DDP-4 as a Novel Biomarker for Inflammatory Bowel Disease: Is It Ready for Clinical Use?

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In this month's Inflammatory Bowel Diseases, Pinto-Lopes et al present an article titled, "Serum Dipeptidyl Peptidase 4 (DPP-4): A Predictor of Disease Activity and Prognosis in Inflammatory Bowel Disease." This study explores the role of DPP-4 as a biomarker of inflammatory bowel disease (IBD) severity and also as a predictor of subclinical disease activity. We read this study with great interest, given the need for new biomarkers of disease activity.

The landmark CALM study supports the utility of biomarkers C-reactive protein (CRP) and fecal calprotectin (FC) to assess disease activity. This study established that Crohn’s disease (CD) patients had better outcomes when therapy escalation was based on biomarker results rather than clinical parameters alone. However, these biomarkers are not without pitfalls. For instance, a subset (>30%) of patients do not mount elevated levels of C-reactive protein, even in the presence of marked intestinal inflammation. Compared with CRP, fecal calprotectin (FC) more reliably detects subclinical inflammation and successfully predicts disease flares before symptom onset. However, FC is known to perform better in ulcerative colitis (UC) as compared with Crohn’s disease (CD), especially among patients with small bowel CD. Furthermore, FC utility is dependent on patient willingness to complete stool testing, and patients with less active (i.e. smoldering) disease may be reticent to comply in the absence of clinical symptoms. Currently, there is an unmet need for IBD biomarkers that perform as well or better than FC. The ideal biomarker would be obtained from blood, which makes DPP-4 an appealing candidate for further investigation.

Dipeptidyl peptidase 4 is a multifaceted enzyme that is nearly ubiquitous and serves an integral role in many metabolic functions. Besides regulating glucose metabolism by degrading glucagon-like peptide-1 (GLP-1), DPP-4 activates cytokines, chemokines, and neuropeptides involved in inflammation, and DPP-4 inhibition has been shown to suppress inflammation and alleviate oxidative stress. Despite these pro-inflammatory functions, there are conflicting reports on the role of DPP-4 as it applies to IBD. A recent prospective cohort analysis of type-2 diabetics concluded that patients treated with DPP4i/metformin combination therapy have reduced risk of autoimmune disease (including IBD) when compared with non-DPP4i/metformin treatment. An inverse correlation between IBD activity and serum DPP-4 (sDPP4) has been demonstrated previously, and DPP-4 inhibitors (DPP4i) have been associated with increased IBD risk. This suggests that low levels of DPP-4 reflect increased IBD activity.

Dr. Pinto-Lopes and colleagues aimed to investigate the utility of DPP-4 as both a biomarker and predictor of disease activity. The authors designed a multicenter prospective cohort study, enrolling 195 patients with IBD and measuring DPP-4, CRP, and FC at time of enrollment. Receiver operating characteristic (ROC) curves were used to evaluate the performance (sensitivity and specificity) of each biomarker in identifying disease activity. The authors found that DPP-4 inversely correlated with clinical disease activity, as assessed by Harvey-Bradshaw index (HBI)/partial Mayo Score (pMS), in addition to FC and CRP. Unfortunately, only 68 of the 195 patients had a baseline endoscopy for biomarker comparison. These 68 patients were split evenly (34 UC and 34 CD), and endoscopic activity correlated well with decreased DPP-4 levels for both diseases. Though not directly compared, mean DPP-4 levels for endoscopically proven UC remission (2122 ng/mL) and CD remission (1899 ng/mL) are higher than those deemed to be in clinical remission for UC (1798 ng/mL) and CD (1589 ng/mL). This highlights the importance of pairing biomarker results with a baseline endoscopy, as it is possible that a subset of patients deemed to be in “clinical remission” had smoldering disease.
To assess longitudinal performance of DPP-4 in response to treatment, the authors created a subcohort of 46 patients out of the 195 enrolled. The authors state these 46 patients were chosen based on requirement for induction with a new biologic therapy at the time of study enrollment. Thus, their response could be followed prospectively across clinical encounters. In addition to the baseline measurements at induction, DPP-4, CRP, FC, and clinical scores (pMS or HBI) were obtained at 5 separate points throughout the maintenance-dosing phase of biologic therapy. The authors report a significant difference in median DPP-4 levels among patients responding to therapy vs those deemed “nonresponders,” and this difference was more prominent in UC. However, it is worth noting in Supplemental Table 2, they classify 18 of the 24 CD patients and 17 of the 22 UC patients as “clinical remission” at the onset of their study involvement. This leaves just 11 “clinically active” patients (6 CD and 5 UC) for longitudinal assessment of biomarker performance, which is unlikely to be an adequately powered sample size for each disease category. In this same table, they delineate the number of patients in each subgroup who require “therapeutic escalation.” Therapy changed in 54 patients, exceeding the number enrolled in the subcohort. Thus, underpowered comparisons combined with inconsistent subgroup reporting may limit the strength of data interpretation here.

Finally, the authors investigated the predictive capability of DPP-4 by evaluating baseline levels of DPP-4, CRP, and FC in patients who went on to require therapy escalation in the year that followed. Therapy escalation was defined by (1) introduction of a new drug, (2) switching drug classes, (3) increasing the dose or shortening the interval of biologically treated patients, or (4) the need for surgery. The authors found that FC, DPP-4, and CRP all similarly predicted therapy escalation among their cohort and reported that a DPP-4 cutoff level of ≤1452 for CD and ≤1472 for UC patients correlated with time to treatment escalation. We note in Table 4 that the specificity of DPP-4 is ~65% in both CD and UC, with a PPV of 38.5% in UC and 65.4% in CD. It is also worth noting that the FC cutoff levels assigned for predicting treatment escalation were >840 ug/g for CD and >785 ug/g for UC. These FC values are undeniably elevated, which implies that a significant subset of patients with FC below these cutoffs had active disease requiring treatment escalation. This confounds interpretation of the results and does not support the reported DPP-4 cutoff levels for predicting therapy modification.

What is the verdict on DPP-4 as a tool for disease monitoring? We believe that further prospective evaluation of DPP-4 levels performed in conjunction with endoscopy is the key to determining its clinical value. Ideally, baseline biomarkers are collected within 1 week of endoscopy. Serial measurements over time, as the authors did with their subcohort, are also important for evaluating changes in DPP-4 in response to treatment. In summary, we agree with the authors that DPP-4 holds great promise as a future serum-based biomarker in UC and CD. We posit that further study with adequately powered subsets will be needed before universal acceptance of clinical utility is achieved.

REFERENCES