Personalized treatment in IBD – for another time

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For decades plagued by therapies of limited efficacy, the recent arrival of an embarrassment of riches in effective therapeutics for inflammatory bowel disease [1, 2] – likely to grow further in coming years [3-6] – has made personalization of therapy ever more urgent. Practicing physicians have no other option than to follow a rather mundane step-up and trial-and-error approach. The results of an exemplary biomarker trial conducted by Janssen and published in this issue [7] showcases how hard progress in this area is – and points to the sobering prospect that the current trial-and-error approach may stay for some longer.

The authors started from a transcriptomic biomarker that was associated with endoscopic and histological response in pre-treatment colonic biopsies in 22 patients of the ACT1 trial of infliximab in ulcerative colitis [8, 9]. This complex biomarker consisting of 109 probe sets corresponding to 81 genes and published in 2009, was then retrospectively validated in biopsies from PURSUIT, the clinical trial that established efficacy of golimumab in ulcerative colitis [10], and further refined to a more tangible 13 gene probe set. In the current trial, Janssen studied this biomarker in a prospective phase 2a study (the PROgECT study) that recruited across 33 centers 103 patients with moderate-severe ulcerative colitis, who received open-label golimumab [7]. With an area under the receiver operating curve (AUC_{ROC}) of 0.688 and 0.671 at weeks 6 and 30, respectively, the biomarker predicted mucosal healing with 87% sensitivity, but only 34% specificity. The biomarker did not identify patients who would achieve clinical response or clinical remission. While this biomarker may not have clinical utility in allocating golimumab treatment in patients, this trial is an important milestone for the field. It carried a properly derived and developed biomarker forward into a prospective, international multi-center trial that could have led to marketing authorization as a companion diagnostic. Though not having the ease of use of a serum biomarker, this biopsy/colonoscopy-based biomarker had many features that made it look robust. Originally developed in a small sub-cohort of a prospective clinical trial, it was replicated in a substantially larger independent cohort of patients undergoing treatment with an in-class alternative therapeutic, and then developed into a clinically applicable robust test. The trial was designed based on contemporary standards, including central reading of endoscopy.

As per its derivation and hence design, it is impossible to tell whether this biomarker would have predicted response to anti-TNF agents or to *any* effective IBD therapeutic. Its individual 13 components may render the latter more likely as there is little indication of a 'TNF signature'. Either way, such a biomarker would have been useful, considering the substantial primary non-response rates to anti-TNFs or other biologics used in IBD. The PROgECT biomarker did not follow a bimodal distribution that would have made dichotomization obvious, and therefore the authors explored two different thresholds – with the expected inverse relationship between specificity and sensitivity. Many examples of effective and

clinically useful biomarkers in cancer medicine, a field substantially better developed in that regard than immune/inflammatory diseases, indeed follow such a bimodal distribution [11]. These biomarkers are typically directly related to the mechanism of action of the therapeutic and hence based on the disease process that is targeted. There are also some examples in inflammatory diseases where this paradigm is followed. One is serum periostin, which is useful to identify patients with asthma who will respond to interleukin-13 blockade [12]. It tracks in serum the basolateral secretion of periostin from interleukin-13-stimulated bronchial epithelium. Some therapeutics currently in late phase development in IBD had pharmacodynamic and biomarker discovery efforts included in their phase 2 trials, which were linked to the mechanism of action of the investigational drug. Examples are serum IL-22, a target cytokine of IL-23, which is targeted by MEDI2070 [13], and colonic integrin α_E expression for the anti-β_7 integrin antibody etrolizumab designed to target $\alpha_4\beta_7$ and $\alpha_E\beta_7$ integrin-expressing immune cells [14]. It remains to be seen whether these biomarkers hold up in phase 3 programs. There is also the prospect that biomarkers might drive the development of new therapeutics. An intriguing example is Oncostatin M, which predicts anti-TNF failure, and at the same time might be an effective therapy target in such patients [15].

There are also examples of *a priori* mechanism-agnostic biomarkers that have proven utility in management of disease, again primarily in cancer medicine. One example is a 21-gene expression signature to guide adjuvant chemotherapy in breast cancer [16]. An interesting example in IBD is a transcriptomic biomarker in $CD8^+$ T cells that predicts at diagnosis the severity of the ensuing condition, and which has been replicated in independent cohorts [17, 18]. Intriguingly, this biomarker emerged to track $CD8^+$ T cell exhaustion, which might also explain why it predicts severe disease not only in Crohn's disease and ulcerative colitis, but across a range of immune-related conditions such as lupus erythematosus [19]. Since need for treatment escalation has been associated with this $CD8^+$ T cell biomarker, it will be interesting to see if patients with a predicted poor prognosis will respond to *any* of the currently approved therapeutics, or whether T cell exhaustion itself would need to be targeted. The utility of this biomarker across diseases that have little in common with regard to effective therapeutics make the latter a plausible possibility. This may also need consideration in light of high rates of primary non-response across different classes of therapeutics and across different diseases.

Returning to PROgECT, golimumab serum levels lower than expected in some patients who were predicted to respond are cited as a possible reason for the relatively poor test characteristics of the biomarker [7]. A genetic association between HLA-DQA1 and development of anti-drug antibodies during anti-TNF therapy is therefore interesting [20]. It might turn out that predicting drug clearance may be a better predictor of response than specifics of the disease process itself that PROgECT would have assessed.

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