

DIGESTIVE DISEASES

The Classical Immunosuppression: Overrated or Underused?

Deep Remission: A New Concept?

Jean-Frédéric Colombel ^a

Edouard Louis ^c

Laurent Peyrin-Biroulet ^b

William J. Sandborn ^d

Remo Panaccione ^e

a Department of Hepatogastroenterology, CHU Lille, Université Lille Nord de France, Lille;

b Department of Hepato-Gastroenterology, University Hospital of Nancy, Université Henri Poincaré 1, Vandoeuvre-lès-Nancy, France;

c Department of Gastroenterology, CHU Liège and GIGA Research, University of Liège, Liège, Belgium;

d University of California San Diego, La Jolla, Calif., USA;

e Inflammatory Bowel Disease Clinic, Division of Gastroenterology, University of Calgary, Calgary, Alta., Canada

Abstract

Crohn's disease (CD) is a chronic inflammatory disorder characterized by periods of clinical remission alternating with periods of relapse defined by recurrent clinical symptoms. Persistent inflammation is believed to lead to progressive bowel damage over time, which manifests with the development of strictures, fistulae and abscesses. These disease complications frequently lead to a need for surgical resection, which in turn leads to disability. So CD can be characterized as a chronic, progressive, destructive and disabling disease. In rheumatoid arthritis, treatment paradigms have evolved beyond partial symptom control alone toward the induction and maintenance of sustained biological remission, also known as a 'treat to target' strategy, with the goal of improving long-term disease outcomes. In CD, there is currently no accepted, well-defined, comprehensive treatment goal that entails the treatment of both clinical symptoms and biologic inflammation. It is important that such a treatment concept begins to evolve for CD. A treatment strategy that delays or halts the progression of CD to increasing damage and disability is a priority. As a starting point, a working definition of sustained deep remission (that includes long-term biological remission and symptom control) with defined patient outcomes (including no disease progression) has been proposed. The concept of sustained deep remission represents a goal for CD management that may still evolve. It is not clear if the concept also applies to ulcerative colitis. Clinical trials are needed to evaluate whether treatment algorithms that tailor therapy to achieve deep remission in patients with CD can prevent disease progression and disability.

Introduction

Crohn's disease (CD) is a chronic, progressive, destructive and ultimately disabling disease [1]. In other chronic destructive diseases such as rheumatoid arthritis (RA), treatment paradigms have evolved beyond partial symptom control alone toward the induction and maintenance of sustained biological remission, also known as a 'treat to target' strategy, with the goal of improving long-term disease outcomes i.e. reduced structural damage and disability [2]. In CD, there is currently no accepted well-defined, comprehensive treatment goal that requires the treatment of both clinical symptoms and biologic inflammation; it is important that such a treatment concept begins to evolve. Patients may potentially benefit by experiencing a 'deep' remission beyond the control of clinical symptoms, which might ultimately impact on important outcomes such as the need for surgery and the development of disability. Similarly, this concept may be useful when designing the next generation of clinical trials that could determine if treating beyond symptoms to deep remission can change the natural history of the disease.

Rationale for Exploring the Concept of Deep Remission in CD

The characterization of CD as a progressive, destructive disease that leads to irreversible bowel damage has become better recognized through longitudinal followup studies of large cohorts of CD patients. In 2002, Louis et al. [3] and Cosnes et al. [4] demonstrated that 74% of patients with CD had a nonpenetrating, nonstricturing phenotype at diagnosis, and that 60% of patients progressed to stricturing and/or penetrating lesions in the long term. Recently, the results from these referral center studies have been confirmed in a cohort based on a North American population [5], showing that the natural history of CD is a dynamic process, leading to irreversible bowel damage and intestinal resection in the large majority of patients. Overall, the cumulative risk of surgery in CD patients is 50% after 10 years of evolution, with no dramatic change in recent years [6]. These studies reflect the outcomes of current treatment paradigms, which are based on the induction of symptomatic response and remission followed by maintenance of symptomatic remission. As the majority of patients experience disease progression and accumulation of bowel damage over time with this treatment paradigm, it would be attractive to develop an alternative where patients are treated to achieve a composite end point comprising both clinical and biological remission. The goal would be to block the progression of CD and to prevent damage progression.

Lessons from Other Chronic and Destructive Inflammatory Diseases

There are similarities between CD and other therapy areas. In hypertension, type 2 diabetes and RA, a failure to treat early and effectively can lead to serious complications and disability. Disease management has evolved over time towards a 'treat to target' approach to achieve 'tight control'. Several studies have shown that this approach leads to improved outcomes compared to conventional care. In the TICORA (Tight Control of Rheumatoid Arthritis) study, which allocated outpatients with RA to either intensive management (aiming for sustained, tight control of disease activity) or conventional care, patients in the intensive-management group experienced improved control of disease activity, reduced radiographic disease progression, improved physical function and a better quality of life [7]. Similar benefits have been reported in other diseases. The early improvement of blood pressure control in patients with both type 2 diabetes and hypertension was associated with a reduced risk of complications [8]. Tight blood pressure control reduced morbidity and mortality in patients with hypertension [9].

What Is Deep Remission in CD?

Deep remission in CD is an evolving concept and there is currently no definition that is widely agreed upon. At its most fundamental level, deep remission is a state of remission with little or no risk of disease progression. If accepted, this definition likely implies an absence of biological evidence of inflammation. Most physicians would agree that clinical remission (symptom control) and endoscopic remission (also known as mucosal healing) would appear to be vital components of deep remission. However, it is still under debate whether complete mucosal healing offers any substantial benefit over partial mucosal healing with a low level of residual endoscopic activity, and if there is also a need for radiographic transmural healing as demonstrated by computed tomography or magnetic resonance imaging enterography. There is an increasing interest in the utility of these biomarkers for monitoring disease activity. Biomarkers are indeed good candidates for inclusion as a component of deep remission. Ideally, they could replace mucosal healing and radiographic healing as surrogate measures of biological remission. However, studies are still needed to demonstrate that they are reliable and adequate surrogate measures. An important point to consider is that the treatment goal should probably be different in patients with early versus late disease due to the progressive nature of CD, as is the case in RA. Patients diagnosed late in the CD course who have already experienced a disease complication or required surgery may not be capable of achieving a state where there is a complete absence of clinical symptoms

(due to irreversible structural damage). Several sub-analyses of clinical studies have suggested that higher clinical and endoscopic remission rates may be achieved in patients with early disease defined by time from diagnosis [10, 11]. Based on these principles, a working definition of deep remission has been proposed. In patients with no bowel damage or disability, deep remission is the resolution of one or more objective measures of inflammation (endoscopy, imaging and markers) and of symptoms, preventing damage and disability. In patients with existing damage and disability, deep remission is the resolution of one or more objective measures of inflammation (endoscopy, imaging and markers) and the improvement of symptoms, preventing further damage and disability and reverse damage if possible (unpubl. data).

Is Deep Remission Achievable?

Even though there are many available data regarding clinical remission or mucosal healing across clinical trials, very few studies have looked at composite end points. Recent data from the EXTEND (Extend the Safety and Efficacy of Adalimumab through Endoscopic Healing) study of adalimumab show that sustained deep remission can be achieved with an anti-TNF antibody. EXTEND was a 1-year trial comparing the efficacy of adalimumab versus placebo in inducing and maintaining mucosal healing [12]. The study included a prespecified secondary analysis of deep remission, defined as clinical remission [CD activity index (CDAI) < 150 points] and mucosal healing (absence of mucosal ulceration). In this study, 19.4% of patients receiving adalimumab every other week achieved deep remission at 1 year (compared to none of the patients receiving placebo; $p < 0.001$) (unpubl. data). As anticipated, patients with a shorter disease duration tended to have a better chance of achieving deep remission at 1 year: 33% of patients with a disease duration ≤ 2 years compared to 25% for ≤ 5 years and 16% for > 5 years. We had the opportunity to investigate deep remission according to different definitions in the STORI (Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission on Combined Therapy with Immunosuppressors) trial [13]. This study looked at the impact of maintenance infliximab withdrawal in patients with CD. One hundred and fifteen patients (with a median disease duration of 7.8 years) were treated with combined scheduled infliximab and azathioprine therapy for > 1 year. When infliximab was stopped, they had to be in steroid free clinical remission for > 6 months. Among the 115 patients in clinical remission, 39 (34%) had a CDAI < 150 and a CD endoscopic index of severity (CDEIS) of 0, 98 (85%) had a CDAI < 150 and a CDEIS < 4, 83/109 (76%) had a CDAI < 150 and a CRP < 5 mg/l, and 63/85 (74%) had a CDAI < 150 and a stool calprotectin level < 250 mg/g (unpubl. data).

Is Deep Remission Desirable?

In RA, studies have shown that structural deterioration is closely related to clinical disease activity but that radiographic progression may occur in patients in symptomatic remission. Several explanations have been provided: synovitis and damage may be independent processes, clinical measures are not sensitive to detect low disease activity and remission criteria are not stringent enough. Very few studies have looked at the impact of deep remission in CD and no study has compared the benefit of deep remission over clinical or endoscopic remission only.

The achievement of deep remission was associated with improved outcomes in EXTEND (unpubl. data). Patients who achieved early deep remission had fewer hospitalizations and CD-related surgeries after 1 year than patients who did not achieve it. These patients also had a better quality of life and their productivity and activity in the workplace were less impaired. Patients with early deep remission experienced fewer dose escalations, and early deep remission was associated with health-care cost savings of approximately USD 9,000 at 1 year. In STORI, several parameters that may define deep remission such as a CDEIS of 0, a calprotectin level > 250 mg/g and an hsCRP < 5 mg/l were associated with a reduced risk of relapse when infliximab was stopped [13] .

Does the Concept of Deep Remission Apply to Ulcerative Colitis?

Until now, major end points of natural history studies of ulcerative colitis (UC) have been colectomy rates, cancer, disease activity and disease extension. The deleterious consequences of ongoing inflammation in the colonic physiology have not been adequately studied [14] . Being only a mucosal disease, UC is not typically accompanied by the stricturing and fistulizing complications that can be seen in CD; hence, the tendency among physicians to consider it a less progressive disease [14] . This attitude results in a reluctance to introduce more potent treatments earlier in the course of disease, even if this approach has been shown to have better outcomes.

Evaluation of UC severity and activity is based on clinical symptoms and on endoscopic indices of inflammation. In most clinical trials and in clinical practice, therapeutic goals for UC have translated into achieving mucosal healing. The impact of mucosal healing was demonstrated in the ACT (Active Ulcerative Colitis) trials. Infliximab-treated patients with lower endoscopy subscores at week 8 were less likely to progress to colectomy over 54 weeks of follow-up ($p = 0.0004$) [15] . This trend was not observed in placebo-treated patients ($p = 0.47$). Moreover, patients with lower endoscopy subscores at week 8 achieved better clinical outcomes for symptomatic

remission, corticosteroid-free symptomatic remission and mucosal healing, and were more likely to discontinue corticosteroids at weeks 30 and 54 ($p < 0.0001$ for infliximab and $p < 0.01$ for placebo). Nevertheless, it has not yet been shown that treating patients beyond clinical remission in order to get a state of deep clinical and full endoscopic remission is indeed associated with better outcomes.

Conclusion

Even though the concept of deep remission is appealing in IBD, there are still many uncertainties regarding its definition and clinical relevance. Prospective studies such as the CALM study are ongoing to demonstrate that a tight control approach using biomarkers targeting deep remission is superior to a classic approach based on clinical symptoms. Caution is nevertheless advised: in diabetes patients, it was shown that a very tight blood glucose control was actually associated with an increased mortality [16]. A careful evaluation of the risk/benefit ratio is important.

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