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BRIEF REPORT

Gene Expression Signature for Prediction of Golimumab Response in a Phase 2a Open-label Trial of Patients With Ulcerative Colitis

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Golimumab, a tumor necrosis factor antagonist, is an effective treatment for patients with moderate-to-severe ulcerative colitis (UC); however, more than 50% of initial responders lose their response to the drug within the first year of therapy. A gene expression signature identified in colon biopsies collected before treatment was associated with response to infliximab, and was subsequently refined to associate with mucosal healing in response to golimumab. We performed a phase 2a open-label study of 103 golimumab-treated patients with moderate-to-severe UC to test whether the baseline gene expression signature could be used to predict which patients would achieve mucosal healing, clinical response, and clinical remission at weeks 6 and 30 of treatment. The gene expression signature identified patients who went on to achieve mucosal healing at treatment week 6 with an area under the receiver operating characteristic curve (AUC_{ROC}) of 0.688 ($P = .002$) and at week 30 with an AUC_{ROC} of 0.671 ($P = .006$). The signature identified patients with mucosal healing with 87% sensitivity, but only 34% specificity, limiting its clinical utility. The baseline gene expression signature did not identify patients who went on to achieve clinical remission or clinical response with statistical significance. Further studies are needed to identify biomarkers that can be used to predict which patients with UC will respond to treatment with anti–tumor necrosis factor agents. ClinicalTrials.gov no: NCT01988961.

Keywords: PROgECT; Transcriptomics; Gene Signature; Prediction of Response.

Golimumab (SIMPONI), an anti–tumor necrosis factor drug, has demonstrated efficacy vs placebo in patients with moderate-to-severe ulcerative colitis (UC); however, many patients are primary anti–tumor necrosis factor nonresponders, defined as a lack of clinical response to induction therapy.[1] Additionally, more than 50% of initial responders experience loss of response within the first year of therapy.[2] Predicting whether a patient will respond to a particular treatment would allow for a patient-specific treatment plan, with expectations of improved safety and efficacy.[3,4] The development of biomarkers that predict individual patient responses to specific inflammatory bowel disease (IBD) therapies has been challenging, partially due to disease complexity, cohort variability, and heterogeneity of molecular, endoscopic, and clinical endpoints. Here we describe the identification and prospective replication of a colonic gene expression signature to predict golimumab mucosal healing response in patients with moderate-to-severe UC.

The predictive gene expression signature was initially identified from colon biopsies collected in the ACT1

Abbreviations used in this paper: AUC_{ROC}, area under the receiver operating characteristic curve; CI, confidence interval; IBD, inflammatory bowel disease; MPS, molecular prediction signature; UC, ulcerative colitis.

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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infliximab study (Supplementary Methods).[5] Baseline expression levels of a panel of 109 probe sets distinguished responders (n = 12) from nonresponders (n = 10) at week 8 with >90% sensitivity and specificity. Response was defined as complete mucosal healing and histologic normalization (a Mayo endoscopic subscore of 0 or 1 and a grade of 0 or 1 on the Geboes histological scale).[6] The predictive panel of 109 probe sets, representing 81 unique genes, was refined using baseline gene expression from colon biopsies (Supplementary Methods) collected in the PURSUIT golimumab study.[7] A 13-gene signature (Table 1) achieved the maximum area under the receiver operating characteristic curve (AUC_{ROC}) value for predicting week 6 mucosal healing response in PURSUIT (AUC_{ROC} of 0.768). Hereafter, the length-13 gene signature is referred to as the molecular prediction signature (MPS).

The MPS was then prospectively evaluated for prediction of mucosal healing, clinical response, and clinical remission in an open-label study (PROgECT; NCT01988961) of 103 patients treated with golimumab (Supplementary Methods).

The primary objective of the PROgECT study was to evaluate the accuracy of the MPS derived from gene expression in colon biopsies collected at screening to predict mucosal healing at week 6. Secondary objectives were to evaluate the accuracy of the MPS to predict clinical response and clinical remission at weeks 6 and 30 and mucosal healing at week 30.

For the primary endpoint, a receiver operating characteristic (ROC) curve for MPS was generated for mucosal healing based on the fraction of true positives and false positives at week 6. The AUC_{ROC} was 0.688 ($P = .002$; Table 2), indicating a better-than-chance accuracy of the MPS to predict week 6 mucosal healing. Two thresholds were applied (Threshold A: −3.8234; Threshold B: 1.0000) to dichotomize patients into mucosal healing responder or nonresponder (see Supplementary Methods for explanation of threshold selection). An analysis based on Threshold A showed superior sensitivity: 1.000, with a lower bound of 95% confidence interval (CI) of 0.878, $P < .001$, and a low specificity of 0.186. An analysis based on Threshold B also showed superior sensitivity: 0.870, with a lower bound of 95% CI of 0.696, $P < .001$, and a low specificity of 0.343.

Additionally, the MPS predicted mucosal healing at week 30 (AUC_{ROC}: 0.671, $P = .006$, lower bound of 95% CI: 0.569; Table 2). In contrast, the ROC curves for clinical response at weeks 6 and 30 and for clinical remission at week 6 showed that the accuracy of prediction was no better than chance (Table 2). Prediction of clinical remission at week 30 showed a positive trend (AUC_{ROC}: 0.633, $P = .059$; Table 2).

The PROgECT study prospectively tested the ability of a gene transcript panel measured in colon biopsies to predict golimumab mucosal healing response in patients with

Table 1. Genes Included in the MPS Panel

Gene symbol	Gene name
cmtm2	CKLF-like MARVEL transmembrane domain containing 2
C5ar1	complement C5a receptor 1
fgf2	fibroblast growth factor 2
gk	glycerol kinase
hgf	hepatocyte growth factor
il1rn	interleukin 1 receptor antagonist
lilra2	leukocyte immunoglobulin like receptor A2
nampt	nicotinamide phosphoribosyltransferase
pappa	pappalysin 1
snca	synuclein alpha
sod2	superoxide dismutase 2; mitochondrial
steap4	STEAP4 metalloreductase
zbed3	zinc finger BED-type containing 3

MPS, molecular prediction signature.

Table 2. MPS Prediction of Primary and Secondary Endpoints

Parameter	AUC_{ROC}	Lower Bound of 1-sided 95% CI	1-sided *P*
Week 6 (N = 93)			
Mucosal healing	0.688	0.589	.002
Clinical response	0.520	0.419	.740
Clinical remission	0.558	0.429	.462
Week 30 (N = 93)			
Mucosal healing	0.671	0.569	.006
Clinical response	0.588	0.488	.148
Clinical remission	0.633	0.517	.059

Note: Of the 103 treated patients, 93 patients were included in the primary analysis (4 patients from 1 site were excluded due to site compliance issues and 6 patients from other sites were excluded due to lack of valid biomarker samples).
AUC_{ROC}, area under the receiver operating characteristic curve; CI, confidence interval; MPS, molecular prediction signature; N, number of patients.