncontrolled IBD	22	VDZ + UST/ Anti-TNF, UST + Anti-TNF	15/24 (62.5%)	39	43% endoscopic improvement 26% endoscopic remission 50% clinical response 41% clinical remission	3/22 adverse events (13%: 1 drug-induced lupus, 1 pneumonia, 1 recurrent C. difficile infection)	Retrospective	C
Privitera et al[57]	2021	Italy (multicenter)	Both uncontrolled IBD and active EIM	11	UST+CRZ, VDZ+UST, UST+IFX, VDZ+IFX	0/5	28	Out of 5 patients with CD, initiating treatment for uncontrolled IBD, 100% clinical improvement at 2 months, 42.8% clinical response at 6 months, 14.2% clinical remission at 6 months	1 perianal abscess	Retrospective cohort	C
Alayo et al[100]	2021	United States (multicenter)	Uncontrolled IBD	10	Tofa + Anti-TNF, Tofa + UST, Tofa + VDZ	20/35 (57.1%)	16	68.4% clinical response by week 16 70.0% clinical remission by week 16 85.7% endoscopic/radiographic response 34.8% endoscopic remission	5.7% of patients experienced adverse events, with one serious adverse event of Clostridium difficile infection leading to hospitalization.	Retrospective cohort	C
Kwapisz et al[59]	2021	United States (single)	Uncontrolled IBD	14	VDZ + Anti-TNF/UST, UST + Anti-TNF/ VDZ	1/15 (6.7%)	144	73% clinical response 67% reduction in steroid use 44% endoscopic or radiological improvement 20% required surgical intervention.	Four patients (27%) had infections requiring antibiotics, 3 patients were hospitalized	Retrospective	C
Goessens et al[55]	2021	European (multicenter)	Both uncontrolled IBD and active EIM	58	Anti-TNF + VDZ/UST, VDZ + UST, TOFA +antiTNF, TOFA+VDZ, UST+ Anti IL	45%	32	70% clinically improved in IBD activity; complete (26%) or partial improvement (44%) 81% clinical improved in IMID/EIM activity	42 significant adverse events: serious infections leading to hospitalization and/or opportunistic infection were observed in 10 out of 98 patients (10.2%). No deaths. 1 skin cancer reported.	Retrospective	C

Llano et al[62]	2021	United States (single)	Uncontrolled IBD	3	VDZ + Anti-TNF, VDZ + UST, Tofa + VDZ	5/14 (35.7%)	31	1 patients underwent colectomy, the other 2 patients had biochemical response to the add-on therapy	66,6% of CD patients included had infectious adverse events	Retrospective cohort	C
Lee et al[101]	2022	United States (single)	Both uncontrolled IBD and active EIM	19	Tofa + Anti-TNF, Tofa + UST, Tofa + VDZ	5/19 (26.3%)	38,4	80.0% clinical response 60.0% clinical remission 54.5% Endoscopic improvement 18.2% endoscopic remission 18.2 endoscopic healing	36.8% of the patients experienced adverse events, mainly infections, no serious AE	Retrospective cohort	C
Eronen et al[102]	2022	Finland (multicenter)	Uncontrolled IBD	15	Anti-TNF + USTE, Anti-TNF + VDZ, USTE + VDZ	3/22 (13.6%)	36	In the study, a total of seven out of the 22 trials of dual biological therapy (DBT) achieved remission, representing approximately 32% of the trials. 32% clinical remission	19% (3/16) had Infection complications such as erysipelas, recurring Clostridium difficile infection, perianal abscess, and conjunctivitis	Retrospective cohort	C
Miyatani et al[103]	2024	United States (single)	Both uncontrolled IBD and active EIM	10	UPA + UST	1/10 (10%)	40	5/6 patients, achieved remission.	50% experienced adverse events, mainly mild respiratory symptoms and nausea	Retrospective cohort	C

Notes: The studies were graded based on the study design in A: Randomized Controlled Trials (RCTs) or Meta-analysis of RCTs; B: Prospective Studies, C: Retrospective Studies, D: Case Series.
Abbreviations: AE, Adverse Events; Anti-TNF, Anti-tumor necrosis factor therapy; CD, Crohn's Disease; CRZ, certolizumab; Discontinued due to Toxicity, DT; EIM, Extraintestinal manifestations; IFX, Infliximab; n, Number of trials discontinued; N, Total number of trials; IBD, Inflammatory Bowel Disease; Tofa, Tofacitinib; UPA, Upadacitinib; UST, Ustekinumab; VDZ, Vedolizumab.

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myelodysplastic syndrome observed a clinical remission during a follow-up that could range from 3 months to 10 years. Currently, evidence on HSCT in CD is still limited to phase I/II studies, small prospective single-arm retrospective studies or case reports. According to data from the European Bone Marrow Transplantation registry, between January 1997 and July 2023, 232 patients underwent HSCT for CD. Out of them, 210 (91%) were adults and 22 (10%) were children under 18 years old at the time of transplantation. Among the procedures, 223 (96%) were performed in the autologous setting and nine (4%) in the allogeneic setting. The ASTIC trial, conducted between July 2007 and September 2011, involved 11 European transplant units. The primary endpoint of the trial was achieving clinical remission for a minimum of 3 months within the year following HSCT, without the use of immunosuppressives or biological treatments, and demonstrating a normal gastrointestinal tract according to endoscopic and radiologic assessments. Patients with CD younger than 50 years who had at least three unsuccessful treatment attempts with immunomodulators or biologics and were not suitable for surgery were included. All patients received mobilization with cyclophosphamide and G-CSF. Consequently, 23 patients underwent HSCT, and 22 were controls. ASTIC trial showed that HSCT was associated with a high burden of adverse events, particularly infections linked to pancytopenia induced by the conditioning regimen, resulting in one patient fatality.[108] The stringent primary endpoint criteria were met by only two patients who underwent immediate HSCT and one patient who underwent delayed HSCT. Complete endoscopic healing was noted in half of the patients, and the combined primary endpoint of clinical remission with a CDAI < 150 and no corticosteroids for at least three months was achieved by 38% of patients after one year. It was also observed that an inflammatory phenotype, colonic disease location, and a high endoscopic disease score were associated with treatment response. In contrast, smoking and perianal disease were identified as risk factors for adverse effects.[109] A single-center cohort assessed 37 patients with CD for HSCT in Barcelona. Relapse occurred in most patients within five years after transplant; these patients retreated, and 80% gained clinical remission.[110] In 2020, Burt et al conducted a pilot study of non-myeloablative allogeneic HSCT in patients with CD. Three patients received unselected matched sibling peripheral blood stem cells, and six received umbilical cord blood when a matched sibling donor was not available. During 5-year follow-up, there was not clinical, imaging, endoscopic, or histologic evidence of disease.[111]

A breaking point is the safety of HSCT because this procedure is associated with febrile neutropenia, bacteremia, septic shocks, and acute Graft Versus Host Disease. Due to the risk of HSCT-related mortality and morbidity in CD, the risks and benefits of performing such a high-risk therapeutic procedure have to be carefully weighed.[108,111,112] The hematopoietic cell transplantation comorbidity index (HCT-CI) could estimate pre-transplant comorbidities that predict non-relapse mortality and survival.[113] Besides, mortality occurred in one of the 23 transplanted patients of the ASTIC trial (sinusoidal obstructive syndrome), the Barcelona cohort (due to CMV infection) and a multicenter trial in Brazil (due to disseminated adenovirus infection). The ASTIClite trial implemented a reduced-intensity conditioning regimen to mitigate toxicity. Its primary goal, achievable within a 48-week follow-up, centered on the absence of endoscopic ulceration without necessitating surgery or resulting in mortality. The trial compared the safety and efficacy of autologous HSCT with a lower dose of cyclophosphamide during stem-cell mobilization and conditioning against the standard of care. However, due to a significant occurrence of serious adverse events and two fatalities, the trial was prematurely halted.[114]

Stem cell therapy holds promise for patients with CD by modulating immune responses and inducing remission. More investigation is required to define uniform dosing schedules and stems cell quantities protocols. Stem cell mobilization reduces patient immunity, heightening infection susceptibility.[115] Due to its associated morbidity and mortality, HSTC should be reserved for highly selected patients or within clinical trials.[21] Currently, three ongoing trials in the United States are actively enrolling patients for autologous HSCT in CD (NCT04224558, NCT00692939, NCT03219359), with the third trial investigating vedolizumab post-autologous HSCT as maintenance therapy.

Mesenchymal Stem Cell Therapy

Stem cell transplantation is a valuable adjunctive therapy for CD, with mesenchymal stem cells (MSCs) demonstrating lower immunogenicity and more excellent immunomodulatory effects than HSCs.[116] MSCs are multipotent stem cells capable of both self-renewal and differentiation into diverse cell lineages.[117] MSCs exhibit differentiation potential into adipocytes, osteocytes, and chondrocytes in vitro. Various sources contribute to the availability of MSCs, including bone marrow, adipose tissue, muscle, peripheral blood, umbilical cord, placenta, fetal tissue, and amniotic fluid. MSC has been

used intravenously to treat luminal CD, locally to treat perianal CD fistulas and CD strictures, even though its exact mechanism in this condition is yet to be understood.[118,119]

RCTs have demonstrated that administering intravenous MSCs can enhance CD-related immune tolerance and alleviate CD symptoms.[120–125] A meta-analysis conducted in 2019 identified 13 RCTs of MSCs, indicating both efficacy and safety.[126] Regarding luminal refractory CD, Phase I trials have confirmed the safety and feasibility of MSC therapy.[120,121] Moreover, Phase II studies and case reports have shown promising results in reducing disease activity scores with allogeneic bone marrow and cord blood-derived MSCs.[122,124] In phase IIa double-blind study, 50 patients with moderate to severe CD were randomly assigned to placebo or placenta-derived MSC (PDA-001).[127] Clinical improvement in patients treated with PDA-001 compared to placebo. Only one treatment-related serious adverse event occurred (systematic hypersensitivity reaction). A recent systematic review and meta-analysis examined 28 animal studies and 18 human trials on CD and stem cells.[128] In the MSC treatment group, disease activity decreased compared to the control group. Animals that received MSC treatment exhibited lower histopathological scores and reduced myeloperoxidase levels. Similarly, clinical trials showed reduced CD activity and endoscopic severity indices in patients. Patients with CD maintained high remission rates for 3–24 months after transplantation. Interestingly, subgroup analysis by the source of stem cells revealed that autologous stem cells had a more favorable effect on the CDAI than allogeneic stem cells.

More recently, a study evaluated MSC injection in CD strictures. In a Phase I–II clinical study, allogeneic bone marrow-derived MSCs injected into non-passable strictures of patients with CD showed partial or complete resolution in some cases, with good tolerability but no statistically significant evolution in clinical scores over time.[118] For an overview of the selected studies in this review focusing on hematopoietic stem cell transplantation for refractory luminal CD, please refer to Table 3.

A Cochrane review published in 2022 examined the efficacy and safety of stem cell transplantation (SCT) for refractory CD and found that SCT showed uncertain effects on achieving clinical remission and CDAI <150 at 24 weeks, with low to very low certainty evidence.[141] However, it was likely to achieve fistula closure both in short and long-term follow-up, albeit with low-certainty evidence. There was no significant difference in total adverse events between SCT and control, but SCT increased serious adverse events with low-certainty evidence. Withdrawal due to adverse events was slightly higher in the control group. Limitations include small sample sizes and varying blinding methods across studies.

Despite the short-term safety and feasibility of MSC therapy, challenges such as long-term side effects and poor engraftment need to be addressed for wider clinical adoption. Strategies like cell priming and genetic modification could enhance engraftment, while exosome therapy offers a promising alternative with its better engraftment potential, albeit hindered by low yield.[142] Ultimately, preconditioned MSC-derived exosomes warrant further investigation and development.

Fecal Microbiota Transplantation

Several pilot studies have evaluated the safety, feasibility, and efficacy of fecal microbiota transplantation (FMT) in patients with refractory CD. However, the safety data for FMT in CD are limited due to the absence of long-term follow-up studies. Furthermore, the lack of RCTs hinders confirmation of these findings, and data on maintenance therapy are also scarce.[143] Additionally, the ideal donor characteristics of stool and the optimal route of administration as well as engraftment remain unclear.[144–146] A recent systematic review and meta-analysis investigating the efficacy of FMT in inducing remission among patients with CD encompassed 11 non-comparative cohort studies and 1 non-placebo controlled randomized trial, involving a total of 228 patients.[147] The results revealed that FMT led to a reduction in CDAI scores within 4 to 8 weeks post-treatment, with consistent decreases also observed in biochemical outcomes in studies reporting them. A Cochrane review published in 2023 assessed the effectiveness and safety of FMT for inducing and maintaining remission in CD.[143] However, none of the included studies reported data on the use of FMT for inducing remission in CD. For the maintenance of remission, only one study was available, which reported very uncertain evidence regarding the use of FMT.[148] Additionally, serious adverse events were reported, but the data lacked specificity in terms of event breakdown between the FMT and control groups. Therefore, no definitive conclusion could be drawn

Table 3 Description of Selected Studies for Hematopoietic Stem Cell Transplantation of Refractory Luminal Crohn's Disease

Study	Publication Year	Country	Number of Patients with CD Included	Type and Source of Stem Cells	Amount	Delivery Method	Conditioning Regimen	Sessions of SCT	Median Duration of Follow-Up (weeks)	Main Findings	Safety	Transplantation-Related Mortality	CD34+ Selection	Study design	Level of Evidence
Burt et al[129]	2003	USA (single)	2	Autologous HSC	NA	Intravenous infusions	Cy 200 mg/kg + ATG	1	54	2/2 clinical remission, 2/2 endoscopic improvement	Febrile neutropenia (2)	None	Yes	Case series	D
Craig et al[130]	2003	USA (single)	4	Autologous HSC	NA	Intravenous infusions	Cy 200 mg/kg + ATG	1	NA	4/4 clinical remission	Febrile neutropenia (4)	None	Unknown	Case series	D
Oyama et al[131]	2005	USA (single)	12	Autologous HSC	CD34+ 5,64x10^6 CD3+ 0,59x10^4/kg body weight	Intravenous infusions	Cy 200 mg/kg + ATG	1	74	11/12 clinical remission	Viral gastroenteritis (1), Line related bacteremia (1)	None	Yes	Phase 1 pilot study.	B
Cassinotti et al[132]	2008	Italy (single)	4	Autologous HSC	11*10^6/kg body weight	Intravenous infusions	CY 100 mg/kg + ATG	1	66	4/4 clinical remission, 2/3 endoscopic remission at 3 months	Febrile neutropenia (4), perianal abscess (1), pleural and pericardial effusions (1), BK virus-related macrohematuria (1)	None	No	Phase I/II, prospective	B
Duijvestein et al[121]	2010	The Netherlands (single)	9	Autologous BM-MSC	1–2* 10^6/kg body weight	Intravenous infusions	NA (expanded ex vivo)	2	14	Three patients exhibited clinical response (CDAI decrease ≥70 from baseline) at 6 weeks post-treatment. Endoscopic improvement was observed in two patients with extensive colonic Crohn's disease.	BmMSC infusion was well tolerated, with only one patient experiencing a mild allergic reaction likely due to cryopreservant DMSO.	None	No	Phase I study	B
Burt et al[133]	2010	USA (single)	24	Autologous HSC	6.35*10^6/kg body weight	Intravenous infusions	CY 200 mg/kg + ATG.	1	260	clinical relapse-free survival: 91% after 1 year, 19% at 5 years	Febrile neutropenia, bacteremia (6)	None, 1 accidental death	Yes	Phase I/II, prospective	B
Clerici et al[134]	2011	Italy (single)	6	Autologous HSC	10.9* 10^6/kg body weight	Intravenous infusions	CY 200 mg/kg + ATG.	1	52	6/6 reached clinical remission, 70% endoscopic remission, 5/6 long term maintenance	NA	None	No	Pilot, non-randomized, single-arm clinical trial.	B

Hommes et al[135]	2011	Netherlands (single)	3 (2 transplanted)	Autologous HSC	3.5–539*10^6 cells/kg	Intravenous infusions	CY 200 mg/kg + ATG + prednisolone 500 mg/day (3 days)	1	248	2/2 clinical and endoscopic improvement at 8 to 10 weeks	Febrile neutropenia (1/2), allergic reaction to ATG (1/2), bacteremia (1), *C. difficile* infection (1), Rotavirus Infection (2)	None	Yes	Case series	D
Liang et al[122]	2012	China (multicenter)	4	Allogeneic MSC	1 * 10^6/kg body weight	Intravenous infusions	N/A	1	76	CD patients achieved clinical remission at the 3-month follow-up post-allogeneic MSCT. Endoscopic improvement in all patients.	No significant adverse events related to allogeneic MSCT were reported in patients with CD during the follow-up period.	None	No	Retrospective cohort	C
Hasselblatt et al[136]	2012	Germany (single)	12	Autologous HSC	5.78* 10^6/kg body weight	Intravenous infusions	CY 200 mg/kg	1	162	4/8 clinical remission after 6 months, 5/9 mucosal healing at 9 months	Febrile neutropenia (8/12), bacteremia (2), *C. difficile* infection (2)	None	Yes	Phase I/II, prospective	B
Forbes et al[124]	2013	Australia (multicenter)	15	Allogeneic BM-MSC	2*10^6/kg body weight	Intravenous infusions	NA	4	6	8/15 clinical remission	Dysgeusia (15) Headache (3) Infection: self-limiting presumed viral gastroenteritis (1), vaginal candidiasis (1) Nausea (2) Lymphopenia (3) Normalization of pre-existing lymphopenia (3) Increased alanine aminotransferase level (3)	None	No	Phase II, open-label trial.	B
Mayer et al[137]	2013	USA (multicenter)	12	PDA-001	2*10^8-8 *10^8/kg body weight	Intravenous infusions	NA	2	104	3/6 clinical remission in the low dose group; none in the high-dose group	Headache (7) Nausea (2) Fever (2) Hematuria (3) Anemia (3) Infusion-related reaction (6) Limb discomfort (1) Hyperesthesia (1) Cough (1) Photosensitivity reaction (1)	None	No	Phase I, open-label trial.	B
Snowden et al[138]	2014	UK (multicenter)	6	Autologous HSC	NA	Intravenous infusions	CY 200 mg/kg + ATG	1	348	5/6 clinical remissison at 3 months, 5/6 endoscopic remission	Febrile neutropenia, bacteremia, upper gastrointestinal hemorrhage (1)	None	Yes (2/6)	Case series	D

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Table 3 (Continued).

Study	Publication Year	Country	Number of Patients with CD Included	Type and Source of Stem Cells	Amount	Delivery Method	Conditioning Regimen	Sessions of SCT	Median Duration of Follow-Up (weeks)	Main Findings	Safety	Transplantation-Related Mortality	CD34+ Selection	Study design	Level of Evidence
Melmed et al[127]	2015	USA (multicenter)	46	Placenta-derived cells, allogeneic	placebo vs 1.5*10^8 cells vs 6*10^8 cells	Intravenous infusions	All active and placebo subjects received hydrocortisone (50 mg, intravenously) and diphenhydramine (50 mg, intravenously) 15 to 30 minutes before infusion of investigational product (IP). Subjects in the Phase 2a randomized study also received oral hydrocortisone (100 mg) the night before or up to 4 hours before infusion of IP.	2	96	Clinical Response: Achieved by 38.5% of subjects receiving 4 units of PDA-001 and 33.3% receiving 1 unit, 0% in the placebo group (P = 0.013 for 4 units vs placebo, P = 0.042 for 1 unit vs placebo). Clinical Remission: Achieved by 15.4% of those receiving 4 units and 13.3% receiving 1 unit, 0% in the placebo group.	Serious Adverse Events (SAEs): Fourteen subjects experienced one or more SAEs. Three SAEs were possibly related to treatment: hypersensitivity reaction, gastric ulcer perforation, and anal cancer. Nonserious Adverse Events: pyrexia, headache, infusion-site pain, anemia (most common), CD flare, abdominal pain, nausea, and headache.	None	NA	phase 2a RCT	A
Hawkey et al[108]	2015	European (multicenter)	45 (23 transplanted)	Autologous HSC	9.0*10^6 cells/kg	Intravenous infusion	CY 200 mg/kg + ATG +methylprednisolone 1 mg/kg/d	1	52	No statistically difference for sustained disease remission between two groups. HSCT group were able to stop immunosuppressive drugs (p=0.01)	76 serious adverse events (viral infections (9), neutropenic sepsis (8)	1 (SOS)	No	RCT	A
Dhere et al[120]	2016	USA (single)	16	Autologous BM-MSC	2*10^6, 5*10^6, 10*10^6/kg body weight	Intravenous infusions	N/A	1	9	Efficacy: 5 out of 11 patients showed a clinical response based on CDAI change.	Safety: All 12 patients tolerated cell infusion well, with stable vital signs and no significant changes in safety measures; 7 experienced serious adverse events, 1 possibly related to infusion (C. difficile colitis).	None	None	Phase 1 open label study	B
Lopez-Garcia et al[110]	2017	Spain (single)	35 (29 transplanted)	Autologous HSC	10*10^6/kg body weight	Intravenous infusions	CY 200 mg/kg + ATG	1	52	Clinical and endoscopic relapse-free survival: 61% at one year, 15% at five years	Febrile neutropenia (23), septic shock (1), CMV infections (2: one death, one colectomy)	1 (CMV infection)	No	Phase I/II, prospective	B

Ruiz et al[139]	2017	Brazil (single)	14	Autologous HSC	13.4* 10^6/kg body weight	Intravenous infusions	CY 200 mg/kg + ATG	1	4	13/14 clinical remission at 30 days	Diarrhea during mobilisation phase, 5 identified bacterial infections	None	No	Phase I/II, prospective	B
Zhang et al[123]	2018	China (single)	82	UC-MSCs, allogenic	1*10^6 cells/kg	IV infusion	UC-MSCs obtained from full-term neonatal umbilical cords. Processing involved centrifugation, washing, collagenase and trypsin treatment, and culture under specific conditions. Cells were cryopreserved and phenotypically characterized before infusion.	4	52	Clinical response: CDAI decreased by 62.5±23.2 in the UC-MSC group (control group by 23.6±12.4). HBI decreased by 3.4 ±1.2 in the UC-MSC group (control group by 1.2±0.58).	Fever post-infusion (4), upper respiratory tract infection (7). No serious adverse events.	None	No	RCT	A
Gregoire et al[125]	2018	Belgium (single)	13	Allogeneic BM-MSC	1.5–2.0* 10^6/kg body weight	Intravenous infusions	N/A	2	12	Patients achieving clinical response at Week 2 4 (30.8% Intention to Treat, 23.1% Per Protocol) Patients achieving clinical response at Week 4 3 (23.1% Intention to Treat, 27.3% Per Protocol) Patients achieving clinical response at Week 12 2 (15.4% Intention to Treat, 22.2% Per Protocol)	One patient developed a mild upper respiratory tract infection treated with antibiotics.	None	None	phase I–II open-label	B
Brierley et al[112]	2018	Europe (multicenter)	82	Autologous HSC	5.4 *10^6 cells/kg	Intravenous infusions	CY 200 mg/kg + ATG	1	164	51/80 clincial remission at 100 days	Infection within 1 year (22), secondary autoimmune diseases (9), malignancies (5)	1 (CMV infection), 1 (sepsis at 8 years)	9 out of 82	Retrospective survey	C
Hernanz et al[140]	2018	Spain (single)	7	Autologous HSC	NA	Intravenous infusions	CY 200 mg/kg + ATG	1	192	3/7 clinical and endoscopic remission, 1/7 clinical improvement at 6 months	Febrile neutropenia and mucositis (6), *C. difficile* infection (1)	None	No	Case series	D

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Table 3 (Continued).

Study	Publication Year	Country	Number of Patients with CD Included	Type and Source of Stem Cells	Amount	Delivery Method	Conditioning Regimen	Sessions of SCT	Median Duration of Follow-Up (weeks)	Main Findings	Safety	Transplantation-Related Mortality	CD34+ Selection	Study design	Level of Evidence
Burt et al[111]	2020	USA (single)	9	Allogeneic umbilical cord blood (UCB) and peripheral blood stem cells (PBSC)	NA	Intravenous infusions	CY 200 mg/kg + Fludarabine + Alemtuzumab	NA	260	8/8 remission at 5 years	*C. difficile* infection (1), bacteremia (3), chronic limited GvHD (1)	1 (adenovirus infection)	No	Pilot study	B
Lindsay et al[114]	2024	UK (multicenter)	23	Autologous HSC	5.4*×10^6 cells/kg	IV infusion	Patients in the intervention group fludarabine 125 mg/m2, cyclophosphamide 120 mg/kg, and rabbit anti-thymocyte globulin [thymoglobulin] 7·5 mg/kg in total	1–2	48	At week 48, absence of endoscopic ulceration without surgery or death was reported in three (43%) of seven participants in the intervention group and in none of six participants in the control group with available data	serious adverse reactions in six (46%) patients in the intervention group (renal failure due to proven thrombotic microangiopathy (3)	2 (1 pulmunary veno-occlusive disease, 1 respiratory and renal failure)	No	RCT	A

Notes: The studies were graded based on the study design in A: Randomized Controlled Trials (RCTs) or Meta-analysis of RCTs; B: Prospective Studies, C: Retrospective Studies, D: Case Series.

Abbreviations: ATG, Anti-Thymocyte Globulin; BM-MSC, Bone Marrow Mesenchymal Stem Cells; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CY, Cyclophosphamide; GvHD, Graft-versus-Host Disease; HSC, Hematopoietic Stem Cells; IV, Intravenous; MSC, Mesenchymal Stem Cells; MSCT, Mesenchymal stem cell transplantation; NA, Not Available; PBSC, Peripheral Blood Stem Cells; RCT, Randomized Controlled Trial; SCT, Stem Cell Transplantation; SOS, Sinusoidal Obstruction Syndrome; UC-MSCs, Umbilical Cord Mesenchymal Stem Cells.

about the risk of serious adverse events associated with FMT in CD patients. In terms of safety, FMT for indications such as recurrent *Clostridioides difficile* infection is generally considered safe and well-tolerated, with most short-term adverse effects being mild.[149] However, although rare, serious adverse events have been reported, including the transmission of infections like multi-drug-resistant organisms from donor stool. These risks can be mitigated through careful and rigorous donor screening. Table 4 provides a comprehensive summary of selected studies investigating FMT in the management of refractory luminal CD.

In conclusion, FMT holds promise as a potential treatment for refractory CD, yet further placebo-controlled trials are imperative to substantiate its efficacy, especially focusing on endoscopic parameters. Additionally, uncertainties persist regarding optimal donor characteristics, administration routes, and engraftment, highlighting the need for comprehensive research to elucidate these aspects and optimize FMT's therapeutic potential in CD management.

Immunomodulators

Calcineurin-Inhibitors

Tacrolimus and cyclosporine are calcineurin inhibitors, constituting the cornerstone of immunosuppressive therapy in organ transplantation.[160,161] They exert their effect by binding to intracellular proteins, primarily cyclophilin in the case of cyclosporine and FKBP12 in the case of tacrolimus. This complex formation inhibits calcineurin, a phosphatase enzyme crucial for T-lymphocyte activation. By blocking calcineurin, these medications downregulate the IL-2 pathway, thereby suppressing T-cell proliferation and cytokine production, leading to overall immune system inhibition.

RCTs assessing the effectiveness of oral or intravenous tacrolimus in luminal CD are currently unavailable. A systematic review conducted in 2011 summarized six studies investigating the role of tacrolimus in luminal refractory CD. Among these studies, complete remission was achieved in 31 patients (44.3%, range 7–69%), while partial response was observed in 26 patients (37.1%, range 14–57%).[162] However, several important questions regarding the long-term efficacy of tacrolimus remain unanswered due to the absence of RCTs. More studies are needed in this regard.

A Cochrane review published in 2005 assessed the efficacy of oral cyclosporine for inducing remission in active CD.[163] While a study by Brynskov in 1989 found statistically significant clinical improvement with high-dose cyclosporine (7.6 mg/kg/day) at 12 weeks compared to placebo, other trials using low-dose cyclosporine (5 mg/kg/day) alone or in combination with corticosteroids did not demonstrate significant benefits. Cyclosporine treatment was associated with a higher incidence of adverse events and withdrawals due to adverse events compared to placebo. Overall, low-dose oral cyclosporine was not found to be effective for inducing remission in CD and was instead found to lead to adverse effects, including renal dysfunction. Higher doses or parenteral administration have not been sufficiently evaluated in controlled trials.

As such, while calcineurin inhibitors offer a therapeutic avenue, their use in CD warrants careful consideration, with a preference for alternative interventions supported by stronger evidence and a better safety profile. Further research, particularly RCTs assessing long-term efficacy and safety, is essential for establishing their role in the management of CD.

Thalidomide

Thalidomide, originally introduced for its sedative properties, was withdrawn from the market in 1961 due to severe teratogenic effects, notably phocomelia.[164,165] However, in recent years, it has been repurposed as a potent anti-inflammatory and immunosuppressive agent, demonstrating efficacy in conditions like erythema nodosum leprosum, sarcoidosis, Behcet syndrome as well as recurrent bleeding due to small-intestinal angiodysplasia.[166–170] Thalidomide's mechanism involves shifting the immune response from Th1 to Th2, inhibiting TNF-α, IFN-γ, and IL-12 while stimulating IL-4 and IL-5, and blocking NF-κB activation.[171]

Prior research, including a RCT in children and adolescents, has supported thalidomide's ability to induce clinical remission in refractory CD.[172] Although mainly documented in open-label trials and retrospective studies, thalidomide's efficacy has been noted in refractory CD cases where biological agents failed or were unsuitable.[173–176]

Despite its potential, thalidomide is known for its adverse effects, including peripheral neuropathy.[177,178] However, a recent double-blind RCTs has demonstrated promising results: patients treated with thalidomide showed significantly

Table 4 Description of Selected Studies for FMT of Refractory Luminal Crohn's Disease

Study	Publication Year	Country	Number of Patients with CD Included	Median Duration of Follow-Up (Weeks)	Main Findings	Safety	Donor	Route	Frequency	Fresh/ Frozen	Pre-antibiotic	Inclusion Criteria	Severity	Duration of Disease	Study Design	Level of Evidence
Cui et al[144]	2015	China (single)	30	60	The percentages of clinical improvement and remission, based on clinical activity, at different time points are as follows: 1 week: 83.3% (25/30) and 60% (18/30) respectively; 1 month: 86.7% (26 out of 30) and 76.7% (23 out of 30) respectively; 3 months: 80% (24 out of 30) and 70% (21 out of 30) respectively; 6 months: 66.7% (20 out of 30) and 60% (18 out of 30) respectively; 9 months: 57.1% (12 out of 21) and 52.3% (11 out of 21) respectively; 12 months: 60% (9 out of 15) and 53.3% (8 out of 15) respectively. 15 months: 85.7% (6 out of 7) and 57.1% (4 out of 7) respectively.	No serious adverse events were reported.	Unrelated and related	Mid-gut through gastroscope	Single	Fresh or frozen	No	Moderate to severe CD; HBI ≥ 7	HBI: 11.7 ± 4.5	7.4 ± 5.3 years	Open-label trial	B
Gutin et al[150]	2019	United States (single)	10	52	At 1-month, clinical remission was observed in 1/10 patients (10%) and clinical response in 3/10.	The study was halted prematurely because of a presumed CD flare in two patients within a few days of undergoing FMT.	Unrelated	Colonoscopy	Single	Frozen	Rifaximin taken for 5 days in three patients was discontinued 3 days before FMT	Active CD; HBI ≥ 3	HBI 8.2 ± 4; SES CD: 8.2 ± 6.2	15.8 ± 14.1 years	Open-label trial	B

Wei et al[151]	2015	China (single)	3	4	The mean CDAI score decreased from 345.00 ±77.78 to 135.00 ±7.07 (P=0.082) two weeks after FMT and further decreased to 149.00 ±20.07 (P=0.024) four weeks after FMT.	No serious adverse events were reported.	Unrelated	Colonoscopy or nasojejunal tube infusion	Single	Fresh	Patients were maintained on vancomycin until 12 hours before FMT,	Mild to moderate CD; CDAI score of >150 and <400; C-reactive protein >10 mg/L	CDAI: 345.00 ± 77.78	Median 3.5 (IQR 1.1–6)	Open-label trial	B
Vermeire et al[152]	2016	Belgium (single)	6	26	The median values of CDAI, CRP, CDEIS, and SES-CD from Week 0 to Week 8 showed changes, but none were statistically significant	2 serious adverse events were reported in patients with CD, including fever	Unrelated and related	Nasojejunal or rectal tube.	Two doses over two days	Fresh	No	IBD; refractory to immunomodulators and anti TNF alpha	CDAI: 290 (243–359); CDEIS 11.8 (9.5–17.2); SES-CD 17.5 (17–19.5)	Median 8 (IQR 4.5–13,75)	Open-label trial	B
Vaughn et al[153]	2016	USA (single)	19	26	Clinical response was observed in 58% of patients	No serious adverse events were reported.	Unrelated	Colonoscopy	Single	Frozen	No	Active CD; HBI ≥ 5; >3 years duration; Refractory to standard therapy	NS	12.5 ± 10.6 years	Open-label trial	B
Wang et al[154]	2018	China (single)	139	NR	Clinical response and remission rates were evaluated based on the FMT preparation methods. For manual preparation, 77.6% (52/67) of patients achieved clinical response, and 58.2% (39/67) achieved clinical remission. For automatic preparation, the rates were slightly lower, with 65.3% (47/72) achieving clinical response and 55.6% (40/72) achieving clinical remission.	No serious adverse events were reported.	Unrelated or related	Mid-gut through a naso-jejunal tube or gastroscopic infusion	Single/ multiple (33)	Fresh	No	Mild to severe CD; HBI > 7	HBI: 9 dovrebbe essere > 4	Median 5 years	Open-label trial	B

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Table 4 (Continued).

Study	Publication Year	Country	Number of Patients with CD Included	Median Duration of Follow-Up (Weeks)	Main Findings	Safety	Donor	Route	Frequency	Fresh/ Frozen	Pre-antibiotic	Inclusion Criteria	Severity	Duration of Disease	Study Design	Level of Evidence
Xiang et al[155]	2020	China (single)	174	Median follow-up duration was 43 months (interquartile range, 28–59 months)	Clinical response was observed in 75.3% of patients at 1 month post-FMT. Moreover, 50% of steroid-dependent patients achieved steroid-free remission after FMT.	In this study, no long-term (> 1 m) FMT-related AEs were observed. Four deaths during the follow-up in this study were considered unrelated to FMT. No FMT-related serious adverse events (SAEs) occurred during the follow-up as well.	Unrelated and related	Gastroscopy, nasojejunal tube, mid-gut transendoscopic enteral tubing (TET), and colonic TET.	Frequency: Multiple FMT courses were administered, with a median frequency of 3.5 (interquartile range, 2–5) courses.	Fresh and frozen FMTs were used	No	CD with any therapeutic target	HBI: 8 (6–10)	Median 5 (IQR 2–9) years	Open-label trial	B
Osaki et al[156]	2021	Japan (single)	20	8	Clinical response rates were 75%, with clinical remission rates at 25%.	No serious adverse events were reported.	Unrelated and related	Colonoscopy or antegrade balloon-assisted enteroscopy.	Single	Fresh	Patients with inflammatory bowel disease (IBD) were instructed to undergo antibiotic pretreatment consisting of amoxicillin (1500 mg/day), fosfomycin (3000 mg/day), and metronidazole (750 mg/day) for 2 weeks until 2 days before fecal microbiota transplantation (FMT). Alternatively, if patients declined this pretreatment due to concerns about diarrhea, they were recommended to undergo single-agent therapy with metronidazole (750 mg/day) for 1–2 weeks.	Active CD; CDAI ≥ 9	Mean CDAI 226.5, surgery 50%	NR	Open-label trial	B

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Sokol et al[148]	2020	France (multicenter)	17	24	Steroid-free clinical remission rate at 10 and 24 weeks: 87.5% and 50.0% in the FMT group.CDEIS decreased significantly 6 weeks after FMT (p = 0.03).	No serious adverse events were reported.	Unrelated	Colonoscopy	Single	Fresh	No	Active CD at screening (HBI > 4); clinical response to corticosteroid induction (HBI < 5)	HBI: 2.0 (0.0–3.0); CDAI 62.0 (41.0–109.0); CDEIS 4.6 (0.2–10.5)	Median 9 (IQR 5–15) years	RCT	A
He et al[146]	2017	China (single)	25	Minimum 52	At 3 months post-initial FMT, 68.0% (17/25) of patients achieved clinical response and 52.0% (13/25) achieved clinical remission. Sustained clinical remission with sequential FMTs was achieved by 48.0% (12/25) of patients at 6 months, 32.0% (8/25) at 12 months, and 22.7% (5/22) at 18 months. Additionally, 9.5% (2/21) of patients achieved radiological healing, while 71.4% (15/21) showed radiological improvement.	No serious adverse events were reported.	Unrelated	Gastroscopy or transendoscopic enteral tubing	Multiple	Fresh	7/25 patients received antibiotics (3 to 7 days), including metronidazole by oral or/and enema, or a combination with levofloxacin by intravenous infusion.	Moderate to severe CD complicated by abscess/phlegmon on MRI/CT; HBI ≥ 7	HBI: 11 ± 2.68	6.2 ± 3.91 years	Open-label trial	B
Li et al[157]	2019	China (single)	69	NR	At 1 month, 47/69 were in clinical remission. After the second FMT, 64.3% maintained clinical response over 125 days.	No serious adverse events were reported.	Unrelated or related	Gastroscopy or transendoscopic enteral tubing	Multiple	Fresh	NR	Active CD; HBI score > 4 despite standard treatment; clinical response to FMT	HBI: 1st FMT 8.51 ± 2.55, 2nd FMT 5.48 ± 2.92	7 ± 5.48 years	Open-label trial	B
Zou et al[158]	2019	China (single)	11	NR	8/11 had clinical response 3 days after FMT	No serious adverse events were reported.	Unrelated or related	Midgut through a gastroscope	Single	Fresh	NR	Moderate to severe CD; HBI ≥ 7	NS	NS	Open-label trial	B

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Table 4 (Continued).

Study	Publication Year	Country	Number of Patients with CD Included	Median Duration of Follow-Up (Weeks)	Main Findings	Safety	Donor	Route	Frequency	Fresh/ Frozen	Pre-antibiotic	Inclusion Criteria	Severity	Duration of Disease	Study Design	Level of Evidence
Li et al[159]	2021	China (single)	32	Mean ± SD 50.9 ± 24.4	Among the 32 patients, the clinical response rates after FMT were 75.0% (24/32) at one month, 78.1% (25/32) at three months, and 71.9% (23/32) at six months. Clinical remission rates were 59.4% (19/32) at one month, and 62.5% (20/32) at both three and six months.	No serious adverse events were reported.	Unrelated or related	Gastroscopy or transendoscopic enteral tubing	Single or multiple	Fresh and frozen FMTs were used	No	Active CD (HBI ≥ 5); patients who failed to achieve satisfactory efficacy from the previous therapies and had prior loss of response or intolerance to IFX	Baseline HBI had a median of 9.0 with an interquartile range (IQR) of 6.0 to 13.0.	Median 6.5 (IQR 3.0–10.0)	Open-label trial	B

Notes: The studies were graded based on the study design in A: Randomized Controlled Trials (RCTs) or Meta-analysis of RCTs; B: Prospective Studies, C: Retrospective Studies, D: Case Series.
Abbreviations: CDAI, Crohn's Disease Activity Index; CD, Crohn's Disease; CR, Clinical Remission; CRP, C-Reactive Protein; FMT, Fecal Microbiota Transplantation; NR, Not Reported; PEN, Partial Enteral Nutrition; Plt, Platelets; SES-CD, Simple Endoscopic Score for Crohn's Disease; SD, Standard Deviation; TR, Treatment Response.

higher clinical remission rates, as described by the CDAI index at 8th week of treatment, compared to placebo recipients, with subsequent treatment extension for responders.[179] Adverse events, though prevalent, were predominantly mild and tolerable.

Similarly, a retrospective study evaluated the combination of thalidomide with azathioprine in CD patients unresponsive to azathioprine alone.[180] The combination therapy resulted in positive clinical outcomes, with 70.5% of patients (86 individuals) achieving clinical remission by week 24. However, during follow-up, 22.4% (22 out of 98) of the patients who continued with the combination therapy experienced a clinical relapse. Notably, adverse events were reported but rarely led to therapy discontinuation.

Conclusively, although thalidomide offers a potential solution for refractory CD, clinicians must carefully balance its benefits with its well-documented adverse effects, necessitating vigilant patient monitoring and thoughtful consideration of alternative therapies. While current guidelines do not endorse its widespread use due to the limited quality of available data, it may be a viable option, especially in regions with limited access to biologic therapies and resources.

Dietary Treatments

Exclusive Enteral Nutrition

Exclusive enteral nutrition (EEN) represents an intensive dietary intervention wherein individuals rely solely on commercially available oral liquid meal replacements for their entire caloric intake, typically over a 6- to 8-week period.[181–184] EEN is predominantly administered orally and is commonly initiated in pediatric patients with CD as a first-line, steroid-sparing therapy, demonstrating clinical remission rates comparable to corticosteroids (approximately 60% to 80%).[183] While less frequently prescribed for adult patients with CD, several studies suggest that EEN, when tolerated, may effectively induce clinical and biochemical remission and provide an effective bridge to safer interval elective surgery.[185] However, challenges in trial recruitment and poor adherence to the EEN regimen contribute to the scarcity of definitive data in adults. Efficacy of EEN is influenced by product fatigue, which adults may find particularly challenging in group settings where food consumption occurs. Although the exact therapeutic mechanism of EEN success remains undefined, hypothesized factors include its potential modulatory effect on the microbiome.[186]

A Cochrane review published in 2019 included 27 studies involving 1011 participants to assess the efficacy of enteral nutritional therapy for induction of remission in CD.[187] Overall, the evidence suggested that corticosteroid therapy was more effective than EEN for inducing clinical remission in adults with active CD, even though the data was rated as very low quality. Protein composition did not seem to influence the effectiveness of EEN. However, treatment failures in EEN trials were often due to poor compliance, with common adverse events including nausea, vomiting, diarrhea, and bloating. Recently a real-world, multicenter retrospective study was published regarding the effectiveness of combining biologic treatment with 16 weeks of EEN compared to that of biologics alone in patients with ileum-dominant CD.[188] Of the patients included, approximately 70% of patients exhibited either structuring or fistulizing disease and 40% had previously undergone anti-TNF treatment. The results indicated that the treatment combination led to significantly higher rates of clinical response, clinical remission, endoscopic response, and mucosal healing at both week 16 and week 52 compared to biologics alone.

EEN has shown promise in the treatment of CD. However, compliance remains a significant challenge with EN, with many patients withdrawing due to poor palatability and side effects. Future research should focus on improving the palatability of EN formulations and increasing adherence to therapy. Additionally, the optimal route of administration and composition of EN formulations warrant further investigation. For further insight into the various approaches to dietetic therapy in refractory luminal CD, please refer to Table 5.

Crohn's Disease Exclusion Diet

The CDED is a dietary approach combining partial enteral nutrition (PEN) with specific food components, initially developed for children and later explored in adults with mild to moderate CD.[196] It involves three phases, gradually introducing select foods while maintaining PEN supplementation. A recent pilot study demonstrated that CDED, with or without PEN, induced clinical remission in 63% of adult patients at week six, with 50% maintaining remission at week 24.[197] Endoscopic remission was achieved in 35% of patients by week 24, with better sustained remission and weight

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Table 5 Description of Selected Studies for Dietetic Therapy of Refractory Luminal Crohn's Disease

Study	Publication Year	Country	Number of Patients with CD Included	Therapeutic Option	Median Duration of Follow-Up (Weeks)	Main Findings	Safety	Study Design	Level of Evidence
Heerasing et al[185]	2017	England (single)	51	EEN	52	25% (13/51) of patients treated with EEN avoided surgery. EEN significantly reduced serum CRP levels, The median length of surgery was shorter in patients pre-optimised with EEN than controls (3.0 vs 3.5) hours respectively, EEN patients had fewer surgical complications.	No safety concerns reported	Retrospective cohort study	C
Sigall Boneh et al[189]	2017	Israel (single)	21 (11 adults and 10 children)	12 patients in CDED plus PEN; 4 patients in CDED alone; 5 patients in modified EEN plus CDED	12	13 of 21 patients with failing biological therapy obtained clinical remission.	No safety concerns reported	Retrospective cohort study	C
Chen et al[190]	2019	China (single)	29	EEN followed by PEN	NR (long-term EEN therapy until MH)	After oral EEN treatment, 79% of patients achieved complete mucosal healing in an average of 123 days. Although only 17% achieved transmural healing, there was a significant reduction in bowel-wall thickness and improvement in complications	A number of patients (NR) initially experienced diarrhea or abdominal distension, which eased after 3–4 days by drinking more slowly.	Prospective non-randomized cohort study	B
Szczubelek et al[191]	2021	Poland (single)	32	CDED plus 50% PEN for 6 weeks followed by CDED with 25% PEN for another 6 weeks	12	Clinical remission was obtained in 76.7% patients after 6 weeks and in 82.1% after 12 weeks of CDED. FCP improved vs baseline.	No safety concerns reported	Prospective non-randomized cohort study	B
Sharma et al[192]	2021	India (single)	31	EEN ± other therapies	8	CDAI improved significantly at 4 weeks (290 to 240) and 8 weeks (290 to 186). Clinical response rates were 37.3% at 4 weeks and 80.4% at 8 weeks.	Due to initial intolerance, 4 patients discontinued EEN	Retrospective cohort study	C

Wang et al[188]	2024	China (multicenter)	197	EEN combined with biologics	52	Compared to biologics alone, BioEEN treatment resulted in higher rates of clinical response (95.0% vs 66.0%), clinical remission (87.0% vs 52.6%), endoscopic response (91.4% vs 47.4%), including mucosal healing (85.7% vs 23.7%) at week 16. This superiority was sustained in maintenance, with 84.7% (vs 49.1%) clinical response, 77.8% (vs 38.6%) clinical remission, 69.2% (vs 32.6%) endoscopic response, and 51.9% (vs 18.6%) mucosal healing at week 52.	GI intolerance was the most common adverse event in 31% of patients receiving BioEEN treatment. This mainly manifested as mild EEN-related diarrhea but did not lead to discontinuation of enteral nutrition until 16 weeks later.	Retrospective cohort study	C
Zhou et al[193]	2024	China (single)	56	EEN (16), PEN (21) + ADA	12	Results showed significant improvements in fecal calprotectin, CRP, Alb, Hb, Plt, ESR, CDAI, SES-CD, and BMI in the ADA+EN group compared to the ADA group alone. The differences in all factors before and after treatment between the ADA+PEN group and the ADA +EEN group were statistically significant ($p < 0.05$).	No safety concerns reported	Prospective non-randomized cohort study	B
Nardone et al[194]	2024	Italy (single)	30	PEN with escalated biologic treatment vs biologic treatment alone	24	At 24 weeks, 9 patients (64.3%) in the PEN group achieved CR, compared to 4 patients (25%) in the BT group ($P = 0.03$). The TR rate was 64.9% in the PEN group and 25% in the BT group ($P = 0.03$). The treatment response rate was significantly higher in the PEN group (64.9% vs 25% biologic treatment group). The Biological group experienced a higher rate of therapy changes (68.7% vs 14.2% in the PEN group)	53.3% discontinued PEN due to intolerance, mainly nausea or vomiting, abdominal pain and lack of palatability	Retrospective cohort study	C

(*Continued*)

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Table 5 (Continued).

Study	Publication Year	Country	Number of Patients with CD Included	Therapeutic Option	Median Duration of Follow-Up (Weeks)	Main Findings	Safety	Study Design	Level of Evidence
Wall et al[195]	2018	New Zealand (single)	38	Patients were sequentially recruited to use 2 weeks of EEN followed by either 6 weeks of EEN or PEN with usual diet.	8	84% completed 2 weeks of EEN with significant improvements in disease symptoms, CRP and FC. Initial improvements were sustained over the next 6 weeks on both EEN and PEN. FC non-significantly increased in some PEN patients, with no significant difference in clinical outcomes between EEN and PEN groups at week 8.	No safety concerns reported, 6 patients experienced intolerance due to nausea or diarrhea	Prospective non-randomized cohort study	B

Notes: The studies were graded based on the study design in A: Randomized Controlled Trials (RCTs) or Meta-analysis of RCTs; B: Prospective Studies, C: Retrospective Studies, D: Case Series.
Abbreviations: ADA, Adalimumab; Alb, Albumin; BioEEN, Biologic-Exclusive Enteral Nutrition; BMI, Body Mass Index; BT, Biologic Treatment; CDAI, Crohn's Disease Activity Index; CDED, Crohn's Disease Exclusion Diet; CD, Crohn's Disease; CR, Clinical Remission; CRP, C-Reactive Protein; EEN, Exclusive Enteral Nutrition; ESR, Erythrocyte Sedimentation Rate; FCP, Fecal Calprotectin; GI, Gastrointestinal; Hb, Hemoglobin; MH, Mucosal Healing; NR, Not Reported; PEN, Partial Enteral Nutrition; Plt, Platelets; SES-CD, Simple Endoscopic Score for Crohn's Disease; TR, Treatment Response.

gain observed in the CDED + PEN group compared to CDED alone. Although not adequately powered, the combination of CDED + PEN has shown effectiveness in adult CD patients, including those unresponsive to biologic therapy. Additional studies support its efficacy, with one study reporting clinical remission rates of 76.7% after 12 weeks of therapy.[191] The combination of CDED + PEN has shown effectiveness in a small cohort of adult patients with CD who did not respond to biologic therapy with anti-TNFs despite dose adjustments: 13 out of 21 (61.9%) achieved clinical remission within six weeks of treatment.[189] In a prospective study in Poland involving 32 adult patients with CD with active disease, clinical remission was achieved in 76.7% after six weeks and 82.1% after 12 weeks of therapy, with significant improvement in fecal calprotectin levels by week 12 compared to baseline.[191] Additionally, a case report documented the successful use of CDED + PEN as the sole therapy in a pregnant woman diagnosed with CD from week 14 of gestation until after delivery.[198]

Despite promising results, caution is warranted in employing restrictive diets, particularly in pregnant women, necessitating close medical monitoring.

Further research is needed to validate these findings and elucidate the optimal use of CDED in adult CD management.

Partial Enteral Nutrition

The limitations of conventional therapies could potentially be addressed by PEN, which allows patients to consume a portion of selected foods daily, potentially enhancing both therapeutic tolerance and overall quality of life. However, research on the efficacy of PEN for inducing remission in CD is limited, with sparse evidence available, mainly recommending it for maintenance therapy. Nevertheless, systematic reviews comparing PEN with EEN show comparable results, with both therapies demonstrating high response rates and clinical remission.[199] These findings contrast with earlier randomized clinical trials, such as that conducted by Jonhson et al in 2011 which reported lower remission rates in the PEN group compared to EEN.[200] Several factors, including concurrent corticosteroid use or dietary variations, may have influenced these results. Conversely, Nardone et al published a pilot study investigating the efficacy of PEN as an adjunct to escalated biological therapy in adults with refractory CD.[194] Results showed that PEN combined with escalated biologics led to higher rates of clinical remission and response compared to escalated therapy alone. Additionally, PEN was associated with improved nutritional status.

Additional research is required to establish the role of dietary interventions as a supplementary treatment in individuals with refractory CD.

Optimizing Current Medical Treatments for Refractory Perianal Fistulizing CD

In CD, the progression of transmural inflammation can lead to the development of adhesions, transmural fissures, intra-abdominal abscesses, and fistula tracts. The risk of fistula formation in patients with CD ranges from 14% to 38%, with a high likelihood of abscesses and fistulae in the anus, particularly in those with proctitis, in which this percentage reaches 90%.[201,202] Up to 40% of cases have already developed fistulae by the time of diagnosis, causing significant morbidity and impacting quality of life.[203–205] Perianal fistulae are an aggressive disease phenotype and need a multidisciplinary approach.[206] Despite advances in treatment, the recurrent disease affects up to two-thirds of patients, sometimes necessitating fecal diversion when medical and local surgical management fails, and approximately 20% of patients may require proctectomy with a permanent colostomy.[207–210] Refractory perianal fistulizing CD was defined by the 2021 ECCO topic review on refractory IBD as the lack of response to at least one surgical intervention and anti-TNF therapy.[21]

As CD follows a chronic course, addressing this complication becomes progressively more complex over time, especially following unsuccessful surgical interventions. While various treatments have been evaluated, only immunomodulators and anti-TNFs have demonstrated apparent efficacy. Traditional anti-inflammatory drugs such as aminosalicylates or corticosteroids have shown low effectiveness and high recurrence rates in perianal fistulizing CD. Corticosteroids alone are associated with a high recurrence rate post-treatment. Immunomodulators often require combination therapy, while infliximab stands out as the only TNF inhibitor proven effective for treating fistulizing CD.[211] A recent meta-analysis by Shehab demonstrated the efficacy of TNF antagonists in inducing response and remission in fistulizing disease, with infliximab showing superiority over adalimumab in response induction.[212]

Adalimumab has demonstrated superiority over placebo in a post-hoc analysis for fistula healing after 56 weeks of treatment.[213] As for certolizumab pegol, in the PRECiSE 3 study investigating fistulizing CD, clinical advancements were noted in a restricted subset of patients with perianal fistulas. By the 26th week, 36% of individuals who had previously drained fistulas in the certolizumab pegol group achieved complete fistula closure, contrasting with 17% of those on placebo. However, subsequent trials have not consistently reproduced these findings concerning certolizumab pegol, especially in perianal fistulizing disease.[214] Additionally, while some small uncontrolled trials in the 2010s reported promising results with local injections of infliximab and adalimumab in refractory complex perianal fistulae in CD, with reported healing rates around 70–80%, subsequent studies have not consistently replicated these findings.[215] Guidelines recommend considering alternative anti-TNF therapies or optimizing current ones if there is a loss of response in refractory CD.[37]

This section will describe potential medical treatments for refractory perianal CD. Refer to Table 6 for an overview of selected studies examining medical therapy for refractory perianal CD. It is essential to evaluate and consider these options in collaboration with surgeons, as the management of this complication requires multidisciplinary care.

Antibiotics

Antibiotics lack robust clinical support from high-quality evidence. Indeed, in a single RCT with three arms, 25 patients with active draining perianal fistula were assigned to receive ciprofloxacin, metronidazole, or placebo for ten weeks.[299] Neither ciprofloxacin nor metronidazole demonstrated superior efficacy compared to placebo in achieving complete fistula closure. However, cohort studies report that antibiotics could help improve clinical symptoms in this patient category.[211,299] Further studies are necessary to draw any conclusion on the effectiveness of antibiotics in this setting.

Biologic Drugs

Ustekinumab

Ustekinumab, an IL12/23 inhibitor, is currently undergoing an RCT to evaluate its' efficacy in this patient's population. The Ustekinumab in Fistulizing Perianal CD (USTAP) trial, sponsored by GETAID (NCT04496063) is now active.

Induction outcomes for fistulizing CD were evaluated in a post-hoc analysis of the UNITI-1 and UNITI-2 trials.[300] 24% of patients treated with ustekinumab achieved a fistula response compared to 15.6% of those on placebo, with no statistically significant difference observed. Similarly, ustekinumab did not demonstrate superiority over placebo for inducing fistula remission. Regarding maintenance of fistula response, a subgroup analysis from the IM-UNITI and CERTIFI-M studies revealed that ustekinumab was associated with a significantly higher fistula response rate (58.8%) compared to placebo (26.8%). Within a subset of patients presenting fistulas in the SEAVUE trial, which compared ustekinumab and adalimumab for initiating and maintaining in biologic-naïve individuals with moderately to severely active CD, no statistically notable distinction was observed between the two treatments in preserving fistula remission.[301] Moreover, in a subset investigation derived from the STARDUST trial, patients with moderate-to-severe CD who were biologic-naïve or had previously failed biologic therapy been administered ustekinumab intravenously at approximately 6mg/kg at baseline followed by subcutaneous ustekinumab at 90mg at week 8. By week 16, patients were randomized to receive maintenance therapy following either standard care or a treat-to-target approach, with dosage being modulated according to SES-CD scores. Approximately 47.4% of patients, encompassing both treatment groups, attained complete resolution of fistulas by week 48.[301] On the other hand, the majority of the data is derived from retrospective studies.[302] Attauabi et al conducted a meta-analysis encompassing nine studies involving 396 patients with perianal CD treated with ustekinumab. The combined proportions of patients achieving a fistula response were 41%, 40%, and 55% at weeks 8, 24, and 52, respectively. Correspondingly, the pooled proportions for fistula remission were 17%, 18%, and 16.7% at these time points.[303]

While observational data suggest the potential benefits of ustekinumab in patients unresponsive to anti-TNF agents, the evidence level remains relatively low, emphasizing the anticipation for the results of the USTAP study.

Table 6 Description of Selected Studies for Medical Therapy of Refractory Perianal Crohn's Disease

Class of Therapeutic Option	Type of Therapeutic Option	Study	Publication Year	Country	Main Findings	Type of Study	Level of Evidence
Local mesenchymal stem cell injection	Autologous adipose-derived stem cells	Garcia-Olmo et al[216]	2005	Spain (single)	By the end of week 8, 6/8 (75%) had fistula healing and 3/8 response (25%).	Open-Label Trial	B
	Autologous adipose-derived stem cells	Garcia-Olmo et al[217]	2009	Spain (multicenter)	71% (17/24) achieved healing with MSCs + fibrin glue at 8 weeks	RCT	A
	Autologous bone marrow-derived stem cells	Ciccocioppo et al[218]	2011	Italy (single)	Closure of fistula tracks in 7/10 and incomplete closure in 3/10.	Open-Label Trial	B
	Autologous adipose-derived stem cells	Herreros et al[219]	2012	International (multicenter)	The findings showed that after 24 to 26 weeks, the healing rates for the groups treated with MSCs alone and MSCs + fibrin glue were 39.1% and 43.3%, respectively. By the 1-year mark, these rates increased to 57.1% and 52.4%.	RCT	A
	Autologous adipose-derived stem cells	Guadalajara et al[220]	2012	Spain (single)	Out of the 12 patients included in the retrospective follow-up of the complete closure group treated with MSCs plus fibrin glue, only 7 maintained freedom from recurrence.	Retrospective	C
	Autologous adipose-derived stem cells	Cho et al[221]	2013	Korea (multicenter)	At a dosage of 1 × 10^7, there were instances of partial healing in all 3 cases. With a dosage of 2 × 10^7, 2 / 3 cases achieved complete healing. At a higher dosage of 4 × 10^7, only 1/3 cases achieved complete healing.	Open-Label Trial	B
	Autologous adipose-derived stem cells	Lee et al[222]	2013	Korea (multicenter)	A modified per-protocol analysis revealed that complete fistula healing was achieved in 27/33 patients (82%) within 8 weeks following ASC injection. Of these 27 patients, 26 participated in an additional 1-year observation study, and 23 of them (88%) maintained complete closure.	Open-Label Trial	B
	Autologous adipose-derived stem cells	Choi et al[223]	2013	Korea (multicenter)	At 8 weeks, complete closure was observed in 69.2% (9/13) of patients. 5/9 (83.3%) showed persistent response at 6 months	RCT	A
	Allogeneic adipose tissue derived stem cells	De la Portilla et al[224]	2013	Spain (multicenter)	Complete healing was achieved in 56% of cases, while 69% displayed partial healing, out of a total of 24 patients.	Open-Label Trial	B
	Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cells	Molendijk et al[225]	2015	Netherlands (single)	Partial healing was observed in 38% (8/21) of patients at week 6, 33% (7/21) at week 12, and 42.8% (9/21) at week 24. Complete healing occurred in 57.1% (12/21) at week 6, 52.4% (11/21) at week 12, and 66.6% (14/21) at week 24.	RCT	A

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Table 6 (Continued).

Class of Therapeutic Option	Type of Therapeutic Option	Study	Publication Year	Country	Main Findings	Type of Study	Level of Evidence
	Autologous adipose-derived stem cells	Cho et al[226]	2015	Korea (multicenter)	In the modified intention-to-treat analysis, 80.0% of patients (28/35) exhibited a complete response at 12 months, and 75.0% of patients (27/36) showed a complete response at 24 months.	Retrospective	C
	Allogeneic adipose tissue derived stem cells	Park et al[227]	2015	Korea (multicenter)	2/3 patients in the group treated with 1 × 10^7 cells/mL, achieved complete fistula closure while 1/3 patient in the group treated with 3 × 10^7 cells/mL, achieved complete closure at 8 weeks	Open-Label Trial	B
	Autologous bone marrow-derived mesenchymal stem cells	Ciccocioppo et al[228]	2015	Italy (single)	The probability of fistula relapse-free survival was 88% at 1 year, 50% at 2 years, and 37% during the subsequent 4 years.	Prospective	B
	Autologous adipose-derived stem cells	Wainstein et al[229]	2016	Chile (single)	All 5 patients achieved complete healing after 12 months, totalling 100%.	Prospective	B
	Allogeneic adipose tissue derived stem cells	Garcia -Arranz et al[230]	2016	Spain (single)	At the 52-week mark, complete healing was observed in 60% of cases.	Open-Label Trial	B
	Autologous adipose-derived stem cells	Dietz et al[231]	2017	USA (single)	By the end of 3 months, complete clinical healing was achieved in 9/12 patients. At 6 months, the number of patients achieving complete clinical healing increased to 10/12 (83.3%). MRI evaluation revealed promising therapeutic potential, with 10/12 patients (83%) showing radiographic response.	Open-Label Trial	B
	Autologous adipose-derived stromal vascular fraction	Serrero et al[232]	2017	France (single)	Complete healing rates were 70% at 24 weeks and increased to 80% at 48 weeks.	Open-Label Trial	B
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Panes et al[233,234]	2016; 2018	International (multicenter)	At 24 weeks, combined remission was achieved by 51.5% of patients. By week 52, 56.3% achieved combined remission and 59.2% clinical remission.	RCT	A
	Autologous adipose-derived stem cells	Dozois et al[235]	2019	USA (single)	At the 6-month mark, complete clinical healing was observed in 3 patients, partial healing in 8 patients, and 4 patients showed no clinical improvement. Radiographic improvement was noted in 11/15 patients.	Open-Label Trial	B

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	Mixed types of MSCs	Herreros et al[236]	2019	Spain (single)	Complete healing was achieved in 46% of cases, involving 18 patients with CD. Specifically, the healing rates were 51/124 for the MSCs group, 22/59 for the MSCs with fibrin glue group, and 26/60 for the fibrin glue alone group at the 24-week mark.	Retrospective	C
	Autologous adipose-derived stem cells	Dige et al[237]	2019	Denmark (single)	Complete healing was observed in 76% of the total patients, comprising 21 individuals.	Open-Label Trial	B
	Autologous adipose-derived stem cells	Barnhoorn et al[238]	2020	Netherlands (single)	The fistula closure rates after 4 years were: 100% in the 3 x 10^7 cells group (4 patients); 63% in the 1 x 10^7 cells group (4 patients); 43% in the 9 x 10^7 cells group (5 patients)	Prospective	B
	Autologous adipose-derived stem cells	Zhou et al[239]	2020	China (single)	At 12 weeks, complete healing was achieved in 90% of cases, at 24 weeks it was 72%, and at 48 weeks it was 63%.	Open-Label Trial	B
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Schwander et al[240]	2021	Germany (single)	The healing rate was 66%, with 8/12 patients showing improvement.	Retrospective	C
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Cabalzar-Wondberg et al[241]	2021	Switzerland (single)	72.7% (8/11) achieved complete closure of the fistula, while 27.3% (3/11) showed no response.	Retrospective	C
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Nikolic et al[241]	2021	Austria (single)	Clinical healing was observed in 25% of cases, representing 1/4 patients.	Retrospective	C
	Allogeneic adipose tissue derived stem cells	Gutierrez et al[242]	2021	Mexico (single)	Complete healing was achieved in 69% of cases/a total of 20 patients.	Open-Label Trial	B
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Panes et al[243]	2022	International (multicenter)	Clinical remission rates at 52-, 104-, and 156-weeks post-treatment were 67.4%, 53.5%, and 53.5%, respectively	Retrospective	C

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Table 6 (Continued).

Class of Therapeutic Option	Type of Therapeutic Option	Study	Publication Year	Country	Main Findings	Type of Study	Level of Evidence
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Colombo et al[244]	2022	Italy (single)	Despite a history of refractory perianal disease, 2 patients showed clinical improvement at 6 months, although fistula tracts persisted radiologically. One patient experienced perianal fistula recurrence with abscess formation.	Retrospective	C
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Garcia-Olmo et al[245]	2022	International (multicenter)	At week 104, clinical remission was achieved in 56% of patients in the darvadstrocel group compared to 40% in the control group, suggesting sustained clinical benefit up to 2 years post-treatment.	RCT	A
	Autologous adipose-derived stromal vascular fraction (ADSVF)	Guillo et al[246]	2022	France (single)	7 patients (70%) achieved combined remission, which correlated with a notable enhancement in the MAGNIFI-CD MRI score	Open-Label Trial	B
	Autologous bone marrow-derived mesenchymal stem cells	Vosough et al[247]	2022	Iran (single)	1/5 patient experienced complete remission, marked by fistula closure, cessation of fistula discharge, and closure of the external opening.	Case series	D
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Furukawa et al[248]	2023	Japan (multicenter)	At Week 24, combined remission was achieved in 59.1% of patients, with maintenance observed at Week 52 (68.2%).	Open-Label Trial	B
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	White et al[249]	2023	Israel (multicenter)	Clinical remission was sustained in 61% of patients (20/33) during the mean follow-up period. Furthermore, 73% (24/33) achieved at least 3 months of clinical remission. Recurrence within 3–12 months occurred in 4 patients. Partial remission was observed in 6% (2/33) of patients, while signs of response without achieving remission were seen in another 6% (2/33). Conversely, 15% (5/33) showed no signs of healing.	Prospective	B
	Allogenic bone marrow-derived mesenchymal stem cells	Reenaers et al[250]	2023	Belgium (single)	At weeks 12 and 48, complete closure of fistulae was achieved in 9/16 and 8/16 patients, respectively, while at least partial closure was noted in 11/16 patients.	Prospective	B

	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Fathallah et al[251]	2023	France (single)	The rates of complete clinical and radiological responses at month 12 were 51.9% and 50%, respectively. The combined rate of complete clinical and radiological response, indicating deep remission, was 34.6%.	Prospective	B
	Allogenic bone marrow-derived mesenchymal stem cells	Lightner et al[252]	2023	USA (single)	At twelve months, a combined clinical and radiographic healing was achieved in 70% of perianal fistulas.	Open-Label Trial	B
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Fathallah et al[253]	2024	International (multicenter)	Regarding clinical response, defined as the closure of at least 50% of external openings, the All-Treated cohort exhibited a rate of 79.9% (107/134 patients), while the Per-Protocol cohort showed a similar rate of 79.8% (99/124 patients). For clinical remission, characterized by the closure of all external openings, the All-Treated cohort achieved a rate of 76.1% (102/134), with the Per-Protocol cohort slightly higher at 76.6% (95/124 patients).	Prospective	B
	Allogenic bone marrow-derived mesenchymal stem cells	Swaroop et al[254]	2024	India (single)	In the intention-to-treat analysis at week 24, 20% achieved fistula remission, while 70% exhibited fistula response. By week 52, remission and sustained response rates remained at 20% and 70%, respectively. At 104 weeks, response was maintained in 20% of patients, with one patient (10%) achieving remission.	Open-Label Trial	B
	Non specified	Pronk et al[255]	2024	Netherlands (single)	Clinical closure of fistula(s) was attained in 21 patients (70.0%). However, 3 patients (14.3%) experienced recurrence during long-term follow-up, despite clinical closure of the fistula(s) without radiological remission.	Case series	D
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Herreros et al[256]	2024	Spain (multicenter)	A clinical response was achieved in 63/73 patients (86.3%), complete clinical closure in 50/73 patients (68.5%), and radiological closure in 45/73 patients (69.2%). A combined clinical and radiological response was observed in 41/73 patients (63.1%).	Retrospective	C
	Allogenic bone marrow-derived mesenchymal stem cells	Husman et al[257]	2024	Germany (single)	At the last observation, 8 of 13 fistulas (62%) exhibited complete closure.	Retrospective	C

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Table 6 (Continued).

Class of Therapeutic Option	Type of Therapeutic Option	Study	Publication Year	Country	Main Findings	Type of Study	Level of Evidence
	Darvadstrocel (expanded allogeneic adipose-derived mesenchymal stem cells)	Dawoud et al[258]	2024	Austria (multicenter)	After a median follow-up of 92 weeks, successful fistula closure was observed in 57.1% (n = 8) of treated patients.	Prospective	B
Hyperbaric oxygen therapy	2–2.4 ATA × 90 min × median 21 (18–30)	Agrawal et al[259]	2015	Australia (single)	All 9 cases achieved complete clinical healing of fistulas, while 3/4 showed complete fistula healing according to MRI scans.	Case series	D
	2.4 ATA × 120 min × median 20 (10–86)	Feitosa et al[260]	2016	Brazil (single)	10/16 improvements	Open-Label Trial	B
	2.5 ATA × 90 min × 30	Piotrowicz et al[261]	2017	Poland (single)	5/7 cases showed regression of lesions based on MRI and endoscopy, while 5/7 exhibited improved CDAI scores.	Prospective	B
	243–253 kPa × 40×80 min	Lansdorp et al[262]	2021	Netherlands (single)	12/20 demonstrated a clinical response, while 4/20 achieved fistula remission.	Open-Label Trial	B
Small molecules	Upadacitinib	Colombel et al[263]	2023	International (multicenter)	By week 12, 20.8% of patients achieved external closure of fistula openings, while 47.7% experienced complete resolution of draining, and 50% attained at least a 50% reduction in draining. Moreover, 54.3% achieved complete resolution of fissures.	RCT	A
	Filgotinib	Reinish et al[264]	2024	International (multicenter)	The combined fistula response rate at week 24 was 47.1% (8/17) for the filgotinib 200 mg group, 29.2% (7/24) for the filgotinib 100 mg group	RCT	A

Combined medical therapy	IFX and thiopurines	Present et al[265]	1999	International (multicenter)	No benefit from the combination.	RCT	A
	Ciprofloxacin + IFX	West et al[266]	2004	Netherlands (single)	Clinical response in 73% (8/11) of patients in the IFX + ciprofloxacin group	RCT	A
	IFX and thiopurines	Sands et al[267]	2004	International (multicenter)	No benefit from the combination	RCT	A
	IFX and thiopurines or methotrexate	Fefferman et al[268]	2004	USA (multicenter)	No benefit from the combination	Prospective	B
	Ciprofloxacin, azathioprine or 6-mercaptopurine and IFX	Schwartz et al[269]	2005	USA (single)	Initially, 86% of the patients (18/21) experienced complete cessation of drainage. Additionally, 76% of the patients (16/21) sustained long-term cessation of drainage.	Retrospective	C
	IFX or Adalimumab and thiopurines	Tozer et al[270]	2012	UK (single)	Of the 41 patients included, 58% of all patients experienced clinical benefit (remission or response) by the end of the follow-up period.	Prospective	B
	IFX and thiopurines or methotrexate	Bouguen et al[271]	2013	France (multicenter)	After a median follow-up of 250 weeks, 69% of patients experienced at least one fistula closure, with cumulative probabilities of first fistula closure at 40% and 65% at 1 and 5 years, respectively	Retrospective	C
	Ciprofloxacin + adalimumab	Dewint et al[272]	2014	Netherlands (multicenter)	Clinical response in 71% (24/34) of patients in the adalimumab + ciprofloxacin group.	RCT	A
	Metronidazole and/or ciprofloxacin + azathioprine	Dejaco et al[273]	2003	Austria (single)	Patients treated with azathioprine + metronidazole and/or ciprofloxacin had a significantly better response rate (48%) compared with patients taking only metronidazole and/or ciprofloxacin (15%; P=0.03).	Open-label trial	B
Immunosuppressants	Tacrolimus	González-Lama et al[274]	2005	Spain (single)	4/10 patients (40%) achieved complete clinical response, while 5/10 (50%) experienced partial clinical response, characterized by a reduction in fistula size, drainage, or pain.	Open-Label Trial	B
	Topical tacrolimus	Hart et al[275]	2007	UK (single)	3/4 patients treated with topical tacrolimus for ulcerating disease improved. Complete healing was not achieved.	RCT	A
	Thalidomide	Plamondon et al[276]	2007	UK (multicenter)	Fistula closure was achieved in 82% of patients (9/11)	Case series	D

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Table 6 (Continued).

Class of Therapeutic Option	Type of Therapeutic Option	Study	Publication Year	Country	Main Findings	Type of Study	Level of Evidence
Biologic therapy	UST	Kopylov et al[89]	2014	Canada (single)	An initial response was observed in 69.2% (9/13) of cases. Among these patients, 4/9 who initially responded reached a follow-up period of 12 months, with 3/4 maintaining their clinical response.	Retrospective	C
	UST	Khorrami et al[277]	2016	Spain (multicenter)	Perianal disease improved in 61% of patients with active perianal fistulae.	Retrospective	C
	UST	Battat et al[278]	2017	Canada (single)	At ≥6 months, 66% of patients achieved >50% reduction in draining fistulas, and 33% achieved closure of all fistulas.	Open-Label Trial	B
	UST	Ma et al[279]	2017	Canada (multicenter)	Complete radiologic healing (as assessed by MRI or contrast-enhanced pelvic ultrasound) was achieved in 31.1% of patients.	Retrospective	C
	UST	Sands et al[280]	2017	International (multicenter)	At week 8, 26% reached fistula response and 24.7% fistula resolution	Post-Hoc analysis of RCTs	A
	UST	Tsistrakis and Oikonomou[281]	2017	USA (single)	2/5 experienced a response, characterized by a reduction in fistulous drainage or partial healing of fistulas, while 1/5 achieved complete closure of fistulas.	Retrospective	C

	UST	Krugliack et al[282]	2018	USA (single)	10/16 (62.5%) showed improvement by the six-month follow-up.	Retrospective	C
	UST	Satyam et al[283]	2018	USA (single)	7/21 showed improvement in perianal symptoms according to their treating physician while continuing ustekinumab treatment; 2/21 achieved remission, characterized by the complete absence of perianal symptoms based on medical history, physical examination, and, if applicable, endoscopy.	Retrospective	C
	UST	Wils et al[90]	2018	France, Switzerland (multicenter)	A clinical benefit was observed in 6/9 patients treated for perianal disease, representing a 67% success rate.	Retrospective	C
	UST	Bar-Gil Shitrit et al[284]	2020	Israel (multicenter)	20/26 patients (77%) remained with an active disease, defined as any actively draining perianal fistula, at week 8, while 18/26 patients (69%) remained with the perianal disease at week 24	Prospective	B
	UST	Biemans et al[97]	2020	Netherlands (multicenter)	The clinical remission rates were 14.3% at week 12 and 35.7% at week 24. The clinical response rates were 14.3% at week 12 and 14.3% at week 24.	Prospective	B
	UST	Chapuis-Biron et al[285]	2020	France (multicenter)	For patients with active fistulas, the success rate was 38.5% (57/148), successful seton removal occurred in 33% (29/88) of cases, and recurrence-free survival was 75.1%.	Retrospective	C
	UST	Fumery et al[43]	2020	France (multicenter)	The clinical response rate stands at 61%, while the clinical remission rate is recorded at 22%.	Retrospective	C
	UST	Harris et al[286]	2020	UK (single)	3/8 exhibited a documented response during the post-induction review, 2/8 underwent defunctioning procedures, and 3/8 continued to experience ongoing disease.	Retrospective	C

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Table 6 (Continued).

Class of Therapeutic Option	Type of Therapeutic Option	Study	Publication Year	Country	Main Findings	Type of Study	Level of Evidence
	UST	Attauabi et al[287]	2021	Denmark (multicenter)	The clinical response rates were 53.8%, 50.0%, and 63.6% at weeks 16, 24, and 52, respectively. There were no instances of fistula remissions observed.	Open-Label Trial	B
	UST	Brewer et al[288]	2021	USA (single)	At the six-month mark, provider-based evaluation revealed that 13/27 patients (48.1%) showed a perianal fistula response, but no patients achieved remission. 13/27 (48.1%) had no change, and 1/27 (3.7%) experienced worsened perianal disease. Regarding symptomatic improvement reported by patients, 16/27 patients (59.3%) saw improvement, with 1/27 (3.7%) achieving symptomatic remission. 11/27 (40.7%) reported no change in symptoms, and none reported worsening perianal symptoms.	Retrospective	C
	UST	Manlay et al[289]	2021	France (multicenter)	By Week 14, Week 24, and Week 54, the rates of remaining active perianal lesions were 19/36, 15/30, and 7/21	Retrospective	C
	UST	Plevris et al[290]	2021	Scotland (multicenter)	At six months, the response rate was 12.5%, and it increased to 53.1% at twelve months.	Retrospective	C
	UST	Straatmijer et al[291]	2021	Netherlands (multicenter)	The rates of fistula remission were 17.2%, 37.9%, and 37.9% at 12, 24, and 52 weeks, respectively.	Prospective	B
	UST	Yao et al[292]	2023	China (single)	By the third infusion, clinical remission was noted in 40.7% of patients, while 63.0% showed a clinical response in fistula management.	Retrospective	C
	UST	Newman et al[293]	2023	USA (single)	Fistula still present at 1 year in 20/27 (79%) subjects included	Retrospective	C

	UST	Peyrin-Biroulet et al[294]	2022	International (multicenter)	In the SEAVUE trial, 7/13 (53.8%) with active perianal fistulas at baseline achieved complete fistula resolution at Week 52. In the STARDUST trial, 9/19 patients (47.4%) with active perianal fistulas at baseline achieved complete fistula resolution at Week 48.	RCT	A
	VDZ	Sandborn et al[64]	2013	International (multicenter)	Out of 17 patients receiving VDZ every 8 weeks, 41.2% experienced closure of draining fistulas at 52 weeks. Similarly, among 22 patients receiving vedolizumab every 4 weeks, 22.7% achieved closure of draining fistulas at the same time point.	RCT	A
	VDZ	Feagan et al[295]	2018	International (multicenter)	The rate of fistula closure was 28% and 33% at weeks 14 and 52, respectively, in the treatment group	RCT	A
	VDZ	Chapuis-Biron et al[296]	2020	France (Multicenter)	The treatment achieved success in 23/102 patients (22.5%). Among those with setons at initiation, successful removal was achieved in 9/61 cases (15%).	Prospective	B
	VDZ	Manlay et al[289]	2021	France (multicenter)	By Week 14, Week 24, and Week 54, the rates of remaining active perianal lesions were 9/14, 2/8, and 3/7, respectively	Retrospective	C
	VDZ	Schwartz et al[297]	2022	International (multicenter)	Prompt and consistent closure of fistulas was noted, with 53.6% of patients (64.3% in the VDZ group and 42.9% in the VDZ + week 10 group) achieving a reduction of at least 50% in draining fistulae, and 42.9% of patients (50.0% in the VDZ group and 35.7% in the VDZ + week 10 group) achieving complete closure of all fistulae by week 30.	RCT	A
	VDZ	Newman et al[293]	2023	USA (single)	Fistula still present at 1 year in 7/7 (100%) subjects included	Retrospective	C
Antibiotics	Metronidazole 10% ointment t.i.d.	Maeda et al[298]	2010	International (multicenter)	A decrease in PDCAI score was noted in 32% (10/33) of patients treated with metronidazole	RCT	A

Notes: The studies were graded based on the study design in A: Randomized Controlled Trials (RCTs) or Meta-analysis of RCTs; B: Prospective Studies, C: Retrospective Studies, D: Case Series.
Abbreviations: ASC, Autologous Adipose-Derived Stem Cells; ATA, Atmosphere Absolute; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; IFX, infliximab; MRI, Magnetic Resonance Imaging; MSCs, mesenchymal stem cells; PDCAI, Perianal Crohn's Disease Activity Index; RCT, Randomized Controlled Trial; UST, Ustekinumab; VDZ, Vedolizumab; t.i.d., three times a day.

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Vedolizumab

Vedolizumab, a fully humanized monoclonal antibody that selectively targets α4β7 integrin, has shown promise as a second or third therapy-line option. A post-hoc analysis of the GEMINI-2 trial evaluated the effectiveness of vedolizumab versus placebo in patients with fistulizing CD.[295] 28% of vedolizumab-treated patients achieved fistula remission compared to 11% of placebo patients, but this difference was not statistically significant. Similarly, there was no considerable contrast in maintaining fistula remission compared to placebo. In a phase IV, double-blind, RCT called ENTERPRISE trial, a standard dose of vedolizumab was compared with the standard dose plus an additional intravenous infusion at week 10. At week 30, the two dosing regimens had no statistically significant disparity in fistula response or remission.[297] A recent meta-analysis of four studies, including two RCTs, two retrospective cohort studies, and almost 200 patients affected by perianal fistulizing CD, found that vedolizumab resulted in complete healing in 27.6% of patients and partial healing in 35%.[304] In a comparative study examining the efficacy of biologic therapies in fistulizing CD, Shehab et al analyzed data from 10 RCTs.[212] Their findings revealed that ustekinumab was more effective than placebo in inducing response (Odds ratio, 0.48; 95% CI, 0.26–0.860) but not in inducing remission (Odds ratio, 0.50; 95% CI, 0.13–1.93) and vedolizumab did not demonstrate superiority over placebo in inducing remission (Odds ratio, 0.32; 95% CI, 0.04–2.29). Moreover, no significant difference was observed in inducing remission when comparing different biologic therapies. Firm recommendations cannot be made due to limited published data and lack of head-to-head trials comparing different biologic drugs in IBD patients.

Immunosuppressants

In the past, immunomodulators and immunosuppressants were commonly utilized for treating fistulizing CD. Azathioprine and 6-mercaptopurine have been employed in fistula treatment, but data supporting their efficacy are limited. A meta-analysis of five RCTs suggested that thiopurines could effectively induce fistula closure.[305] Nevertheless, many patients had to discontinue the therapy due to side effects like allergy, leukopenia, pancreatitis, and nausea. Due to insufficient evidence, ECCO guidelines do not advocate using thiopurines in monotherapy.[305]

In a 1998 study by Egan et al, seven out of nine patients with fistulizing CD partially responded to intravenous cyclosporine, with four of six maintaining or improving the response during subsequent oral therapy. However, all patients experienced a relapse within 1 to 17 weeks after discontinuing the treatment.[306] In a 2002 Spanish study, these findings were not replicated, as the response to intravenous cyclosporine was observed in refractory CD but not in fistulizing/perianal disease.[307]

Tacrolimus has been utilized as an oral and topical rescue therapy for fistulizing CD. However, give its safety profile and limited tolerability, long-term studies to assess its efficacy and safety are scarce.[308–311] A RCT was undertaken to evaluate the effectiveness of topical tacrolimus treatment to address potential systemic adverse effects. Nineteen patients were stratified according to whether they presented with ulcerating (7 patients) or fistulizing (12 patients) CD. Subsequently, they were randomly allocated to receive topical tacrolimus or a placebo for 12 weeks. For individuals with fistulizing disease, topical tacrolimus showed no efficacy.[275] In 2011, a systematic review examined eight studies involving 49 patients with perineal CD treated with oral or intravenous tacrolimus. Among patients who received oral tacrolimus, there was a reported partial or complete response rate of 67.4%.[162]

A study conducted by Plamondon and Kamm and published in 2007 proposed that thalidomide might be effective as a short-to-medium-term treatment for specific patients with refractory luminal and fistulizing CD.[276] Out of 11 patients with active fistulizing disease included in this study, nine responded positively to thalidomide treatment, with six experiencing improvements and three achieving remission. Despite its potential efficacy, long-term use of thalidomide was limited due to toxicity issues, including sedation, abdominal pain, leukopenia, and neuropathy.[276] A subsequent systematic review conducted in 2016 aimed to describe the efficacy of thalidomide in luminal and fistulizing CD. It included ten studies and 81 patients with fistulizing CD. Despite varying definitions used by different authors, improvement in perianal fistulas was documented in 49 out of 81 patients (60.5%), with closure achieved in 28 out of 81 patients (34.6%).[312] A recent systematic review and meta-analysis analyzed pharmacological therapies for fistulizing CD and found that on pooled analysis fistula response but not fistula remission was achieved with immunosuppressants against placebo.[313]

In conclusion, while immunosuppressants have historically been used in the treatment of fistulizing CD, their efficacy remains uncertain, and their use is often limited by adverse effects.

Combined Medical Therapy

Combined Anti-TNF and Antibiotics

The most common combination includes anti-TNF drugs (such as infliximab and adalimumab) paired with antibiotics (typically ciprofloxacin), outperforming anti-TNF monotherapy. The ADAFI trial demonstrated that combining adalimumab with ciprofloxacin was more effective than adalimumab alone in achieving fistula closure in perianal fistulizing CD.[272] After 12 weeks of treatment, the combination therapy resulted in significantly higher rates of clinical response and remission compared to adalimumab monotherapy.[272] However, this beneficial effect was not sustained after discontinuation of antibiotic therapy. Similarly, an RCT investigated the efficacy of combining ciprofloxacin with infliximab in treating perianal fistulae in CD.[314] In a double-blind placebo-controlled trial, patients received either ciprofloxacin or a placebo for 12 weeks alongside infliximab. The primary endpoint, clinical response defined by fistula reduction, showed a trend favoring the ciprofloxacin group (73% vs 39% in the placebo group), although not statistically significant. However, secondary endpoints such as the Perianal Disease Activity Index score showed significant improvement in the ciprofloxacin group. However, the improvement in fistulas was restricted to the duration of antibiotic use.[272]

Combining anti-TNF drugs like infliximab and adalimumab with antibiotics, particularly ciprofloxacin, has emerged as a promising approach for treating perianal fistulizing CD. However, the sustained benefit may be limited to the duration of antibiotic therapy.

Combined Anti-TNFs and Immunomodulators

Contrary to previous assumptions, introducing thiopurines after anti-TNF therapies does not seem beneficial. A 2015 meta-analysis based on 11 RCTs found no clear advantage with combined therapy concerning partial or complete fistula closure compared to anti-TNF monotherapy.[315] Presently, ECCO guidelines stress the need for further research due to insufficient evidence supporting a definitive recommendation for or against using immunomodulators in this context.[37]

Dual-Targeted Therapy

Specific clinical trials suggest the potential of utilizing a combined medical approach to address this condition. A small retrospective cohort study examined 22 patients who received treatment with dual biologics, finding that 33% of patients with perianal fistulas experienced fistula healing post-treatment.[61] These findings imply that combining two biologics could be an alternative for managing refractory fistulizing CD. Nevertheless, additional research is necessary to validate the efficacy and safety of this approach.

Small Molecules

Utilizing small molecules in treating fistulizing CD remains a topic of debate. A study by Colombel et al explored the efficacy of upadacitinib in patients with CD complicated by fistulas. The group receiving treatment exhibited higher rates of external closure and fistula drainage resolution than the placebo group. Interestingly, the incidence of adverse events was comparable between the upadacitinib and placebo groups.[263] Nevertheless, current data is very limited.

Local Mesenchymal Stem Cell Injection

As previously mentioned, there is clear evidence that combining medical and surgical treatments is superior to single medication therapy in achieving fistula closure (53% vs 43%, $P < 0.05$).[316] Additionally, autologous MSC transplantation has emerged as a potential therapy for perianal fistulas in CD alongside traditional methods like fistula drainage and ligation. Administering a MSC preparation into a carefully prepared fistula tract has shown increased rates of fistula healing compared to surgery alone.[233,234] The rationale behind these therapies resides in the unique properties of mesenchymal cells, including their potential to differentiate into various mesodermal cell lineages and their ability to modulate immune cell activation, proliferation, differentiation, and maturation, making them promising candidates for therapeutic use.[317] These cells can be sourced from adipose tissue or bone marrow or be allogeneic or autologous. A recent meta-analysis incorporating five RCTs

reaffirmed the safety and efficacy of MSC treatment in this patient population.[211] Patients treated with MSCs exhibited a significant likelihood of remission (odds ratio of 2.06), with consistent findings across studies. Regarding treatment-emergent adverse events, perianal abscesses and proctalgia were commonly reported in trials, with no notable difference compared to the control group. However, in the clinical application of MSCs, determining the optimal dose or injection site remains challenging. Interestingly, in the review, as mentioned earlier, the group receiving 3×10^7 MSCs demonstrated superior fistula healing compared to the 9×10^7 MSCs group, possibly due to a lower cell survival rate.

Darvadstrocel consists of 120 million expanded human allogeneic adipose-derived MSCs, which showed great promise in perianal CD. Two Phase III studies analyzing the efficacy and safety of Darvadstrocel have been recently published. In the phase III multi-center ADMIRE-CD study, 212 patients diagnosed with treatment-refractory perianal CD underwent examination under anesthesia with curettage of fistula tracts and surgical closure of their internal openings.[233] These patients received two operations, which included the closure of the internal opening and were randomly assigned to receive either a placebo or a single injection of darvadstrocel. The study found that 56% of patients treated with stem cells achieved combined radiological and clinical remission at 52 weeks, defined as closure of external openings and absence of fistula drainage, compared to 39% of those in the control group. Furthermore, extended follow-up indicated that remission rates persisted beyond 104 weeks, with no observed safety concerns.[243] The global ADMIRE-CD II phase III study aimed to assess the efficacy and safety of treating complex perianal fistulas in CD.[318] Patients were randomized to receive either darvadstrocel or a placebo. The primary endpoint was combined remission at 24 weeks, with secondary endpoints including combined remission at 52 weeks, clinical remission at 24 and 52 weeks, and time to clinical remission at 24 weeks. Overall, darvadstrocel was well tolerated, with a safety profile consistent with previous studies. Although there were no statistically significant differences in remission rates between darvadstrocel and placebo at 24 weeks, a post hoc analysis suggested lower placebo response rates in patients randomized before COVID-19.

Given the limited available data, further trials are warranted to establish optimal dosing and injection sites for MSC therapy in this patient subset. Therefore, more research is needed to define these individuals' most appropriate treatment approaches.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) shows promising effectiveness in treating perianal CD and enterocutaneous fistulas, as indicated by uncontrolled observational studies and prospective case series. A recent systematic review and metanalysis found that HBOT in luminal and perianal CD resulted in an overall clinical response rate of 75% and a clinical remission rate of 55%, with no major differences observed in sensitivity analyses.[319] For rectovaginal fistulas, clinical response occurred in 62.5% of patients and clinical remission in 37.5%. Radiographic assessment revealed significant improvements in fistula tracts, with some studies reporting complete resolution in up to 75% of cases. In enterocutaneous fistulas, the clinical response rate was 85%, with partial closure achieved in 50% of cases. These findings suggest that HBOT may be a valuable adjunctive therapy for fistulizing CD.

Regarding safety, a total of 15% of patients experienced an adverse event to HBOT, none of which were serious, and the majority of which did not impact treatment. Ear barotrauma was the most frequently reported adverse event, occurring in 3% of patients, and was less common than what has been reported in prior studies, possibly as a result of fewer predisposing risk factors (intubation, concomitant cardiovascular disease, head and neck cancers, diabetes, and sinus infections) in patients with IBD compared with non-IBD patients with chronic wounds.[320,321]

In a study involving 20 patients, treatment with 40 hyperbaric oxygen sessions resulted in marked improvements in clinical outcomes, including decreased scores of perianal disease activity and modified van Assche index.[262] Additionally, a substantial proportion of patients achieved clinical response and remission, with many showing inactive perianal disease by week 16. Furthermore, reductions in inflammatory markers such as C-reactive protein and fecal calprotectin levels were observed.

These findings suggest that hyperbaric oxygen therapy holds promise as a therapeutic option for managing perianal fistulas in patients with CD.

Conclusion

Despite advancements in treatment and the biologic era, some patients with CD exhibit inadequate responses to medical therapy. Refractory CD, although rare, poses a formidable challenge in treatment. Despite efforts over the past two decades to discover new drugs, data remain limited, albeit preliminary findings may seem promising. We reviewed the evidence on various treatments for both luminal and perianal CD, including combined therapies, HSCT, FMT, immunomodulators, HBOT and dietary approaches. While the evidence is promising, it remains limited. Further research is imperative to comprehend refractoriness mechanisms and innovate new medicines.

Disclosure

Edoardo Vincenzo Savarino has served as speaker for Abbvie, Agave, AGPharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, MayolyBiohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as a consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, DiademaFarmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Nestlè, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici. Fabiana Zingone has served as a speaker for EG Stada Group, Fresenius Kabi, Janssen, Pfizer, Takeda, Unifarco, Malesci, and Kedrion and has served as a consultant for Galapagos. Brigida Barberio has served as a speaker for Abbvie, Agave, Alfasigma, AGpharma, Janssen, Lilly, MSD, Pfizer, Sofar, Takeda, and Unifarco. Edoardo Vincenzo Savarino and Brigida Barberio are co-senior authors. The other authors declare no conflict of interest.

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