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EDITORIAL

Timely Use of Biologics in Early Crohn's Disease: The Return of "Hit Hard and Early"?

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Abbreviations

CD Crohn's disease
TNF Tumor necrosis factor

Crohn's disease (CD) has long been recognized as a destructive and disabling inflammatory bowel disease, leading to progressive and cumulative bowel damage [1], encompassing strictures, fistulas, and/or abscesses. Almost 20% of patients with CD experience penetrating or stricturing complications within 90 days of diagnosis, whereas half of patients will eventually experience these complications 20 years after diagnosis [2]. These complications often require bowel resection, leading to inherent additional bowel damage. Moreover, postoperative recurrence is frequent and may lead to further surgical bowel resection. Current "treat-to-target" strategies aim at avoiding long-term bowel damage and subsequent disability by using disease-modifying therapy in high-risk patients, followed by closely monitoring and adjusting treatment according to a predefined objective goal. Consequently, therapeutic targets have progressively shifted from focusing on clinical outcomes to achieving "deep remission," including clinical remission combined with mucosal healing [3]. In this respect, anti-tumor necrosis factor (anti-TNF) therapy reverses or at least slows the development of bowel damage [4, 5]. The concept of a "therapeutic window of opportunity" in early CD is growing, as an international expert opinion process developed the Paris definition of early CD for use in future disease modification trials, based on the duration of disease after diagnosis ($\leq$ 18 months) and previous use of disease-modifying agents (no previous or current use of immunomodulators and/or biologics) [6]. Whether the timing of initiating biologic therapy impacts the long-term progressive course of CD remains unclear. Yet, since the presence of bowel damage in early CD is associated with an inferior outcome, with increased risks of surgery and hospitalization [7], the premise for early aggressive treatment is compelling.

With regard to quantifying disease progression, the Lémann index has been developed to measure cumulative structural bowel damage in patients with CD, based on small bowel imaging, upper endoscopy, colonoscopy, and perianal assessment [8]. This index proved to be accurate for assessing bowel damage at a definite time point, but its sensitivity to change needs to be further explored. Indeed, although several studies conducted recently assessed the variation in the Lémann index over time, the index calculation was done at discrete time points and not during longitudinal follow-up [9].

In this issue of *Digestive Diseases and Sciences*, Panchal et al. [10] explored the impact of the timing of introducing biologic therapy on the rate of progression of bowel damage by using serial assessment of the Lémann index, testing the hypothesis that early introduction of anti-TNF therapy delays CD progression. To validate this hypothesis, a longitudinal study was conducted in 88 patients, 58 of them receiving biologics before or within 3 months of inclusion and 30 patients who either did not receive biologics at all or received them 3 months after inclusion. The Lémann index was assessed for each patient at two different time points at least a year apart (t_1 and t_2). Rates of change in the Lémann index were calculated as a function of time between the disease onset and initiation of biologic therapy. The authors found that disease duration correlated with Lémann index at both time assessments, t_1 ($r = 0.442$, $p = 0.001$) and t_2 ($r = 0.426$; $p < 0.001$) and that median time to initiation of biologics among patients whose index improved was

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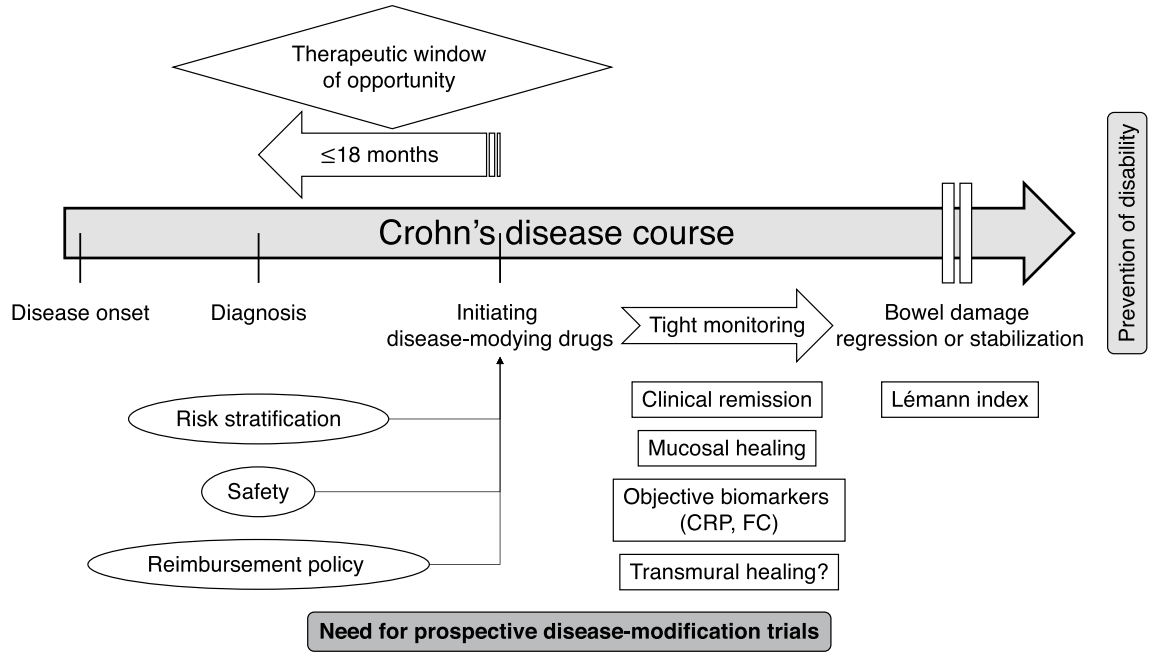

Fig. 1 Schematic representation of the concept of "therapeutic window of opportunity" in early Crohn's disease. Early intervention in the first 18 months after diagnosis of Crohn's disease through treating patients with disease-modifying drugs should prevent long-term bowel damage and subsequent disability. Risk stratification, safety profile, and reimbursement policy would still have to be taken into account when considering the introduction of biologic therapy in patients with Crohn's disease. Close monitoring based on clinical, endoscopic, imaging, and biologic data would still be required under treatment. Nevertheless, evidence is lacking and prospective disease modification trials are needed to settle whether this approach should be used in routine clinical practice. *CRP* C-reactive protein, *FC* fecal calprotectin

nominally shorter as compared to that in patients whose index worsened (8 vs. 15 years). Earlier introduction of biologics nonsignificantly correlated with a slower rate of progression (rho = 0.241; $p = 0.069$), whereas no association was noted between the rate of change in the Lémann index and time of initiating biologic therapy in patients never introduced to anti-TNF therapy or after 3 months of study inclusion (rho = − 0.024; $p = 0.934$). After application of a multivariable logistic regression analysis, the authors demonstrated that later introduction of anti-TNF by 10 years decreased the odds of disease regression or stabilization by 91%.

This is the first study to quantify disease progression as the rate of change in Lémann index, to use this calculation as the primary outcome and to correlate this outcome measure with the time from presumed disease onset to the first introduction of anti-TNF therapy as the independent and continuous variable. Calculation of Lémann index was based on a rigorous protocol established after multiple meetings that included institutional radiologists and gastroenterologists. Two previously trained investigators together calculated the Lémann index, with an excellent interreader interclass coefficient (97.7). Intra-rater reliability was also excellent (99.4).

This study has some limitations. The retrospective design is important to note, as association is not causation, and randomized controlled trials would be required to confirm these findings. Moreover, this study was based on a small cohort with an imbalance in the size of the two groups to compare (58 vs. 30 patients), which might contribute to selection bias. Referral bias may also emerge from the observation that all included patients were seen at a tertiary care center. This study was conducted from 2009 to 2014, prior to the implementation of the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) guidelines [3]. Since then, the use of biologics has been constantly increasing, especially in early CD (≤ 18 months). Yet, in this study, the median time from disease onset to the introduction of biologics was 9.5 years (range 0–42 years), clearly demonstrating that this cohort does not fit with the current definition of "early CD," confirmed by the high proportion of patients (62.5%) who had already undergone at least one surgical resection prior to the first Lémann index assessment. Furthermore, the median duration between the two calculations of Lémann index was 2.1 years (range 1–6.6), which might be too brief for changes in bowel damage to manifest, even though the change in the Lémann index over the two time points (t_1 and t_2) was noticeable (mean ± standard deviation: 4.0 ± 8.6). Finally, the analysis did not include information with regard to the type of payer, which might have influenced decision making for the use of biologics,

and a stratified analysis according to the concomitant use of immunomodulators would also have been interesting, as about half of patients in both groups were treated by immunomodulators at the time of inclusion.

In summary, the present study interestingly tries to address the question regarding the optimal time to initiate biologic therapy during the course of CD. Earlier introduction of anti-TNF agents somewhat correlated with a slower rate of progression of cumulative bowel damage, consistent with the growing concept of rapidly achieving disease control through intense treatment of CD patients at an early stage in order to avoid long-term bowel damage and subsequent disability (Fig. 1). In this respect, prospective disease modification trials are eagerly awaited to settle whether this approach should become routine in clinical practice. Identification and early referral of appropriate patients for such trials may be challenging, possibly facilitated by use of the easy-to-calculate Red Flags Index, which is still under validation [11]. Apart from therapeutic implications, Panchal et al. also suggest that the rate of progression of the Lémann index may be a useful outcome measure for use in these proposed future studies, although this index remains excessively complex for routine use in practice, all the more so as cutoffs to discriminate the presence of bowel damage and clinically meaningful changes over time still need to be determined.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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