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Review Article

Review Article

Predictors of Primary Response to Biologic Treatment [Anti-TNF, Vedolizumab, and Ustekinumab] in Patients With Inflammatory Bowel Disease: From Basic Science to Clinical Practice

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Abstract

Background: Inflammatory bowel diseases [IBD]–ulcerative colitis and Crohn's disease–are commonly treated with biologic drugs. However, only approximately two-thirds of patients have an initial response to these therapies. Personalised medicine has the potential to optimise efficacy, decrease the risk of adverse drug events, and reduce costs by establishing the most suitable therapy for a selected patient.

Aim: The present study reviews the potential predictors of short-term primary response to biologic treatment, including not only anti-tumour necrosis factor [TNF] agents [such as infliximab, adalimumab, certolizumab, and golimumab] but also vedolizumab and ustekinumab.

Methods: We performed a systematic bibliographical search to identify studies investigating predictive factors of response to biologic therapy.

Results: For anti-TNF agents, most of the evaluated factors have not demonstrated usefulness, and many others are still controversial. Thus, only a few factors may have a potential role in the prediction of the response, including disease behaviour/phenotype, disease severity, C-reactive protein, albumin, cytokine expression in serum, previous anti-TNF therapy, some proteomic markers, and some colorectal mucosa markers. For vedolizumab, the availability of useful predictive markers seems to be even lower, with only some factors showing a limited value, such as the expression of $\alpha 4\beta 7$ integrin in blood, the faecal microbiota, some proteomic markers, and some colorectal mucosa markers. Finally, in the case of ustekinumab, no predictive factor has been reported yet to be helpful in clinical practice.

Conclusion: In summary, currently no single marker fulfils all criteria for being an appropriate prognostic indicator of response to any biologic treatment in IBD.

Key Words: Adalimumab; anti-TNF; biologics; Crohn's disease; certolizumab; golimumab; inflammatory bowel disease; infliximab; predictive; response; ulcerative colitis; ustekinumab; vedolizumab

1. Introduction

Inflammatory bowel diseases [IBD]—ulcerative colitis [UC] and Crohn's disease [CD]—are chronic idiopathic inflammatory diseases affecting the gastrointestinal tract. The use of anti-tumour necrosis factor [anti-TNF] agents has revolutionised the treatment of IBD. Their use avoids the need for steroid therapy, promotes mucosal healing, reduces hospitalisations and surgeries, and therefore dramatically improves the quality of life of IBD patients.[1] However, only approximately two-thirds of the IBD patients treated with anti-TNF drugs have an initial response to therapy.[2]

For many years, anti-TNF agents were the only type of biologics used for IBD treatment. However, two new biologic drugs that target different inflammatory pathways have been approved for IBD in recent years: vedolizumab[3] and ustekinumab.[4] However, similar to anti-TNF agents, a significant number of patients do not respond to these drugs and their place relative to anti-TNF therapy [before or after] remains unclear.

Since the aforementioned biologic medications do not work in everyone, are associated with rare but serious side effects, and have a high cost, it would be important to selectively treat patients who have the highest chance of responding. Until now, the strategy for testing these biologics in clinical settings used to be 'one drug suits all', although they may be beneficial in only a subset of patients characterised by a specific target.[5–9] Recent evidence suggests that the mechanisms underlying primary non-response are multifactorial and include disease characteristics, drug, and treatment strategy-related factors. Personalised medicine is a relatively new concept that has the potential to optimise efficacy, decrease the risk of adverse drug events, and reduce costs by establishing the most suitable therapy for a selected patient.[10] In other words, personalised medicine refers, precisely, to a medical model using characterisation of an individual's phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time.[11]

The present review will summarise the current data on predictors of short-term primary response to biologic treatment in IBD patients, including not only anti-TNF agents [such as infliximab, adalimumab, certolizumab, and golimumab] but also more recently approved biologics such as vedolizumab and ustekinumab.

A systematic bibliographical search was designed to identify studies reporting on predictive factors of response to biologic therapy in patients with IBD. An electronic search was performed in PubMed up to January 2019 using the following algorithm: ['inflammatory bowel disease' OR 'ulcerative colitis' OR 'Crohn's disease'] AND [predictor OR predictors OR predictive OR prediction] AND [response OR remission] AND [infliximab OR adalimumab OR certolizumab OR golimumab OR anti-TNF OR antiTNF OR vedolizumab OR ustekinumab OR biologic]. With this search strategy, 494 citations were identified. In addition, the reference lists from the selected articles were reviewed to identify additional studies of potential interest.

Only studies conducted in humans were included and animal models were excluded. Available data from both clinical trials and 'real life' studies were included. In general, primary non-response to treatment is best assessed after at least three infusions or injections of anti-TNF medication.[12] In clinical practice, primary non-response to anti-TNF agents should not be assessed before Weeks 8–12, as successful induction of remission may still be achieved after three infliximab infusions at Weeks 0, 2, and 6[12]. Therefore, the short-term response [or non-response] in the included studies had to be assessed after an induction period [generally within approximately 12–14 weeks, but up to 16 weeks]. Pharmacokinetic studies [e.g., therapeutic drug monitoring] were excluded. Studies evaluating the response in patients with postoperative recurrence of CD were also excluded. Finally, predictive markers had to be measured at the time the biologic treatment was initiated [i.e., at baseline], and therefore changes between biomarkers before and after therapy were not considered. Articles published in any language were included.

2. Predictors of Primary Response to Anti-TNF Treatment

We have schematically divided the predictive factors of efficacy for anti-TNF agents in IBD patients into three groups: i] patient-related factors; ii] disease-related factors; and iii] immune-epithelial biomarkers.

Potential predictors of favourable response to biologic agents [anti-TNF, vedolizumab, and ustekinumab] in CD and UC are included in Tables 1 and 2, respectively, and the most relevant information of each study evaluating predictors of response to these agents [such as drug treatment, IBD type, number of patients, study design, predictors considered and predictors of response] is summarised in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online.

2.1. Patient-related factors

2.1.1. Age and gender

In CD, younger age has been associated with better response to anti-TNF treatment in some studies, mainly including infliximab.[13,14] However, many other studies were not able to find any relationship between age and response to infliximab,[15–21] adalimumab,[19,21–23] or certolizumab.[19,24,25] Furthermore, some studies have reached opposite conclusions, showing that older age is associated with a higher probability of response.[26] Similarly in UC patients, controversial results have also been reported, with studies showing an association between younger age,[27] older age[28,29] or, most frequently, no relation at all.[30–42]

Several studies have evaluated the association between gender and the response of CD patients to anti-TNF agents, and most of them have not found any relationship, either with infliximab,[14,15,18,21] adalimumab,[21–23] or certolizumab.[24] One single study has suggested a better response in male CD patients.[20] Similarly in UC patients, no association has been reported, in general, between gender and response to infliximab,[29–37] adalimumab,[38] or golimumab,[41,42] although there are some exceptions suggesting a more favourable response in females.[39,40,43] In summary, the age or the gender of the IBD patient when anti-TNF therapy is administered cannot be used as a reliable marker to predict the response to these drugs.

2.1.2. Weight

Observational studies in various rheumatic diseases have shown a negative impact of obesity on response to therapy, including both anti-TNF agents that are dosed based on body weight [infliximab] as well as fixed-dosing regimens [adalimumab, golimumab, certolizumab, or etanercept].[44] This may be attributed to low systemic drug exposure resulting in low trough concentrations in obese individuals [as has been observed in population pharmacokinetic studies], or may be attributed to obesity-induced low-grade inflammation, which can lead to higher systemic inflammatory burden.[44]

However, these results have been inconsistent in patients with IBD. In CD, some studies have found a higher response rate in

Table 1. Predictors of favourable response to biologic agents in Crohn's disease.

Parameter	Infliximab	Adalimumab	Certolizumab	Golimumab	Vedolizumab	Ustekinumab
Age	Yes: - Younger: [13,14] - Older: [26] No: [15–21]	Yes: - Older: [26] No: [19,21–23]	No: [19,24,25]		No: [80,169–174]	Yes: - Younger: [184] No: [81,185–188]
Gender	Yes: - Male: [20] No: [14,15,18,21]	No: [21–23]	No: [24]		No: [80,90,169–174]	Yes: - Female: [184] No: [81,185–188]
Weight	Yes: - Low: [20,45] - High: [14]	Yes: Low: [45]				Yes: - Low: [189] No: [186,187]
Smoking [no]	Yes: [49–52] No: [13–21,26,50,54–56]	Yes: [52,53] No: [19,21,22,26]	No: [19]		Yes: [80] No: [90,169,170,172–174]	No: [81,185,186]
Disease duration [short]	Yes: [21,60–63] No: [13–16,18–20,49,50,69]	Yes: [21,64,65] No: [19,22,23]	Yes: [66–68] No: [19,24]		No: [80,90,169–174]	Yes: [184] No: [81,185–188]
Disease location/extension [colon]	Yes: [13,20,50,68] No: [14,17,18,21,26,49,69]	No: [21,22,26,72]	No: [24]		Yes: [171] No: [80,169,170,172–174]	Yes: [184] No: [186,188,189]
Disease behaviour [inflammatory]	Yes: [13,15,26,52] No: [14,17,26,49]	Yes: [26,52,53,72]			No: [80,90,169,172–174]	Yes: No: [185–188]
Disease severity [less severe]		No: [23]	Yes: [25,65]		Yes: [80,169,174] No: [90,170,172]	No: [189] [better response if more severe]
Extraintestinal manifestations	No: [14]				No: [80,169,170]	
Previous surgery [no]	Yes: [13,14,17] No: [15,18,21,26,50,80,81]	Yes: [23] No: [21,22,26]		Yes: [25]	Yes: [174] No: [90,170,171]	Yes: [186] No: [188]
CRP [high]	Yes: [71,72,84–91] No: [15,93 14,20,21,193]	Yes: [64,72] No: [21,23]	Yes: [67,92] No: [24]		Yes: [90] No: [169,174] [better response if low levels]	No: [81,186,187]
Haemoglobin [high]	No: [20]	No: [23]			No: [170,174]	
Leukocyte count [high]		No: [23]			No: [169]	
Platelet count [high]	Yes: [95]	No: [23]				
pANCA-/ASCA+	No: [50,100]					
cANCA+	Yes: [111]					
TNF levels [low]	Yes: [145] No: [84,91,146]					
Faecal calprotectin	Yes: - Low: [102] - High: [103]				No: [170] [better response if low levels]	
Vitamin D levels [low]	Yes: [194]					
Peripheral regulatory T cells	Yes: [195]					
Genetic polymorphisms	Yes: [19,111–125] No: [13,84,127–136]	Yes: [19,118,123,126] No: [137]	Yes: [19]			
FcγRIIIa genotype	Yes: [140]					
Apoptosis genes [Fas ligand–843CC/CT, caspase-9 93 TT]	Yes: [55,139]					
Concomitant steroids [yes]	Yes: [50,145] No: [15,84,196]				Yes: [169] No: [80,172]	No: [81,185,188]
Previous anti-TNF [no response]	Yes: [141]	Yes: [23]			Yes: [80,175,176] No: [90,170,172–174]	Yes: [184,188] No: [185,186]
Expression of α4β7 in blood [T, B, and NK cells]					Yes: [179]	
Proteomics	Yes: [150–152,197]				Yes: [180]	
Cytokines expression in colonic mucosa	Yes: [148,165]			Yes: [148]		
TNF in the intestinal mucosa	Yes: [162] [high]					
Intestinal mTNF[+] immune cells [molecular imaging with fluorescent antibodies]	Yes: [161]					
Plasma cells and inflammatory macrophages in colonic mucosa	Yes: [168]					
CD19+ cells in colonic mucosa	Yes: [159]					
Faecal microbiota					Yes: [178]	

TNF, tumour necrosis factor; CRP, C-reactive protein; pANCA, perinuclear antineutrophil cytoplasmic antibody; ASCA, anti-*Saccharomyces cerevisiae* antibody; sANCA, speckled antineutrophil cytoplasmic antibody.

Table 2. Predictors of favourable response to biologic agents in ulcerative colitis.

Parameter	Infliximab	Adalimumab	Certolizumab	Golimumab	Vedolizumab
Age	Yes: - Younger: [27] - Older: [28,29] No: [30–37]	No: [38–40]		No: [41,42]	No: [80,169–173]
Gender	Yes: - Female: [43] No: [30–32 29,33–37]	Yes: -Female: [39,40] No: [38]		No: [41,42]	No: [80,90,169–173]
Weight	Yes: - Low: [45] No: [31]	Yes: - Low: [45,47]			
Smoking [no]	Yes: [37] [active smokers and never smokers [vs ex-smokers] No: [27,29–36]	Yes: [39,40] No: [38]			Yes: [80] No: [90,169,170,172,173]
Disease duration	Yes: - Shorter: [36] - Longer: [71] No: [28,30,32v]	No: [38,40]		Yes: [41] [shorter] No: [42]	No: [80,90,169–173]
Disease location/extension [pancolitis]	Yes: [32] [more extensive disease] No: [30,31,33–36]	Yes: [47] [less extensive disease] No: [40]		No: [42]	No: [80,169,170,172,173]
Disease severity [less severe]	Yes: [33,37,77,78] No: [28,29,31,33,34,36,71,79]	Yes: [40,47,78]		Yes: [97]	Yes: [80,169,172] No: [90,170,173]
Extraintestinal manifestations					No: [80,170]
CRP [low]	Yes: [27,29] No: [32,34,35,37]	Yes: [47] No: [38,39][high][40]			Yes: [90,169]
Haemoglobin [high]	Yes: [33,35,89]				No: [170]
Albumin [high]	Yes: [29,35,37,78,96] No: [14,36,91]	Yes: [78]	Yes: [97]		
pANCA-/ASCA+	Yes: [79,91,99]				
TNF levels [low]	No: [14,146]				
Cytokines expression in serum	Yes: [34,147–149]			Yes: [148]	
Faecal calprotectin [high]	Yes: [36] No: [34,35,104]				No: [170]
Genetic polymorphisms	Yes: [118,120,125]	Yes: [118]			
Cultured blood T cell responses	Yes: [198,199]	Yes: [198]		Yes: [198]	
Concomitant steroids [yes]	No: [33–35]	No: [38]			No: [80,169,172]
Previous anti-TNF [no response]	Yes: [141]	Yes: [40]		Yes: [41,42] [2 or more]	Yes: [80,176,177] No: [90,170,172,173]
Proteomics	Yes: [152,197]				Yes: [180]
TNF in colorectal mucosa	Yes: [160,200]				
Gene expression in colorectal mucosa	Yes: [156,157,160,163,164]			Yes: [167]	
Cytokines expression in colonic mucosa	Yes: [34]				
Plasma cells and inflammatory macrophages in colonic mucosa	Yes: [168]				
Mucosal expression of transcription factor Th1-Tbet and Th17-Rorc	Yes: [166]				

CRP: C-reactive protein; TNF, tumour necrosis factor; pANCA perinuclear antineutrophil cytoplasmic antibody; ASCA, anti-*Saccharomyces cerevisiae* antibody; sANCA, speckled antineutrophil cytoplasmic antibody .

patients with lower weight treated with either infliximab[20,45] or adalimumab,[45,46] whereas others have reached opposite results [that is, better results in patients with a higher weight].[14] Similarly, controversial results have also been reported for UC patients [better response in lower weight[45,47] in some studies, and no association in others[31]]. Nevertheless, the lack of an association between body mass index [BMI] and response to infliximab in particular might simply reflect the weight-based dosing of infliximab [i.e., higher in heavier patients].

Recently, Singh *et al.* assessed whether obesity may affect response to infliximab, conducting an individual participant data pooled analysis using data from four clinical trials of infliximab in IBD [ACCENT-I, SONIC, ACT-1, and ACT-2, including 1205 patients], using the Yale Open Data Access [YODA] Project.[44] Obesity was not associated with odds of achieving clinical remission. These results were consistent across strata based on disease type [CD and UC] and trial design [induction and maintenance therapy]. Therefore the authors concluded that, based on individual participant data

pooled analysis, obesity is not associated with inferior response to infliximab in patients with IBD.

In summary, obesity [or low weight] does not seem to have a clear impact on response to anti-TNF therapy, although more studies evaluating this potential association specifically for each anti-TNF agent [infliximab, adalimumab, etc.] are required to definitively clarify this issue.

2.1.3. Smoking

Smoking is known to negatively influence disease course in CD patients.[48] Smokers with CD have a more complicated disease course than non-smokers, and quitting smoking may ameliorate this.[48] However, although some studies have suggested that CD non-smokers tend to respond better to anti-TNF therapy, either with infliximab[49–52] or with adalimumab,[52,53] most of the studies have not been able to find any relationship between smoking habit and treatment efficacy.[13–22,26,50,54–56]

Two meta-analyses have evaluated the role of smoking habit in treatment response of CD patients. The first, published in 2009, found no effect of tobacco smoking on the efficacy of infliximab in CD patients.[57] A second meta-analysis, published in 2015, also concluded that the relative risk of non-response was not significantly different in smokers.[58] However, the studies included in this last meta-analysis were all conducted to assess induction, not maintenance. Finally, it should be noted that studies examining the epidemiology of smoking and CD have used various definitions of smoking, in terms of both the number of cigarettes per day and the length of time the individual has smoked, which constitutes an additional limitation of the aforementioned meta-analyses.

In UC patients, the influence of smoking habit on anti-TNF treatment response has also been controversial, most studies reporting no relationship[27,29–36,38] and only a few studies suggesting a negative effect of smoking.[37,39,40]

In summary, although smoking is known to have an indisputable negative effect on the course of CD as well as other organ systems, its impact on the efficacy of anti-TNF therapy for CD has not been confirmed. Therefore, although it is reasonable to aggressively discourage smoking, it should not influence the decision to initiate anti-TNF treatment.

2.2. Disease-related factors

2.2.1. Disease duration

Disease duration has been evaluated with the hypothesis that patients with shorter disease duration will have a better response to early treatment.[59] This was demonstrated in post-hoc analyses from large clinical trials where patients with a disease duration shorter than 2 years had a higher chance of responding to anti-TNFs than those with more long-standing disease.[59] Thus, some studies have confirmed that CD patients with a shorter disease duration tend to respond better to anti-TNF treatment, either with infliximab,[21,60–63] adalimumab,[21,64,65] or certolizumab.[66–68] However, many other authors could not confirm this association in patients treated with anti-TNF agents [infliximab,[13–16,18–20,49,50,69] adalimumab,[19,22,23] or certolizumab[19,24]].

Intuitively though, treating patients earlier, when inflammatory disease predominates over fibrosis, is appealing.[70] On the other hand, worse response to treatment in patients with longer disease duration may be due to several factors, including a selection bias of patients with more severe disease and also a greater proportion of advanced fibrosing organ damage. In rheumatoid arthritis, there is already considerable support for the use of anti-TNF in early disease to modify favourably the disease course.

In UC patients, however, this correlation between shorter disease duration and a better response to anti-TNF treatment has not been shown. In fact, some studies have suggested that patients with longer disease duration tend to respond better to anti-TNF agents,[71] but others reported opposite results[36,41] or, most frequently, no association at all.[28,30,32–35,37,38,40,42]

In summary, those patients with a shorter CD duration may have a higher chance of responding to anti-TNF agents than those with more long-standing disease. However, this association has not been consistently reported, so more studies are necessary to confirm it.

2.2.2. Disease location/extension

Some studies have suggested that CD patients with isolated colonic disease tend to have a better response to anti-TNF treatment [specifically to infliximab], whereas isolated ileitis has been associated with poor response.[13,20,50,68] This observation could be explained by the fact that localised ileal stricturing disease may be associated with primary non-response to anti-TNF agents [see next section], but data have been conflicting. In fact, many other studies have been unable to find any association between disease location and probability of therapeutic response to infliximab,[14,17,18,21,26,49,69] adalimumab,[21,22,26,72] or certolizumab.[24] Moreover, in UC patients, disease location/extension has not been associated in general with anti-TNF response,[30,31,33–36,40] although some exceptions exist [better[32] or poorer[47] response in more extensive disease]. In summary, there does not seem to be a consistent pattern of response related to the disease location or extension, either in CD or in UC patients.

2.2.3. Disease behaviour/phenotype

Disease phenotype of CD patients, as defined by the Montreal classification, may potentially be associated with anti-TNF treatment response. In general, patients with a simple inflammatory disease behaviour should be expected to have more benefit from anti-TNF-therapy than patients with a complicating [stenosing or fistulising] phenotype,[13,15,26,52,53,72] although not all the studies are in agreement.[14,17,26,49] In particular, fibrostenotic disease may have lower response rates and may be more suitable for surgical resection or endoscopic dilatation therapy. However, some patients with a stricturing phenotype may still respond well, especially when an inflammatory component is also present.[73] In summary, luminal inflammatory CD seems to be associated with a better response to anti-TNF treatment, whereas a stricturing phenotype has been associated with reduced response.

2.2.4. Disease severity

In CD, only a few studies have assessed the influence of disease severity on probability of response to anti-TNF therapies, with controversial results [better response in less severe CD,[25,65] or no association[23]]. In CD, the lack of a clear agreement on disease severity definition is more evident [compared with UC] with a consequently less defined scenario. On the other hand, anti-TNF therapies have shown lower efficacy [and higher risk of colectomy] in more severe UC patients due, possibly, to a greater drug clearance and loss of drug in the stools.[74–76] Faecal loss of anti-TNF into the stool via the ulcerated, denuded mucosa has been hypothesised as the mechanism for primary non-response in patients with very high inflammatory disease burden. Reduced UC severity has been associated with higher response rates,[33,37,40,47,77,78] although not all authors have confirmed

this observation.[28,29,31,33,34,36,71,79] It has been suggested that, from the purely clinical standpoint, the best candidate for anti-TNF administration may be an outpatient with moderate to severe UC but not severe disease requiring hospitalisation, although this hypothesis has not been validated. In summary, some studies appear to support the notion that severe UC shows a less favourable response to treatment with anti-TNF, although this association needs to be confirmed in future studies.

2.2.5. Previous surgery

Some studies in CD patients have reported that a history of previous resectional surgery is a negative predictive factor of response to anti-TNF treatment.[13,14,17,23] It may be speculated that this group of patients might correspond to those that are prone to stricturing and may represent a more aggressive disease phenotype and therefore a more refractory disease. Nevertheless, most of the studies have not been able to find an association between previous surgery and anti-TNF response.[15,18,21,22,26,50,80,81] In summary, the influence of a history of previous surgery on anti-TNF therapy has not been clearly demonstrated.

2.2.6. C-reactive protein

Among the various laboratory biomarkers of inflammation, C-reactive protein [CRP] has been the most extensively applied to clinical practice.[82] However, it is unclear whether pre-treatment CRP, *per se*, is predictive of response to anti-TNF therapy. Thus, whether an elevated CRP is truly predictive of response to anti-TNF or simply a marker that symptoms are due to active inflammatory disease remains to be proven.[83] Many studies have confirmed an association between elevated CRP and response to anti-TNF treatment in CD, including infliximab,[71,72,84–91] adalimumab,[64,72] and certolizumab.[67,92] On the contrary, in UC patients, several studies have confirmed an association between low CRP levels and a better response to anti-TNF treatment, including infliximab[27,29] and adalimumab.[47] Moreover, several authors could not find any association between CRP levels and response to anti-TNF treatment either in CD[14,15,20,21,23,24,93] or in UC.[32,34,35,37,38,40] These discrepancies may be due to the fact that CRP is associated with an inflammatory phenotype, but also with more severe disease. Thus, it has been suggested that an elevated baseline CRP may be a double-edged sword. Whereas a high baseline CRP weeds out some patients with non-inflammatory functional symptoms and predicts higher overall response, it may also reflect a higher inflammatory load, contributing to faster drug elimination, leading to a decreased response in some patients with elevated CRP.[94] In summary, although in general there seems to be an association between elevated CRP and response to anti-TNF treatment in CD, these drugs should not be restricted to patients with an elevated CRP, as almost 50% of those with a normal value respond.[84] In this respect, it is well established that the sensitivity of CRP is limited in CD, as almost 30% of patients have a normal level despite clinically active disease.[94]

2.2.7. Blood count parameters

Some studies have reported a correlation between higher haemoglobin levels and response of UC to anti-TNF treatment,[33,35,89] whereas others could not confirm this finding in CD.[20,23] Only one study has evaluated the possible association between leukocyte count and response to anti-TNF treatment [adalimumab in CD], and no correlation was found.[23] Finally, only two studies have evaluated the possible association between platelet count and the probability to respond to anti-TNF agents, with controversial results.[23,95]

2.2.8. Albumin

The association between albumin levels and response to anti-TNF treatment in CD patients has not been properly evaluated. However, this association has been assessed by several studies in UC patients. In patients with acute severe UC, infliximab levels were significantly lower in comparison with moderate UC during the induction phase, and were significantly correlated with albumin levels.[94] Thus, several studies have reported higher response rates in UC patients with higher albumin levels, treated with either infliximab,[29,35,37,78,96] adalimumab,[78] or certolizumab.[97] Nevertheless, other studies [although a minority] could not confirm this association.[14,36,91] In summary, low serum albumin levels have been consistently associated with diminished response to anti-TNF treatment. This relationship was also reflected by the lower infliximab serum levels in hypoalbuminaemic patients, and is probably explained by the common mechanism responsible for protection from catabolism of both albumin and monoclonal antibodies [which belong to the IgG class of immunoglobulins], namely the neonatal Fc receptor [FcRn].[75,94,96]

2.2.9. Perinuclear anti-neutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies

Perinuclear anti-neutrophil cytoplasmic antibodies [pANCA] and anti-*Saccharomyces cerevisiae* antibodies [ASCA] are serological markers that have been associated with UC and CD, respectively.[98] Most recently, these antibodies have been studied as predictors of response to anti-TNFs. Some studies have suggested that positivity of pANCA could predict response to infliximab in UC patients,[79,91,99] but others could not confirm this in CD patients.[50,100] A meta-analysis determined that pANCA-positive patients had almost a 2-fold lower response compared with pANCA-negative patients[101]; however, the results were not impressive: serological testing for pANCA+ predicting non-response to infliximab therapy showed a sensitivity of 25%, a specificity of 85%, a positive predictive value of 41%, and a negative predictive value of 74%. In summary, despite data supporting their value in predicting response to anti-TNF therapy, pANCA and ASCA have not been used widely as they are not sufficiently predictive of response when analysed in isolation.[98] These serological markers may be of greater utility when applied as part of a predictive model with clinical and other predictive factors.[83]

2.2.10. Faecal markers

Faecal calprotectin and lactoferrin are surrogate markers of luminal disease activity, which have been suggested to predict clinical response to anti-TNF therapy[83] [see above], and this capacity has been demonstrated in a few studies, both in CD[102,103] and in UC[36] patients. However, in some studies a higher calprotectin level was predictive of a better response,[103] whereas in others the association was inverse.[102] Furthermore, there are also studies that have not been able to confirm any of the aforementioned associations.[34,35,104] In summary, it seems that the levels of faecal calprotectin are not useful in predicting the response of a particular patient to anti-TNF therapy. Finally, it has been reported that metabolic network reconstruction and assessment of metabolic profiles of faecal samples might be used to identify patients with IBD likely to achieve clinical remission following anti-TNF therapy.[105]

2.2.11. Genetic polymorphisms

Pharmacogenetic studies may help identify patients likely to benefit from a given treatment and also the pathways by which a drug works. Furthermore, the identification of genetic profiles characterising the non-responders may lead to understanding of the mechanisms that are active in these patients and may suggest targets for treatment strategies.[6] Genetic biomarkers have the advantage that they do not change over time. Most studies have investigated genes related to cytokines and their receptors [especially TNF] or immunoglobulin receptors.

Genome-wide association studies [GWAS] have already indicated that it is unlikely that there are genetic variants with large effect sizes on the composite disease-response scores routinely measured in clinical practice.[106] However, certain genetic polymorphisms have been proposed to predict the probability of response to anti-TNFs in IBD.[70,107–109] A connection has been observed between some genes described as possible predictors of response to anti-TNF drugs in IBD and the cytokines and molecules involved in the T helper 17 pathway.[110] In particular, several studies have found an association between several polymorphisms and the response to infliximab, both in CD[19,111–125] and in UC.[118,120,125] This association has also been reported in patients treated with adalimumab[19,118,123,126] or certolizumab.[19] However, many other studies have concluded that different polymorphisms are not able to predict the efficacy of anti-TNF treatment.[13,84,127–137] Importantly, none of the described genetic factors could be reproduced in a large and well-designed study, and currently no specific polymorphism or gene is a reliable marker for prediction of response to biologics.[94,106]

A meta-analysis performed in 2013 explored whether TNFα promoter -308 A/G and -857 C/T polymorphisms have an association with responsiveness to anti-TNF agents in IBD.[138] In total, 392 IBD patients were included. The results showed that the common allele [G and C, respectively] showed a better responsiveness than the minor allele [A and T, respectively]. More recently, another systematic review and meta-analysis aimed to identify polymorphisms and candidate genes from the literature which are associated with anti-TNF treatment response in patients with IBD, considering available studies including at least 100 IBD patients.[6] Polymorphisms in *FCGR3A* [rs396991], *TLR4* [rs5030728], *TNFRSF1A* [rs4149570], *IFNG* [rs2430561], *IL6* [rs10499563], and *IL1B* [rs4848306] genes were significantly associated with improved response, whereas *TLR2* [rs3804099] and *TLR9* [rs352139] variants were associated with reduced response.[6]

Finally, induction of apoptosis is a key mechanism by which infliximab and adalimumab exert their anti-inflammatory effects, suggesting that apoptosis-related genes may also influence response to therapy. Hlavaty *et al*. developed and studied an apoptotic pharmacogenetic index in a small retrospective study using three single nucleotide polymorphisms [SNPs]: Fas ligand-843 C/T, Fas-670 G/A, and Caspase9 93 C/T. They found that higher apoptotic pharmacogenetic index score correlated with better response rates to anti-TNFs.[55,139] Other authors have found an association between FcγRIIIa genotype and response to infliximab.[140]

In summary, emerging GWAS suggest that there may be a number of genes with modest effects on treatment response, rather than a few genes with large effect.[106] Many genes have been explored, and despite some polymorphisms emerging with a great potential, particularly in members of the TNF family, the overall results are poor and no good predictive biomarkers for anti-TNF response adequate for use in the clinic have been established.[6,109] Therefore, hypothesis-free approaches, testing a large number of polymorphisms in large, well-characterised cohorts, are required in order to identify genetic profiles with larger effect sizes, which could be employed as biomarkers for treatment selection in clinical settings.[6]

2.2.12. Previous anti-TNF therapy

Some studies have shown that in IBD patients, previous anti-TNF therapy is a risk factor for treatment failure with another anti-TNF agent, including either infliximab,[141] adalimumab,[23,40,41,42] or golimumab.[41,42] A systematic review and meta-analysis concluded that the efficacy of a second anti-TNF in CD patients largely depends on the cause for switching[142]: the remission rate is higher when the reason to withdraw the first anti-TNF is intolerance [61%] compared with secondary [45%] or primary failure [30%].[142] More information regarding switching to a second anti-TNF agent, after a first one fails, comes from a review of 15 studies [including only two randomised controlled trials] which identified patients who had discontinued infliximab [most of them because of loss of response or intolerance to infliximab] and switched to adalimumab.[143] Remission rates were highly variable across the different studies, with short-term rates between 41% and 83%. Finally, a more recent review also evaluated the efficacy of adalimumab in CD patients for whom infliximab had failed, including 10 studies [one randomised controlled trial][144] where disease remission rates ranged from 5% to 67% during induction therapy.

2.3. Immune-epithelial biomarkers

In a small study, patients who did not respond to infliximab had higher baseline TNF levels.[145] However, a larger study of 226 patients did not find a relationship between treatment response and TNF levels,[84] and these results have been confirmed in two additional more recent studies.[91,146]

Some authors have reported an association between the severity of pro-inflammatory cytokine profile in serum and the response of UC patients to infliximab or golimumab.[147–149]

Up to now, only a few studies have evaluated the role of serum proteomics in the prediction of response to treatment in IBD patients.[150,151] Initially, in 2008, Meuwis *et al*. evaluated 20 CD patients receiving infliximab, and assessed their serum proteomic profiling on Surface Enhanced Laser Desorption Ionization-Time of Flight-Mass Spectrometry [SELDI-TOF-MS].[150] This pioneer proteomic pilot study suggested an association between platelet metabolism and response to infliximab.[150] More recently, Gazouli *et al*. employed proteomics technologies in order to monitor for differences in protein expression in a cohort of patients following infliximab administration.[151] Proteins apolipoprotein A-I, apolipoprotein E, complement C4-B, plasminogen, serotransferrin, beta-2-glycoprotein 1, and clusterin were found to be up-regulated in the primary non-responder and responder groups. Additionally, leucine-rich alpha-2-glycoprotein, vitamin D-binding protein, alpha-1B-glycoprotein, and complement C1r subcomponent were significantly increased in the serum of the remitter group.[151] Finally, Eftekhari *et al*. used physiological intermolecular modification spectroscopy [PIMS] to discriminate IBD patients according to response to anti-TNF treatment.[152] Protein extracts of peripheral blood mononuclear cells from 30 outpatients diagnosed with UC or CD and treated with infliximab were subjected to PIMS analysis, which predicted response to anti-TNF therapy with an accuracy of 96%. Although the aforementioned results seem encouraging, these are preliminary results that should be confirmed/validated on larger cohorts.

We expect the findings at the cell level to be more robust and reproducible than gene biomarkers and more suitable to derive immunological insights and mechanistic hypotheses. This highlights one potential advantage of analysing tissue samples over serum,[153,154] although it is unknown which would produce better results.[11] Concentrations of candidate IBD biomarkers may be higher in the intestinal tissue compared with serum, potentially reducing the chance of false discoveries. On the other hand, although this approach produces valuable physiological information, it has the disadvantage of requiring a pretreatment endoscopy.

Gene-array analysis on colonic mucosal biopsies from IBD patients before starting therapy with infliximab showed a differential gene expression between responders and non-responders.[155] An approach that has been pursued by several groups is the use of microarray analysis to simultaneously measure the RNA expression of thousands of genes to investigate whether gene expression profiles within certain tissues or cell types are associated with treatment outcomes.[155] For example, in a microarray study of pre-treatment rectal mucosal biopsy samples from patients with active UC, a panel of the top five differentially expressed genes [osteoprotegerin—*TNFRSF11B*—, stanniocalcin-1, prostaglandin-endoperoxidesynthase 2, *IL13Rα2*, and *IL11*; all of which are involved in the adaptive immune response] was able to separate responders from non-responders with 95% sensitivity and 85% specificity.[156] In a similar but smaller study of gene expression profiles from pre-treatment mucosal biopsy samples in patients with CD, the same group showed that, in colonic CD, analysis of the top five differentially expressed genes [*TNFAIP6*, *S100A8*, *IL11*, *G0S2*, and *S100A9*] predicted infliximab response with 100% accuracy.[157] A more recent study identified low TREM-1 as a specific biomarker for anti-TNF induced endoscopic remission.[158]

Ferkolj *et al*. conducted, in 2005, the first study that found that a high percentage of CD19+ cells [by flow-cytometry] in the inflamed intestinal mucosa may predict response to infliximab in CD patients.[159]

It has been suggested that high mucosal expression of TNF could be associated with effectiveness of anti-TNF therapy in patients with IBD. Thus, Olsen *et al.* showed an inverse association between pre-treatment TNF expression levels in colorectal mucosa and clinical and endoscopic remission achieved with infliximab treatment in UC patients.[160] Similarly, Atreya *et al.* applied a fluorescent anti-membrane-bound TNF [mTNF] antibody, finding that CD patients with high numbers of mTNF[+] cells on confocal laser endomicroscopy showed significantly higher short-term response rates upon subsequent anti-TNF therapy.[161] Finally, Vatansever *et al.* found that favourable parameters such as clinical remission and mucosal healing were increased in CD patients with high mucosal TNF levels, although results were not statistically significant.[162]

Rismo *et al*., in 2012, reported that high mRNA expression of mucosal IFN-gamma and IL-17A in biopsies obtained before therapy started was associated with anti-TNF induction therapy response in UC patients.[163] Halloran *et al*., in 2014, studied 56 colon biopsies from patients with UC and used microarrays to define the mRNA phenotype.[164] Biopsies manifested coordinate transcript changes resembling rejecting transplants, with effector T cell, IFNG-induced, macrophage, and injury transcripts increasing while parenchymal transcripts decreased. When assessed in microarray results from published studies, the disturbance in gene expression, summarised as principal component 1 [PC1], predicted response to infliximab.

Dahlen *et al*., in 2015, collected mucosal biopsies from 48 UC patients before anti-TNF therapy and evaluated response to the therapy at Week 14[34]. At baseline, responders had lower mucosal mRNA expression of IL-1b, IL-17A, IL-6, and interferon g [IFN-gamma] than non-responders. In this same way, Zhang *et al*. reported, in 23 patients with CD treated with infliximab, that IL-17 and IL23 tissue expression was much higher in responders than in non-responders.[165]

West *et al*., in 2017, analysed more than 200 patients with IBD, including two cohorts from phase 3 clinical trials of infliximab and golimumab, and demonstrated that high pre-treatment expression of oncostatin M was strongly associated with failure of anti-TNF therapy.[148] Viazis *et al*., in 2017, studied a group of 67 patients with UC receiving anti-TNF treatment.[166] Mucosal healing was associated with lower pre-treatment mucosal expression of Th1 transcription factor Tbet and higher expression of Th17-Rorc. In 2018, Telesco *et al.* showed that the gene expression signature identified UC patients treated with golimumab with mucosal healing, with 87% sensitivity but only 34% specificity, limiting its clinical utility.[167]

Finally, in 2018, Gaujoux *et al.* identified altered abundance of plasma cells and inflammatory macrophages in pre-treatment intestinal biopsies of anti-TNF responders versus non-responders. Pathway analysis of the cell-adjusted differentially expressed genes in biopsies suggested an up-regulation of the triggering receptor expressed on myeloid cells 1 [TREM-1] and chemokine receptor type 2 [CCR2]–chemokine ligand 7 [CCL7] axes in non-responders.[168]

3. Predictors of Primary Response to Vedolizumab

Vedolizumab is a monoclonal antibody directed against the gut-homing integrin, α4β7. Integrin α4β7 is expressed on T cells, B cells, and NK cells as well as subsets of innate immune cells, and binds to mucosal addressin cell adhesion molecule [MAdCAM-1] expressed on the endothelium of gastrointestinal and gut-associated lymphoid tissue.[3]

Among patient-related factors, age[80,169–174] and gender have not been associated with better or worse response to vedolizumab, either in CD or in UC patients.[81,167–172] In agreement with that reported in anti-TNF treated patients, some studies have suggested that CD smokers tend to respond less to vedolizumab.[80] However, the association between smoking habit and response to vedolizumab has not been confirmed by most of the studies.[90,169,170,172–174]

When evaluating disease-related factors, disease duration has not been associated with a higher or lower probability of response to vedolizumab either in CD or in UC.[80,90,169–174] Some studies have suggested that CD patients with isolated colonic disease tend to have a better response to vedolizumab.[171] However, most of the studies have not been able to confirm this association.[80,169,170,172–174] In contrast with anti-TNF treatment, a pure inflammatory disease-behaviour of CD has not been associated with an increased benefit from vedolizumab.[80,90,169,172–174] Only a few studies have assessed the influence of IBD disease severity on the probability of response to vedolizumab, with controversial results: some studies reported better response in less severe CD patients[80,169,174] and others found no association.[90,97,170,172] Most studies could not find any association between previous CD surgery and vedolizumab response.[90,170,171]

Regarding laboratory markers, some studies have confirmed an association between elevated CRP and response to vedolizumab in CD patients[90] [although other authors reached opposite results[174]]. Conversely, in UC patients, several studies have reported an association between low CRP levels and a better response to vedolizumab.[90,169] A correlation between haemoglobin levels[170,174] or

leukocyte count[169] and response to vedolizumab treatment has not been confirmed either in CD or in UC. Faecal calprotectin was not associated with a better or worse response to vedolizumab in a single study.[170]

It was initially suggested that the concomitant use of steroids could increase the efficacy of vedolizumab treatment in CD patients.[169] However, more recently, this association could not be confirmed by other authors, either in CD patients[80,172] or in UC patients.[80,169,172] As previously reviewed in the anti-TNF section, the risk of primary non-response to anti-TNF treatment is higher among patients previously exposed to biologics compared with bio-naïve patients.[3,4] Some studies have shown that previous anti-TNF therapy is also a risk factor for failure of treatment with vedolizumab,[80,175–177] whereas others have reached opposite results, that is the response to vedolizumab is independent of previous anti-TNF failure,[90,170,172–174] in IBD patients.

The composition of the microbiome might affect the clinical response to vedolizumab therapy, but there is a paucity of studies addressing this question. One study showed that baseline community alpha diversity was significantly higher, and *Roseburia inulinivorans* and *Burkholderiales* spp. more abundant, in patients with CD who achieved remission at Week 14 of vedolizumab treatment than in patients who did not achieve remission.[178] Furthermore, 13 pathways including branched chain amino acid synthesis were significantly enriched in baseline samples from patients who achieved remission. Thus, the longitudinal course of early microbiome changes could represent a marker of response to vedolizumab treatment.

Regarding immune-epithelial biomarkers, one study found that the expression of α4β7 in blood [T, B, and NK cells] was a superior biomarker for vedolizumab response than any reported outcomes associated with disease severity [CRP, albumin, and clinical scores].[179] A retrospective single-centre cohort study of 28 patients with IBD receiving vedolizumab applied Multiplex ELISA to quantify 47 preselected plasma proteins based on their putative involvement in the inflammatory process in IBD.[180] Vedolizumab non-responders had significantly higher levels of circulating IL-6 than those responding to vedolizumab. A small pilot study that used molecular imaging of α4β7 integrins suggested that low or absent integrin expression in the colonic mucosa before treatment might result in primary non-responsiveness to vedolizumab in patients with CD.[181] In this respect, in the randomised controlled phase II trial of another anti-integrin therapy, etrolizumab [a humanised monoclonal antibody that selectively binds the β7 subunit of the heterodimeric integrins α4β7 and αEβ7], the presence of baseline colonic αE expression detected by flow cytometry assays improved response to the drug.[182] In this same line, Tew *et al.* compared differences in colonic expression [by immunohistochemistry and gene expression profiling] of the integrin αE gene between UC patients who achieved clinical remission with etrolizumab versus those who did not.[183] Colon tissues collected at baseline from patients who had a clinical response to etrolizumab expressed higher levels of T cell-associated genes than patients who did not respond.

4. Predictors of Primary Response to Ustekinumab

Ustekinumab is a monoclonal antibody directed against the p40 subunit shared by IL-12 and IL-23[4]. Few studies have investigated associations between clinical, biological, or pharmacological parameters and responsiveness to ustekinumab. With respect to patient-related factors, with some exceptions,[184] age,[81,185–188] gender,[81,185–188] and smoking habit[81,185,186] have not been associated with better or worse response to ustekinumab. Regarding disease-related factors, disease duration[81,185–188] or location[185,187,188] have not been associated with a higher or lower probability of response to ustekinumab, although some exceptions have been reported.[184] In contrast with anti-TNF treatment, a pure inflammatory disease-behaviour of CD has not been consistently associated with an increased benefit from ustekinumab.[185–188] A single study has suggested a better response to ustekinumab in patients with a more severe CD.[189] One study has reported that a history of previous surgery is a negative predictive factor of response to ustekinumab treatment,[186] but this has not been confirmed by another study.[188] Unlike anti-TNF treatments, an association between high CRP levels and a favourable response to treatment has not been reported for ustekinumab in CD patients.[81,186,187] The concomitant use of steroids has not been associated with a higher response rate to ustekinumab.[81,185,188] Finally, some studies have shown that previous anti-TNF therapy is a risk factor for treatment failure with ustekinumab,[184,188] whereas others have reported that the response to ustekinumab is independent of previous anti-TNF failure.[185,186]

5. Limitations of Studies Evaluating Predictors of Response

The studies carried out so far evaluating predictors of response to biologic treatments in IBD have relevant limitations, which are summarised as follows.

1] The first and most obvious limitation is that the number of studies performed in patients with IBD which have assessed the association between each biologic drug and each of the potential predictive factors is still relatively small.
2] Most studies have a relatively small sample size, and consequently have insufficient statistical power.
3] Most of the studies have a retrospective design, with the consequent shortcomings of this.
4] Another limitation is the heterogeneity of the type of patients who have been included in the studies. Thus, some studies included IBD patients [without separation between CD and UC], and others included only CD or UC. Furthermore, much of our knowledge regarding biologic therapies derives from registrational trials, where patient selection is dramatically different from what actually happens in real life. Finally, in almost all the studies, patients had received different medical treatments—in addition to the biologic drug—which potentially could affect the efficacy results. On the other hand, for some 'inconsistent correlations' of predictors with outcome, this could be due to a U-shape correlation, rather than a linear one; this is especially true for weight variables where probably both the very lean and the very obese are more prone to fail.[190,191] This U-shape phenomenon is probably true also for CRP where normal [suggesting irritable bowel syndrome symptoms] and very high [indicating inflammatory burden and/or infectious complication] are both associated with no response in several studies.
5] The vast majority of predictive studies have only evaluated serum biomarkers, and only a few studies have assessed biomarkers in intestinal mucosa from IBD patients. As previously mentioned, although due to its non-invasive nature serum measurements would seem ideal, it is not evident that blood

markers faithfully reflect the pathogenic process that actually occurs in the intestinal mucosa.

6] Most of the studies carried out to date on response prediction in IBD patients have evaluated anti-TNF drugs. However, in current clinical practice, physicians can choose among several other biologic treatments, including also vedolizumab and ustekinumab, where the information is much more limited.

7] Most of the studies which have evaluated the relationship between biomarkers and the efficacy of biologic therapy in IBD have been based solely on pre-treatment determinations, and therefore do not allow the evaluation of their evolution after treatment. A determination of the biomarkers both before and after administration of the biologic treatment would allow study of the kinetics of these biomarkers and correlate them with the therapeutic response.

8] A final limitation is the lack of a clear definition of effectiveness, which often varies according to the different studies. First, the time frame within which primary response or non-response is determined has varied between trials and clinical practice. Second, in the performed studies, response to biologic treatment has generally been determined by clinical parameters [mainly the Crohn's Disease Activity Index and the Harvey–Bradshaw Index in CD, and the Mayo score in UC[83]], whereas it is well known that the correlation between clinical and endoscopic response is low.[192] In fact, mucosal healing currently represents the true reference standard of therapeutic response, given that the resolution of endoscopic lesions has been associated with a better evolution of the disease, including longer clinical remission, lower rate of hospitalisations, and lower surgical requirements.[192]

6. Conclusions

As the number of new biologic therapies increase in IBD, identifying patients who are most likely to benefit from specific agents is of paramount importance to help best position IBD therapies. In particular, the increasing availability of biologic therapies against other specific targets and different from TNF, such as vedolizumab and ustekinumab, has expanded the therapeutic armamentarium. In this context, personalised medicine is emerging and will become a requirement in the management of patients with IBD. Therefore, there is an urgent unmet need for predicting response before treatment initiation, to reduce health care costs and avoid unnecessary treatment, allowing a more rational use of the resources.

In the present article we have reviewed the potential predictors of favourable response to biologic agents in CD and UC [Tables 1 and 2; and Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online]. For anti-TNF agents, most of the evaluated factors have not demonstrated utility, and many others are still controversial [Table 3]. Thus, only a few factors may have a potential role in the prediction of the response to anti-TNF treatment, including disease behaviour/phenotype, disease severity, C-reactive protein, albumin, cytokine expression in serum, previous anti-TNF therapy, some proteomic markers, and some colorectal mucosa markers [Table 3]. For vedolizumab, the availability of useful predictive markers seems to be even lower, with only some factors showing a limited value, such as the expression of α4β7 in blood, the faecal microbiota, some proteomic markers, and some colorectal mucosa markers [Table 4]. Finally, in the case of ustekinumab, no predictive factor has been reported yet to be helpful in clinical practice [Table 5].

Table 3. Predictive factors of response to anti-TNF agents.

Patient-related factors	Predictive value
Age	Controversial
Gender	None
Weight	Controversial
Smoking	None
Disease-related factors	
Disease duration	Controversial
Disease location/extension	Controversial
Disease behaviour/phenotype	Possible [inflammatory phenotype is a predictive factor of response, in contrast with stricturing phenotype]
Disease severity	Controversial in CD; possible in UC [severe UC is a predictive factor of therapeutic failure]
Extraintestinal manifestations	None
Previous surgery	Controversial
Biochemical markers	
C-reactive protein	Possible in CD [high baseline C-reactive protein levels are predictive of response]; controversial in UC
Haemoglobin	Controversial
LeuKocyte count	None
Platelet count	Controversial
Albumin	None in CD; possible in UC [low serum albumin levels are negatively correlated with response]
Perinuclear anti-neutrophil cytoplasmic antibodies and anti-*Saccharomyces cerevisiae* antibodies	Controversial
TNFα levels in serum	None
Cytokines expression in serum	Possible in UC [the severity of pro-inflammatory cytokine profile in serum is predictive of response]
Faecal markers	Controversial
Genetic polymorphisms	Controversial
Concomitant steroids	Controversial in CD; none in UC
Previous anti-TNF therapy	Possible [previous anti-TNF therapy is a risk factor for treatment failure]
Proteomics	Possible
Predictors at the colorectal mucosa [tissue] level	Possible

CD, Crohn's disease; UC, ulcerative colitis; TNF, tumour necrosis factor.

In summary, currently no single marker fulfils all criteria for being an appropriate prognostic indicator for response to any biologic treatment in IBD, and therefore the suggested biomarkers appear of limited clinical utility. Thus, as previously reviewed, available predictors of response to biologic therapy have shown variable and frequently conflicting results, and most of them suffer from relevant methodological limitations. Thus the basis for personalised medicine, i.e., the ability to stratify the patients according to the expected response to biologic treatment, is not yet available and remains an unmet need in daily clinical practice.

In the near future, novel markers could improve our ability to direct treatment and personalise therapy, especially if we consider that a considerable number of drugs for the treatment of IBD will soon be available. Better knowledge of predictors of response would allow correct prioritisation of both the currently available and

Table 4. Predictive factors of response to vedolizumab.

Factor	Predictive value
Age	None
Gender	None
Smoking	None
Disease duration	None
Disease location/extension	None
Disease behaviour/phenotype	None
Disease severity	Controversial
Extraintestinal manifestations	None
Previous surgery	None
C-reactive protein	Controversial
Haemoglobin	None
Leukocyte count	None
Expression of α4β7 in blood	Possible
Faecal calprotectin	None
Faecal microbiota	Possible
Concomitant steroids	None in ulcerative colitis; controversial in Crohn's disease
Prior anti-TNF therapy	Controversial
Proteomics	Possible
Predictors at the colorectal mucosa [tissue] level	Possible

TNF, tumour necrosis factor.

Table 5. Predictive factors of response to ustekinumab.

Factor	Predictive value
Age	None
Gender	None
Smoking	None
Disease duration	None
Disease location/extension	Controversial
Disease behaviour/phenotype	Controversial
Disease severity	Controversial
Previous surgery	Controversial
C-reactive protein	None
Faecal microbiota	Possible
Concomitant steroids	None
Previous anti-TNF therapy	Controversial

TNF, tumour necrosis factor.

upcoming drugs. Furthermore, future research is needed to develop a comprehensive predictive model incorporating patient- and disease-related factors, including genetic, clinical, biochemical, proteomic, mucosal, etc., factors. Hopefully, further work in this area, along with multivariate clinical prediction modelling, may soon allow us to deliver personalised medicine by predicting individualised treatment response in patients with IBD.

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Author Contributions

JPG wrote the first draft of the manuscript and critically reviewed the final version. MC complemented draft sections and critically reviewed the final version.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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