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Predicting durable response or resistance to antitumor necrosis factor therapy in inflammatory bowel disease

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***Abstract*:** Monoclonal antibodies to tumor necrosis factor (TNF) have become a mainstay of the therapeutic armamentarium in inflammatory bowel disease (IBD) over the last 15 years. Although highly effective, primary and secondary nonresponse are common and associated with poor clinical outcomes and significant costs. Multiple clinical, genetic and immunopharmacological factors may impact the response to anti-TNFs. Early stratification of IBD patients by the expected risk of therapeutic failure during the induction and maintenance phases of treatment may allow for treatment optimization and potentially optimal short- and long-term outcomes. The aim of this review is to summarize the current data concerning the potential predictors of therapeutic success and failure of anti-TNFs in IBD.

Keywords: anti-TNF agents, inflammatory bowel disease, therapeutic drug monitoring

Introduction

Biological therapy using antitumor necrosis factor alpha (anti-TNF) monoclonal antibodies has been used successfully for the treatment of inflammatory bowel diseases (IBDs) for over 15 years. However, treatment failures are common. Primary nonresponse was reported to occur in 13–40% of patients in clinical trials [Ben-Horin *et al.* 2014; Ding *et al.* 2016]. Secondary loss of response (LOR) has been observed in another 23–46% of patients when defined by need to dose adjust within the first 12 months of treatment [Gisbert and Panes, 2009; Ben-Horin *et al.* 2011; Ding *et al.* 2016]. An additional 5–13% fail secondarily as defined by drug discontinuation [Ding *et al.* 2016]. Treatment with anti-TNF is associated with significant costs, and when it fails, therapeutic options are somewhat limited. Therefore, the early identification of patients at risk of nonresponse to anti-TNF is of major clinical importance. Timely identification of these patients may allow us to ascertain which patients might be in need of dose optimization, define the need for concomitant immunosuppression or point out the necessity of therapeutic drug monitoring (TDM). Multiple genetic, clinical and immunopharmacological variables were described to be associated with the risk of therapeutic failure with anti-TNF antibodies. The purpose of this review is to summarize the currently available data regarding the predictors of primary response and secondary LOR to anti-TNF in IBD. The main studies addressing the predictors of response to anti-TNFs are summarized in Table 1.

Definition of response

Primary nonresponse is generally defined as a failure to achieve initial clinical response to induction doses of an anti-TNF. However, the definition of primary nonresponse varies across IBD trials [Ben-Horin *et al.* 2011]. In clinical practice, primary nonresponse to anti-TNFs should not be assessed prior to weeks 8–12, as successful induction of remission may still be accrued after 3 infliximab (IFX) infusions at weeks 0, 2 and 6, or after 3–5 bi-weekly adalimumab (ADA) injections [D'Haens *et al.* 2011]. For vedolizumab, the more recently approved antiadhesion monoclonal molecule, onset of therapeutic benefit may take even longer. A secondary LOR is generally defined as a LOR after achieving a primary response [Kopylov *et al.* 2014b]. Importantly, clinical assessment of response alone is frequently unreliable and may underestimate the true disease burden. The

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Table 1. Predictors of response to antitumor necrosis factors in IBD.

Disease-related factors		Serology		Genetic polymorphisms		Immunopharmacological factors	
Short duration of disease	+	pANCA	_	rs975664 2p12/ TACR1	_	Adequate drug levels	+
Young age	+	Anti-OmpC	–	rs4855535 3p14/ FAM19A4	–	Antidrug antibodies	_
Elevated biomarkers (CRP, FCP)	+			rs6100556 20q13 / PHACTR3	–	Concomitant immunomodulators	+
Stricturing disease	_			rs2836878 21q22 / BRWD1	–	Episodic treatment	_
Previous failure of corticosteroids or cyclosporine	–			rs1568885	+	Hypoalbuminemia	_
Initial response to anti-TNF treatment	+			rs1813443	+	Obesity	_
Need for dose optimization	_			rs10210302/ *ATG16L1*	+	Tissue TNF burden	–
Smoking	_			Apoptosis genes: Fas ligand-843/670 Caspase 9-93	+	Fecal drug loss	_

CRP, C-reactive protein; FCP, fecal calprotectin; pANCA, perinuclear antineutrophil cytoplasmic antibodies; OmpC, outer membrane protein C; TNF, tumor necrosis factor.

importance of guiding the therapy by objective and quantitative endoscopic and imaging parameters is widely recognized [Peyrin-Biroulet *et al.* 2014].

Disease-related factors

The clinical course of IBD is often unpredictable for individual patients. Crohn's disease (CD) in particular is often subject to a progressive clinical course associated with periods of ongoing chronic inflammation resulting in progressive fibrotic complications [Cosnes *et al.* 2002]. The current therapeutic arsenal in IBD, including anti-TNFs, targets the mechanism of inflammation that might not directly impact the course of fibrotic remodulation and associated complications [Cosnes *et al.* 2011]. It is thus not surprising that a higher efficacy of anti-TNF treatment is achieved when used early in active disease. Generally, a shorter duration of disease is associated with an improved response to biologics. In the CHARM study, remission rates with ADA approached 60% in patients who had CD for up to 2 years compared with 40% ($p < 0.05$) in those with a longer duration of disease [Colombel *et al.* 2007]. Similar results were observed with certolizumab (CZP) in the PRECIZE trial [Schreiber *et al.* 2007]. This infers a likely explanation for lower response rates in older patients [Vermeire *et al.* 2002a], in patients with previous CD-related surgery [Vermeire *et al.* 2002a] or a stricturing phenotype [Peters *et al.* 2014]. In the pediatric REACH trial, the rate of response to IFX appeared to be higher than that described for adult CD for both induction and maintenance therapy [Hyams *et al.* 2007], likely due in part to lower overall disease duration.

Inflammatory biomarkers

It has been reported that patients with active inflammation, characterized by elevated levels of inflammatory biomarkers such as C-reactive protein (CRP), are more responsive to anti-inflammatory therapy [Sandborn *et al.* 2007; Colombel *et al.* 2010]. In a real life cohort of 438 CD patients, an elevated CRP was associated with a threefold higher response rate to induction therapy with ADA [Peters *et al.* 2014]. Similar results were observed for IFX [Jurgens *et al.* 2011; Reinisch *et al.* 2012]. However, anti-TNF treatment should not be restricted to patients with an elevated CRP, as almost 50% of those with a normal value respond [Louis *et al.* 2002]. Moreover, not all studies support the association between elevated

CRP and response to treatment in IBD. In a recent Portuguese study, baseline CRP levels were higher in CD patients with primary nonresponse, and baseline levels greater than 15 mg/l predicted primary nonresponse with 67% sensitivity and 65% specificity. At week 14, CRP levels greater than 4.6 mg/l predicted nonresponse with similar accuracy [Magro *et al.* 2014]. An elevated baseline CRP may also predict a worse outcome. In a group of ulcerative colitis (UC) patients treated with IFX, an elevated baseline CRP was recently shown to predict a higher likelihood of drug failure and need for colectomy [Arias *et al.* 2015]. An elevated baseline CRP may thus be a double-edged sword. Whereas a high baseline CRP weeds out some patients with noninflammatory 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 [Ben-Horin *et al.* 2015].

CRP levels after initiation of anti-TNF are also predictive of response. In a recent study, the CRP level in a group of UC patients at week 2 after initial dose of anti-TNF was significantly lower in responders *versus* partial responders ($p = 0.0135$) or nonresponders ($p = 0.0084$), in spite of similar trough IFX levels. Furthermore, the median CRP (week 2/week 0) ratio was significantly lower in patients who responded *versus* partial responders or nonresponders. A cut-off value set at 0.19 for the CRP (week 2/week 0) ratio could predict partial responders with 79.1% sensitivity and 75.9% specificity. Patients with a CRP (week 2/week 0) ratio greater than 0.19 were likely to be partial responders, with an odds ratio (OR) of 10.371 [$p < 0.0001$; 95% confidence interval (CI), 3.596–33.440] [Iwasa *et al.* 2015].

It is well established that the sensitivity of CRP is limited in CD, as almost 30% of patients will have a normal level despite clinically active disease. In a significant proportion of these patients, active inflammation may still be detected using other biomarkers such as fecal calprotectin [Kopylov *et al.* 2014c]. The calprotectin level has been shown to be a sensitive marker of response to treatment. In a study that included 90 patients hospitalized for severe colitis, fecal calprotectin was significantly higher in patients requiring colectomy (1200 *versus* 887; $p = 0.04$), with a trend toward significance when comparing corticosteroid nonresponders and responders (1100 *versus* 863.5; $p = 0.08$), as well as between IFX nonresponders and responders (1795 *versus* 920.5; $p = 0.06$) [Ho *et al.* 2009]. An early decrease in fecal calprotectin levels was associated with superior clinical response [Kolho and Siponnen, 2014] and mucosal healing [Guidi *et al.* 2014] in pediatric- and adult-onset IBD, respectively, treated with an anti-TNF. An elevation in fecal calprotectin is also a reliable predictor of pending relapse in patients with clinical remission in UC and CD [De Vos *et al.* 2013; Molander *et al.* 2012; Ferreiro-Iglesias *et al.* 2015].

Response to previous therapies, disease phenotype and location

Patients with severe disease failing corticosteroids or immunomodulators pose a higher risk of therapeutic failure to anti-TNF agents. Previous failure of corticosteroid or cyclosporine treatment is also associated with increased risk of therapeutic failure in UC [Ferrante *et al.* 2008; Oussalah *et al.* 2010]. Initial response to treatment, manifested by early clinical remission and mucosal healing, is associated with improved durability of response [Colombel *et al.* 2011]. On the other hand, the need for dose optimization due to insufficient response is an adverse prognostic factor [Ben-Horin *et al.* 2014]. Disease phenotype has been shown to influence outcomes. An inflammatory phenotype was associated with a higher response rate and sustained clinical benefit [hazard ratio (HR) 0.55, $p < 0.03$] at 24 months in CD [Sprakes *et al.* 2012]. Fibrostenosing CD phenotype is associated with a lower response rate to anti-TNFs and may be more amenable to dilatations or surgical resection. A retrospective cohort study of 425 CD patients found that a fibrostenosing phenotype more often required surgical resection despite anti-TNF therapy (adjusted HR 6.17; 95% CI, 2.81–13.54) [Moran *et al.* 2014].

The association between disease location and likelihood of response to biologics is less clear cut. Isolated colonic disease is associated with an improved response to anti-TNFs in CD [Vermeire *et al.* 2002a; Arnott *et al.* 2003]. Another study showed that isolated colonic CD is associated with shorter duration to ADA dose escalation [Cohen *et al.* 2012].

Smoking

Smoking has often been associated with significantly lower rates of response to anti-TNF for CD [Arnott *et al.* 2003; Cohen *et al.* 2012;

Juillerat *et al.* 2015; Ungar *et al.* 2015a]. Other reports did not observe this association [Fefferman *et al.* 2004; Orlando *et al.* 2005]. The relative risk of nonresponse was not significantly different in smokers in one recent meta-analysis [Inamdar *et al.* 2015]. The explanation for the discrepancy in the results in regards to the impact of smoking on clinical response is unclear. It may be attributed to differences in study design, patient cohort and outcome definitions. However, a recent prospective cohort study in CD patients on IFX or ADA in combination with azathioprine reported that LOR among smokers was significantly more frequently observed (74%) *versus* nonsmokers (5%) ($p < 0.0001$) [Viazis *et al.* 2015]. Overall, it is reasonable to discourage smoking aggressively, but it should not influence the decision to initiate anti-TNF treatment [Narula and Fedorak, 2009].

Serological predictors

Multiple studies addressed the prognostic utility of serological biomarkers in IBD, especially CD [Lichtenstein *et al.* 2011]. Nevertheless, very few studies addressed the correlation of serological parameters with the probability of response to anti-TNFs. The presence of perinuclear antineutrophil cytoplasmic antibodies (pANCA) [Jurgens *et al.* 2010; Arias *et al.* 2015], as well as anti-OmpC positivity [Kevans *et al.* 2015], was associated with diminished long-term response to anti-TNFs in UC. However, the current consensus is that IBD serological tests, when used alone, do not have a significant predictive role [Ding *et al.* 2016].

Genetic predictors

Certain genetic polymorphisms were proposed to predict the probability of response to anti-TNFs in IBD [Urcelay *et al.* 2005; Siegel and Melmed, 2009; Ben-Horin *et al.* 2014]. To date, a clear relationship between TNF alpha polymorphisms and response to anti-TNFs has not been established [Mascheretti *et al.* 2002; Siegel and Melmed, 2009]. Polymorphisms in the NOD2/CARD15 were not associated with response to IFX [Vermeire *et al.* 2002b]. However, a recent Spanish study reported that the proportion of patients on an intensified biological therapy was significantly higher among CD patients with a NOD2-variant [Gutierrez *et al.* 2014]. Four polymorphisms were associated with response to IFX in a pediatric IBD study: rs975664 2p12/TACR1, rs4855535 3p14/FAM19A4, rs6100556 20q13/PHACTR3 and rs2836878 21q22/BRWD1 [Dubinsky *et al.* 2010]. In a recent Greek study, TT and AT genotypes of the rs1568885 and the CC and GC genotypes of the rs1813443 were associated with nonresponse to IFX in CD [Thomas *et al.* 2014]. A recent study from Slovenia suggested that *ATG16L1* SNP rs10210302 influences response to ADA [Koder *et al.* 2015]. Interestingly, these polymorphisms were also associated with response to anti-TNFs in rheumatoid arthritis [Umicevic Mirkov *et al.* 2013]. Jurgens and colleagues demonstrated that IL23R-genotype status is associated with early response to IFX in UC [Jurgens *et al.* 2010].

A Belgian study focused on apoptosis genes and response to IFX in CD. Polymorphisms in the Fas ligand-843 and caspase-9 93 gene alleles were associated with improved response to IFX [Hlavaty *et al.* 2005]. Interestingly, the effect of Fas ligand-843 C/T, Fas-670 G/A and caspase-9 93 C/T polymorphisms on the response to IFX was cumulative, demonstrating a strong correlation using a compound score incorporating the burden of these mutations with clinical response [Hlavaty *et al.* 2007].

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. Further GWAS studies will hopefully allow a better understanding between genetic polymorphisms and response to anti-TNF therapy.

Immunopharmacological predictors

Antitumor necrosis factor levels

TDM of anti-TNF therapy has become standard of care in the clinical setting for many clinicians. There is a well established correlation between serum trough levels of anti-TNF medications and clinical response [Baert *et al.* 2003; Maser *et al.* 2006; Yanai *et al.* 2015] Adequate trough levels were also associated with improved rates of mucosal healing and decreased incidence of long-term complications [Colombel *et al.* 2010, 2014; Paul *et al.* 2013] in both UC and CD. However, there is no clear consensus as to what constitutes ideal trough levels of anti-TNFs. Moreover, there is no method of reliably comparing trough anti-TNF levels across different assays employed. A meta-analysis of 2021 serum samples from 532 CD patients included in prospective

randomized-controlled trials and cohort studies demonstrated that week 8 trough IFX concentration greater than 3 μg/ml was predictive of significantly lower disease activity, as measured by CRP [Feagan *et al.* 2012]. Lukas and colleagues demonstrated that this cut-off value at start of maintenance treatment (week 14 or 22) was predictive of sustained remission (median 2-year follow up) with a positive and negative predictive value of, respectively, 85% and 45% [Lukas *et al.* 2012].

For ADA, the data are less abundant and consistent. A recent French study evaluated the correlation between ADA levels and mucosal healing, demonstrating that a level of up to 4.9 μg/ml was found to be associated with an absence of mucosal healing with a positive predictive value of 88% and negative predictive value of 51% [Roblin *et al.* 2014]. In a recent study from Israel, a cut-off drug level of 5.85 μg/ml yielded optimal sensitivity, specificity and a positive likelihood ratio for prediction of clinical response [Mazor *et al.* 2013]. Another study from the same group evaluated the correlation between IFX and ADA levels with clinical assessment, biomarkers and endoscopic response. Median drug levels were significantly higher in IBD patients with mucosal healing *versus* patients with endoscopically active disease, for both IFX and ADA (4.3 *versus* 1.7 μg/ml, $p = 0.0002$, 6.2 *versus* 3.1 μg/ml, $p = 0.01$, respectively). Higher drug levels were also associated with normalization of CRP (3.95 *versus* 2.2, $p = 0.03$ for IFX, 5 *versus* 2.3, $p = 0.03$ for ADA). An IFX level above 5 μg/ml [area under the curve (AUC) = 0.75, $p < 0.0001$] and an ADA level above 7.1 μg/ml (AUC = 0.7, $p = 0.004$) had a specificity of 85% for achieving mucosal healing. [Ungar *et al.* 2015b]. Interestingly, the gained benefit from increasing the drug level achieved a plateau (for IFX levels above 8 μg/ml were associated with only minimal additional gain in mucosal healing, while the correlation between higher ADA levels and increased mucosal healing rate reached a plateau at 12 μg/ml). These results suggest the existence of a 'therapeutic window' for biologics in IBD, with a low likelihood of incremental gain in clinical and endoscopic response with further dose optimization once the 'plateau' trough level is reached.

For steroid refractory UC, Seow and colleagues reported that a detectable serum trough IFX level was associated with higher rates of remission (69% *versus* 15%; $p < 0.001$) and endoscopic improvement (76% *versus* 28%, $p < 0.001$). Most importantly, an undetectable serum trough IFX level predicted an increased risk for colectomy for steroid refractory UC (55% *versus* 7%, OR, 9.3; 95% CI, 2.9 to 29.9; $p < 0.001$) [Seow *et al.* 2010]

The vast majority of data using TDM in IBD pertains to trough level measurements. There are some data available in regard to earlier time points. A serum level of IFX greater than 12.0 μg/ml at 4 weeks from the last infusion was independently correlated with clinical response for CD [Baert *et al.* 2003]. In a recent Japanese study, peak IFX level at week 2 predicted clinical improvement at week 14 and mucosal healing at week 30 in UC [Kobayashi *et al.* 2015]. Early achievement of target drug levels may have a significant impact on long-term effect and durability of anti-TNF treatment. Post-induction (week 14) trough levels of IFX were correlated with long-term (week 54) clinical response in a subgroup analysis of the ACCENT 1 study [Cornillie *et al.* 2014].

Authors of the trough level adapted IFX treatment (TAXIT) study investigated whether dosing of IFX based on TDM during the maintenance phase was superior compared with clinically based dosing in CD. During the optimization phase, all patients were dose-optimized to achieve IFX trough levels between 3 and 7μg/ml. During the maintenance phase, patients were randomized 1:1 to continue drug concentration-based dosing or to switch back to clinically based dosing (52-week follow up). The percentage of patients in clinical remission was not significantly different between the arms. However, in the maintenance phase, patients managed using TDM required less drug optimization and had fewer flares. Successful de-escalation was possible in 93% of the patients with IFX levels above 7 μg/ml, resulting in a more efficient use of the medication [Vande Casteele *et al.* 2015].

Antidrug antibodies

It is known that several factors are correlated with trough levels of anti-TNFs. Among the most studied is the presence of antidrug antibodies [Vermeire *et al.* 2003, 2007; Yanai and Hanauer, 2011; Yanai *et al.* 2015]. As monoclonal antibodies are a foreign protein, the development of antibodies against different epitopes is to be expected. While it is still unclear which epitopes induce antibody production that is clinically relevant, it was demonstrated that the antibodies bind to

the Fab segment [Ben-Horin *et al.* 2011]. Antimonoclonal antibodies interfere with their biologic activity by inhibiting the binding of TNFα inhibitors to both serum and membrane-bound TNFα molecules, and by the generating of immune complexes that are eliminated by the reticuloendothelial system [Rojas *et al.* 2005; Yamada *et al.* 2010]. In a recent large retrospective study from Israel, antibodies to IFX were detected in 47% of patients with secondary LOR, and to ADA in 23% [Yanai *et al.* 2015]. The risk of LOR development in patients with detectable anti-IFX is increased by at least threefold [Moss *et al.* 2013; Vande Casteele *et al.* 2014]. A similar risk of future LOR was also associated with antibodies against ADA [Baert *et al.* 2015].

The rate of detection of antidrug antibodies is highly dependent on the laboratory technique employed. The first generation of 'bridging' ELISAs are incapable of detecting antidrug antibodies in the presence of the drug in the serum, as the monoclonal anti-TNF served as both the substrate and the detection antibody [Vermeire *et al.* 2003]. Modified ELISA techniques such the antihuman lambda chain assay (AHLC ELISA) [Kopylov *et al.* 2012] and alternative methods such as a radioimmunoassay (RIA) [Ainsworth *et al.* 2008] or the homogenous mobility shift assay [Wang *et al.* 2012] are currently able to more accurately detect both antibodies and drug levels in the same sample. Interestingly, the first study describing the prevalence and impact of anti-ADA antibodies using the first generation bridging ELISA reported a prevalence of 9.2% [Karmiris *et al.* 2009]; when the same samples were analyzed using the HMSA technique, the prevalence of antibodies more than doubled [Baert *et al.* 2015]. Despite the difference in sensitivity between the techniques, it appears that the clinical impact of those discrepancies is limited, as most patients with antibodies have undetectable trough levels [Vande Casteele *et al.* 2012]. Earlier studies that used first-generation ELISA suggested that emergence of antidrug antibodies is indicative of the need to switch to a different formulation, within class [Afif *et al.* 2010]. Importantly, the ELISA assay could only demonstrate antidrug antibodies in the absence of detectable drug in the serum, limiting the ability to inform whether there is presence of high-level antibodies leading to the elimination of IFX from the serum. With the newer assays, we now understand that low- and high-level ADA may not have similar clinical consequences. Moreover, serum anti-TNF levels and antidrug antibodies most likely represent a continuous process that may frequently start with low-titer antibodies that do not initially hamper levels of the drug significantly, progressing to high-titer antibodies leading to a complete elimination of the drug and LOR. Frequently, detection of antidrug antibodies will precede the development of LOR by several weeks, or alternatively, will be detected after LOR has developed [Ungar *et al.* 2013]. Transient (appearing on a single measurement without recurrence) antibodies to IFX are a frequent phenomenon, described in up to 28% of patients [Vande Casteele *et al.* 2013]. In contrast to persistent antibodies to IFX, that rarely (<10%) appear after 1 year of treatment, transient antibodies may be detected at any point during the treatment without a significant impact on LOR-free survival [Ungar *et al.* 2013].

Another issue is establishing the cut-off to consider antibodies to the monoclonal anti-TNF as being significant as well as permanent. Titers of antibodies-to-ADA greater than 4 mcg/mEq and antibodies-to-IFX greater than 9 mcg/mEq were 90% specific for failure to respond to dose intensification [Yanai *et al.* 2015]. These results suggest that low-level antidrug antibodies, in the presence of an insufficient trough drug level, is amenable to dose intensification, while therapeutic failure with high-level antibodies or drug levels is unlikely to respond to drug intensification. Again, the inability of the first generation ELISA method to detect antidrug antibodies in the presence of drug needs to be considered, as well as the variability on results across different assays.

Concomitant treatment with immunomodulators was repeatedly associated with improved trough levels, diminished production of antibodies to IFX and improved clinical outcomes [Vermeire *et al.* 2007; Colombel *et al.* 2010; Sokol *et al.* 2010; D'Haens *et al.* 2011]. This advantage is mostly evident during the initial treatment phase; after more than 6 months of treatment no clear clinical benefit of combination therapy was demonstrated [Van Assche *et al.* 2008]. For other anti-TNFs, the available data are sparse. No strong evidence of long-term clinical benefit could be demonstrated for the combination therapy with immunomodulators with ADA or CZP [Kopylov *et al.* 2014a; Jones *et al.* 2015]. For ADA, a recent study from the Leuven group demonstrated a lower level of antidrug antibody formation with combination therapy [Baert

et al. 2015]. However improved clinical outcomes were not reported [Karmiris *et al.* 2009]. In the COMMIT study in CD, the combination of IFX with methotrexate resulted in a significantly lower prevalence of antidrug antibody formation and a trend towards higher serum IFX levels; however, no significant difference in clinical efficacy was found [Feagan *et al.* 2014].

Addition of an immunomodulator may be a valid strategy for some patients developing LOR to anti-TNF monotherapy accompanied by low drug levels with or without antidrug antibody formation. In a recent report, in a small cohort of IBD patients who have developed LOR to IFX accompanied by ATI, an addition of an immunomodulator in patients on monotherapy (azathioprene in three patients and methotrexate in two patients) resulted in a gradual restoration of clinical response, decrease in antidrug antibody titers and augmentation of IFX levels [Ben-Horin *et al.* 2013]. The results of this small pilot study must be taken with caution, however.

Episodic treatment with IFX was associated with a significantly greater risk of antibody formation, decreased drug levels and adverse clinical outcomes [Hanauer *et al.* 2004; Rutgeerts *et al.* 2004, 2006]. Currently, most clinicians employ anti-TNFs according to an established maintenance schedule.

To date, there are few studies evaluating the genetic factors associated with the emergence of anti-TNF antibody formation. The human leukocyte antigen (HLA) region, involved in the detection of foreign proteins, would be a potential candidate. A recently published small study from the Leuven group, published in letter form, suggested an association between HLA DRB1 and formation of anti-TNF antibody formation [Billiet *et al.* 2015]. In an Israeli study, Ashkenazi Jewish origin was associated with a less frequent formation of anti-TNF antibody formation compared with the prevalence in Jews of Sephardic origin, in both UC and CD. However, genetic analysis was not performed [Ungar *et al.* 2015a].

Serum albumin, obesity and other factors

In addition to the presence of antidrug antibodies, anti-TNF titers are negatively influenced by low serum albumin levels and by excessive body weight. These factors had a similar impact in both adult and pediatric patients and are valid for both CD and UC [Fasanmade *et al.* 2009, 2010, 2011]. To date, the most clinically important clinical setting that demonstrates the important interplay of these factors is in the setting of severe colitis. In these patients, the consequence of IFX failure frequently results in the need for total colectomy, which may be associated with increased risk of complications [Scoglio *et al.* 2014].

In patients with acute severe colitis, IFX levels were significantly lower in comparison with moderate colitis during the induction phase, and were significantly correlated with albumin levels [Ungar *et al.* 2015c]. Low serum albumin levels were consistently associated with diminished response to IFX [Fasanmade *et al.* 2010; Arias *et al.* 2015]. This relationship was also reflected by the lower IFX serum levels in hypoalbuminemic patients, and is probably explained by the common mechanism responsible for protection from catabolism for both albumin and monoclonal antibodies such as IFX, namely the neonatal Fc receptor (FcRn). The FcRn facilitates immunoglobulin G and albumin homeostasis by recycling across cell membranes back to the circulation [Fasanmade *et al.* 2010].

Additionally, still poorly defined factors that have a significant impact on the clearance of IFX include the burden of inflammatory disease in the tissue [Yarur *et al.* 2015]. In a recent study comparing tissue levels of TNF alpha and anti-TNF antibodies in the mucosa of IBD patients, a significant correlation was observed between serum and the tissue levels in the noninflamed mucosa. However, in areas of active inflammation, the correlation was poor, and the ratio of TNF alpha to anti-TNF was skewed [Yarur *et al.* 2015]. In a novel study by Atreya and colleagues that applied a fluorescent antimembrane-bound TNF (mTNF) antibody, CD patients with high numbers of mTNF(+) cells on confocal laser endomicroscopy showed significantly higher short-term response rates (92%) at week 12 upon subsequent anti-TNF therapy when compared with patients with low amounts of mTNF(+) cells (15%). This clinical response in the former patients was sustained over a follow-up period of 1 year and was associated with mucosal healing observed in follow-up endoscopy. These results suggest that molecular imaging with fluorescent antibodies has the potential to predict therapeutic responses to biological treatment and can be used for personalized medicine in CD [Atreya *et al.* 2014].

Significant fecal losses of anti-TNF monoclonal antibodies were associated with therapeutic failure in patients with acute severe colitis [Brandse *et al.* 2015]. These findings support the concept of a 'sponge-and-sieve' effect in patients with severe UC, with increased gut losses of anti-TNF antibodies secondary to the high inflammatory burden, as well as possibly heightened elimination of TNF-anti-TNF complexes by the hyperactive reticuloendothelial system [Rosen *et al.* 2015]. These patients may indeed require a more flexible and intensified infusion protocol. TDM to aggressively aim for adequate peak IFX levels may prevent risk of colectomy. This hypothesis was supported by a small retrospective study, in which a flexible individualized dosing of IFX was associated with a decreased short-term risk of colectomy in acute severe UC [Gibson *et al.* 2015]. The optimal dosing schedule for acute severe colitis merits further evaluation in a large-scale prospective study.

Obesity was also associated with a shorter duration of response to IFX in IBD [Harper *et al.* 2013]. For ADA, there was a weak association between clearance and body mass index (BMI) [Lie *et al.* 2014]. However it appears that LOR is somewhat more frequent in obese patients [Bhalme *et al.* 2013], perhaps due to the fixed, rather than weight-based dosing of ADA. In patients with rheumatoid arthritis, obesity appears to be significantly associated with the risk of nonresponse to second-line anti-TNF following the failure of the first medication [Iannone *et al.* 2015]. For IFX, the relationship between obesity and clinical response would appear to be somewhat paradoxical, as IFX dosing is weight based. However, it is likely that the correlation between the distribution volume of IFX and weight is not linear. TDM-based dosing optimization is potentially beneficial for patients with a high BMI. In addition, IFX clearance was reported to be higher in male IBD patients. However, this finding was not reproduced in the majority of later pharmacokinetic studies [Ternant *et al.* 2008].

Future directions

Despite the abundance of available clinical and pharmacological data, the variability in response to biologics in IBD patients can be only partially explained by the factors described above. A better understanding of the microbiome impact in the pathogenesis of IBD and its interactions with the innate and adaptive immune system may shed more light into the mechanism of response and LOR to treatment. A recent original study by Kolho and colleagues examined the microbiome. The host microbial diversity and similarities to the microbiota of controls increased in patients who responded to anti-TNFs by week 6, but not among nonresponders. The abundance of six groups of bacteria including those related to *Eubacterium rectale* and *Bifidobacterium* spp. predicted the response, assessed by fecal calprotectin levels in this study [Kolho *et al.* 2015]. Other novel research strategies, such as the study of metabolome and epigenetics, may yield additional data that will allow for prediction of response and early stratification of patients by the likelihood of their response to different medication types.

Conclusions

Multiple clinical, genetic and immunopharmacological factors are associated with response to anti-TNF medications in IBD. Future research is needed to develop novel, accurate tools, such as a comprehensive model using these predictors early in the course of treatment, or even before treatment initiation, in order to optimize the utilization of these medications, potentially improving patient outcomes and reducing treatment costs. Ideally, such a model should also predict the likelihood of response to a specific therapeutic mechanism, aiding in selection of the first-line agent and guiding the strategy for management of LOR and selection of a second-line agent. Such data may arise from alternative and novel research strategies and fields that have not been employed to date.

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The authors declare that there is no conflict of interest.

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