Redefining Early Intervention and the Window of Opportunity in Crohn's Disease

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Abstract: Crohn's disease is a chronic, progressive inflammatory bowel condition characterized by unpredictable episodes of flare and remission. Inflammation that is not controlled, and even in instances when inflammation is controlled, often has a substantial impact on quality of life for individuals with Crohn's disease, affecting relationships, education, and work productivity. The concept of a therapeutic window of opportunity has long been recognized as a period within which to maximize effectiveness of interventions and potentially modify the course of disease. However, there has been considerable uncertainty over the years on when the window of opportunity is, or how early should early effective intervention be in Crohn's disease. In recent years, there has been a growing body of evidence supporting early intervention to maximize benefit and improve outcomes for patients, and several seminal studies have provided insights into the true window of opportunity. This article summarizes the latest evidence for early effective intervention and considers when to intervene in the therapeutic window of opportunity to maximize outcomes and quality of life for people living with Crohn's disease.

Keywords
Crohn's disease, inflammatory bowel disease, early intervention, therapeutic window of opportunity

Crohn's disease is an inflammatory bowel disease characterized by variable and alternating periods of disease activity and remission, typically on a background of chronic disease progression. It is a condition that can present with a range of intestinal and extraintestinal manifestations, resulting in a major impact on quality of life for most patients.[1] Although the areas of greatest prevalence of Crohn's disease have typically been in high-income countries, the incidence is now rapidly rising in lower- and middle-income countries, highlighting that these regions will likely be the areas of greatest disease burden in the coming decades.[2] Early theoretical depictions have suggested an almost

relentless progression towards disease complications such as strictures, fistulas, and abscesses—with associated need for hospitalizations and surgeries. Considering both the rising global burden and the progressive course of Crohn's disease, clinical focus in recent years has shifted away from *reactive* strategies and simply managing complications after they occur towards more *proactive* strategies to ensure maximal bowel healing and preventing complications from occurring in the first place.

Although largely theoretical in the first instance, a window of opportunity was proposed in Crohn's disease as a period when interventions were most likely to be effective and result in beneficial outcomes for patients.[3] However, there has been considerable uncertainty over the years on when the window of opportunity is, and in particular how early should early intervention be. An ongoing area of debate has also centered around whether the course of Crohn's disease is modifiable and whether it might be possible to change the disease trajectory with early intervention. Recently, there have been new insights into these questions and into whether a preclinical phase, characterized by immune dysregulation, microbial shifts, and barrier defects, may open avenues for disease prevention. This article summarizes the latest evidence on the therapeutic window of opportunity and considers how best to optimize outcomes—and ultimately explore preventative strategies—for people living with Crohn's disease.

Initial Evidence for Early Treatment of Crohn's Disease

The transmural and patchy nature of Crohn's disease has been appreciated for many decades, and while early descriptions focused on terminal ileal involvement, it is now well appreciated that Crohn's disease can affect any part of the gastrointestinal tract.[1] The evidence base supporting the notion of Crohn's disease being a progressive condition has steadily accumulated over the years, in particular from data demonstrating progressive bowel damage, which occurs in patients over time.[4-7] In the pre-biologic era, it was recognized that in the absence of effective treatments, the vast majority of patients with Crohn's disease developed a stricturing or perforating complication over time, requiring at least one or more abdominal operations in their lifetime.[8,9] It should be noted that a small proportion of patients with much milder disease have also been identified, being marked by lack of disease progression over time.[10,11] However, the majority with moderate and severe inflammatory disease have consistently been demonstrated to have substantially worse outcomes and disease course consistent with the classic picture of disease progression in Crohn's disease.[12,13]

Highly variable definitions have been used for what might constitute early intervention and how wide or narrow the window of opportunity really is.[14] Some studies have used very relaxed definitions and labeled early intervention as a decade or more after diagnosis. Perhaps unsurprisingly in studies intervening 10 years or more after diagnosis, benefits from early treatment have been either minimal or difficult to establish.[15] Moreover, in the pre-biologic era, the mainstay of maintenance treatment for Crohn's disease was based on treatment with immunomodulators such as thiopurine medications. In 2 distinct and well-conducted randomized controlled trials (RCTs) with follow-up durations of 1.5 years and 3 years, respectively, early initiation of azathioprine demonstrated no superiority over conventional management for achieving clinical remission in patients with newly diagnosed Crohn's disease.[16,17] Based on these findings, there were some suggestions that the benefits of early intervention may have been overstated. However, it was recognized that failure to demonstrate benefit of early intervention using thiopurines may simply reflect the limited effectiveness of these medications, and that early intervention would be important to study in the context of more effective treatment options.

Accordingly, important preliminary evidence was provided by the step-up vs top-down RCT conducted in Belgium, Germany, and the Netherlands.[18] In this trial, 133 treatment-naive patients with moderate and severe Crohn's disease diagnosed within 4 years were randomized to either conventional step-up care or top-down treatment consisting of 3 doses of intravenous infliximab induction. The top-down infliximab induction group had substantially better outcomes at week 26. At the time, however, knowledge was still developing on how best to use biologic therapies, so there was no maintenance biologic treatment arm. Perhaps unsurprisingly, given there was no maintenance therapy, outcomes between the 2 groups were similar over time, with no discernible difference at the end of the longer-term extension period.[19] Therefore, although a promising early signal, the lack of sustained benefit resulted in few clinicians changing their clinical practice at the time.

Introduction of a New Crohn's Disease Treatment Paradigm

Evidence accumulated over the next 10 years, mostly from post hoc analyses of RCTs, suggesting that the window of opportunity in Crohn's disease may be less than 2 years after diagnosis. Indeed, post hoc analyses from a few trials, the PRECiSE 2 trial of certolizumab pegol[20] and the CHARM and EXTEND trials of adalimumab,[21] demonstrated that both anti–tumor necrosis factor (TNF) molecules were more effective in patients when used less

than 2 years after diagnosis, compared with patients who had medication initiated 5 or more years after diagnosis. Similarly, the EXTEND study, which assessed endoscopic healing and clinical remission with adalimumab, found improved outcomes significantly associated with a disease duration of less than 2 years.[22] Not only was disease control itself shown to be improved, but the risk of associated complications was also shown to be reduced when anti-TNF therapy was initiated within 2 years of diagnosis, with lower rates of both osteoporosis and anemia.[23]

An additional post hoc analysis of the SONIC trial compared treatment outcomes between patients with early disease (duration ≤18 months) and nonearly disease (>18 months).[24] This analysis included 188 patients, of whom 63 had early Crohn's disease, and showed that using a combination of intravenous infliximab and azathioprine was significantly more effective in the early intervention group.[22] This post hoc analysis also highlighted the key role of combination therapy, demonstrating that the infliximab-azathioprine combination was more efficacious than either drug alone in achieving composite remission markers, including clinical remission, endoscopic healing, and normalization of inflammatory markers such as C-reactive protein.[24]

In addition to medical intervention, important data began to accumulate about the benefits of earlier surgical intervention, particularly for patients with limited short-segment ileal Crohn's disease. The LIR!C trial included 143 patients with Crohn's disease who had nonresponse or intolerance to conventional treatment (corticosteroids and thiopurines at the time) at approximately 18 months after diagnosis. Patients were randomized to receive either ileocecal resection or intravenous infliximab, and quality-of-life outcomes between the 2 groups were demonstrated to be comparable.[25] Greater time free from either medical treatment or repeat surgery was reported in the ileocecal resection group over longer-term follow-up.[26]

Despite this evidence, a clear consensus on what should be considered either early medical or surgical intervention in Crohn's disease was lacking until the Paris consensus meeting was convened in 2012. At this meeting, an international consensus group of experts developed an opinion statement suggesting that the window of opportunity and definition of early intervention should be considered 18 months or less after diagnosis.[27] Additional subsequent efforts have sought to synthesize data across available studies and concluded that the window of opportunity and definition of early intervention may be considered up to 2 years from diagnosis.[14]

A lingering question has been whether the maximal window of opportunity in Crohn's disease could be much earlier. It is important to note that in analogous immune-mediated inflammatory disorders (IMIDs), such as rheumatoid arthritis (RA), early intervention has been defined as weeks or months after diagnosis, not in the context of years.[28] This may reflect the fact that active joint inflammation is more readily discernible to both patients and clinicians, and the progression to joint damage and permanent disability is clear; therefore, it is much more readily acknowledged that effective treatment needs to start as soon as possible.[29]

Redefining the Therapeutic Window of Opportunity

A pivotal step towards progress and better understanding of the nature of early treatment in Crohn's disease was provided by the CALM trial.[30] In CALM, 244 patients with moderate and severe Crohn's disease were treated with adalimumab approximately 1 year after diagnosis and then managed with either a tight control approach or reactive treatment using symptom-based escalation. A combination of this earlier treatment and tight control demonstrated the best clinical outcomes that had been reported in a Crohn's disease trial until that date, with endoscopic remission rates of approximately 45%. This was particularly important, given that achievement of endoscopic remission was associated with subsequent improved longer-term outcomes for patients.[31,32]

Further data demonstrated that treating patients with anti-TNF biologic therapy within that first year of diagnosis led to even better outcomes, with greater transmural healing rates in the early biologic therapy group when assessed using magnetic resonance imaging.[33,34] Indeed, in one of these early biologic therapy studies from Portugal, achievement of higher transmural healing rates was associated with lower risk of bowel damage (adjusted hazard ratio [aHR], 0.28; 95% CI, 0.10-0.79; *P*=.03), fewer Crohn's disease–related surgeries (aHR, 0.21; 95% CI, 0.05-0.88; *P*=.03), and decreased need for therapy escalation (aHR, 0.35; 95% CI, 0.14-0.88; *P*=.03).

These studies provided insights that the window of opportunity was likely to be at least less than 1 year after diagnosis. To explore whether the optimal window for early treatment might be even earlier would need very early disease cohorts, recruited ideally as soon as possible after diagnosis. In this regard, building on 2 decades of progress, the PROFILE trial has helped to redefine the role of early effective intervention and provided many novel insights into the true window of opportunity. PROFILE was an RCT of 386 newly diagnosed, treatment-naïve patients with moderate and severe Crohn's disease who received either early combined immunosuppression with infliximab and immunomodulator (top-down strategy) or an accelerated step-up conventional treatment strategy.[35]

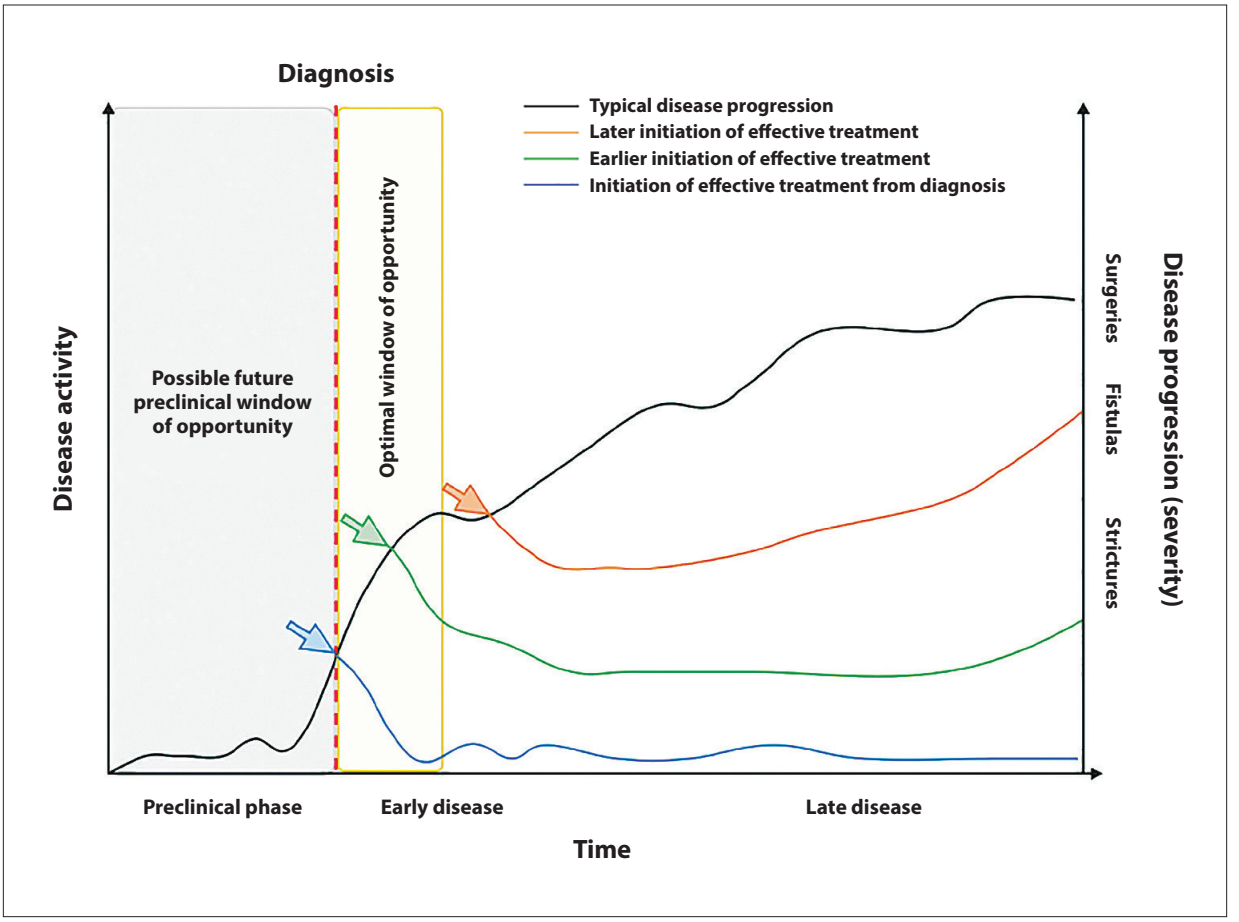

Figure. Redefining the therapeutic window of opportunity in Crohn's disease. The classical picture of disease progression in Crohn's disease presented with variable attenuation of disease severity (represented by the wavy lines) based on timing of effective intervention being initiated after diagnosis. Possible preclinical window of opportunity depicted as a future aspirational interventional period.

Maintenance biologic therapy was included in the top-down arm of PROFILE, distinguishing it from the historic step-up vs top-down trial, and a tight control approach to care was used for all patients. Crucially, patients were enrolled within days of diagnosis, making this by far the earliest early-intervention clinical trial conducted in Crohn's disease.

The results from PROFILE showed that the use of a top-down early effective treatment strategy from the point of diagnosis led to higher rates of remission than previously reported.[35] The primary endpoint was sustained corticosteroid-free and surgery-free remission at week 48 and was achieved by 79% in the early effective top-down therapy arm, compared with only 15% in the conventional accelerated step-up therapy arm. When focusing on objective outcomes, especially a stringent endpoint of endoscopic remission, for most registrational trials of licensed therapies in Crohn's disease, remission rates have typically been reported at approximately 30% to 40%. However, in PROFILE, ulcer-free endoscopic remission was achieved by 67% of patients receiving top-down early effective therapy. In addition to demonstrating high rates of endoscopic remission, all secondary endpoints (adjusted for multiple testing) showed efficacy for patients with early top-down treatment, including higher quality-of-life scores. These findings for the benefit of top-down infliximab after diagnosis were also shown in the pediatric Crohn's disease setting in the TISKids RCT.[36]

It is fair to say that the benefit for early effective therapy in Crohn's disease was already being recognized many years before either PROFILE or TISKids reported their findings. However, these trials have helped deliver robust and definitive data demonstrating the true magnitude of benefit from early treatment and provided an indication that the window of opportunity is even earlier than had previously been appreciated (Figure).

Implementation of Early Intervention Within the Window of Opportunity

Many would point out that the efficacy data from these studies could perhaps have been predicted based on accumulating signals in Crohn's disease and from evidence in analogous IMIDs. However, an important fact is that despite this awareness of the benefit for most patients with early effective therapy, step-up approaches to care have persisted in the management of Crohn's disease for decades, even when examining recent real-world evidence cohorts, with high rates of corticosteroid use being reported in parallel to low levels of advanced therapy use.[37,38] One major reason for this lack of implementation for early use of biologic treatment in Crohn's disease has likely been concerns about the potential risk of overtreatment and whether efficacy benefits may be offset by increased toxicity or safety concerns. In this regard, an important finding from PROFILE was that not only was the top-down arm more efficacious, but early effective control of inflammation was also the safer treatment strategy for patients. Indeed, patients in the early effective therapy top-down arm had fewer flares and fewer serious adverse events requiring hospitalization.[35] These data would be entirely consistent with recent findings from the PYRAMID registry data, demonstrating that anti-TNF treatment also helped decrease infections and serious infectious disease.[39] Taken together, these studies all highlight an important point, that the safest treatments in Crohn's disease are the ones that most effectively control inflammation. Moreover, these safety findings are in line with growing evidence on patient preferences, and that a key goal for patients is to feel better and have inflammation as well controlled as possible.[40] A further crucial point is that cost has also been considered a limiting factor for early use of biologic therapies. In this regard, recent formal health economic analyses have demonstrated that early and effective control of inflammation is not only more efficacious and safer, but also more cost-effective (ie, cheaper for health care services).[41]

Potential for Disease Modification With Early Intervention During the Window of Opportunity

One of the most intensely debated questions over the last 2 decades has been whether it is possible to modify the course of Crohn's disease.[42] Arguments for disease modification being possible have been put forward based on data showing that treatments such as anti-TNF biologics can help reduce progression towards stricturing and penetrating phenotypes and reduce the rates of hospitalization and surgery.[43,44] According to data from the PROFILE trial, even within a 1-year period after diagnosis, a 10-fold reduction was noted in need for urgent abdominal surgeries.[35] When considering the indications for these urgent abdominal surgeries, every abdominal surgery in the conventional accelerated step-up treatment group occurred for a stricturing or penetrating complication of Crohn's disease in patients who rapidly progressed within a 1-year period, whereas the only abdominal surgery in the top-down group was unrelated to Crohn's disease. These data for the ability to reduce disease complications requiring urgent abdominal surgery may be even more stark when compared with recent population-based data highlighting that rates of abdominal surgery in Crohn's disease still remain high (in conventionally treated cohorts).[45] Furthermore, recent evidence that Crohn's disease is modifiable with early intervention in the window of opportunity has been provided from the RISK study in pediatric Crohn's disease. In this cohort, a reduced progression towards stricturing and penetrating disease phenotypes was reported with early infliximab treatment within 3 months of diagnosis.[46,47] In addition, based on a further post hoc analysis from the RISK study, a significant reduction in development of perianal fistulizing Crohn's disease was noted among patients treated with early infliximab.[48] Notably, early infliximab initiation reduced the odds of developing perianal fistulizing disease by 82% (odds ratio [OR], 0.18; 95% CI, 0.05-0.66; P=.01). In selected groups, such as those with any perianal lesions at diagnosis, early infliximab treatment decreased the odds even further, by as much as 94% (OR, 0.055; 95% CI, 0.006-0.50; P=.010).

Taken together, the data from both PROFILE and RISK have provided clear evidence that disease modification is possible if there is very-early effective intervention in Crohn's disease. These data have also highlighted that if the window of opportunity is going to be defined by a period after diagnosis, then the maximal opportunity appears to exist immediately from diagnosis.

It should be noted that the majority of evidence for disease modification being possible in the window of opportunity has been related to anti-TNF medications, particularly with rising availability and affordability of these medications in the biosimilar era.[50] However, more treatments have become licensed and available for Crohn's disease in the last 20 years.[51] There is now a growing body of evidence that use of other advanced therapies may also be effective in the early disease setting.[52] Although most data currently have been gleaned from studies using historic definitions of less than 2 years after diagnosis, an important future step will be to assess the role of other therapies when used soon after diagnosis, including cost-effectiveness of non–anti-TNF options, when it appears the window of opportunity is

greatest. Additionally, it will be important to explore early intervention in this period with nonmedication interventions, including dietary, psychological, and surgical interventions.

To date, the window of opportunity has been considered as a time frame from diagnosis or duration of disease. However, patients have highly heterogeneous presentations and variable pathways before a diagnosis is even established. There is now a plethora of evidence demonstrating that significant diagnostic delay occurs for patients with Crohn's disease, often owing to its insidious presentation and that it can commonly be mistaken for other conditions such as irritable bowel syndrome.[53] Diagnostic delay has been attributed as the major cause for patients presenting with already more advanced stricturing and penetrating phenotypes.[54] Moreover, diagnostic delay has consistently been associated with worse outcomes, including higher risk of hospitalizations and abdominal surgeries.[55,56] One of the major challenges to overcoming diagnostic delay has been the appreciation that no single factor is to blame, rather a multitude of health care and individual factors contribute to it,[57] and these factors can vary between countries. Nevertheless, any strategies to maximize benefit for patients will need to consider how to ensure both timely/early diagnosis and timely/early effective treatment.[58]

Aspirations for a Future Paradigm on the Window of Opportunity

The question has now emerged as to whether it might be possible to go even earlier than the point of diagnosis. In conditions such as type 1 diabetes mellitus and RA, there has been intense focus on investigating preclinical disease and whether it may be possible to intervene before diagnosis to deliver better outcomes for patients. Several studies have demonstrated promising initial findings supporting a preclinical period of Crohn's disease, when it might be possible to predict which individuals may either develop disease or potentially be at higher risk for complications from disease. This preclinical period has been noted to be diverse but includes changes in factors such as dysregulation of the adaptive and innate immune systems, compositional shifts in the gut microbiome, increased intestinal permeability, and changes in protein structure or function (eg, through processes such as glycosylation).[59-62]

With the potential to identify individuals at risk for developing disease, hope has arisen that it might be possible to intervene in this preclinical period.[63] Through intervention in this preclinical window of opportunity, it may be that immune tolerance could be restored, with prevention or even cure of Crohn's disease as major aspirations. Even if prevention or cure was not to be achieved through this pathway, it is hoped that such an approach of intervening even earlier than before might improve the outcomes possible for patients and achieve longer-lasting periods of remission and treatment effectiveness. An important aspect going forward will be to understand which interventions could be used, at what time, and for which patients to realize the benefits of preclinical intervention[64] and move towards the ultimate and aspirational goal of preventing or curing Crohn's disease.

Conclusions

Although initially only a theoretical concept, the window of opportunity in Crohn's disease has become an accepted treatment paradigm, supported by accumulating evidence over the last 2 decades showing that there is a period to intervene early and modulate the disease course. Initially, intervention within several years of diagnosis was thought to be good enough in Crohn's disease. However, recent evidence has challenged the old paradigm and helped to redefine and reshape our understanding of the true therapeutic window of opportunity. It is now clear that at the point of diagnosis, the clock is already ticking and has likely been doing so for quite some time, with inflammation slowly building and bowel damage accumulating for many months or years in most patients. This has underlined that the maximal therapeutic window of opportunity is at diagnosis and that early intervention likely needs to be considered as soon as possible in this window to prevent progressive damage in Crohn's disease, much like in other IMIDs such as RA. Importantly, early effective intervention within the therapeutic window of opportunity should not be limited to medication intervention but encompass a range of other interventions, including dietary, psychological, and surgical approaches. These interventions or combinations of them will likely need to be tailored to individual patients based on disease severity, patient characteristics, availability, and patient preferences.

Now that the window of opportunity is recognized to be earlier than previously appreciated, a further step going forward will be to better understand the process of preclinical Crohn's disease and to investigate whether even earlier intervention, before diagnosis, might lead to improved outcomes for patients, with the hope that such strategies might provide a pathway towards prevention and/or cure. However, it should be noted that studies for preclinical Crohn's disease are in their infancy, and these goals are currently aspirational. In the meantime, there should be appropriate focus on early recognition, early diagnosis, and especially early effective intervention to help prevent complications and deliver the best possible outcomes for people living with Crohn's disease.

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