Probing the Microbiome to Predict Response to Biologic Therapy in Inflammatory Bowel Disease—One Step Closer to Precision Medicine?

Lee JWJ, Plichta D, Hogstrom L, et al. Multi-omics reveal microbial determinants impacting responses to biologic

therapies in inflammatory bowel disease. Cell Host Microbe 2021;29:1–11.

Current treatment algorithms in inflammatory bowel disease (IBD) rely on a "trial and error" approach, and therefore, patients may receive ineffective and costly therapy for many months, with associated risks. Furthermore, after failure of the first biologic, response rates to second-line therapies drop considerably. Personalized medicine, which seeks to identify biomarkers that predict disease course and treatment efficacy, thus remains a significant unmet need in IBD.

In a prospective study, Lee et al sought to define novel microbial, metabolomic, and proteomic predictors of remission with anti-cytokine (anti-tumor necrosis factor [TNF] or anti-interleukin [IL]12/23) or anti-integrin therapy in IBD (Cell Host Microbe 2021;29:1294–1304). Included were 185 patients with moderate-to-severe disease (108 with Crohn's disease [CD], 77 with ulcerative colitis [UC]), with the study nested within a longitudinal prospective cohort, Prospective Registry in IBD Study at MGH (PRISM), at Massachusetts General Hospital, Boston. Of these, 100 patients received anti-cytokine therapy (n = 79 anti-TNF [infliximab, adalimumab, golimumab, certolizumab pegol] and n = 21 anti-IL12/23 [ustekinumab]) and 85 received anti-integrin therapy (vedolizumab). Stool and blood samples were collected at baseline for metagenomic sequencing, followed by microbial community profiling and metabolomic and proteomic profiling, respectively.

All patients were assessed for clinical remission at week 14 and 52, with endoscopic remission also assessed at week 52 in the 86 patients (46%) in whom colonoscopy was performed. At week 14, 91 patients (49%) achieved clinical remission, rising to 113 patients (61%) at week 52, and 48% (41 of 86) achieved endoscopic remission at week 52. Greater baseline fecal microbial diversity was associated with clinical and endoscopic remission with anti-cytokine but not with anti-integrin therapy.

Two distinct metacommunities with differing responses to anti-cytokine therapy were identified: group 1 consisting predominantly of the Firmicutes phyla and with a more diverse community profile, with group 2 consisting of Bacteroides phyla among others. Group 1 was associated with higher rates of clinical remission at both week 14 (73% vs 41%, $P = .02$) and week 52 (67% vs 36%, $P < .01$). The endoscopic remission rate showed a similar trend but failed to reach statistical significance (group 1 65% vs group 2 38%, $P = .09$). In contrast, group 1 was not associated with better response to anti-integrin therapy, and indeed both clinical and endoscopic remission at week 52 was inferior to group 2. This preferential response to anti-cytokine therapy over anti-integrin therapy among patients in group 1 was independent of baseline disease severity (with moderate-severe disease defined as Harvey Bradshaw index >8 for patients with CD and simple clinical colitis activity index >5 for patients with UC) or IBD subtype (UC vs CD).

Serum metabolomic analysis found secondary bile acid enrichment to be associated with week 14 clinical remission with anti-cytokine therapy, which correlated with a greater abundance of bile acid dehydroxylation enzymes necessary for secondary bile acid production in patients with the baseline group 1 metacommunity. Additional serum proteomic profiling suggested that cytokines that correlated with microbial diversity were also associated with remission.

Finally, a random forest classifier model incorporating clinical, metagenomic, metabolomic and proteomic markers (albeit only in 21 patients with all available baseline profiles), produced a remarkable area under the curve of 96% (95% confidence interval, 0.88–1) for prediction of week 14 remission with anti-cytokine therapy.

Comment. The key importance of the microbiome in the pathogenesis of IBD is underlined by several observations including that gastrointestinal inflammation is either significantly or entirely suppressed in germ-free IBD models, that transfer of pro-inflammatory microbiota from diseased to healthy mice induces gastrointestinal inflammation, and that diversion of the fecal stream in patients with Crohn's disease ameliorates inflammation (J Allergy Clin Immunol 2020;145:16–27). Earlier work has consistently demonstrated alterations in the gut microbiome between responders and nonresponders to IBD therapy (Clin Gastroenterol Hepatol 2020;18:1054–69). Interpretation has, however, been hindered by issues, including small sample size, lack of prospective data, assessment of single therapeutic classes in isolation, complexities of analysis, and uncertainty over whether these observations are cause or effect. It is also clear that lifestyle and physiological variables distinct from IBD subtype and severity, such as diet and alcohol consumption, exert significant effects on the gut microbiome and may confound study design (Nature 2020;587:448–45).

The study by Lee et al has the advantage of being a larger and prospective study cohort with longer follow-up out to 52 weeks and 3 different drug classes allowing for a direct comparison of the role of the microbiome in therapies with quite separate mechanisms of action. Despite the promising results pointing to potential biomarkers of response, this study is not without limitations.

The primary outcome was measured by clinical outcomes, with fewer than half undergoing objective endoscopic assessment of response, and by the incomplete provision of stool and blood samples allowing only a small subset (21 of 185) to be included in the final predictive model. In an era of more stringent treatment targets, this limitation makes their results difficult to interpret.

Further, although pre-existing data from 2 independent cohorts were used to validate the metagenomic and metabolomic association of increased secondary bile acid production in anti-TNF and anti-IL12/23 responders, the final multiomics predictive model still requires validation. Indeed, it is noteworthy that geographic location leads to significant variance in microbiota composition in IBD and that the predictive model here was based on patients from a single center (Gut 2021;70:499–510).

Lee et al again highlight the importance of microbial diversity, which was positively associated with treatment response to anti-cytokine therapy and inversely associated with serum cytokine profiles that favored nonresponse. It is

already well established that lower alpha diversity is associated with a broad range of diseases, including IBD, where it also correlates with disease severity and lower remission rates (Aliment Pharmacol Ther 2020;52:1453–1468).

The beneficial effects of greater diversity are likely to be multifactorial. Firstly, it may lead to a more stable and resilient ecosystem. Secondly, it may favor a tolerogenic intestinal immune state, including maintenance of gut barrier function and regulation of regulatory T cells/T helper 17 cells balance, which is central to intestinal inflammation (Pathogens 2019;8:26). Thirdly, there is clear evidence that greater microbial diversity positively correlates with metabolite diversity and abundance, including reduced medium- and short-chain fatty acids levels linked to the pathogenesis of IBD (Nature Commun 2020;11:4322).

The association, at both metagenomic and metabolomic levels, between secondary bile acid production and response to anti-TNF or anti-IL12/23 described by Lee et al is both intriguing and plausible. Emerging data have linked secondary bile acids to key intestinal immunoregulatory roles, including Paneth cell homeostasis, the innate immune response, and T-cell differentiation (Cell Host Microbe 2021;29:988–1001, Front Immunol 2021;12:658354, Nature 2019;576:143–148). Further, secondary bile acid supplementation reduces intestinal inflammation in both acute and chronic murine colitis models (Cell Host Microbe 2020;27:659–670). This raises the possibility that secondary bile acids might represent both a useful biomarker and a potential novel treatment modality.

Comparisons with earlier studies are complicated by differences in methodology and reference databases used for analysis as well as heterogeneity of patient cohorts, while lifestyle habits that are known to impact the microbiome are not included in most of the work (Aliment Pharmacol Ther 2020;52:1453–1468). It is notable that no reproducible predictive microbial signature has yet emerged, although patients with greater baseline microbial diversity do consistently show a better response to anti-TNF therapy, ustekinumab, and vedolizumab, with a lower abundance of proinflammatory bacteria and greater abundance of short-chain fatty acid producers also apparently favorable (Aliment Pharmacol Ther 2020;52:1453–1468).

While it is tempting to theorize that the different mechanism of action of vedolizumab might explain why the predictive factors for anti-cytokine response described by Lee et al do not translate to vedolizumab, an earlier predictive model using both clinical features and the microbiota (vedoNet), developed by the same group, predicted response to both vedolizumab and anti-TNF therapy (Cell Host Microbe 2017;21:603–610), highlighting the need to develop larger studies and validation data sets.

A key question yet to be answered is whether a causal relationship exists between the microbiome and treatment response. It has been shown in cancer that chemotherapy and immunotherapy efficacy are both modulated by the gut microbiome, but similar data are still lacking in IBD (Immunity 2016;45:931–943, Science 2015;350:1079–1084). This new discipline of pharmacomicrobiomics is dedicated to elucidating microbial effects on drug bioavailability, action, and toxicity, and particular attention will be directed to drugs that are taken orally, such as Janus kinase inhibitors, that directly interact with the gut microbiome (Nat Rev Rheumatol 2020;16:282–292).

Lee et al have taken us a step closer to probing the vast potential of the microbiome and associated metabolic profile for response prediction in IBD, but we still remain some way off routine adoption of a cost-effective and reproducible assay to truly personalize care. A concerted effort of different stakeholders, including pharmaceutical companies and different research centers, is necessary to allow for a transition from individual-omics studies to larger multiomics trials in order to identify definite prognostic markers that can contribute to a tailored IBD management.

On this path to precision medicine in IBD, the use of different systems biology is emerging; future research priorities should focus on the optimization of study design for biomarker development to clearly differentiate prediction from association, allowing for appropriate validation and incorporation of biomarkers into clinical trials and into clinical practice (Gastroenterology 2022; S0016-5085:04069-5, Gastroenterology 2022; S0016-5085:04081-6).

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