The Evolution of Treatment Options in Crohn's Disease

Introduction

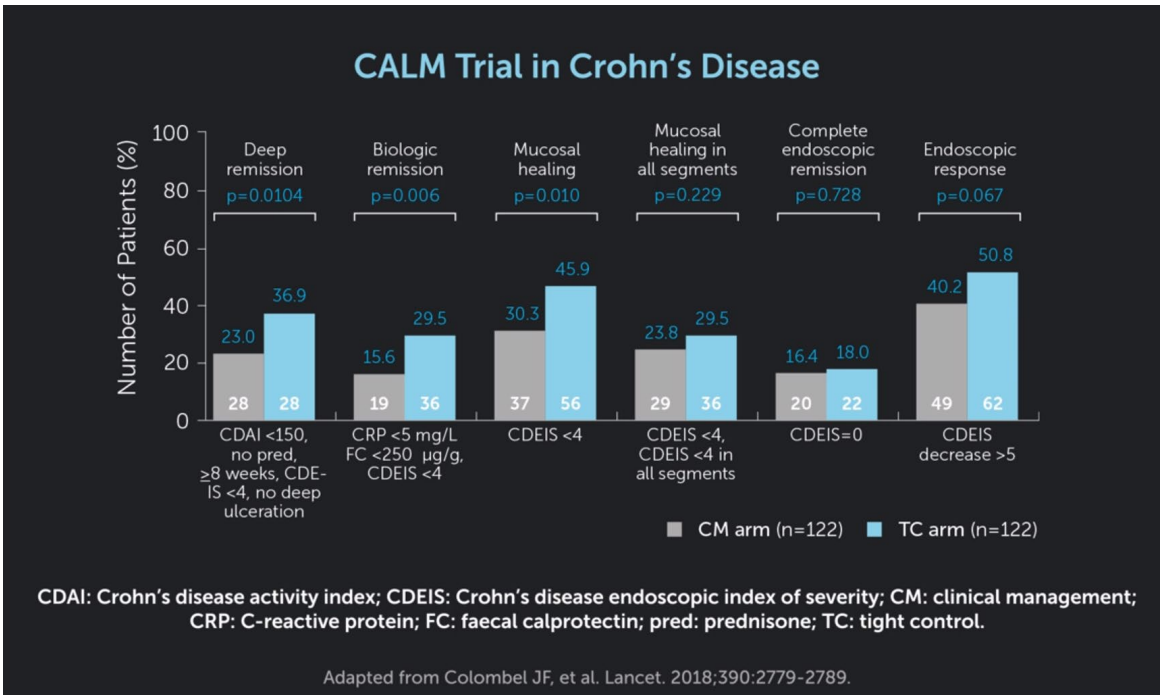
Crohn's disease is an idiopathic inflammatory disorder of unknown etiology with genetic, immunologic, and environmental influences.[1] Hallmark symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, recurrent fistulas, and extraintestinal manifestations including, but not limited to, arthropathy, ocular and hepatic disease, metabolic bone disease, thromboembolism, cholelithiasis, and nephrolithiasis.[1] Crohn's disease is diagnosed clinically; the presence of chronic intestinal inflammation confirms its diagnosis.[1] Treatment for Crohn's disease is based on disease location and severity, related complications, and disease prognosis. Pharmacotherapy for Crohn's disease has been typically divided into induction and maintenance therapy. To date, however, few clinical trials have evaluated endoscopic mucosal healing as a primary outcome.

Evolution in Management of Crohn's Disease: Treating-to-Target vs. Symptoms

The evolution of management for Crohn's disease can best be described as a fundamental change in focus from that of symptom control to that of improving inflammation, promoting mucosal healing of the gastrointestinal lining, and achieving and/or maintaining remission in patients with Crohn's disease. Key principles in this evolution are: 1) identification of patients who may benefit from biologic therapy; and 2) initiating aggressive therapy earlier in the disease course. By treating Crohn's disease aggressively before complications arise allows medications to be more effective in reducing inflammation and lessens the risk of future serious complications and surgery that may be associated with Crohn's disease.

The principles of symptom control versus a treating-to-target approach were tested in the CALM trial.[2] The CALM trial evaluated clinical management based on symptom control against that of tight control through continuous monitoring of disease activity (CDAI), as well as fecal calprotectin and CRP, which are biomarkers of intestinal inflammation, in patients (18-75 years of age) with active endoscopic Crohn's disease. Patients received 8 weeks of prednisone induction therapy, followed by escalation therapy with adalimumab with both treatment arms, ultimately receiving weekly adalimumab plus azathioprine. However, the difference between treatment arms was based on differing treatment failure criteria (i.e., tight control versus clinical management). The primary endpoint was mucosal healing (CDEIS <4) with absence of deep ulcers after 48 weeks of treatment. The study protocol called for modifying treatment until therapeutic targets were achieved.

The CALM trial is the first study to demonstrate that timely escalation with TNF-alpha inhibitor therapy based on clinical symptoms combined with biomarkers results in better clinical and endoscopic outcomes than clinical management based on symptoms (see Table).[2] The most common adverse events associated with tight control were nausea (17%), nasopharyngitis (15%), and headache (15%); worsening of Crohn's disease (29%), arthralgia (16%), and nasopharyngitis (15%) were observed with clinical management.[2]



The results of CALM fortify previously published data that indicate achieving mucosal healing is associated with increased rates of long-term clinical remission and suggest that maintenance of mucosal healing is a reasonable therapeutic target in patients with active Crohn's disease.[3] Additional data suggest that targeting mucosal healing or inflammation rather than symptoms may also be cost-effective with an impact on disease progression.[4]

Factors for physicians to consider when contemplating early and aggressive therapy with a biologic in patients with active Crohn's disease may include:[5]

- Younger patient age
- Extensive bowel involvement or Crohn's disease that affects the upper GI tract
- Perianal disease or severe rectal inflammation
- Penetrating or stenosing disease at diagnosis
- Presence of deep ulcerations at endoscopy

Current Treatment Options for Crohn's Disease

Treatment options for Crohn's disease include both biologic and non-biologic agents. The safety and efficacy of these agents is well-established and includes such agents as:[1,5]

Biologics:

- Anti-integrin
  - Natalizumab
  - Vedolizumab
- TNF-alpha inhibitors
  - Adalimumab
  - Certolizumab

    - Infliximab
- Anti-IL-12/IL-23 antagonists
    - Ustekinumab

Non-biologics:

- Immunosuppressants
    - Azathioprine
    - Mercaptopurine
- Aminosalicylates (5-ASA)
- Corticosteroids
- Methotrexate

Despite the number of biologic agents, there are no head-to-head comparative clinical trials in patients with Crohn's disease; thus, any comparison must be based on observational cohort level data. The SONIC trial compared TNF-alpha inhibitor therapy (infliximab) to infliximab plus azathioprine in patients with moderate-to-severe Crohns' disease, study results showed that 43.9% of patients receiving combination therapy with infliximab plus azathioprine had mucosal healing compared to 30.1% of patients receiving infliximab monotherapy and 16.5% of patients receiving azathioprine.[Error! Bookmark not defined.] Importantly, combination therapy with TNF-alpha inhibitor plus azathioprine was more effective in achieving corticosteroid-free clinical remission in patients with moderate-to-severe Crohn's disease.

Supporting aggressive therapy earlier in Crohn's disease is data evaluating recently approved biologic agents—vedolizumab and ustekinumab—as induction therapy in patients with Crohn's disease. In a study of patients with IBD who had failed TNF-alpha inhibitor therapy, approximately one-third achieved steroid-free remission after 14 weeks of induction therapy with IV vedolizumab [see Figure 1].[6] Induction with IV ustekinumab led to a higher response rate than placebo, with SC ustekinumab maintaining remission in approximately 50% of patients with moderate-to-severe active Crohn's disease at 44 weeks [see Figure 2].[7] The availability of several therapies for aggressive management will allow clinicians to determine the right therapy for the right patient by individualizing the decision based on efficacy, safety, and individual patient factors.

Figure 1:

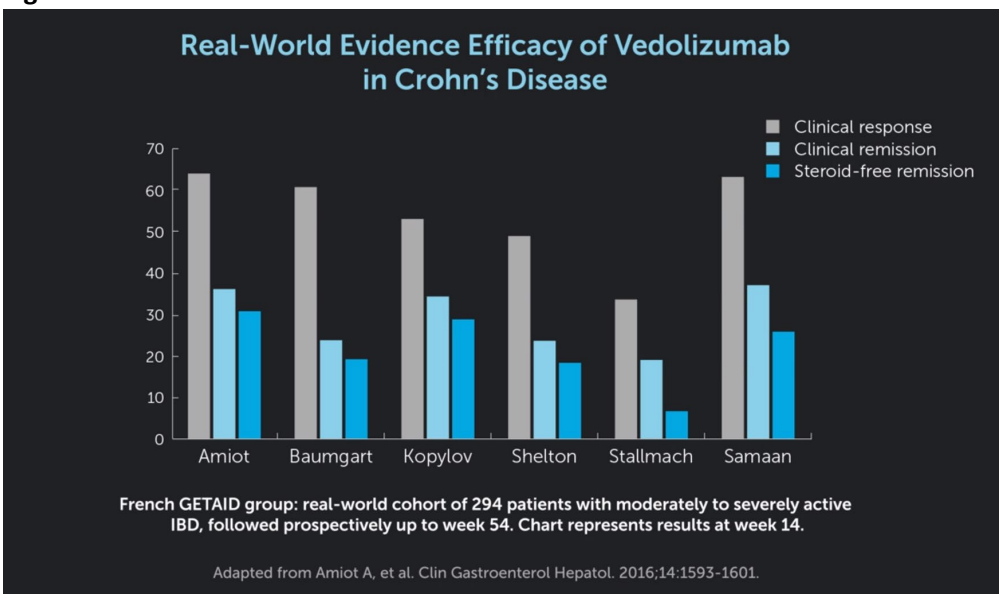
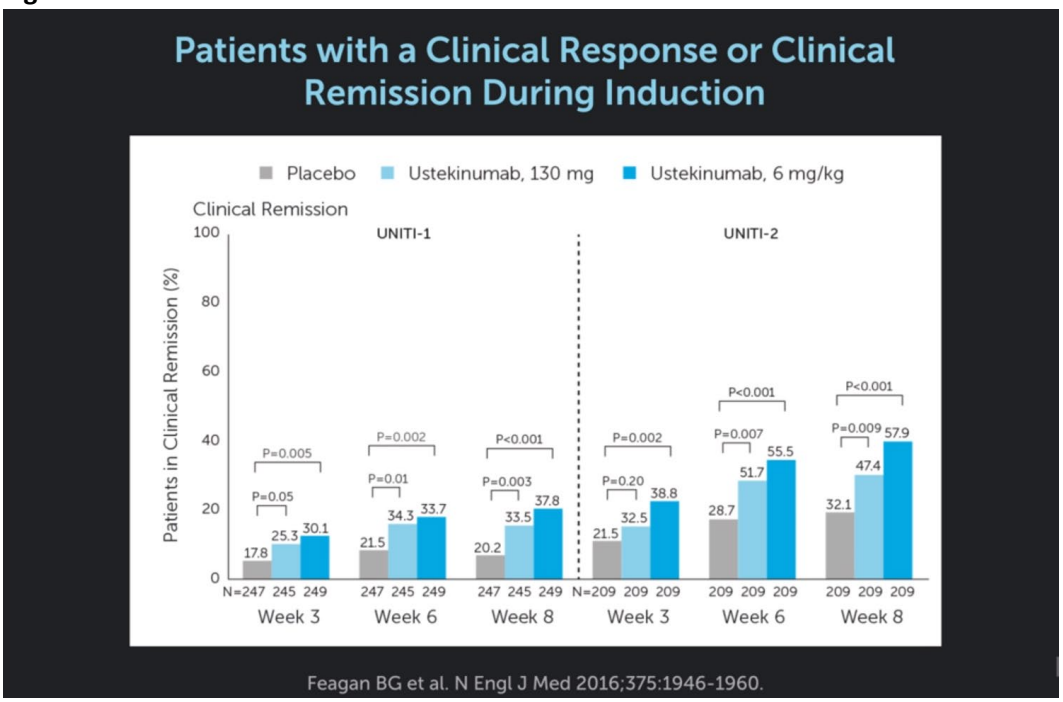


Figure 2:



Conclusions

Hallmark symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, recurrent fistulas, and extraintestinal manifestations including, but not limited to, arthropathy, ocular and hepatic disease, metabolic bone disease, thromboembolism, cholelithiasis, and nephrolithiasis. Thus, Crohn's disease is associated with significant morbidity and potentially mortality. Pharmacotherapy is classified as induction or maintenance therapy. The evolution of management for

Crohn's disease may be shifting, however, from that of symptom control to that of improving inflammation, promoting mucosal healing of the gastrointestinal lining, and achieving and/or maintaining remission in patients with Crohn's disease. Treating Crohn's disease aggressively before complications arise allows medications to be more effective in reducing inflammation and lessens the risk of future serious complications and surgery that may be associated with Crohn's disease.

"I think for too long in the inflammatory bowel disease world, we've been waiting for complications to occur in order to be more aggressive with management. I think we need to change that trajectory – individualize therapy but be early and aggressive."

- Millie D. Long, MD, Associated Professor of Medicine, Gastroenterology & Hepatology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

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