Editorial

Achieving Deep Remission in Crohn's Disease: Treating Beyond Symptoms

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Introduction

Crohn's disease (CD) is a chronic inflammatory disease which is progressively destructive in nature. Persistent inflammation often leads to bowel damage over time, with the development of strictures, fistulae and abscesses. Current standard therapeutic strategies have not modified the course of CD. The focus of effective management of CD has shifted from short-term symptom control to long-term modification of disease course and complications. Traditionally, clinical remission was regarded as a therapeutic endpoint, however mucosal healing (MH) has emerged as a major therapeutic goal in CD. It is associated with lower relapse and hospitalisation rates, less bowel damage and reduced need for surgery. Growing evidence indicates that we have to look beyond clinical symptoms. Hence, achieving deep remission (clinical remission and mucosal healing) may be the way to alter the natural course of CD.

Mucosal Healing

MH is broadly defined as the absence of inflammation on endoscopic assessment. There is no consensus on what truly defines MH and the different grades of inflammation between MH and severe mucosal inflammation. Furthermore, endoscopic remission differs from histological remission.[1] Histological remission is impractical in CD as inflammation in CD tends to be patchy resulting in the need for multiple biopsies for evaluation.

Endoscopic remission to assess for MH is the most well studied method of evaluation. Largely driven by trials with biologic agents, it gained more traction in recent years as a desirable and realistic outcome of treatment. However, a universally accepted system for grading mucosal inflammation is lacking, with various trials using different classifications to measure MH.

MH is important as CD is a progressive disease with a relapsing and remitting course. Most patients will initially present with inflammatory CD without penetrating features and longitudinal studies have shown that chronic inflammation alters the behaviour of disease, eventually leading to fistulae and strictures. The number of surgical interventions a patient will have adds to the disease burden as most CD patients will undergo surgery at some point in their lives.[2,3]

The theory behind MH as an efficacy endpoint is the belief that halting tissue injury promptly and controlling mucosal inflammation over the course of disease will alter the course of disease, and prevent complications of penetration and stricture formation. There is a growing body of evidence from numerous trials that MH translates into higher rates of steroid free remission, less CD-related hospitalisations, lower surgical rates ultimately culminating in better quality of life.

Surrogate Markers for MH

As ileocolonoscopy is an invasive and costly procedure, there is a need for tests that would be accurate surrogates for MH. The time-tested C-reactive protein (CRP) is the most commonly used method for assessing severity of CD but it lacks sensitivity for patients with minimal symptoms. Moreover, it does not predict long-term prognosis.[4]

Cross-sectional imaging like magnetic resonance imaging (MRI) and computed tomography (CT) allow for evaluation of the gastrointestinal tract beyond the ileocolonoscope, give better detail for the anatomy of strictures, fistulae and deep tissue healing. An MRI activity index (MRAI) for CD has been developed and has good correlation with Crohn's disease endoscopy index of severity (CDEIS).[5,6] CT is also comparable to MRI but carries the added risks of radiation for patients who are already at higher risk for malignancies due to disease and treatment.[7]

Faecal calprotectin and lactoferrin remain the most promising candidate biomarkers for MH. Calprotectin is a protein that comprises about 40% of neutrophil's cytosol and is easily measured in faeces. It is fairly resistant to degradation. Faecal lactoferrin is a glycoprotein expressed by activated neutrophil. When raised levels are detected in faeces, they suggest active luminal inflammation. Both faecal calprotectin and lactoferrin correlate well with CDEIS, with falling levels paralleling treatment response and normal levels reflecting MH.[8,9]

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CDEIS is considered to be the gold standard scale, requiring the assessment of ileocolonic segments, area of mucosa involved and ulcer size and depth. There is minimal interobserver variability but does require training and experience. Its complexity restricts its application in clinical practice, and limits its usage to trials.[10]

Rutgeert's scale is a postoperative score used to assess the neoterminal ileum to predict clinical recurrence of disease. Grades i0 to i4 are determined by the number of aphthous ulcers, presence of ileitis, nodules and narrowings. This scale's obvious limitation is its applicability to post-surgical patients.[11]

Therapeutic Choice for Achieving Complete MH

Induction of MH can be attained with thiopurines and anti-TNFα agents. Methotrexate, steroids, 5-aminosalicylate compounds do not have strong data to support its use in MH, but are still useful in inducing clinical remission.

Azathioprine (AZA) has been studied and is superior to placebo in inducing and maintaining mucosal healing. In a study involving patients with ileocolitis, 54% to 70% achieved MH at 24 months.[12] Mantzaris et al demonstrated that patients with steroid dependent ileocolitis were more likely to achieve histologic remission at 1 year with AZA than budesonide (83% vs 24%).[13] A Cochrane review also showed that AZA was more effective than 5-aminosalicylate compounds in reducing the recurrence of postoperative CD.[14]

Anti-TNFα agents initially sparked interest in MH and since then led to a large body of literature demonstrating efficacy over placebo in their respective trials. Infliximab has been proven to induce and maintain MH in ACCENT 1 trial, adalimumab in EXTEND trials. In ACCENT 1, patients who received infliximab and achieved MH at week 54 after induction and maintenance therapy, there was a longer median time to clinical relapse as well as lower hospitalisation rates when followed up beyond that.[15] SONIC (infliximab vs azathioprine vs combination of both) showed that up to 43.9% of patients achieve MH at 26 weeks if infliximab and azathioprine combination treatment is introduced early in disease, compared to infliximab alone (30.1%) and azathioprine alone (16.5%).[16]

Step-up vs top-down study which compared patients who underwent early induction therapy with infliximab and azathioprine vs patients who were gradually progressed from steroids to ultimately infliximab, showed 73% vs 30% MH at 2 years respectively.[17] Schnitzler demonstrated that patients who received infliximab and managed to achieve mucosal healing, had a higher rate of remaining in clinical remission at 5 years (65% (83/128) vs 40% (34/86)).[18]

EXTend the Safety and Efficacy of Adalimumab Through ENDoscopic Healing (EXTEND) study compared induction and maintenance therapy with adalimumab (ADA) to induction with ADA followed by placebo. Complete mucosal healing was achieved at 12 weeks in 27.4% of patients in the group receiving continuous ADA and 13.1% of patients in the induction-only group. At 52 weeks, rates of complete MH were 0% and 24.2% in the 2 groups, respectively.[19]

In addition, post-hoc analysis revealed that MH at 12 weeks predicted lower CDAI scores at 1 year. Higher Simple Endoscopic Index for Crohn's Disease (SES-CD) scores were associated with higher CDAI score and lower chance of clinical remission.[20]

Prior to EXTEND, Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance (CHARM) evaluated adalimumab with clinical remission as an endpoint. Treatment with ADA translated into a 56% reduction for all cause hospitalisations at 1 year.[21] Once healing is achieved with a biologic, continuous therapy appears to be appropriate. This was shown in the CHARM study. Data from this study showed that ADA maintenance therapy conferred better Health Related Quality of Life scores for patients up to 56 weeks. It can be inferred that this culminates from decreased CD-related hospitalisations, fewer symptoms and less surgeries.[22]

Deep Remission

Deep remission has been discussed extensively in recent years and is defined as CDAI of <150 and complete MH by some. This concept arose from observations that patients with MH can remain symptomatic. Possible explanations for this phenomenon include the presence of irritable bowel syndrome (IBS) in this group of patients, presence of histological remission that was not documented due to sampling error, submucosal inflammation not visible macroscopically and inflammation that occurs at a cellular level, not seen microscopically. It seems logical that complete absence of inflammation would result in a combination of both symptom control and MH.[23] The EXTEND trial involving ADA showed that regular dosing was superior to placebo in inducing and maintaining deep remission (DR) at 12 (16.1% vs 9.8%) and 52 (19.4% vs 0%) weeks, with lower hospitalisations, surgeries and better quality of life. Also, patients with DR faired better than patients with MH only.[24,25]

Downside of Biologics

As a potent immunosuppressant, opportunistic infections are a cause for concern, especially intra-cellular pathogens. Inhibition of TNFα affects the ability to form granulomas, therefore increasing the risk of tuberculosis infection. TNFα is also required for immune response against viral pathogens. Patients will need to be screened for tuberculosis, hepatitis B and human immunodeficiency virus (HIV) prior to starting treatment.[26]

More worryingly, there is a small but significant risk of developing non-Hodgkin's lymphoma (NHL) and the highly lethal hepatosplenic T-cell lymphoma (HSTL). Due to the low absolute numbers, it is difficult to quantify the exact risk, however we know that concurrent immunomodulator use, duration of use, age and male gender are risk factors for lymphoma.[27]

Thus, even as anti-TNFα are useful drugs for the management of CD, a clear benefit should be expected before initiating therapy, more so in patients at higher risk of developing them.[26]

Conclusion

In the coming years, the paradigm shift in clinical trials should translate into clinical practice on the ground as potent designer agents become more available. We must not forget that CD has numerous phenotypes affecting people from various backgrounds. Management plans and goals should be discussed with the patient and decision on the course of action undertaken should be jointly made. Deep remission will increasingly become a viable goal for patients who seek to reduce debilitating complications and have a decent quality of life with lower disease burden.

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