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Potential molecular biomarkers used to predict the response to biological therapies in ulcerative colitis

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Ulcerative colitis (UC) and Crohn's disease (CD) are two major types of inflammatory bowel disease (IBD). In recent decades, the use of biological agents, including antitumor necrosis factor (TNF), anti-integrins, anti-interleukin (IL)-12/IL-23, and Janus kinase (JAK) inhibitors, has promoted clinical remission and mucosal healing and reduced surgeries, hence significantly improving the quality of life of IBD patients. However, it was reported that approximately 20% to 30% UC patients did not respond to anti-TNF treatment in clinical trials (primary nonresponders), and the response in an additional 15% to 30% of patients was lost over time.[1] Additionally, it was reported that primary nonresponse to anti-integrin therapy occurred in 43% of UC patients in clinical trials.[2] In a real-world multicenter study, 32.1% of UC patients treated with vedolizumab did not reach clinical response at week 14.[3] For long-term efficacy, only 33% of UC patients maintained clinical response at 400 treatment weeks.[4]

The early recognition of nonresponders to certain biological therapies is an urgent need in clinical practice, which will help to avoid exposure to unnecessary medications, decrease costs, and find alternative appropriate medications in a timely manner. However, the need to provide novel markers is still unmet due to the limitations and lack of efficiency of the clinical manifestations, C reaction protein, and fecal calprotectin. In the past twenty years, the predictive values of novel molecular biomarkers for the response to IBD biological agents, including genomics, transcriptomics, proteomics that focus on adaptive or innate immunity, inflammatory cytokines, and cell adhesion, have been explored. Many biological therapies have been adopted into the medications of UC patients. However, few published studies have focused on the molecular predictors of the response to anti-IL12/23 therapy, selective IL-6 transduction inhibitors, and JAK inhibitors in UC patients. Here, we summarize the most potential molecular predictors of the response to anti-TNF and anti-integrin agents in UC, according to the pathophysiology. All the potential molecular predictors are illustrated in Supplementary Figure S1, http://links.lww.com/CM9/A465.

Anti-TNF-α agents are the first line of biological agents used for IBD treatment. The activation of TNF-α-independent pathways has been thought to be the key for the primary nonresponse of anti-TNF-α agents, including IL-17/Th17 and IL-6, and proteolytic degradation. Interferon (IFN)-γ and IL-17A are characteristic cytokines of Th1 and Th17 cells, respectively. Dahlen *et al*[5] identified that UC responders to anti-TNF therapy showed lower mucosal *IFN-γ*, *IL-17A*, *IL-1β*, *IL-6*, and *TNF-α* mRNA expression at baseline. Rismo *et al*[6] showed that higher mucosal *IL-17A* and *IFN-γ* mRNA expression at baseline was associated with clinical remission. These conflicting results might be due to the differences in endpoint times, disease severity, the definition of response, and the ethnicity of the participants.

IL-12 and IL-18 can induce IFN-γ synthesis and contribute to Th1 cell differentiation. Bank *et al*[7] found 21 SNPs in 14 genes that regulate inflammation in 738 anti-TNF-naive IBD patients. The variant allele of *IL-12B* (rs3212217), associated with increased IL-12 levels in the serum, predicted nonresponse to anti-TNF therapy. Meanwhile, the variant allele of *IL-18* (rs1946518), associated with reduced IL-18 levels in the serum and peripheral blood mononuclear cells (PBMCs), predicted response.

Several molecular biomarkers in the innate immune system were indicated to have a predictive potential of the response to biological therapies in UC, such as the

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ATG16L1 and *IRGM* genes [Supplementary Table 1, http://links.lww.com/CM9/A465]. In intestinal biopsies from IBD patients with active disease, highly upregulated Triggering receptor 1 expressed on myeloid (*TREM-1*) mRNA and protein levels were identified. Verstockt *et al*[8] found that lower whole blood *TREM-1* mRNA expression at baseline could predict the response to anti-TNF therapy (area under the curve [AUC]: 0.777). Similar accuracy could be achieved in patients with lower mucosal *TREM-1* mRNA levels. However, a recent study with 22 CD patients showed controversial results. The serum TREM-1 protein level did not show a predictive value.

IL-6 is a pro-inflammatory cytokine that plays a central role in activated B cell growth and terminal differentiation, T cell activation, and cytotoxic T cell proliferation and differentiation.[9] Sato *et al*[10] measured the serum levels of 17 cytokines in UC patients. When assessing the response at week 26, there were no significant differences in the baseline levels of any involved cytokine between clinical responders and nonresponders, and serum IL-6 levels at week 8 were remarkably lower in clinical responders. However, Nishida *et al*[9] showed that lower serum IL-6 levels at baseline were independently associated with response to infliximab at week 14. Dahlen *et al*[5] reported that mucosal *IL-6* mRNA levels at baseline were lower in responders than in nonresponders, but there were no significant differences in the serum IL-6 levels between the two groups. This discrepancy could be partially explained by the differences in the times of response and disease severity.

Oncostatin M (OSM) is a member of the IL-6 pro-inflammatory family. West *et al*[11] focused on OSM in IBD patients and proposed it as a novel potential predictor and therapeutic target. First, they confirmed that OSM, IL-6, IL-1A, and IL-1B expression levels were higher in 227 IBD patients obtained from five databases than in non-IBD controls. They found that higher pretreatment mucosal *OSM* mRNA expression was associated with decreased responsiveness to anti-TNF therapy. It was reported that serum or whole blood OSM expression could not accurately predict the response.[8]

Proteolytic degradation may contribute to nonresponse to anti-TNF agents. A recent study[12] reported serum matrix metalloproteinase 3 (MMP3) as a possible biomarker because it cleaved infliximab and adalimumab *in vitro*, and it was correlated with an increase in pro-inflammatory cytokine levels. UC patients, whose response to infliximab was lost at week 52, showed higher MMP3 levels at week 14. This distinction was maintained until week 52.

Due to the limited potential of a single biomarker, several studies have focused on the development of predictive models using multiple genes, cytokine panels, and complex models comprising phenotypes and genotypes. Dubinsky *et al*[13] designed a genome-wide association study (GWAS) to investigate the potential role of IBD susceptibility loci in the prediction of response. The most predictive model comprised pANCA, UC diagnosis, 3 SNPs from the pharmacogenetic GWAS, and a susceptibility SNP reported on pediatric IBD. This model identified a nonresponder with a remarkable AUC of 0.98. Bank *et al*[14] assessed 37 SNPs that regulate inflammation, particularly genes of the NF-κB pathway. They found that 19 SNPs were associated with the response to anti-TNF therapy. Burke *et al*[15] developed two genetic-clinical combined models of primary nonresponse and durable response. When the SNP predictive models were combined with clinical factors (age at diagnosis, disease duration, etc.), the predictive values of the resultant models were higher than that of a clinical-only model. An adaptive immunity gene array (encoding osteoprotegerin-TNFRSF11B, stanniocalcin-1, prostaglandin-endoperoxide synthase 2, IL-13 receptor alpha 2, and IL-11) in UC patients could identify primary responders with 89.1% accuracy. These high accuracy models suggested the potential clinical utility of genomic variants, especially in combination with traditional predictors.

RNAs have recently emerged as essential mediators of immune functions, such as autophagy, indicating their potential effectiveness as biomarkers. Morilla *et al*[16] validated a nine-mRNA signature using a deep learning-based algorithm with 84% accuracy. Accurately measuring cytokines in serum is simple and inexpensive. Obraztsov *et al*[17] established a model with a subset of serum cytokines (TNF-α, IL-12, IL-8, IL-2, IL-5, IL-1β, and IFN-γ). This model classified patients as primary responders and nonresponders, with 84.2% sensitivity, 93.3% specificity, and 89.8% total accuracy.

Anti-integrin agents mainly include vedolizumab and etrolizumab [Supplementary Table 2, http://links.lww.com/CM9/A465]. Vedolizumab is a humanized monoclonal antibody targeting the α4β7 heterodimer. In the study by Boden *et al*,[18] 14 out of 26 patients treated with vedolizumab reached endpoints, and the baseline α4β7 expression was higher in multiple cell subsets. Verstockt *et al*[19] identified baseline expression levels of four genes (*PIWIL1, MAATS1, RGS13,* and *DCHS2*). The model predicted a response with 80% accuracy in the discovery datasets and 100%, 81.3%, and 76.9% accuracy in three different validation datasets.

Similar to anti-TNF agents, proteomic predictors were found to focus on serum cytokines. Lower baseline serum IL-6 and higher baseline osteocalcin levels predicted clinical response at week 14 after treatment with vedolizumab. An early assessment of serum IL-6 and IL-8 was useful in predicting both clinical remission and mucosal healing after 54 weeks of treatment with vedolizumab.[20]

Etrolizumab selectively binds to α4β7 and αEβ7. UC patients with high integrin αE (*ITGAE*) mRNA expression in their baseline colonic biopsies were more likely to achieve clinical remission. Furthermore, Tew *et al*[21] compared differences in the baseline colonic expression levels of T-cell-associated genes between responders and nonresponders. The results showed that higher baseline granzyme A (*GZMA*) and *ITGAE* mRNA expression levels were linked with clinical remission of etrolizumab, especially in anti-TNF-naive patients.

Although many studies have already explored the potential predictive molecular biomarkers for the response of

biological therapies, few have been conducted in real clinical practice. The biggest challenge is the lack of external validation for these biomarkers. Inconsistent definitions of the response to biological therapies, variable background of biologic agents' exposure, different methodologies of biomarker testing, different genomic backgrounds, and disease behaviors from participants all contribute to the conflicting data in currently published studies. Meanwhile, scientific improvement, including the development of new technologies, the application of big data, and a more precise artificial intelligence algorithm, will likely facilitate the discovery of more predictive molecular biomarkers,[22] which has also been highlighted in some of the abovementioned studies.

The ideal predictive biomarker must be easy to obtain, show high accuracy and have quick feedback in clinical practice. Progress in the awareness of the exact pathogenesis of UC will be the major driver to explore predictive biomarkers. Multicenter cohort studies enrolling a large number of participants with different genomic backgrounds are expected to lead to a comprehensive predictive model that incorporates clinical, environmental, microbiota-related, genomic, transcriptomic, biochemical, and/or proteomic factors.

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Conflicts of interest

None.

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