**Defining biological remission in Crohn’s disease: interest, challenges and future directions**

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**Short title:** Defining biological remission in Crohn’s disease

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This article has been accepted for publication in *Journal of Crohn’s and colitis* Published by Oxford University Press.

<https://doi.org/10.1093/ecco-jcc/jjad086>

**Abstract**

In Crohn’s disease, the treat-to-target strategy has been highly encouraged and became a standard of care. In this context, defining the target (remission) constitutes a major stake which fuels the literature. Currently, clinical remission (symptoms control) is no longer the only objective of treatments since it does not allow to well control inflammation-induced tissue damage. The introduction of endoscopic remission as a therapeutic target was clearly a progress but this examination remains invasive, costly, not well accepted by patients and does not allow a tight control of disease activity. More fundamentally, morphological techniques (eg, endoscopy, histology, ultrasonography) are limited since they do not evaluate the biological activity of the disease but only its consequences. Besides, emerging evidence suggest that biological signs of disease activity could better guide treatment decisions than clinical parameters. In this context, we stress the necessity to define a novel treatment target: biological remission. Based on our previous work, we propose a conceptual definition of biological remission which goes beyond the classical normalisation of inflammatory markers (C-reactive protein and faecal calprotectin): absence of biological signs associated with the risk of short-term relapse and mid/long-term relapse. The risk of short-term relapse seems essentially characterised by a persistent inflammatory state while the risk of mid/long-term relapse implicates a more heterogeneous biology. We discuss the interest of our proposal (guiding treatment maintenance, escalation or de-escalation) but also the fact that its clinical implementation would require overcoming major challenges. Finally, future directions are proposed to better define biological remission.

**Keywords:** biological remission, Crohn’s disease

**1. Introduction**

Historically, treatments for Crohn’s disease (CD) focused on the control of symptoms. Since the end of the nineties, the introduction of biologics (mainly anti-tumour necrosis factor α, TNF-α) allowed to reach more ambitious therapeutic goals than symptoms control and such a change was accompanied by the development of a treatment strategy called “treat-to-target”1. This clinical concept consists in escalating/optimising the treatment (eg, dose, frequency, type of drugs) until reaching a state of remission (target) defined by objective and subjective criteria. In CD as in many areas of medicine, the treat-to-target strategy became a standard of care. Its implementation in clinical practice requires to regularly monitor disease activity (tight control) and to adopt a consensual definition of remission. In this context, the concept of remission became a major stake and showed rapid evolution with the advances in the fields of diagnosis and clinical research2–5. In 2015, the expert committee of the STRIDE (Selecting Therapeutic Targets in Inflammatory Bowel Disease) initiative defined therapeutic targets in CD and this was updated in the STRIDE-II initiative (2021)4,5.

**2. Limitations of clinical and morphological criteria to define remission: need to define remission based on biological grounds**

According to the STRIDE-II consensus5, the formal treatment targets in CD are defined by a combination of clinical, endoscopic and biochemical criteria. Clearly, using clinical remission (symptoms control) as the only treatment endpoint is outdated and insufficient. Indeed, this approach is not adapted for the advocated early intervention preventing bowel damage (eg, ulcers, strictures, fistulae) since symptoms are poorly correlated to endoscopic and biological signs of inflammation6. Consequently, treating beyond symptoms became a consensual idea among clinicians and endoscopic remission (mucosal healing) was recognised as a treatment objective in 2015 by the STRIDE committee4. This recommendation was motivated by convergent studies showing that mucosal healing was associated with better outcomes4. However, when endoscopy was introduced to define remission, it was already anticipated that this situation would be only temporary: “However, mucosal healing as the target should be viewed as a starting place, and it is likely that the target will evolve over time to other less invasive objective measures of inflammation”6. Indeed, evaluation of the disease activity with endoscopy presents major limitations: 1) it is not adapted for a tight control of disease activity given its cost, acceptance and invasive nature4; 2) it remains difficult to assess small bowel disease (only the terminal ileum can be examined); 3) there is no consensual agreement about the definition of endoscopic remission7; 4) it is only a superficial view of disease activity given that endoscopic examination only concerns the mucosa (less than 15% of the gut thickness8) while CD affects all gut layers (transmural disease). Besides, it was reported in CD that mural and extramural abnormalities remain relatively frequent in gut segments in endoscopic remission9.

In CD, remission has also been defined by using histology or cross-sectional imaging techniques (magnetic resonance enterography, computed tomography and ultrasonography). Nevertheless, the STRIDE committees did not recognise histological and transmural remission as formal treatment targets in CD4,5. Briefly, this decision was notably motivated by the insufficient capacity of current treatments to reach these targets (histological and transmural remission) and the lack of validated definition (histological remission). In addition, histological evaluation of disease activity seems particularly challenging in CD given its discontinuous presentation (patchy nature). Indeed, it cannot be guaranteed that histological examination of a few mucosal biopsies can appropriately represent disease activity10,11. Although transmural remission is currently not recognised as a formal treatment target (see above), it shows a growing interest. This trend is notably pushed by: 1) advances in intestinal ultrasonography and its assets: rapid, non-invasive, safe, low cost, broadly available, no preparation; 2) accumulating data showing that transmural remission is associated with better long-term outcomes than endoscopic remission12–14; 3) the advantage to evaluate disease activity in all gut layers. In this context, transmural remission is seen as a future treatment target15.

More fundamentally, in this viewpoint, we stress the fact that whatever the morphological techniques (eg, endoscopy, histology, ultrasonography) used to define remission, they only catch the consequences of disease activity on intestinal tissue. Morphological features result from biological processes which, if caught by biomarkers, could constitute a central piece to define remission (Figure 1). The recent introduction (2021, SRIDE-II initiative) of biomarker normalisation (C-reactive protein: CRP, erythrocyte sedimentation rate, faecal calprotectin) as treatment objective underlines the growing importance of molecular-based evidence of remission5. This evolution was notably pushed by a randomised controlled trial (CALM) showing that escalation of treatment driven by symptoms and biomarkers (CRP and faecal calprotectin) results in a higher proportion of patients achieving mucosal healing compared with treatment decision only guided by symptoms16.

Based on the above discussion, we stress the need to define a novel treatment target: biological remission. Of note, this objective is different from tools such as endoscopic healing index (EHI), a marketed blood test based on the measurement of 13 proteins, which does not propose a new treatment target but surrogate markers of an existing one (endoscopic remission)17. Overall, we think that biomarkers may convey more information on the state of disease activity than simply their association with morphological features. In ulcerative colitis, this idea was supported by transcriptomic data showing that ustekinumab-induced remission at week 44 is better predicted by a low level of molecular inflammation in the gut than endoscopic and histological remission at week 818. Thus, biological signs of disease activity could have a better predictive value than morphological criteria.

**3. Defining biological remission: looking beyond inflammation**

Biological remission is regularly defined by the level of CRP, combined or not with the level of faecal calprotectin20–22. However, these inflammatory markers only provide a restricted view of the complex and various biological dysfunctions implicated in CD (eg, genetics, immune system, intestinal barrier, cellular homeostasis, microbiota)23. Clearly, looking beyond inflammation is needed to define biological remission. We recently demonstrated that this argument is not only theoretical. Indeed, in CD patients in clinical remission and stopping infliximab (STORI cohort)24, a high serum level of inflammatory markers (eg, interleukin-6, acute phase reactants, complement components) was essentially associated with the risk of short-term relapse (< 6 months) but not mid/long-term relapse (> 6 months within a median follow-up period of ~2 years)25,26. This finding was confirmed in an independent cohort (SPARE)27,28. In STORI and SPARE, the risk of mid/long-term relapse was associated with a high or low serum level of proteins implicated in heterogeneous functions (eg, complement system, anti-inflammatory defence, angiogenesis, tissue regeneration)28. Overall, by comparing the results from STORI and SPARE, we confirmed that, after stopping infliximab in CD patients, the risk of short-term and mid/long-term relapse are associated with distinct biological profiles28. All these findings were obtained by stratifying relapsers according to their time to relapse (< 6 or > 6 months). Thus, short-term relapsers, characterised by a high serum level of inflammatory markers, were analysed separately and this allowed to reveal the distinct biological profile of mid/long-term relapsers. In other words, we pointed out that relapse was just the tip of the iceberg, hiding a succession of biological events which culminates with the inflammatory flare. Based on our work, we propose herein a conceptual definition of biological remission which goes beyond the classical normalisation of CRP and faecal calprotectin: absence of biological signs associated with the risk of short-term relapse and mid/long-term relapse (Table 1). Such definition stresses the idea that an absence of residual inflammation (no biological risk factors of short-term relapse) is a necessary but not sufficient condition to define biological remission.

**4. Potential interest of biological remission to guide treatment decisions**

Theoretically, associating biological parameters with prediction time-windows could help to better adjust treatments and, by doing so, improve the implementation of the treat-to-target strategy. For instance, detecting biological risk factors of mid/long-term relapse could be an information encouraging the maintenance of treatment while detecting biological risk factors of short-term relapse could motivate an escalation of treatment to resolve persistent inflammation (Figure 2). On the other hand, a state of biological remission as proposed (absence of biological signs associated with the risk of short-term relapse and mid/long-term relapse) is a situation in which treatment de-escalation could be contemplated and integrated in a treatment cycle (Figure 2). Defining such a state of remission corresponds to a real need since, as currently defined, the remission exhibits an insufficient predictive value to guide treatment de-escalation. A randomised controlled trial recently showed that despite being in stable remission according to classical criteria (clinical, biochemical and endoscopic), 50% of CD patients stopping infliximab relapsed over one year29.

**5. Challenges and future directions**

Precisely monitoring the biological activity of CD with non-invasive biomarkers could present a major interest for the management of patients. However, to our opinion, this attractive and desirable objective is not a short-term perspective since it would require first the development of fundamental knowledge characterising the biological activity of the disease, its dynamics and, more specifically, the succession of pathophysiological events leading to relapse. Although much efforts have been done to find predictors of relapse in CD, the biological aspects of this outcome have received little attention in the literature30–32. Reasonably, we expect that a better understanding of the relapse mechanism could be exploited to better predict its occurrence and define biological remission. To this end, the biological activity of the disease, obtained at blood level, will have to be integrated with molecular examination of gut biopsies and immune cells. In addition, a more general view of what is biological remission could be obtained by studying and comparing clinical situations other than infliximab withdrawal: 1) relapse following treatment maintenance or immunosuppressant withdrawal (eg, SPARE cohort: NCT02177071); 2) relapse following surgical resection (eg, POP-REMIND cohort: NCT03458195); 3) before the diagnosis of CD, i.e., a situation where individuals are treatment-naïve (eg, GEM and PREDICT projects33,34). Finally, another perspective would be to evaluate to which extent biological remission in CD and ulcerative colitis could converge.

As discussed above, the development of fundamental knowledge characterising biological remission is a necessary step guiding the search of novel biomarkers in CD. In a next phase, implementing this knowledge into clinical practice will require to overcome important challenges since demonstrating the clinical utility of biomarkers is a difficult and long task with a low rate of success35. More precisely, biomarkers must comply with a complex combination of constraints: 1) demonstrating a solid external validity: 2) showing a reasonable risk of patient misclassification; 3) dealing with some clinical requirements such as cost, availability of materials, throughput and analytical performance of the selected technology; 4) having a better cost-effectiveness ratio than the use of classical treatment targets in CD (symptoms control, mucosal healing, CRP and faecal calprotectin normalisation). In addition, the heterogeneity of CD phenotypes represents a challenge for the discovery of biomarkers. This difficulty is already perceptible with the disease location since the biomarkers used in clinical routine (CRP and faecal calprotectin) showed lower performance to monitor ileal than colonic CD36–42. Thus, we must expect that any new biomarker will not necessarily be appropriate for all subphenotypes of the disease. Lastly, the association between biomarkers and disease activity could also be influenced by past and present treatments thus making more difficult to define a homogeneous state of biological remission.

**6. Conclusion**

Defining treatment target (remission) in CD primarily aims to implement an appropriate therapeutic strategy, i.e., treatment escalation in case of insufficient disease control, but also treatment de-escalation to optimise benefit/risk ratio for the patient in case of stable remission. It is well known that reaching clinical remission is insufficient to avoid inflammation-induced tissue damage. On the other hand, morphological techniques (eg, endoscopy, histology, ultrasonography) remain insufficient to define remission because they only capture the consequences of the disease process instead of the disease process itself. Thus, the clinical and morphological information cannot fully assist the clinician in optimising treatment strategy. This is why, herein, we would like to stimulate and encourage the development of a novel treatment target: biological remission. To reach this ambitious objective, we do not propose a “ready to use” solution but rather a general frame which would need to be debated and adapted according to future knowledge.

**Funding**

No funding was provided.

**Data Availability Statement**

Data sharing not applicable to this article as no datasets were generated or analysed.

**Conflict of Interest**

No potential conflict of interest to disclose.

**Authors’ contributions**

NP drafted and revised the manuscript with intellectual contributions of all co-authors.

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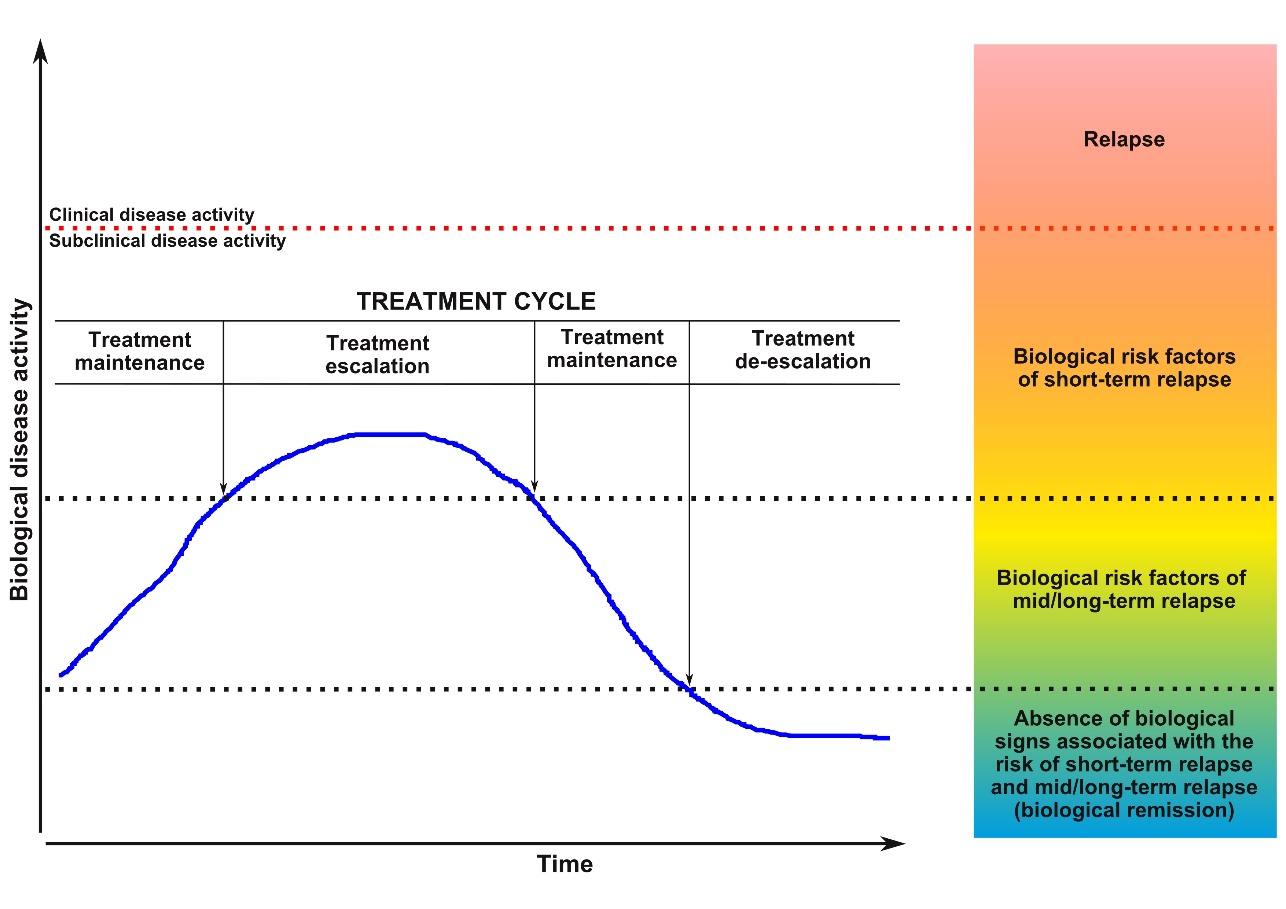
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| **Table 1. Proposed definition of biological remission in Crohn’s disease** |
| Absence of biological signs associated with the risk of short-term relapse and mid/long-term relapse. |

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**Figure 1. Biological remission as a central therapeutic target in Crohn’s disease**

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**Figure 2. Optimisation of the therapeutic strategy according to** **biological risk factors of relapse**