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REVIEW

Optimal Management of Refractory Crohn's Disease: Current Landscape and Future Direction

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Abstract: Refractory Crohn's disease, defined as ongoing inflammation despite the trial of multiple advanced therapies, impacts a number of individuals with Crohn's disease, and leads to significant burden in quality of life and cost. Interventions such as early implementation of advanced therapies, optimization of current therapies prior to switching to an alternative, as well as understanding the overlapping pathophysiology between immune-mediated disorders, however, can help shift the current landscape and reduce the number of patients with refractory disease. As such, in this review we summarize the key takeaways of the latest research in the management of moderate-to-severe Crohn's disease, focusing on maximization of our currently available medications, while also exploring topics such as combination advanced therapies. We also describe evidence for emerging and alternative therapeutic modalities, including fecal microbiota transplant, exclusive enteral feeding, hyperbaric oxygen, stem cell therapy, bone marrow transplant, and posaconazole, with a focus on both the potential impact and specific indications for each.

Keywords: Crohn's disease, surgery, advanced therapies, biologics

Introduction

Crohn's disease (CD) is a chronic immune disorder of the gastrointestinal tract, which along with ulcerative colitis (UC), impacts more than 6.8 million people worldwide.[1] Some estimate the prevalence of CD may rise to 1% in 2030 in the United States (US) and western European countries.[2] The mainstay of therapy among those with moderate-to-severe CD centers around the use of advanced therapies as well as surgical intervention. However, despite recent advances in both medical and surgical therapeutics, as well as in our understanding of the underlying pathophysiology and disease course, a large proportion of individuals will continue to have ongoing inflammation.

Refractory CD, defined as ongoing inflammation despite multiple trials of advanced therapies as well as surgical intervention, can be associated with significant comorbidity and mortality. It can increase the risk of malnutrition, increase the risk of intestinal cancer, and may accelerate aging-related processes such as cardiovascular disease, dementia, and diabetes.[3] Further, it can reduce quality of life for patients, and is associated with rising healthcare costs.[4–7] Thus, understanding how to approach refractory CD is critical to improving care for hundreds of thousands of patient with CD, and can help combat the rising healthcare-related costs seen across the US.[4]

Current Goals of Treatment of Crohn's Disease

In order to understand how to treat individuals with refractory CD, it is first important to review our current standards of practice. Classically, and among many older clinical trials, the focus of therapy in CD has centered around clinical response and the achievement of clinical remission. Although the focus on patient symptoms is highly important, over the past few years, we have learnt that even among those in clinical remission, ongoing endoscopic disease activity can lead to adverse long-term outcomes. As a result, a meta-analysis found that individuals who achieved mucosal healing at first endoscopic assessment were more than twice as likely to remain in long-term clinical remission as compared to those

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who had ongoing endoscopic disease activity (pooled odds ratio (OR) 2.80, 95% confidence interval (CI) 1.91–4.10), and more than twice as likely to avoid CD-related surgery (pooled OR 2.22, 95% CI 0.86–5.69).[8]

Thus, as a result, STRIDE II Guidelines were developed, emphasizing that the most important IBD treatment targets are clinical remission, endoscopic healing, restoration of quality of life, and absence of disability.[9] It should be noted that histological healing in CD is also recognized as an important adjunctive measure, however more data is needed to determine whether this should be included as a target of therapy.[9]

Optimization of Current Advanced Therapies

Despite our growing armamentarium of therapies, achieving persistent endoscopic and clinical remission can be a challenge in CD. However, early implementation of advanced therapies, optimization of these therapies, and selecting therapies that treat overlapping immune-mediated disorders, have the potential to improve our current rates.

Early Implementation of Advanced Therapies

Although classically, IBD for many years had been treated utilizing a "step-up" approach, recent data have supported the use of a "top-down" approach. This early implementation of advanced therapies has been associated with improved long-term outcomes, as well as the prevention of late-stage complications of CD (eg, stricture).[10]

One of the first trials to investigate this studied the efficacy of early combined immunosuppression (infliximab [IFX] and azathioprine) versus conventional management (steroids followed by azathioprine and IFX as needed) in patients with a recent diagnosis of CD.[11] Specifically, it demonstrated that rates of clinical remission (defined as a score <150 on the Crohn's Disease Activity Index [CDAI], absence of bowel resection, and withdrawal of steroid therapy) were significantly higher in the early combined immunosuppression group at 26 weeks as compared to the conventional management group (60% vs 35.9%, $p = 0.006$).[11] Additionally, the patients with early combined immunosuppression had a faster rate of decrease in CDAI scores, a faster reduction in median C-reactive protein (CRP) by week 10, fewer ulcers on colonoscopy at week 104, and a higher rate of 52-week clinical remission, though this latter result was not statistically significant (61.5% vs 42.2%, $p = 0.278$).[11]

Clinical trials assessing the efficacy and safety of additional biologics have similarly shown an improvement in clinical outcomes among individuals who utilize advanced therapies early in the course of their CD.[12–14] For example, the Precise 2 trial assessing the efficacy of certolizumab in CD showed an increased rate of clinical response among patients with a shorter disease duration – at week 26, 89.5% of patients with disease duration <1 year had a clinical response compared to 57.3% in patients with disease duration ≥5 years.[15] At week 26, clinical remission rates were 68.4% for patients with disease duration <1 year and 44.3% for those with disease duration ≥5 years.[15] Similar data were seen among the clinical trials using vedolizumab, with shorter disease duration (<2 years) being significantly associated with a higher rate of steroid-free clinical remission and endoscopic healing at 6 months.[16]

Dose Optimization

In addition to early implementation of advanced therapies, data from prior randomized clinical trials often suggest that individuals who are bio-naïve have a higher likelihood of achieving clinical and endoscopic remission, as compared to those who have previously failed an advanced therapy. For example, in the ADVANCE trial studying risankizumab, 44–50% among those who were bio-naive were able to achieve endoscopic remission as compared to 24–33% among those who had previously failed an advanced therapy (ranges of percentages due to different doses of risankizumab studied 600mg and 1200mg groups).[17] Thus, optimizing each of our therapies before advancing to the next, is of utmost importance.

Among our anti-tumor necrosis factor (TNF) therapies (eg, infliximab, adalimumab), dose optimization is particularly important, since individuals are at higher risk of developing anti-drug antibodies due to the murine component of the medication. As such, when individuals have an incomplete response, or are having breakthrough symptoms, obtaining a drug level and drug antibody level can help determine the need for dose intensification. In a multicenter study of CD patients who had breakthrough symptoms on infliximab, dose intensification led to an improvement in clinical response among 47% of these patients.[18] In another study of CD patients who underwent dose intensification while on infliximab,

75.9% were able to regain response and remain on infliximab at the end of the study (mean follow-up duration 26 ± 8 months).[19] In yet another study assessing long-term durability of infliximab after loss of response, 41% of patients underwent dose escalation, with 56% of patients achieving clinical remission (defined as a Harvey Bradshaw Index [HBI] ≤4 without steroids) and 40% partial clinical response (defined as a decrease in HBI of >3 points) following the first intensified dose.[20]

Further, in specific cases, such as those with perianal disease, studies have shown that higher anti-TNF levels are associated with increased perianal healing, and should therefore prompt dose escalation or combination therapy with an immunomodulator prior to changing therapy.[21,22] Additionally, it should also be noted that older adults are both less likely to receive higher doses of anti-TNF therapy, and may be more likely to make anti-TNF antibodies.[23] This emphasizes the importance of adequate dosing of anti-TNF therapy, particularly among older individuals with CD, particularly since higher levels of anti-TNF therapy have not been associated with an increased risk of adverse events.[24]

Dose optimization not only applies to anti-TNF therapy but also to all advanced therapies. A meta-analysis evaluating the effectiveness of ustekinumab dose escalation among patients with CD with inadequate response/loss of response, found that 55% of these individuals were able to achieve clinical response after dose interval shortening to <8 weeks and/or intravenous reinduction.[25] Analogously, a systematic review found that individuals who had a shortening of vedolizumab dosing were able to achieve a high rate of clinical response (40–73%) as well as clinical remission (30–56%) after dose escalation.[26] Similarly, dose escalation appears to improve response when using small-molecule inhibitors (janus kinase [JAK] inhibitor) such as upadacitinib as well. Among a study of 190 patients who had inadequate or loss of response on upadacitinib maintenance dose of 15mg, dose escalation to 30mg daily achieved 41% endoscopic improvement, and 20% endoscopic remission at week 48, although this was among a population of patients with UC.[27] Among patients with CD, although only older data using differing doses of upadacitinib are available, similar results were seen with dose escalation.[28] Hence, there is a growing body of evidence supporting dose interval shortening or dose escalation for advanced therapies, including for the recently approved drug mirikizumab, which has been approved for the treatment of moderate-severe ulcerative colitis.[29]

Together, these data, in combination with the findings that biologic-experienced patients often have lower treatment efficacy with subsequent therapies, support the notion of a trial of dose optimization prior to switching, particularly among patients who have had a partial but incomplete response, or among those who achieved endoscopic remission and are now having recurrence of disease. Additionally, optimizing therapy prior to a switch is also particularly important given the limited number of drug mechanisms available to treat CD (anti-TNF, IL-23 ± 12, α4β7, JAK-i), despite the growing number of drugs on the market.

Overlapping Immune-Mediated Disease

Since initial therapy has a higher likelihood of inducing endoscopic and clinical remission, which in turn increases the chance of remaining in remission, it is important to select appropriate initial therapy. If a patient has an overlapping immune-mediated inflammatory disorder (IMID), certain biologics that treat overlapping physiology should be considered, as they may have higher efficacy.

One of the most common overlapping disorders with CD is the presence of psoriasis. In both disorders, increased expression of IL-23 can contribute to the underlying disease pathophysiology.[30] Hence, prior data has shown ustekinumab (an anti-IL-12/23) to be effective in treating both CD and psoriasis, as well as the newer biologic available risankizumab (anti-IL-23); a multicenter study of 45 patients with IBD and psoriasis demonstrated clinical remission of psoriasis among 82.2% of individuals treated with ustekinumab.[31] Further, these agents appear to be more effective among individuals with both CD and psoriasis, as compared to individuals with CD and no overlapping psoriasis. Supporting this was a retrospective study of 395 patients with CD, which found that ustekinumab had better efficacy among individuals with concomitant psoriasis when evaluating fecal calprotectin and endoscopy scores as compared to those without psoriasis.[32] Thus, when treating patients with CD and overlapping psoriasis, we preferentially select one of these agents. In particular, we often use risankizumab given results from a head-to-head study suggesting that risankizumab had superior response among patients with moderate-to-severe plaque psoriasis as compared to those treated with ustekinumab.[33] Further, it should be noted that anti-TNF agents also have efficacy in treating psoriasis, though around

6% of individuals with CD can have a paradoxical psoriasiform reaction from their use as well.[34] It is for this reason that we often prefer an initial trial of risankizumab or ustekinumab prior to the use of anti-TNF therapy among those with concurrent psoriasis.

In patients with other overlapping rheumatologic disorders, such as axial spondyloarthritis and rheumatoid arthritis, there is often an upregulation of the TNF as well as the JAK-STAT (Janus kinase-signal transducers and activators of transcription) pathways.[35] Thus, for axial spondyloarthritis, the current standard of management for rheumatologists is to start an anti-TNF agent, IL-17 inhibitor, or JAK inhibitor in patients with persistently high disease activity despite conventional treatment.[36] As these pathways are often upregulated in CD as well, anti-TNF agents and JAK-I inhibitors such as upadacitinib have dual efficacy in treating both conditions, and should be considered first-line for individuals with these coexisting conditions. Of note, there is an association between the use of IL-17 inhibitors (eg, secukinumab) and the development of new onset IBD, which needs further research to understand the underlying pathophysiology contributing to this.[37]

Selecting a Biologic

Although the presence of perianal disease or the presence of overlapping IMIDs may help with initial selection of a specific advanced therapy, there is also a large population of individuals with CD who do not have an overlapping immune-mediated disease. Selecting an initial therapy can be difficult among these individuals, as head-to-head data are limited.

The first head-to-head trial comparing biologics was SEAVUE, which compared the safety and efficacy of adalimumab versus ustekinumab among individuals with moderate to severely active CD.[38] Overall, there was no significant difference in the primary endpoint of clinical remission at week 52 between ustekinumab and adalimumab groups (65% vs 61%, p = 0.42).[38] Similar rates of secondary outcomes, including steroid-free remission, 1-year clinical response, 16-week clinical remission, and endoscopic remission, were found.[38] The frequency of adverse and serious adverse events were also similar in both groups, however more patients taking adalimumab had an adverse event requiring drug discontinuation as compared to ustekinumab (11% vs 6%). Rates of clinical remission, as well as rates of serious infections were also similar between the two medications.

Recently, the SEQUENCE trial compared the safety and efficacy of risankizumab vs ustekinumab among individuals with moderate to severely active CD, and found that risankizumab was non-inferior to ustekinumab for clinical remission at week 24 (58.6% vs 39.5%) and superior for endoscopic remission at week 48 (31.8% vs 16.2%, $p< 0.0001$ for superiority).[39] Risankizumab also showed superiority in all secondary endpoints, with clinical remission at week 48 (60.8% vs 40.8%) and endoscopic response at week 48 (45.1% vs 21.9%).[39]

In an attempt to simulate additional comparisons, Singh et al performed a network meta-analysis including 31 Phase 2 and Phase 3 randomized controlled trials (RCTs) in adults with CD treated with various advanced therapies, and found that among biologic-naive adults, infliximab and adalimumab with or without combination immunomodulator therapy were associated with the highest likelihood of achieving clinical remission.[40] Among individuals with CD who were previously biologic exposed, risankizumab, as well as adalimumab among those who developed immunogenicity or an intolerance to infliximab, were associated with the highest likelihood of achieving clinical remission.[40] It should be noted, however, that these data were published prior to the introduction of upadacitinib, and thus this data is excluded from the analysis.

Additionally, there is a new class of advanced therapies, TL1-A (TNF-like ligand 1A) that have shown early initial promise in CD. Recent data have shown TL1A to be upregulated among individuals with IBD, with levels thought to be closely related to ongoing disease severity. Moreover, PRA-023, a humanized monoclonal TL1A antibody, has been studied in a phase 2a study of patients with moderate-to-severe CD, with results showing that patients treated with PRA-023 achieved endoscopic response (Simple Endoscopic Score for Crohn's Disease [SES-CD] lowered ≥50%) and clinical remission at higher rates as compared with placebo (26% vs 12%, 49% vs 16%, respectively, $p < 0.001$).[41] This is particularly notable as a large proportion of individuals (71%) were bio-exposed, suggesting efficacy even among a more refractory patient population. PRA-023 is also being studied in a phase 2 trial for UC, with similar results reported.[42] Of

note, no serious adverse events have been reported in PRA-023 trials at the time of these publications; however, a phase 3 trial to validate these findings is underway.

Cessation of Therapy

While early therapy, optimization of current medication, and selecting a medication based on overlapping conditions can improve the likelihood of achieving endoscopic remission, data also suggest that remaining on an advanced therapy is important to maintain persistent response and remission. To this end, prior studies have suggested that patients with markers of asymptomatic disease, eg elevated CRP or fecal calprotectin (FC) or lack of mucosal healing, are at increased risk of relapse after cessation of anti-TNF therapy.[43]

Further, among patients in endoscopic remission, cessation of biologic therapy may also lead to high rates of relapse in CD. In the STORI trial of 115 patients with CD who were in deep remission on anti-TNF therapy, 52% had recurrence of disease by two years once infliximab therapy was stopped (patients were able to remain on the immunomodulator if they were previously on). On long-term follow-up, at seven years, 22% of individuals with CD remained without an advanced therapy or major disease-related complications.[44] Similarly, in the SPARE trial, one-third of patients with CD who were in corticosteroid-free clinical remission on combination infliximab and an immunomodulator therapy had recurrence of disease when stopping infliximab (vs 14% among individuals who continued on combination therapy).[45] Thus, in order to limit the possibility of recurring CD, as well as the development of refractory disease, we often recommend continuation of advanced therapy use, even when in clinical and endoscopic remission.

Combination Advanced Therapies

Despite the growing armamentarium of advanced therapies for CD, there is still a therapeutic ceiling, with the majority of medications leading to a one-year endoscopic remission rate of 30–40% among bio-naive individuals.[46] However, advances in our understanding of the underlying pathophysiology of CD suggest that multiple inflammatory pathways may be active, and that a multipronged approach to downregulation of these cascades may improve outcomes. Thus, combination therapy with dual advanced therapies has been of increasing interest, particularly for those with refractory CD.

Data from real-world studies have suggested an overall increased rate of clinical response among those with refractory disease.[47] In a 2022 systematic review of all patients with IBD: vedolizumab plus anti-TNF had pooled clinical response and remission rates of 78% and 55%, respectively, vedolizumab plus tofacitinib had pooled clinical response and remission rates of 60% and 48%, and vedolizumab plus ustekinumab had pooled clinical response and remission rates of 84% and 47%.[48] These improvements in efficacy where also balanced by a relatively safe adverse events profile, with only a small proportion of individuals having adverse outcomes as a result: 9.6% among those on vedolizumab and anti-TNF (8 studies, 56 total patients), 1% among those on tofacitinib and vedolizumab (5 studies, 57 total patients), and 12.3% among those on vedolizumab and ustekinumab (7 studies, 49 total patients).[48]

Building upon these retrospective studies, a recent large-scale clinical trial assessed the efficacy of combination therapy (guselkumab [anti-IL-23] and golimumab [anti-TNF]) among a population of patients with moderate-to-severe UC.[49] The trial randomly assigned 214 patients to either combination biologics or biologic monotherapy.[49] At week 12, 83% of patients on combination biologic therapy achieved clinical response, as compared to 61% on golimumab and 75% on guselkumab monotherapy.[49] Reassuringly, adverse effect profiles were similar for all three groups, suggesting that combination therapy with two advanced therapies may not significantly increase the risk of an adverse event.[49] Although these data are among a population of patients with UC, they provide reassurance and future direction as we investigate the role of dual advanced therapies in the treatment of refractory CD.

In 2023, a Phase 4, single-arm study looked at the efficacy of triple combination therapy with vedolizumab, adalimumab, and methotrexate in 55 biologic-naive patients with moderate-to-severe CD. The resulting rates of clinical and endoscopic remission at week 26 were 54.5% and 34.5%, respectively, suggesting greater efficacy than any individual agent alone.[50] The types and rates of adverse effects and serious adverse effects in this study with triple combination therapy were also similar to those seen in trials and real-world data for vedolizumab, adalimumab, and methotrexate monotherapy.[50] Further, it should be emphasized that ongoing moderate-to-severe IBD carries significant

comorbidity and mortality, and therefore risks of multiple advanced therapies should also be weighed against the risk of undertreated IBD.[51]

The Role of Diet and Fecal Microbiota Transplant as Adjunctive Therapies

Recent data have reinforced the role of environment on both the development and natural history of CD. In particular, there has been much interest in diet, with diets high in ultra-processed foods leading to higher risk of IBD.[52] Similarly, among those with CD, a systematic review found that adherence to the Mediterranean diet (MD) was positively correlated to scores of quality of life and negatively correlated with disease activity.[53] Thus, diet has gained interest in combination with advanced therapies, as it may be an adjunctive treatment option that can help induce remission among those with ongoing disease activity. In a randomized controlled trial comparing the MD with a specific carbohydrate diet (SCD: a diet characterized by strictly excluding foods such as grains, certain starches and processed meats), Lewis et al found that the SCD was not superior to the MD in achieving symptomatic remission, fecal calprotectin response, or CRP response by week 6.[54] Another studied diet is the CD exclusion diet (CDED), a whole food diet that aims to reduce exposure to foods that may be harmful to the gut microbiome, inflammation, or intestinal function. It notably excludes wheat, dairy, animal fat, additives such as artificial sweeteners, processed foods, and red meat. A randomized controlled trial that evaluated CDED plus partial enteral nutrition (PEN) versus EEN in children with mild-to-moderate CD found CDED plus PEN to be better tolerated, and be superior in sustaining corticosteroid-free remission (pediatric CD activity index <10) at week 12.[55] Another randomized trial from Israel compared CDED plus PEN or CDED alone for 24 weeks in adults with mild-to-moderate CD and found both therapies to be effective for induction and maintenance of remission.[56]

These diets, in combination with advanced therapies, particularly in comparison to a traditional Western diet, may increase clinical response among a more refractory population of patients with CD. More research, however, is needed to further explore the role of diet as an adjunctive therapy to help reduce ongoing inflammation and disease activity in CD.

Additionally, there has been interest in the role of fecal microbiota transplant (FMT) for the treatment of CD. Randomized controlled trials in UC have found that FMT may help induce clinical and endoscopic remission, with a meta-analysis finding that clinical and endoscopic remissions were significantly better among patients who received FMT (clinical remission relative risk [RR] 1.73 95% CI 1.41–2.12; endoscopic remission RR 1.74, 95% CI 1.24–2.44).[57] Limited data exist among individuals with CD, with one clinical trial showing that FMT was associated with higher initial rates of corticosteroid-free remission (62.5% vs 33.3%), however results were not significant based on the limited number of patients (n=21).[58] Similarly, a systematic review found that FMT did not impact clinical outcomes among individuals with CD, though multiple FMT doses were associated with an earlier clinical response as compared to just one FMT dose.[59] Additionally, FMT appeared safe and well tolerated, with no serious adverse events reported.[59] However, since the data is largely observational and limited by the number of individuals included, more studies are needed to understand the role of FMT as an adjunctive therapy among individuals with CD, particularly those with refractory disease.

Exclusive Enteral Feeding and Pediatric CD

In addition to diet modifications in CD, exclusive enteral nutrition (EEN) has been studied as a way to decrease mucosal inflammation. Evidence has shown that exclusive enteral feeding can have long-term impacts on the gut microbiota, stripping it of bacterial species that cause sustained inflammation.[60] Results supporting the use of EEN in CD, however, have been mixed. Several earlier reports and meta-analyses have shown EEN to be less effective than traditional corticosteroid therapy in inducing remission among adults with moderate-to-severe CD, though have shown some efficacy in children.[61,62] In particular, a 2018 Cochrane meta-analysis found similar CD remission rates when using EEN as compared to corticosteroids among children, though this was not found in adults; 83% (24/29) of children taking EEN achieved remission compared to 61% (17/28) of children taking corticosteroids (RR 1.35, 95% CI 0.92 to 1.97), while 45% (87/194) of adults using EEN achieved remission as compared to 73% (116/158) taking corticosteroids (RR 0.65, 95% CI 0.52 to 0.82).[63] Thus, enteral feeding can be considered especially for pediatric patients who wish to avoid corticosteroid therapy, however there are challenges including both poor adherence and difficulty tolerating feeding

tubes. Further studies, however, particularly in the preoperative setting where decreasing inflammation can result in improved clinical outcomes, are needed to better understand the role of EEN in treating refractory CD.

Of note, in pediatric CD, there continues to be a smaller body of long-term data regarding the efficacy and safety of advanced therapies, with a significant lag to approval for these drugs in the pediatric population.[64] Currently, infliximab and adalimumab tend to be preferred agents for more severe forms of pediatric CD, with milder forms often treated with aminosalicylates, steroids, or EEN.[65,66] Additionally, in cases of very early onset IBD presenting before 6 years of age, genetic testing should be entertained as there is a higher proportion of patients with monogenic immune diseases such as primary immune deficiencies in this population compared to an adult IBD population.[67]

Surgery

CD that is refractory to medical management, or CD with complex features such as strictures and/or fistulas may ultimately require surgical management. Most CD patients will require surgery at least once in their lifetime (~80%), however the optimal timing of surgery is an area of active research.[68] In recent data from the LIR!C study, almost 50% individuals with limited ileal disease who underwent intestinal resection did not require advanced therapy for CD at 5 years (~half remained on immunomodulator prophylactically after surgery).[69] Further, in a recent real-world study of 1279 patients, similar results were seen. Most notably, upfront surgery among individuals with limited ileocolonic disease had improved long-term outcomes as compared to those who initiated an anti-TNF therapy.[70] Further, among individuals with refractory CD who are likely to require eventual surgical resection, earlier surgery may have improved outcomes, as it may decrease the risk of requiring emergency surgery, as well as developing preoperative sepsis and malnutrition, which can all increase risk of an adverse postoperative outcome.[71]

Hyperbaric Oxygen and Stem Cell Therapy for Ongoing Perianal Disease

Perianal fistulas and complicating abscesses are common in patients with moderate-to-severe CD (~25%).[72] Perianal fistulas are often managed with a combination of surgical or medical therapy including anti-TNF therapy ± immunomodulators. However, persistent non-healing fistulas can continue to generate significant pain and discomfort, and newer therapies beyond our currently available advanced therapies are being evaluated. Hyperbaric oxygen is one such therapy for CD patients with fistulizing disease that has demonstrated promising results. In a 2021 trial conducted in Amsterdam, 20 patients with severe fistulizing CD who had failed conventional treatments were recruited for 40 daily hyperbaric oxygen treatment sessions.[73] The therapy consisted of placing patients for 80 minutes in a chamber of 100% oxygen at 243-253 kilopascal. At week 16, 60% of patients reported a clinical response, with 20% reporting complete fistula healing.[73] Further, an observational study showed similar results; 80% of patients with either fistulizing CD or concomitant pyoderma gangrenosum who were treated with hyperbaric oxygen therapy achieved complete healing.[74]

Stem cell therapy can also be used among individuals with CD who have refractory perianal disease. Although there have been a number of trials assessing differences between allogeneic and autologous transplants of mesenchymal stem cells into the fistula tract, overall the majority have found encouraging results when assessing the likelihood of perianal fistula healing. More specifically, in a meta-analysis, patients with active perianal CD who received stem cell therapy had a higher rate of perianal fistula healing as compared to patients who received placebo (OR 2.21, 95% CI 1.19 to 4.11).[75] Further, a randomized multicenter trial found that allogeneic expanded adipose-derived stem cell therapy significantly increased perianal fistula remission rates as compared to placebo (53/107 [50%] vs 36/105 [34%]).[76] As a result, the European Crohn's and Colitis Organization (ECCO) guidelines recommend allogeneic stem cell therapy as a safe and effective treatment for complex perianal fistula disease, and should be considered among individuals with refractory perianal disease.[77]

Bone Marrow Transplant

Despite the above considerations, there are still a number of patients who will continue to have ongoing and severe CD that is refractory to our conventional therapies. Among these individuals, bone marrow transplant is considered in order to "reset" the immune system, thereby altering the course of the immune-mediated disease.[78] Allogeneic bone marrow transplant in CD was first described in 1998 by Lopez-Cubero et al, when a small cohort of patients with both leukemia

and CD underwent allogeneic hematopoietic stem cell transplant.[79] During follow-up, four patients achieved remission of their CD without relapse, and one patient with mixed chimerism had a relapse of CD 1.5 years after transplantation.[79] Following this study, many small cohort studies have shown an overall reduction in symptom burden as well as an improvement in disease control; a 2021 meta-analysis of clinical trials in humans found that bone marrow transplantation reduced the CDAI (standardized mean difference [SMD] −2.10, p<0.01), Crohn's Disease Endoscopic Index of Severity [CD-EIS] (SMD −3.40, p = <0.01), SES-CD (SMD −1.71, p<0.01), and improved quality of life as compared to controls.[80] In studies that included clinical remission rates after treatment, the remission rates at 12 and 24 weeks from treatment were 54% and 52%, respectively.[80] In a Phase IIa study of autologous stem cell transplant among a population of refractory patients with CD (NCT03219359), after 6 months of transplant, 12 of 13 patients had endoscopic response (defined as a 50% reduction in SES-CD score), and 10 of 13 patients were in endoscopic remission (SES-CD<4).[81] Thus, although more data is needed, in the patient with severely active CD who is refractory to conventional advanced therapies, including the aforementioned treatment considerations, bone marrow transplant may offer a unique and efficacious approach. However, despite the efficacy seen, it should be noted that bone marrow transplant can lead to serious adverse events (one patient in prior trials developed septicemia and died), and thus should be reserved for individuals with severe refractory CD.

Additional Exploratory Therapies

Although exploratory, there is interest in other therapies for patients with refractory CD, particularly ones that target the microbiome. In particular, one randomized trial looks to assess the role of posaconazole among patients with CD who have the caspase recruitment domain family member 9 (CARD9) S12N risk allele (NCT04966585). This allele, which confers innate immunity to fungal organisms, when mutated, allows for unrestricted proliferation of *Malassezia* which results in a pro-inflammatory cascade, and is associated with an increased risk of developing IBD.[82] Thus, among patients who have CD and a polymorphism in this allele, there is reason to believe that anti-fungal agents such as posaconazole may improve rates of clinical response, however studies are first underway. Additionally, vagus nerve stimulation has been hypothesized to reduce inflammatory activity in CD, and a few small exploratory studies have suggested feasibility and tolerability, with reductions in CDAI and SES-CD scores, however these are very early small studies and further research is necessary to generate data on clinical outcomes.[83]

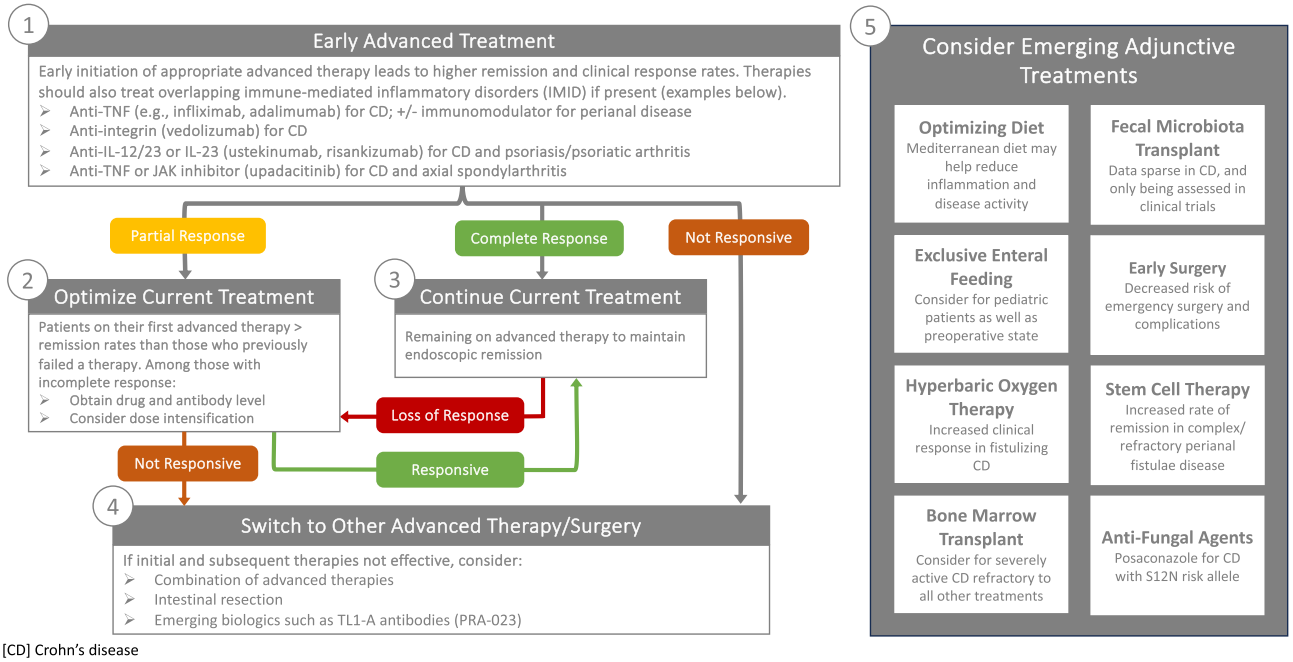

Figure 1 Management of Refractory Crohn's Disease.

Conclusion

Refractory CD is associated with adverse clinical outcomes, decreased quality of life, and increasing costs to both the patient and healthcare system. However, though a fraction of individuals will have refractory CD regardless of interventions, there are a number of initial considerations that can decrease the number of patients with refractory disease. In particular, earlier initiation of advanced therapies, dose optimization of a current therapy before selecting an alternative agent, selection of a medication that treats concurrent IMIDs when present, remaining on advanced therapies once in remission, and targeting endoscopic remission may all reduce the proportion of individuals with refractory CD. Moreover, among the individuals who develop disease that is refractory to our currently available therapies, additional consideration can be given to combining advanced therapies, trialing TL1-A medications as part of a clinical trial, and bone marrow transplant among those who have severely active ongoing disease. Additional research evaluating the use of adjunctive therapies such as diet, EEN, FMT, as well as anti-fungal agents among those genetically susceptible, and hyperbaric oxygen and stem cell therapy for refractory perianal disease, are also underway and should shed additional light on the treatment of refractory CD in the coming decade (Figure 1).

Abbreviations

ADVANCE, A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active Crohn's Disease; CARD9, Caspase Recruitment Domain Family Member 9; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CDED, Crohn's Disease Exclusion Diet; CI, Confidence Interval; CRP, C-Reactive Protein; ECCO, European Crohn's and Colitis Organisation; EN, Enteral Nutrition; FC, Fecal Calprotectin; FMT, Fecal Microbiota Transplant; HBI, Harvey-Bradshaw Index; IBD, Inflammatory Bowel Disease; IFX, Infliximab; IL, Interleukin; IMID, Immune-Mediated Inflammatory Disorder; IOIBD, International Organization for the Study of Inflammatory Bowel Diseases; IV, Intravenous; JAK-STAT, Janus Kinase-Signal Transducers and Activators of Transcription; JAK, Janus Kinase; MD, Mediterranean Diet; OR, Odds Ratio; RCT, Randomized Controlled Trial; RR, Relative Risk; SC, Subcutaneous; SCD, Specific Carbohydrate Diet; SCT, Stem Cell Therapy; SEAVUE, Safety and Efficacy of Adalimumab Versus Ustekinumab for One Year; SEQUENCE, Study Comparing Intravenous(IV)/Subcutaneous (SC) Risankizumab to IV/SC Ustekinumab to Assess Change in CDAI in Adult Participants With Moderate-to-Severe CD; SES-CD, Simple Endoscopic Score for Crohn's Disease; SPARE, A proSpective Randomized Controlled Trial comParing infliximAb-antimetabolites Combination Therapy to Anti-metabolites monotheRapy and Infliximab monothErapy in Crohn's Disease Patients in Sustained Steroid-free Remission on Combination Therapy; STORI, Study of Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission on Combined Therapy with Immunosuppressors; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; TL1-A, TNF-like Ligand 1A; TNF, Tumor Necrosis Factor; US, United States.

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