Early Markers in IBD

Subjects: Immunology

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Inflammatory bowel diseases (IBD) are chronic conditions that primarily affect the gastrointestinal tract, with a complex pathogenesis; they are characterized by a significant heterogeneity of clinical presentations and of inflammatory pathways that sustain intestinal damage. After the introduction of the first biological therapies, the pipeline of therapies for IBD has been constantly expanding, and a significant number of new molecules is expected in the next few years.

inflammatory bowel disease | biological therapy | predictors | biomarkers

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) represent the two main forms of inflammatory bowel diseases (IBD). These are chronic conditions with a relapsing-remitting course that affect more than 5 million people worldwide, mostly in Western countries; their epidemiology is rapidly changing, with a sharp increase in incidence in Western countries registered in the previous decades [1]. IBD carries a significant direct and indirect health-care burden, which is mainly represented by drugs like biologics and small molecules, but also includes hospitalization-related costs and days of absence from work due to the disease [2]. In this scenario, there is an urgent need for a more effective approach than today's trial and error method, when it comes to starting therapies.

To date, IBD treatment is based on corticosteroids (for the acute phases), mesalamine (only for UC), traditional immunosuppressants and targeted therapies; this last category includes: anti-tumor necrosis factor α (TNFα), anti-integrin, anti-interleukin (IL) 12/23 and Janus kinases (JAK) inhibitors [3][4][5]. It has been shown that different pathogenic pathways can sustain bowel damage in IBD [6][7], so that two patients with similar clinical phenotypes can have different inflammatory pathways activated and, thus, respond to different targeted therapies. There is also evidence that, within the same patient, the immune system can exhibit a significant plasticity and change the inflammatory pathways that are activated during the course of disease [8]. Such a complexity can easily explain why current therapies are only of limited efficacy. While the armamentarium for IBD treatment is constantly expanding—with new drugs targeting different pathogenetic pathways—there is still a significant proportion of patients who do not respond to therapy: data from clinical trials and real life report clinical efficacy of a single drug in up to 60% of patients [9][10]. Whether these patients would respond to another agent is not possible to foretell, but there is strong evidence that second- and third-line agents can be effective even in the case of primary failure, although to a lesser extent [11]. Furthermore, a substantial percentage of patients experience secondary failures [12]: in these cases, unless surgery is made mandatory by disease complications, the usual choice is to try another medical treatment.

Taken together, these considerations point to the necessity for the development of new prognostic tools able to identify those patients who would benefit from an early introduction of advanced therapies, to predict their response to a specific therapy and to assess response at an early point in treatment. Some clinical features have been identified so far, but they mainly identify patients who would most benefit from immunosuppressive therapies and/or patients who are more likely to respond to medical treatment, while they do not offer much information about patients' response to a specific drug. Implementation of personalized medicine into IBD routine management represents one of the most compelling challenges of coming years, in order to provide patients with better clinical care in parallel with a reduction of costs for the health-care systems (Figure 1).

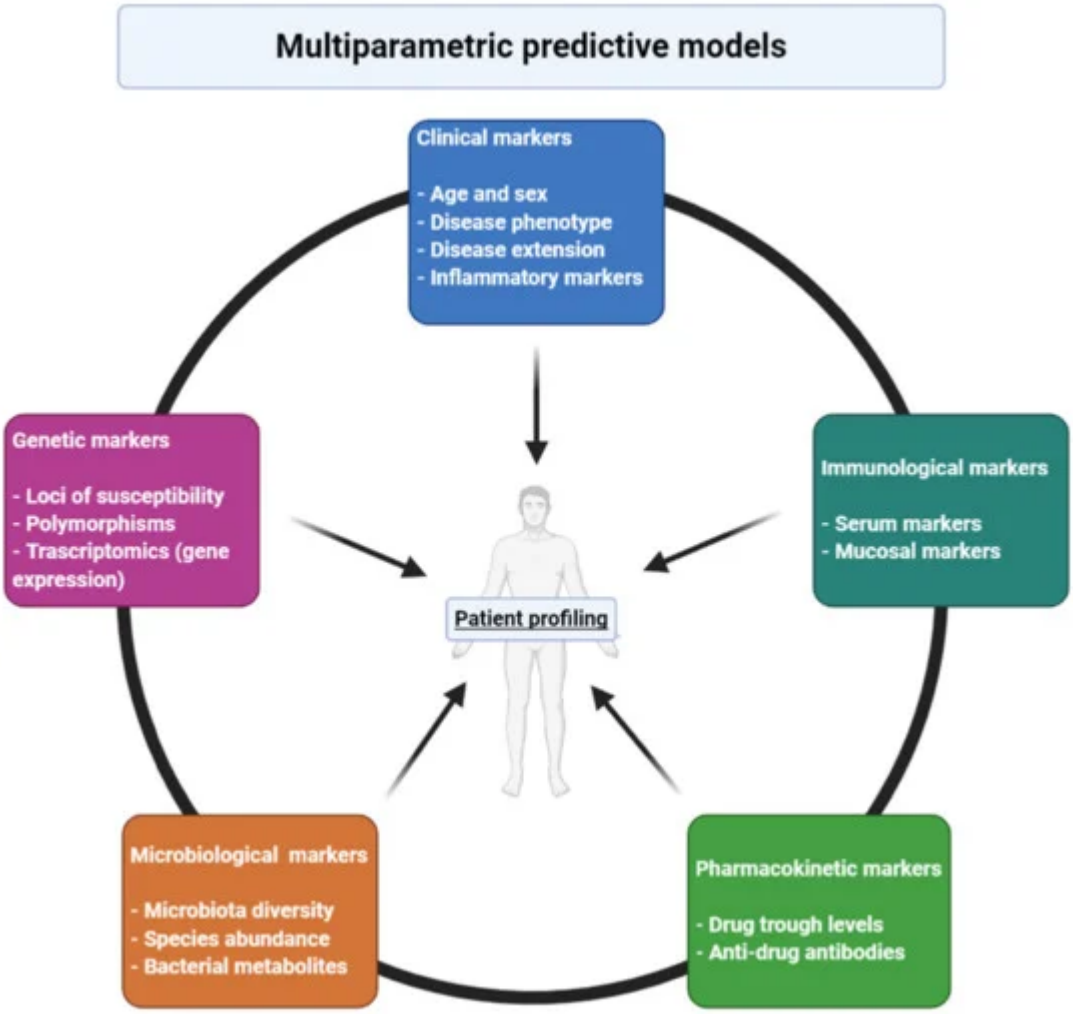

Figure 1. Different features that contribute to responsiveness to a certain drug and that needs to be included in multiparametric models for prediction of response in inflammatory bowel diseases. Created with BioRender.com.

2. Traditional Markers

Associations of patients' and disease characteristics with response to therapy have been widely investigated, but results have been generally discouraging. Age, gender, weight and smoking status have not been confirmed to correlate with response to anti-TNF or other targeted agents [13]. Two recent meta-analysis suggested that early

treatment of CD is associated with better response rates [14][15], and one of those also observed an association with higher rates of mucosal healing [15]; however, no differences between different drugs have been observed so far. In CD patients, disease location has not been found to be associated with treatment outcomes of anti-TNF and ustekinumab [13]; of note, one study reported an association between colonic localization and better responses to vedolizumab [16], that was not confirmed in others. Some studies have reported a correlation, in CD patients, between inflammatory phenotype and better response rates with TNF antagonists, compared to stricturing or penetrating diseases [17][18][19][20]; such findings have not been confirmed for vedolizumab and ustekinumab.

Various serological biomarkers have been investigated for their potential predictive role. In a recent retrospective study on elderly (>60 years old) patients, a higher serum triiodothyronine-to-thyroxine (T3/T4) ratio was found to be associated to mucosal healing, regardless of the biological drug used [21]. C-reactive protein (CRP) levels haves been inconsistently associated with response to biological therapies. A correlation between higher CRP levels and better response to TNF antagonists has been reported in CD patients [22][23][24][25]; conversely, a negative correlation between CRP levels and response rates to TNF inhibitors has been observed in UC [26][27][28]. Similar findings have also been observed with vedolizumab, but not with ustekinumab [13]. However, such results have not been confirmed by many other studies. Higher CRP levels can help identify those patients whose symptoms are actually dependent on active IBD and, in CD, can help discriminate inflammatory vs. stricturing phenotypes; on the other hand, such high levels can also be expression of a higher inflammatory burden, that is comprehensively associated with poorer response to medical treatment. Faecal calprotectin has been tested as a potential predictor of response, with disappointing results. Of note, in a prospective observational study it has been found that lower post-induction calprotectin levels were able to predict sustained clinical response and mucosal healing in IBD patients receiving anti-TNF treatment [29].

Previous exposure to biologics has been associated with poorer response to subsequent lines of therapies. Reason for discontinuation seems to have an impact on the likelihood of responding to second-line therapies: a Spanish retrospective study and 2 meta-analysis concluded that discontinuation due to anti-TNF intolerance was associated with higher rates of response to both second anti-TNF or other biologic agents [11][30][31]. Primary non-response to TNF antagonists seems to correlate with an even lower likelihood of response to second-line therapies, when compared to secondary loss of response (LOR) [30]. A retrospective study on UC patients showed that, in case of primary failure, out-of-class swap seems to be superior to in-class switch with regard to rates of clinical response and remission [32]. However, such findings have not been consistently confirmed in literature.

3. Genetic Markers

More than 240 susceptibility loci for IBD have been identified so far [33]. Such genes have greatly contributed to the understanding of IBD pathogenesis and to the identification of novel therapeutic targets. However, genetic markers have usually performed quite poorly in predicting response to a specific drug [34]. In Table 1, there is an overview of the studies investigating the association between genetic markers and response to therapy.

Table 1. Genetic markers.

Study	Genetic Markers	Outcomes
Bek et al. 2016 [34]	*Polymorphisms in TLR2*, rs11938228, *TLR4*, *TLR9*, *TNFRSF1A*, *IFNG*, *IL6* and *IL1B* (rs4848306)	Clinical response to anti-TNF in IBD patients
Tong et al. 2013 [35]	Polymorphisms in TNF-α promoter (-308 A/G and -857 C/T)	Clinical response to anti-TNF in IBD e SpA patient
Bank et al. 2014 [36]	Polymorphisms implicated in NF-kB pathway: TLR2, TLR4, TLR9, LY96 (MD-2), CD14, MAP3K14 (NIK), TNFA, TNFRSF1A, TNFAIP3(A20), IL1B, IL1RN, IL6, IL17A, IFNG	Clinical response to anti-TNF in IBD patients
Jürgens et al. 2010 [37]	Polymorphisms in IL23R	Early response to infliximab in UC patients
Sazonovs et al. 2020 [38]	HLA-DQA1*05	Development of ADA against infliximab and adalimumab in CD patients
Billiet et al. 2015 [39]	HLA-DRB1	Development of ADA against infliximab in IBD patients
Louis et al. 2004 [40]	Polymorphism in IgG Fc receptor IIIa	Development of ADA against infliximab in CD patients
Niess et al. 2012 [41]	Polymorphisms in NOD2	Clinical response to anti-TNF in CD patients
Juanola et al. 2015 [42]	Polymorphisms in NOD2	Loss of response to anti-TNF in CD patients
Schäffler et	Polymorphisms in NOD2	Lower anti-TNF TLs in CD

Study	Genetic Markers	Outcomes
al. 2018 [43]		patients
Koder et al. 2015 [44]	Polymorphisms in ATG16L1	Clinical response to adalimumab in CD patients
Hlavaty et al. 2007 [45]	Polymorphisms in Fas, Fas ligand and Caspase 9 (Apoptotic Pharmacogenetic Index)	Clinical response to infliximab in CD patients
Barber et al. 2016 [46]	Multiple polymorphisms (Combined clinical-genetic model)	Short- and long-term to anti-TNF in CD patients
Burke et al. 2018 [47]	Multiple polymorphisms (Combined clinical-genetic model)	Short- and long-term response to anti-TNF in UC patients
Wang et al. 2019 [48]	Polymorphisms in *TNFSF4/18*, *PLIN2*, rs762787, rs9572250, rs144256942, rs523781	Clinical response to anti-TNF in IBD patients

leukocyte
se kinase
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sis factor;
ly; IFNG: interferon gamma.

Genome-wide association studies have reported that disease susceptibility loci do not seem to substantially contribute to anti-TNF non-response. For instance, polymorphisms in the genes encoding for TNF or molecules involved in the TNF receptor pathway have been inconsistently associated with treatment response. A 2013 meta-analysis reported an association between 2 polymorphisms in the TNF promoter and responsiveness to TNF inhibition in IBD patients: specifically, the more common alleles were associated with better response rates [35]. Another meta-analysis found a positive correlation between polymorphisms in *FCGR3A*, *TLR4*, *TNFRSF1A*, *IFNG*, *IL6*, *IL1B* genes and better clinical response, whereas variants of TLR2 and TLR9 were negatively correlated [34]. Polymorphism in the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFkB) pathway, TNF pathway and pathways of other cytokines have been linked to treatment response in IBD patients treated with anti-TNF agents [36][49]. IL23 receptor polymorphisms have been associated with response to infliximab in UC patients [37]. Moreover, the HLA-DQA1*05, the HLA-DRB1 allele and polymorphisms at the FCGR3A locus (encoding IgG Fc receptor IIIa) have been correlated with an increased risk of anti-drug antibodies (ADA) formation in CD patients treated with anti-TNF agents [38][39][40]. Being large complex proteins, monoclonal antibodies—especially infliximab, that is a chimeric antibody—can stimulate the production of ADA, which are associated with treatment inefficacy [50]. Identifying patients who are more likely to develop ADA would be of great help, as we know that concomitant immunosuppression (with thiopurines and methotrexate) reduces the risk of their formation [51].

Another marker previously identified by gene array studies in mucosal biopsies of IBD patients is the IL13 receptor alpha 2 (IL13RA2) [52]. This biomarker has been more recently evaluated as mRNA expression in the mucosa of IBD patients prior to therapy and found to be specifically predictive of non-response to anti-TNF in terms of mucosal healing at 6 months with an area under the receiver operating characteristic (AUROC)of 0.90 for infliximab and 0.94 for adalimumab, $p < 0.001$ [53].

The NOD2 gene is associated with CD susceptibility and with a more aggressive course of disease [54][55]; it encodes for a protein that plays a role in eliciting the immune response and is implicated in the inflammatory pathway of TNF. Some studies have found an association between NOD2 variants and worse response to anti-TNF therapy [41][42][43]. Polymorphisms in the ATG16L1 gene have been associated better response rates [44] and longer benefit [46] in CD patients treated with TNF antagonists. An apoptotic pharmacogenetic index (API) has been proposed to predict treatment response to anti-TNF in CD patients. The index was based on single nucleotide polymorphisms of 3 apoptotic genes (Fas, Fas-ligand and caspase-9). The authors elaborated a model, combining API with clinical features, that was able to predict response to infliximab in luminal and penetrating CD [45]. Predictive models combining clinical and genetic features have been shown to be superior to models based on clinical characteristics only for predicting primary non-response to anti-TNF agents in CD (Area Under the Receiver Operating Characteristics [AUROC] 0.93 vs. 0.70, $p < 0.0001$) [46], UC (AUROC 0.87 vs. 0.57, $p < 0.0001$) vs. [47] and IBD patients (AUROC 0.89 vs. 0.72, $p < 0.0001$) [48].

Data on genetic variants associated with response to anti-integrin is scarce. In the phase 2 trial of etrolizumab (anti-β7 integrin) in UC patients, αE gene expression was found to be predictive of clinical remission at week 10 [56]. This result was subsequently enhanced by the finding that also higher levels of Granzyme A (which is highly expressed by αE+ cells) mRNA in colonic biopsies taken at baseline could identify UC patients in clinical remission at week 10 of etrolizumab therapy [57]. No association between genetic markers and anti-IL12/23 response has been identified so far.

4. Other Markers: Transcriptomics, Proteomics and Immunological Markers

Transcriptomics studies have provided some more pleasing results, suggesting that therapy response seems to rely on differential expression of significant genes, more than on genetic variants.

A putative biomarker identified by transcriptomics studies is the triggering receptor expressed on myeloid cells 1 (TREM-1), although with some discordant findings: a study of gene expression described a down-regulation in whole blood of non-responders to anti-TNF. However, these patients showed an up-regulation of TREM-1 and of chemokine receptor type 2 (CCR2)–chemokine ligand 7 (CCL7) in intestinal biopsies. In the same study, plasma cell frequencies were examined in intestinal biopsies by CD138+ staining and were considered able to predict anti-TNF response, being higher in non-responders ($p = 0.0005$). [58] A different study analyzed the expression of TREM1 in whole blood and in mucosal tissue and as protein level in the serum and found a significant reduction in

IBD patients who achieved mucosal healing [59]. This pathway seems to be specific for anti-TNF response as no modifications was detected in patients treated with vedolizumab or ustekinumab.

Measures of TNF production have been studied as putative biomarkers of response to anti-TNF. In vivo imaging by endomicroscopy revealed higher numbers of mTNF+ cells in short-term (12 weeks) responders, after local fluorescent adalimumab administration [60]. A recent study analyzed in 42 IBD patients the in vitro production of TNF from peripheral blood mononuclear cells (PBMC) stimulated with lipopolysaccharide (LPS) and found it to be predictive of clinical response after 6 weeks of infliximab therapy. A cutoff of 500 pg/mL was identified in CD for short-term response with 100% sensitivity and 82% specificity [61].

High expression of a member of the IL6 family, oncostatin M (OSM), in the intestinal mucosa was found to predictive of refractoriness to anti-TNF therapy. The clinical response was assessed at week 8 and 30 in a cohort of patients treated with infliximab (from ACT1/2 studies) and at 6 weeks in a cohort of patients treated with golimumab (from the Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment−Subcutaneous, PURSUIT study) [62]. This biomarker was also studied at baseline in serum and found to be predictive of mucosal healing at 54 weeks of infliximab treatment with an AUC of 0.91 in a study on 45 CD patients [63].

Assays of α4β7 occupancy in peripheral blood T cells showed almost complete blocking of this integrin in patients after vedolizumab treatment, irrespective of clinical response and also of circulating drug levels [64]. However, in a small study, vedolizumab responders had higher pre-treatment α4β7 expression on T effector memory cells (p = 0.0009 for CD4 and.0043 for CD8) and on natural killer (NK) cells (p = 0.0047) [65]. These results were partly confirmed at the tissue level by a preliminary study with confocal endomicroscopy with fluorescein isothiocyanate (FITC) labelled vedolizumab, where only CD patients were responders to subsequent therapy with the anti-integrin showed α4β7+ cells in the mucosa [66]. A study examined the in vitro assay of baseline peripheral blood CD4+ cells dynamic adhesion to recombinant MAdCAM-1 and the decrease of this effect by vedolizumab: these parameters have been suggested as predictors of clinical response at 15 weeks in a study on 21 UC patients [67]. Another small study explored serum markers of response in anti-TNF refractory patients, before starting vedolizumab. They found higher levels of IL6 in IBD patients who were subsequently non-responder, of sCD40L in CD non-responder patients and higher osteocalcin levels in UC responders [68]. More recently serum IL6 and IL8 measured at baseline and at week 10 of vedolizumab treatment were suggested as early markers of clinical response at 12 months [69]. The prognostic value of serum biomarkers measured at baseline and at early intervals during vedolizumab therapy was also explored in two studies. In UC, an increase of s-α4β7 an a decrease of s-MAdCAM-1, s-VCAM-1, s-ICAM-1, and s-TNF were found in clinical and endoscopic remitters at 26 weeks [70]. In CD patients, higher early serum levels of s-ICAM-1 and s-VCAM-1 and lower values of s-α4β7 were found in endoscopic remitters [71].

Limited data of transcriptomic and immunologic predictive biomarkers of response to IL23 inhibition are available. IL22 exerts a role of positive regulation on IL23 signalling. In the phase 2a trial of brazikumab (anti-IL 23) in CD

patients, higher concentration of IL22 at baseline had an association with increased likelihood of response, even though the association did not test statistically significant [72].

Results from transcriptomic and immunologic studies are resumed in Table 2.

Table 2. Immunological markers.

Study	Immunological Markers	Outcomes
Gaujoux et al. 2019 [58]	Higher expression of TREM-1 and CCR2-CCL7 in intestinal biopsies	Nonresponse to anti-TNF treatment
Verstockt et al. 2019 [53]	Lower expression of TREM-1 in whole blood and intestinal biopsies, lower concentration in serum	Mucosal healing in patients treated with anti-TNF
Atreya et al. 2014 [60]	Higher number of mTNF+ cells in intestinal biopsies	Short term (12 weeks) response to adalimumab
Jessen et al. 2020 [61]	TNF production > 500 pg/mL by PBMC stimulated with LPS	Clinical response to infliximab at week 6
West et al. 2017 [62]	Higher expression of OSM in intestinal biopsies	Refractoriness to infliximab (at weeks 8 and 30) and golimumab (at week 6)
Bertani et al. 2020 [63]	Lower serum concentration of OSM	Mucosal healing at week 54 in infliximab-treated patients
Boden et al. 2018 [65]	Higher expression of α4β7 on T effector memory cells and NK cells	Response to vedolizumab
Rath et al. 2017 [66]	Presence of α4β7+ cells in intestinal mucosa	Response to anti-integrin therapy

Study	Immunological Markers	Outcomes
Allner et al. 2020 [67]	Higher dynamic adhesion of peripheral blood $CD4^+$ T cells to MAdCAM-1 and more pronounced reduction of adhesion following treatment	Clinical response to vedolizumab in UC patients
Soendergaard et al. 2020 [68]	Higher serum IL6	Nonresponse to vedolizumab in IBD patients
	Higher serum CD40L	Nonresponse to vedolizumab in CD patients
	Higher serum osteocalcin	Response to vedolizumab in UC patients
Bertani et al. 2020 [69]	Higher serum IL6 and IL8, more pronounced decrease of IL6 after 10 weeks	Clinical response to vedolizumab after 12 months
Battat et al. 2019 [70]	Increase of serum α4β7 and decrease of serum MAdCAM-1, VCAM-1, ICAM-1 and TNF	Clinical and endoscopic remission ate week 26 in vedolizumab-treated patients
Holmer et al. 2020 [71]	Higher serum VCAM-1 and ICAM-1 and lower serum α4β7	Endoscopic remission in vedolizumab-treated patients
Sands et al. 2017 [72]	Higher serum IL22	Clinical response to brazikumab

TREM-1: triggering receptor expressed on myeloid cells 1; CCR2-CCL7: chemokine receptor type 2–chemokine ligand 7; TNF: tumor necrosis factor; mTNF: membrane tumor necrosis factor; PBMC: peripheral blood mononuclear cells; LPS: lipopolysaccharide; OSM: oncostatin M; NK cells: natural killer cells; IL: interleukin; CD40L: ligand of cluster of differentiation 40; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1; VCAM-1: vascular cell adhesion molecule 1; ICAM-1: intercellular adhesion molecule 1.

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