SELECTED SUMMARIES

Selecting the Ideal Candidate for Anti-TNF Discontinuation in Crohn's Disease, Dream or Reality?

Pierre N, Baiwir D, Huynh-Thu VA, et al. Discovery of Biomarker Candidates Associated With the Risk of Short-Term and Mid/Long-Term Relapse After Infliximab Withdrawal in Crohn's Patients: A Proteomics-Based Study [published online ahead of print October 26, 2020]. Gut https://doi.org/10.1136/gutjnl-2020-322100

The topic of anti-TNF therapy discontinuation for patients with inflammatory bowel disease in long-term remission is of significance for both clinicians and patients, due to safety concerns, adverse effects, and cost. In the current pandemic era, it has regained renewed attention. However, disease relapse has been reported to occur in roughly 50% of patients, highlighting the need for the development of biomarkers that could help in selecting the best candidates for successful stopping.

The STORI (Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission in Combined Therapy With Immunosuppressors) study was a prospective, observational study of 115 patients with Crohn's disease (CD) on combination therapy for at least 1 year who discontinued anti-TNF after being in steroid-free clinical remission for at least 6 months (Gastroenterology 2012;142:63–70). The clinical Crohn's Disease Activity Index–based relapse rates at 12 and 24 months were 43.9% ± 5.0% and 52.2% ± 5.2%, respectively, with a median time to relapse of 16.4 months. The long-term follow-up of the cohort (median 7 years) showed that only in approximately 20% of patients, remission was kept without development of major complications or without the need to restart infliximab or another biologic (Clin Gastroenterol Hepatol 2018;16:234–243). Therefore, it seems that, at least in a minor subset of patients, therapy discontinuation could be a feasible strategy. So how to identify the best candidates for this strategy?

Currently, C-reactive protein (CRP) and fecal calprotectin are recognized as the best biomarkers to evaluate the risk of short-term (<6 months) relapse after stopping biologics (J Crohns Colitis 2013;7:820–826). The lack of biomarkers that could predict a mid-/long-term relapse constitutes a clinical concern when the question of stopping anti-TNFα arises. In the work by Pierre et al, investigators from the STORI trial have analyzed the baseline serum from 102 patients included in the STORI trial, collected at the time of infliximab discontinuation. Relapse was defined as a Crohn's Disease Activity Index >250 or a Crohn's Disease Activity Index between 150 and 250 with a 70-point increase from baseline over 2 consecutive weeks, and patients were categorized into short-term relapsers (relapse documented within 6 months after anti-TNF discontinuation) and mid-/long-term relapsers (relapse occurring >6 months after anti-TNF discontinuation). Using mass spectrometry–based proteomics, the authors identified a large set of proteins that were then further validated and selected using a selected reaction monitoring approach. Overall, they observed 44 relapsers with a median time to relapse ranging from 4.8 to 16.4 months. Several biomarkers were associated with risk (hazard ratio) of short-term (15 proteins, 2.9<hazard ratio<16.1; $P < .05$), and mid-/long-term (17 proteins, 2.1<hazard ratio<4.7; $P < .05$) relapse, reflecting distinct pathophysiologic processes. The short-term relapse was characterized by an increased innate immune response with increased circulating levels circulating levels of acute-phase reactants (eg, ceruloplasmin and haptoglobin-related protein) and complement factors. Mid-/longer-term relapse was associated with proteins associated with angiogenesis, proteins involved in the activation of leukocytes, proteins originating from immune cells, and proteins involved in the complement system, which were in most instances down-regulated, suggesting a partial weakening of the immune system. Ten proteins were commonly associated with the risk of both short-term and mid/long-term relapse. Finally, the discriminatory probability of these markers to predict relapse was better compared to CRP and fecal calprotectin. These results could

constitute an important tool for clinicians to identify a subpopulation of patients with CD who could stop anti-TNFα with an optimal risk to benefit ratio.

Comment. As a chronic inflammatory disorder affecting people at a young age and requiring immunosuppressive therapy for a long period, it is not surprising that patients with inflammatory bowel disease inquire about treatment discontinuation, especially when remission has been attained. From a clinical point of view, patients with an aggressive phenotype at diagnosis (deep [ileal] ulcerations, penetrating disease, perianal disease, or acute severe colitis) are presumably not the best candidates to taper therapy once their disease could be fully dampened. However, in the vast majority of patients, we cannot predict up front who might remain in remission without any therapy. The STORI trial has been instrumental in highlighting the high risk of relapse on anti-TNF discontinuation, but also pointed toward a minor subset of patients who could indeed benefit from this strategy.

In the current era of personalized medicine, selecting patients who could safely stop therapy is as important as stratifying patients toward a specific mode-of-action once treatment has to be initiated. This post-hoc analysis of the STORI trial is therefore very timely and tackles one of the relevant unmet needs in inflammatory bowel disease practice. In this treat-to-target era (Gastroenterology 2021;160:1570-1583), one could question steroid-free clinical remission as a minimum to consider treatment de-escalation. However, the STORI trial was designed and conducted more than a decade ago, when the focus was on the symptomatic burden and not yet fully on endoscopic remission. This explains, in part, the predictive role of fecal calprotectin on short- and mid-/long-term clinical relapse, and suggests that some patients might not have been in deep remission at the time of anti-TNF discontinuation. In fact, 34% of patients included in the STORI trial had remaining ulcers at inclusion, with a Crohn's Disease Endoscopic Index of Severity score >3 in 23% of patients. Currently, one should presumably first document deep remission as a composite of both clinical and endoscopic remission before anti-TNF withdrawal, due to the discrepancy between symptoms and active endoscopic disease.

Might a more stringent inclusion based on endoscopic remission and a different definition of relapse, including fecal calprotectin and/or endoscopy, have resulted in different proteomic markers? Presumably yes, although this does not preclude the current reported markers of being clinically relevant. Undoubtedly, the current study by *Pierre et al* is a first step in an individualized treatment algorithm in which various factors, including biomarkers, could guide clinical decision-making on treatment withdrawal. The authors identified different proteins and processes enriched in patients with short- and longer-term relapses, suggesting that both are mechanistically distinct, with either a profound innate immune response or a partial immunologic weaking. Intriguingly, the involvement of the complement system as predictive for a disease flare has previously been identified as up-regulated preceding CD diagnosis in the pivotal PREDICTS study (Gastroenterology 2020;159:96–104). Although the complement cascade is not routinely monitored in patients with CD, subtle changes might inform on smoldering disease before major clinical symptoms, and highlight once more the central role of the innate immune system in CD pathogenesis.

Importantly, validation of the identified markers in an independent larger dataset is required before implementation in daily clinical practice, especially given the limited sample size and large number of markers assessed. The SPARE (Prospective Randomized Controlled Trial Comparing Infliximab-Antimetabolites Combination Therapy to Anti-Metabolites Monotherapy and Infliximab Monotherapy in Crohn's Disease Patients in Sustained Steroid-Free Remission on Combination Therapy; ClinicalTrials.gov ID: NCT02177071) trial might be an excellent validation dataset. The SPARE trial will not only allow validation of the identified proteomic signature in relation to relapse on anti-TNF withdrawal, but could also inform on the anti-TNF specific character of the signature. Indeed, the design of the STORI trial cannot discriminate between a marker specific for relapse after anti-TNF withdrawal vs an overall marker for future flare, regardless of whether the patient discontinues anti-TNF, immunomodulators or any other therapy. In line, the PREdiCCt (Prognostic Effect of Environmental Factors in Crohn's and Colitis) study characterizing inflammatory bowel disease flares from different angles could provide validation of the potential of the proposed markers as predictive for any flare.

The landmark STORI trial identified a clinical risk score (corticosteroid use 6–12 months before anti-TNF withdrawal, no previous surgery, male sex, hemoglobin <145 g/L, leukocyte count $>6 \times 10^9$/L, Crohn's Disease Endoscopic Index of Severity score > 0, high-sensitivity CRP ≥ 5 mg/L, infliximab trough level ≥ 2 mg/L, fecal calprotectin ≥ 300 μg/g), with patients having 3 or fewer deleterious factors flaring significantly less compared to patients with 4, 5–6, or more than 6 factors. Whether the current identified proteomic signal is superior or complementary to this clinical scoring remains to be investigated. Nevertheless, a high number of identified proteomic marker combinations deemed superior to the prognostic value of either CRP or fecal calprotectin, which requires subsequent independent validation. In line, superiority of particular combination of markers over other combinations has to be explored in large, well-powered validation studies.

In conclusion, this post-hoc analysis of the STORI trial sheds the first light on the pathophysiology behind disease flares in CD patients discontinuing anti-TNF therapy. Various 2-protein panels were identified to discriminate patients who did and did not flare on anti-TNF withdrawal on the short- or mid-/long-term. Although independent validation is undoubtedly required, it paves the way for a more tailored treatment approach in patients with CD and could subsequently be investigated in ulcerative colitis.

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