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REVIEW

Predictors and optimal management of tumor necrosis factor antagonist nonresponse in inflammatory bowel disease: A literature review

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Abstract

Tumor necrosis factor-α (TNF-α) antagonists, the first biologics approved for treating patients with inflammatory bowel disease (IBD), are effective for the induction and maintenance of remission and significantly improving prognosis. However, up to one-third of treated patients show primary nonresponse (PNR) to anti-TNF-α therapies, and 23%-50% of IBD patients experience loss of response (LOR) to these biologics during subsequent treatment. There is still no recognized predictor for evaluating the efficacy of anti-TNF drugs. This review summarizes the existing predictors of PNR and LOR to anti-TNF in IBD patients. Most predictors remain controversial, and only previous surgical history, disease manifestations, drug concentrations, antidrug antibodies, serum albumin, some biologic markers, and some genetic markers may be potentially predictive. In addition, we also discuss the next steps of treatment for patients with PNR or LOR to TNF antagonists. Therapeutic drug monitoring plays an important role in treatment selection. Dose escalation, combination therapy, switching to a different anti-TNF drug, or switching to a biologic with a different mechanism of action can be selected based on the concentration of the drug and/or antidrug antibodies.

Key Words: Predictor; Management; Tumor necrosis factor antagonist; Primary nonresponse; Secondary nonresponse; Inflammatory bowel disease

Core Tip: Tumor necrosis factor-α (TNF-α) antagonists play an essential role in the management of inflammatory bowel disease (IBD). However, a significant number of patients experience primary or secondary nonresponse to these drugs. Here, we summarize relevant predictors of anti-TNF nonresponse in IBD and discuss the next steps for treating patients with primary or secondary nonresponse to anti-TNF agents.

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INTRODUCTION

Inflammatory bowel disease (IBD), an immune-mediated inflammation of the gastrointestinal tract characterized by repeated remission and relapse, comprises Crohn's disease (CD) and ulcerative colitis (UC). Traditionally, IBD has been considered a disease of the Western world, but the newly industrialized countries of Asia, Africa, and South America are experiencing a rapid increase in incidence[1-3]; therefore, IBD has become a global disease[4,5].

IBD is a lifelong disease and is incurable. Currently, medical therapy for IBD mainly includes traditional therapeutics such as 5-aminosalicylates, thiopurines, and steroids, biologics such as antitumor necrosis factor (anti-TNF) therapy, vedolizumab and ustekinumab, and novel small-molecule drugs such as Janus kinase (JAK) inhibitors.

Anti-TNF therapies, the first biologics approved for the treatment of patients with IBD, are effective for the induction and maintenance of remission and significantly improve prognosis[6-8]. The development of anti-TNF therapies revolutionized the treatment of IBD and was a landmark event. Anti-TNF drugs are still the most commonly used biological agents in IBD at present[6]. Four TNF antagonists have been used in the treatment of IBD: infliximab, adalimumab, certolizumab, and golimumab[9]. However, up to one-third of treated patients show no primary response to anti-TNF-α therapies[10], and 23%-50% of IBD patients experience loss of response (LOR) to these biologics during subsequent treatment[11,12]. These patients not only fail to benefit from anti-TNF therapies but also suffer from the side effects of anti-TNF drugs, including increased susceptibility to infection, autoimmune diseases, and malignant tumors[13,14]. In addition, they face a serious financial burden. A retrospective study reported that direct healthcare expenditures increased significantly after the initiation of anti-TNF therapy and remained higher than preinitiation costs for up to 5 years[15].

Hence, it is important to assess the therapeutic response to anti-TNF agents in IBD before initiating treatment. In this review, we conducted a comprehensive search of studies to summarize relevant predictors of anti-TNF nonresponse in IBD and discuss the next steps of treatment for patients with primary or secondary nonresponse (SNR) to anti-TNF agents.

LITERATURE SEARCH STRATEGY

We conducted a search on PubMed and Web of Science. Keywords used include “inflammatory bowel disease”, “Crohn's disease”, “Ulcerative colitis”, “Tumor necrosis factor antagonists”, “anti-TNF”, “infliximab”, “adalimumab”, “certolizumab”, “golimumab”, “primary nonresponse”, “secondary nonresponse”, and “loss of response”. This review included articles, reviews and guidelines that investigated predictors of failure of TNF antagonists in IBD or optimized treatment (Supplementary Figure 1).

DEFINITION

Primary nonresponse

There is no consensus on the definition of primary nonresponse (PNR) in IBD patients as definitions vary across studies. Papamichael *et al*[11] defined PNR as a lack of objectively assessed improvement in baseline inflammatory signs after induction treatment in the presence of adequate concentrations of the drug and in the absence of antidrug antibodies (ADAs). In a cohort study, PNR was classified as treatment failure or use of corticosteroids (new prescription or previous dose not discontinued) or failure to reduce C-reactive protein (CRP) to 3 mg/L or less or to decrease by 50% or more from baseline and failure to decrease Harvey-Bradshaw Index score to 4 or less or by 3 or more from baseline before week 14 [16]. In general, PNR refers to the absence of improvement in clinical symptoms or objective measures during the induction phase[17-19]. The incidence of PNR has been reported to range from 13%-40%[7,20,21].

Secondary nonresponse

SNR, also named LOR, describes the clinical phenomenon of patients who have an initial response to biologics but then subsequently lose this response[22]. Notably, the two features of the SNR are that the patient's symptoms improved

during the initial treatment and that the recurrence of symptoms can only be due to the inflammatory response of IBD and not due to concurrent infection, fibrous stenosis, *etc*.[23]. SNR eventually occurs in 20%-50% of patients[12,24,25]. A recent meta-analysis found that the mean percentages of patients with SNR to infliximab, adalimumab, and certolizumab were 37.8%, 35.4%, and 43.3%, respectively[26].

PREDICTORS OF PNR

Clinical features

Age: Real-world data suggest that elderly individuals with CD benefit less from infliximab and adalimumab at 12 wk [27]. In the precision-3 study, CD patients treated with certolizumab had a reduced probability of achieving a primary response as they aged[28]. However, several other studies have reported no correlation between age and PNR to anti-TNF in CD[21,29]. In UC patients, Arias *et al*[30] found that the benefit was greater when the baseline age was less than 40 years, whereas other studies did not show the impact of age on the efficacy[31,32]. Differences between the results may have originated from variations in designs and how outcomes were defined.

Gender: A single-center study in Britain involving CD patients reported that men were significantly less likely to PNR to infliximab[21]. Another Korean study showed that among CD patients, men benefited from clinical remission at week 14 more than women[29]. However, many researchers have not found an association between sex and PNR to anti-TNF therapy in CD[33-35]. Similarly, the influence of gender on anti-TNF therapy cannot be clearly defined in UC patients. Sandborn *et al*[36] reported that women responded better when assessing the efficacy of golimumab at week 6. Other studies did not report that sex could predict TNF antagonists response in UC[30,37].

Smoking: Smoking is an environmental risk factor for CD[38] and appears to be associated with nonresponse to anti-TNF therapy in CD patients. Analysis from the precision-3 study suggested that nonsmokers are more likely to achieve early clinical remission than smokers[28]. Zorzi *et al*[39] identified a positive association between smoking and anti-TNF nonresponse in CD patients by Cox proportional hazards regression. In addition, a meta-analysis published in 2021 revealed that when smoking status was defined smoking was significantly associated with a reduction in response to infliximab or adalimumab in patients with CD[40]. However, the negative effect of smoking on response was not found in another earlier meta-analysis[41]. Studies of UC have also reported inconsistent results. One Italian study found a significantly lower response to infliximab in ex-smokers[42], while others did not reach this conclusion[37,43]. The conflicting findings may be due to different definitions of smoking among the studies. In summary, smoking cessation is recommended for current smokers diagnosed with IBD[44].

Previous surgery: Although treatment strategies for IBD have changed, 17.4%-25% of patients with CD still require surgery[45-47]. Macaluso *et al*[27] used a logistic regression model to identify a history of previous surgery as an independent risk factor for PNR in CD patients. Another group reported similar results, showing that CD patients without previous surgery had a greater chance of achieving initial remission than patients with previous surgery, with a hazard ratio of 1.387[28]. CD patients with previous surgery had a lower response rate[48]. A study involving 201 CD patients also demonstrated that previous surgery was an independent predictor of PNR[34].

Disease duration: The analysis of pooled data from CD studies indicates that CD with a shorter disease duration is associated with a superior early response[49]. In the MODIFY study, patients who received early adalimumab achieved a higher clinical response and remission rate at week 26 than those who received delayed treatment[50]. This correlation has also been confirmed by a recent meta-analysis[51]. Studies have reported that among UC patients, a shorter disease duration is associated with a better response to anti-TNF drugs[32,52]. However, in general, authors did not find a positive association between long disease duration and anti-TNF nonresponse[31,48,53]. Although the current studies available cannot explain the underlying reasons for poorer response to anti-TNF in IBD with a longer disease duration, it is intuitive that a longer disease duration may contribute to the development of fibrosis, making earlier treatment attractive to patients[54].

Phenotype: The disease phenotype seems to be related to anti-TNF treatment response. In CD patients, isolated ileitis was inversely associated with the anti-TNF response, whereas the opposite was true for isolated colitis[29,48].

Pharmacokinetic

The pharmacokinetic (PK) of anti-TNF consists of four processes: absorption, distribution, metabolism, and elimination [55]. PK failures are characterized by undetectable or subtherapeutic drug concentrations associated with rapid nonimmune clearance or immunogenicity as well as the development of ADAs[56].

Drug concentration and antidrug antibodies: Several studies have demonstrated that subtherapeutic drug concentration is a predictor of PNR, with drug concentrations lower in IBD patients who failed to respond to anti-TNF therapy than in responders[16,57]. Post hoc analysis of data from the MUSIC trial data showed that CD patients with higher levels of certolizumab were more likely to achieve endoscopic response and remission at week 10[58]. Ding *et al*[17] suggested that low anti-TNF levels and the formation of ADAs could predict PNR in CD patients. The same results were reported in another study involving patients with UC[59].

Weight: Weight is a predictor of anti-TNF nonresponse. In a multicenter cohort study, high body mass index (BMI) at baseline in CD patients was associated with an increased risk of PNR[16]. Similar results were reported in another study [60]. In UC patients, Kurnool *et al*[61] reported that an increase in BMI had a negative impact on the response to anti-TNF drug therapy. The reason may be that, on the one hand, obesity induces a proinflammatory state[62], and on the other hand, the proteolytic clearance of immunoglobulins is usually related to weight, that is, the higher the weight is, the faster the clearance[63,64].

Serum albumin: Serum albumin levels predict the PK of anti-TNF therapy. A recent prospective study noted that low albumin levels at baseline in IBD patients predicted low infliximab concentrations at week 14[16]. Several other studies have reached similar conclusions[57,63]. One study of patients with UC found significantly higher serum albumin in responders than in primary nonresponders[65]. This effect occurs because albumin is the main transporter of drugs in blood, and serum albumin binds anti-TNF drugs to protect against degradation[66].

Fcγ receptor type IIIA: Single nucleotide substitutions within the Fcγ receptor type IIIA (FCGR3A) gene result in allelic variations, one valine (V) or one phenylalanine (F) at amino acid position 158. Functional polymorphisms in FCGR3A are significantly associated with response to anti-TNF therapy in CD patients[67]. Bek *et al*[67] used mono-compartmental population modeling to describe the PK of infliximab and found that the FCGR3A-158V/V genotype was associated with increased elimination of infliximab[67]. Further studies identified the FCGR3A VV phenotype as an independent predictor of ADAs generation and associated with a reduced clinical response in IBD patients at the end of induction[68].

Pharmacodynamic

Pharmacodynamic (PD) failure is associated with underlying non-TNF-driven inflammation characterized by no improvement in symptoms even at sufficient concentrations and without ADAs[56].

Pharmacokinetic/pharmacodynamic modeling: Kimura *et al*[69] developed Pharmacokinetic/pharmacodynamic (PK/PD) modeling to predict IBD response to infliximab during induction therapy. Another team of researchers in Japan developed a PK/PD model to calculate the $K^{anti\text{-}TNF\alpha}{}_0/K^{else}$ ratio to predict the PNR to TNF in IBD patients at the second administration[70]. The validity of this model remains to be tested in larger populations.

Biologic markers

C-reactive protein: Several studies have investigated the relationship between CRP levels and anti-TNF responses. A multicenter retrospective study in Korea demonstrated that UC patients with CRP ≥ 3 mg/dL were more likely to achieve clinical remission at week 8[71]. This was also observed in CD treated with certolizumab[72]. However, opposite results were reported in another retrospective study of CD patients[73]. Presumably, high baseline CRP will exclude some patients with noninflammatory functional symptoms and predict a higher response, but it may also reflect a higher inflammatory load with increased drug loss[74].

Antineutrophil cytoplasmic antibody and anti-*Saccharomyces cerevisiae* antibody: In a cohort study involving 90 UC patients, a greater proportion of antineutrophil cytoplasmic antibody (ANCA)-negative patients achieved clinical response during infliximab induction than ANCA-positive patients[75]. Another study in CD patients found that positive perinuclear ANCN (pANCA) is a predictor of anti-TNF nonresponse[76]. In a meta-analysis, pooled results showed that pANCA-negative patients with IBD had a nearly twofold higher response to anti-TNF therapy than pANCA -positive patients[77]. A single-center study evaluating pANCA and anti-*Saccharomyces cerevisiae* antibody (ASCA) simultaneously found that pANCA+/ASCA- serotypes significantly reduced early clinical response to infliximab in CD patients[78].

Fecal calprotectin: Fecal calprotectin (FC) is an indicator of gut inflammation and disease burden in IBD. Beltrán *et al*[79] noted that FC was higher in PNR patients with CD than in responders at weeks 0, 6, and 14, with a statistically significant difference only at week 0. Another study in UC patients also showed that early high FC was predictive of infliximab nonresponse[52]. Pavlidis *et al*[80] suggested that a decrease in FC of less than 70% after induction with anti-TNF drugs could predict PNR in patients with CD. However, some authors have not shown a relationship between FC and anti-TNF PNR in UC patients[81,82].

Fecal lactoferrin: Fecal lactoferrin (FL) can be used to monitor intestinal inflammation in IBD[83]. A retrospective study involving IBD demonstrated that dynamic monitoring of FL could distinguish responders from primary nonresponders, with two sustained drops in FL observed in responders during induction therapy[84].

Genetic markers

TNF and TNF-receptor superfamily genes: Genetic polymorphisms associated with TNF and TNF receptors have been widely studied for their ability to predict the response to anti-TNF therapy. In a clinical trial studying CD, patients homozygous for the TNF/Lymphotoxin alpha (LTA) polymorphism, the LTA NcoI-TNFc-aa13L-aa26 haplotype 1-1-1-1, showed early nonresponse to infliximab[76]. Another study demonstrated that TNF-308 (rs1800629) was associated with response to anti-TNF therapy, and the presence of the minor allele (A) was associated with increased odds of nonresponse to anti-TNF therapy in IBD[85]. For TNF-receptor superfamilies (TNFRSF), Steenholdt *et al*[86] found that CD patients carrying the TNFRSF1B minor allele rs1061622 had a better response to infliximab induction therapy. In a Japanese study, TNFRSF1A (rs767455_G) and TNFRSF1B (rs1061624_A-rs3397_T) were associated with poor response in CD patients[87] and these results were replicated in another Spanish study[88]. Additionally, a meta-analysis indicated

that TNFRSF1A (rs4149570) significantly improved anti-TNF responses in IBD[67].

Autophagy-related 16 like 1: Autophagy-related 16 like 1 (ATG16L1) is a risk factor for CD[89]. Koder *et al*[90] found a strong association between ATG16L1 (rs10210302) and response to adalimumab treatment in the CD population, with the TT genotype showing a better response after 12 wk of adalimumab treatment. Future studies on the relationship between ATG16L1 and the anti-TNF response are necessary to clarify these effects.

Apoptosis genes: Infliximab and adalimumab induce apoptosis by binding to membrane-bound TNF-α, which is the main mechanism of their efficacy[54]. An earlier study observed the strongest association between the Fas ligand -843 TT genotype and nonresponse to infliximab in CD patients[91]. Furthermore, Hlavaty *et al*[92] developed a novel apoptotic pharmacogenetic index based on three single nucleotide polymorphisms (Fas ligand-843 C/T, Fas-670 G/A, and Caspase9 93 C/T), with a higher score indicating a better response to anti-TNF therapy.

Nucleotide-binding oligomerization domain 2: Nucleotide-binding oligomerization domain 2 (NOD2) mutations predict an increased risk of complications related to CD[93]. Further studies showed that NOD2 mutations were less responsive to anti-TNF therapy than wild-type NOD2 in CD patients[94]. Another study demonstrated that CD patients with either NOD2 variants alone or in combination with ATG16L1 variants were more likely to receive intensive biologic therapy, which may indicate that NOD2 variants have a negative impact on response to biologic therapy[95]. However, this effect was not observed in another trial[96].

Cytokines

Interleukin: One study conducted in CD patients found that primary nonresponders had significantly higher interleukin-8 (IL-8) concentrations at baseline[97]. In addition, the level of IL-6 in responders was significantly lower than that in primary nonresponders at week 2 and week 6[97]. Another study of CD noted that IL17A and IL1B expression was significantly upregulated in anti-TNF refractory patients during anti-TNF therapy[98]. Oncostatin M (OSM), a member of the IL-6 cytokine family, has been shown to disrupt epithelial barrier function and drive intestinal inflammation[99]. An analysis of more than 200 IBD patients treated with anti-TNF therapy found higher baseline levels of OSM expression in those who failed anti-TNF therapy[100]. A cross-sectional study suggested that higher levels of OSM in the colon were associated with PNR to anti-TNF in patients with IBD[101].

Triggering receptor expressed on myeloid cells 1: Triggering receptor expressed on myeloid cells 1 (TREM1) expression has been proposed as a potential marker for predicting response to anti-TNF therapy in IBD patients. Gaujoux *et al*[102] demonstrated that TREM1 can be an ex-ante predictor of the anti-TNF response and that TREM1 Levels were downregulated in nonresponders, with a prediction accuracy of 94%. This phenomenon is also found in the inflamed mucosa.

Gut microbes

Several studies have shown that gut microbes predict nonresponse to anti-TNF treatment in IBD. Magnusson *et al*[103] found that responders had lower dysbiosis indexes, a higher abundance of *Faecalibacterium prausnitzii* (*F. prausnitzii*) at baseline, and an increase in the abundance of *F. prausnitzii* during induction therapy compared with nonresponders. Another study found that high abundances of the genera *Blautia*, *Faecalibacterium*, *Roseburia*, and *Negativibacillus* at baseline were inversely associated with responsiveness to infliximab in CD[104]. In the same study, a high abundance of *Sutterella*, *Roseburia*, and *Intenstinibacter* appeared to predict response to infliximab in UC patients[104]. Alatawi *et al*[105] detected a reduction in the abundance of short-chain fatty acid-producing bacteria, including *Anaerostipes*, *Coprococcus*, *Lachnospira*, *Roseburia*, and *Ruminococcus,* in IBD patients unresponsive to anti-TNF therapy[105]. Nevertheless, a European multicenter study found no differences in the microbiota of anti-TNF therapy responders *vs* nonresponders in IBD[106]. Indicators that predict PNR to anti-TNF agents in patients with IBD are listed in Table 1.

PREDICTORS OF SECONDARY NONRESPONSE

Clinical features

Gender: A retrospective study identified that women were more likely to develop SNR to anti-TNF[107]. Another multicenter retrospective study found a similar result in the CD subgroup[108]. An earlier systematic review noted the male sex was a predictor of LOR in CD[109]. A single-center study demonstrated a significantly higher likelihood of SNR in men with UC[110]. However, no association has been reported between gender and SNR in most studies[21,30,31,37].

Smoking: Sandborn *et al*[28] found that current smoking was associated with LOR in individuals diagnosed with CD. This result was also validated in another single-center study[39]. Chaparro *et al*[111] reported that smoking was associated with the occurrence of LOR in CD.

Previous surgery: A Sicilian study of CD reported that previous surgery was associated with a low rate of clinical remission at 1 year[27]. However, many studies have not demonstrated a relationship between previous surgical history and SNR to anti-TNF therapy in CD[16,112].

Disease duration: Panaccione *et al*[49] showed that patients with CD whose duration was less than 1 year benefited more in maintaining remission. A retrospective cohort study reported that CD patients with a disease duration of more than 2 years had a significantly higher rate of SNR[113]. A subgroup analysis of the placebo-controlled CHARM trial also

Table 1 Predictors of primary nonresponse in Crohn's disease and ulcerative colitis

Predictor	Crohn's disease	Ulcerative colitis
Clinical features		
Age	Yes: Older[27,28]; No[21,29]	Yes: Older[30]; No[31,32]
Gender	Yes: Male[21], female[29]; No[33-35]	Yes: Male[36]; No[30,37]
Smoking	Yes: Smoker[28,39,40]; No[41]	Yes: Ex-smoker[42]; No[37,43]
Previous surgery	Yes[27,28,34,48]	
Disease duration	Yes: Longer[49-51]; No[48]	Yes: Longer[32,52]; No[30,53]
Phenotype	Yes: Isolated ileitis[29,48]	
Pharmacokinetic		
Drug concentration	Yes: Low[16,17,57,58]	Yes: Low[57,59]
Antidrug antibodies	Yes[17]	Yes[59]
Weight	Yes: High[16,60]	Yes: High[61]
Serum albumin	Yes: Low[57]	Yes: Low[57,65]
FCGR3A	Yes: FCGR3A-158V/V[67,68]	Yes: FCGR3A-158V/V[68]
Pharmacodynamic		
PK/PD model	Yes[69,70]	Yes[69,70]
Biologic markers		
CRP	Yes: Low[72], High[73]	Yes: Low[71]
ANCA and ASCA	Yes: pANCA+[76,77]	Yes: ANCA+[75], pANCA+[77], pANCA+/ASCA-[78]
Fecal calprotectin	Yes: High[79]	Yes: High[52]; No[81,82]
Fecal lactoferrin	Yes: High[84]	Yes: High[84]
Genetic markers		
TNF genes	Yes: Lymphotoxin alpha NcoI-TNFc-aa13L-aa26 haplotype 1-1-1-1[76], TNF-308A[85]	Yes: TNF-308A[85]
TNFRSF	Yes: TNFRSF1A (rs767455_G)[87], TNFRSF1B (rs1061624_A-rs3397_T)[87]	
ATG16L1	Yes: ATG16L1 (rs10210302_CC)[90]	
Apoptosis genes	Yes: Fas ligand-843 TT genotype[91]	
NOD2	Yes: NOD2 mutation[94,95]	
Cytokines		
Interleukin	Yes: IL-8 (high)[97], IL-6 (low)[97], IL17A (high)[98], IL1B (high)[98], OSM (high)[100,101]	Yes: OSM (high)[100,101]
TREM1	Yes: Low[102]	Yes: Low[102]
Gut microbes	Yes: Abundance of short-chain fatty acid-producing bacteria (decreased)[105]	Yes: Dysbiosis indexes (high)[103]; Abundance of short-chain fatty acid-producing bacteria(decreased)[105]

FCGR3A: Fcγ receptor type IIIA; PK/PD model: Pharmacokinetic/pharmacodynamic modeling; CRP: C-reactive protein; ANCA: Antineutrophil cytoplasmic antibody; ASCA: Anti-*Saccharomyces cerevisiae* antibody; pANCA: Perinuclear anti-neutrophil cytoplasmic antibody; TNF: Tumor necrosis factor; TNFRSF: TNF-receptor superfamily; ATG16L1: Autophagy-related 16 like 1; NOD2: Nucleotide-binding oligomerization domain 2; OSM: Oncostatin M; TREM1: Triggering receptor expressed on myeloid cells 1.

obtained a similar conclusion[114].

Phenotype: A recent study reported that accumulation of the upper digestive tract and the presence of fistulas at baseline were associated with SNR to adalimumab and infliximab in CD patients[27]. Another study involving 93 individuals verified that nonstructuring nonpenetrating CD was associated with sustained remission[39]. CD with concurrent fistula or stenosis had a lower clinical remission rate[115].

Pharmacokinetic

Drug concentration and antidrug antibodies: A multicenter cohort study confirmed that concentrations of infliximab < 7 mg/L and adalimumab < 12 mg/L were independently associated with SNR in CD patients[16]. A prospective study indicated that the trough level (TL) of infliximab < 5.5 μg/mL in patients with IBD was the best threshold to predict LOR [116]. Alternatively, the generation of ADAs, which in combination with circulating drugs also leads to a reduction in drug concentration, is associated with anti-TNF LOR in IBD[117].

Weight: Kennedy *et al*[16] found that obesity at baseline was associated with adalimumab treatment failure at week 54 in patients with CD. Another study also reported that IBD patients with a high BMI displayed a high rate of LOR[118]. In IBD patients treated with adalimumab, SNR was increased in those with BMI ≥ 30 kg/m^2 compared with those with BMI < 30 kg/m^2[119].

Serum albumin: In CD patients treated with certolizumab, low albumin predicted SNR[28]. Higher albumin levels were associated with lower LOR in IBD patients treated with infliximab[119]. A prospective study found that IBD patients with low albumin serum concentrations at baseline had a significantly increased risk for SNR to anti-TNF and that normalization of albumin levels during treatment did not reduce this risk[120].

Serum γ-globulin: A German study from IBD found a positive association between elevated serum γ-globulin concentrations and the risk of SNR to anti-TNF therapy[120]. Higher γ-globulin concentrations imply increased B-cell activity, resulting in increased ADAs production[120].

Matrix metalloproteinase 3: Matrix metalloproteinase 3 (MMP3) expression is significantly upregulated in inflamed colonic segments of IBD patients, suggesting the possible involvement of this enzyme in the inflammatory process[121, 122]. A retrospective study from Italy showed that in IBD patients, MMP3 levels were significantly lower in responders (11.48 ng/mL) than in nonresponders (25.96 ng/mL) at week 52[123]. In the same study, MMP3 levels tended to be higher in patients without ADAs than in those with ADAs[123]. According to a previous report, MMP3 cleaved infliximab and adalimumab which may result in reduced drug efficacy[124].

Fcγ receptor type IIIA: A Spanish team found higher serum concentration levels of both infliximab and adalimumab in FCGR3A FF carriers than in FCGR3A VV carriers during maintenance therapy in IBD and found that the proportion of VV patients who developed ADAs was significantly higher than that of FF patients diagnosed with IBD[125].

Human leukocyte antigen: The value of human leukocyte antigen-DQA1*05 (HLA-DQA1*05) in predicting anti-TNF-ADAs production has been reported in several studies. A genome-wide analysis of 1240 subjects in the PANTS cohort revealed that approximately 40% of Europeans carried HLA-DQA1*05 and significantly increased rates of ADAs production[126]. Wilson *et al*[127], using genotypic analysis, showed that HLADQA1*05 was independently associated with LOR to infliximab and increased ADAs in IBD.

Biologic markers

C-reactive protein: Post hoc analysis of ACCENT I, indicated that high levels of CRP before treatment predicted an increased likelihood of maintaining remission[128]. A study of IBD found that CRP > 5 mg/L was an independent predictor of SNR[116]. However, a Hungarian study reported that low levels of CRP at week 12 were associated with clinical remission at week 52 in CD patients on adalimumab[129]. Additionally, Angelison *et al*[82] did not find an association between CRP and SNR to anti-TNF agents in UC.

Antinuclear antibody: Among patients with IBD, those with positive antinuclear antibody (ANA) at baseline had higher odds of LOR to anti-TNF[130]. More studies are needed to investigate the relationship between ANA and response to anti-TNF therapy in the future.

Fecal calprotectin: Analyses from the 7-year PRECiSE 3 study revealed that an increase in FC implies an increased risk of LOR to anti-TNF[28]. However, Deshpande *et al*[131] reported that FC levels at week 14 could not predict the recurrence of CD one year later. Differences in the timing of FC measurement and sample size may have contributed to this discrepancy.

Fecal lactoferrin: Sorrentino *et al*[132] found that FL levels before and after anti-TNF treatment could be used to distinguish responders, partial responders, and nonresponders in IBD patients with suspected LOR[132]. In the same study, they proposed that responders had normal FL both before and after administration, partial responders had elevated FL before administration, partial FL decreased after administration but remained well above the normal threshold, and FL increased after LOR administration[132].

Genetic markers

TNF and TNF-receptor superfamily genes: Currently, only a retrospective cohort study of CD has demonstrated that carrying the TNFRSF1B minor allele rs976881 was associated with LOR to infliximab[86]. More studies are urgently needed to explore the relationship between TNF and TNFRSF genes and SNR to anti-TNF therapy.

Cytokines

Interleukin: Higher baseline OSM in IBD patients with SNR to infliximab was found in a UK study[100]. Bertani *et al*[133]

demonstrated that in CD patients treated with infliximab, those with low OSM levels at baseline and week 14 were more likely to achieve clinical remission at week 54[133]. Moreover, the level of OSM in patients with mucosal healing was significantly lower than that in patients without mucosal healing at week 54[133]. We summarize the predictors of SNR in Table 2.

OPTIMAL MANAGEMENT OF ANTI-TNF NONRESPONSE

Assessment

PNR or SNR to anti-TNF therapy was determined according to clinical symptoms, laboratory tests, endoscopy, imaging examinations, *etc.* It is worth noting that conditions such as poor adherence[134], improper drug storage medication storage[135], and co-infection[23] need to be excluded during assessment.

Therapeutic drug monitoring

The British Society of Gastroenterology consensus defines therapeutic drug monitoring (TDM) as, the measurement of the drug (± ADAs) levels to assess compliance, drug metabolism, and immunogenicity with a view to guide dose adjustments or switch off therapy[136]. TDM can be used reactively or proactively. The American Gastroenterological Association recommends reactive TDM for adults who fail to respond to anti-TNF therapy[9]. A target TL of at least 5 μg/mL, 7.5 μg/mL, and 20.0 μg/mL for infliximab, adalimumab, and certolizumab, respectively, is suggested[9]. Papamichael *et al*[137] recommend a minimum drug concentration of at least 2.5 μg/mL at week 6 and a trough concentration of at least 1 μg/mL of golimumab during maintenance therapy. Several recent reviews showed that TDM was more beneficial than empirical strategies in terms of cost-effectiveness[138-140]. TDM plays an important role in optimizing anti-TNF therapy.

Management of PNR

There is no consensus on the optimal management of PNR to TNF antagonists. A review proposed that the management of IBD patients with PNR to anti-TNF therapy consists of three major steps: prediction, prevention, and therapeutic intervention[11]. Clinical features, pharmacokinetics, genetic phenotypes, *etc*., can predict the development of PNR. Preventive measures to avoid PNR to anti-TNF include counseling patients to quit smoking, weight intervention, *etc*.[11, 17]. For IBD patients with PNR, empirical intervention can be performed, switching to another TNF antagonist, or switching to a biological agent of a different mechanism, is desirable[141]. Ding *et al*[17] suggested that a second TNF antagonist be administered when the patient is PNR to the first TNF antagonist. If the treatment fails again, switching out of class should be considered.

Some scholars have also proposed that the medication of primary nonresponders can be adjusted according to TDM. With the help of TDM, rational and optimal treatment can be provided[136]. If patients have low TLs and no or low titer ADAs formation, dose optimization or the addition of an immunomodulator is recommended. When TLs are low and high-titer ADAs are detected, switching to another TNF antagonist or biologic agent with a different mechanism may be considered. For patients with therapeutic concentrations, switching out of class is suggested (Figure 1).

Management of secondary nonresponse

The detection of TNF antagonist and ADAs concentration is helpful to guide the next treatment of SNR (Figure 2).

Dose escalation: Dose intensification can reverse nonresponse to anti-TNF in IBD patients with subtherapeutic concentrations and no or low concentrations of ADAs. A meta-analysis reported a 34% need for anti-TNF dose escalation in CD at a median follow-up of 1 year, with pooled rates of 38%, 32%, and 2% for infliximab, adalimumab, and certolizumab, respectively[26]. A multicenter cohort study in Belgium found that 34% of CD patients treated with adalimumab required an increased dose to maintain clinical response, and clinical response was induced again in 67% of these patients[142]. Billioud *et al*[109] concluded that among CD patients who experienced LOR to adalimumab, 71.4% regained response and 39.9% achieved remission after dose optimization. Interestingly, a post hoc analysis of the TAXIT trial showed a significantly higher rate of clinical response with dose intensification, regardless of the presence of ADAs[143]. Meanwhile, Bodini *et al*[144] have suggested that, based on clinical need, anti-TNF doses can be increased, even in older patients of patients receiving combination therapy, with little risk of adverse reactions occurring.

Addition of an immunomodulator: The addition of an immunomodulator is a good option for IBD patients receiving anti-TNF therapy in whom subtherapeutic and no or low concentrations of ADAs are detected. For example, van Schaik *et al*[145] observed a significant increase in mean trough concentrations and a significant decrease in the incidence of ADAs in the infliximab combined with azathioprine group compared with infliximab alone in patients with IBD, whereas no differences were observed in the adalimumab combination *vs* monotherapy groups[145]. Another study involving patients with CD reported that, for both infliximab and adalimumab, combined immunomodulators reduced the risk of ADAs formation[16]. In the SONIC trial, the response rate in corticosteroid-free clinical remission at week 50 was significantly higher with infliximab adding immunomodulator than with monotherapy (55.6% *vs* 39.6%)[146]. In the UC-SUCCESS trial, infliximab plus an immunomodulator was also superior in achieving corticosteroid-free clinical remission [147]. In a 2-year cohort study of 46 patients with IBD, the addition of a low-dose immunomodulator, either azathioprine, methotrexate, or mycophenolate mofetil, reversed clinical response in approximately 50% of IBD patients who had failed to respond to anti-TNF monotherapy[148]. With regard to when to discontinue immunomodulators, Drobne *et al*[149]

Table 2 Predictors of secondary nonresponse in Crohn's disease and ulcerative colitis

Predictor	Crohn's disease	Ulcerative colitis
Clinical features		
Gender	Yes: Female[107,108], male[109]; No[21]	Yes: Female[107], male[110]; No[31,37]
Smoking	Yes: Smoker[28,39,111]; No[41]	
Previous surgery	Yes[27]; No[16,112]	
Disease duration	Yes: Longer[49,113,114]	
Phenotype	Yes: Upper digestive tract[27], fistula[27,115], stenosis[115]	
Pharmacokinetic		
Drug concentration	Yes: Low[16,116]	Yes: Low[116]
Antidrug antibodies	Yes[117]	Yes[117]
Weight	Yes: High[16,118,119]	Yes: High[118,119]
Serum albumin	Yes: Low[28,119,120]	Yes: Low[119,120]
Serum γ-globulin	Yes: High[120]	Yes: High[120]
MMP3	Yes: High[123]	Yes: High[123]
FCGR3A	Yes: FCGR3A VV[125]	Yes: FCGR3A VV[125]
HLA	Yes: HLADQA1*05[127]	Yes: HLADQA1*05[127]
Biologic markers		
CRP	Yes: Low[128], high[129]	No[82]
ANA	Yes: ANA+ [130]	Yes: ANA[130]
Fecal calprotectin	Yes: High[28]; No[131]	
Fecal lactoferrin	Yes: High[132]	Yes: High[132]
Genetic markers		
TNFRSF	Yes: TNFRSF1B (rs976881)[86]	
Cytokines		
Interleukin	Yes: OSM (high)[100,133]	Yes: OSM (high)[100]

MMP3: Matrix metalloproteinase 3; FCGR3A: Fcγ receptor type IIIA; HLA: Human leukocyte antigen; CRP: C-reactive protein; ANA: Antinuclear antibody; TNFRSF: Tumor necrosis factor receptor superfamily; OSM: Oncostatin M.

suggest that at least 6 mo of combination therapy is required. Mahmoud *et al*[150] compared different durations of combination therapy in relation to LOR and found no significant difference between durations of combination therapy (< 0.5 years, 0.5-1 year, 1-2 years, and > 2 years); however, durations of combination therapy longer than 2 years were associated with a lower risk of ADAs formation.

Switch within class: In the case of subtherapeutic concentrations with high titers of ADAs, switching within class to another anti-TNF agent should be considered. A retrospective study of IBD showed that when ADA titers of infliximab and adalimumab were > 9 μg/mL and 4 μg/mL, respectively, switching within class achieved a longer duration of response compared with dose intensification[151]. In another study of IBD, switching patients positive for ADAs to another anti-TNF agent achieved a response rate of 92%, whereas dose optimization achieved a response rate of 17%[152]. In cases where the first anti-TNF drug failed, switching to another drug achieved remission in approximately 50% of patients, an effect that has been reported in several other studies[153,154]. Moreover, a systematic review reported that switching to a second anti-TNF agent led to successful induction of remission in 46% of patients with IBD who had failed the first anti-TNF agent[155]. Of note, the previous generation of anti-TNF antibodies increases the risk of the generation of a second anti-TNF antibody in IBD[156]. Therefore, when switching to another anti-TNF agent, a combination of immunosuppressive agents is appropriate[136,157].

Switch out of class: If TL is sufficient with high ADAs, it is recommended that the patient switches to a drug that exerts its effects through another mechanism of action, considering that TNF-α is not the primary pathogenesis. Alternatively, for low TLs with high titers of ADAs, switching out of class is also effective. Subgroup analyses of trials investigating vedolizumab[158], ustekinumab[159,160], and tofacitinib[161] all showed that patients who had failed anti-TNF therapy

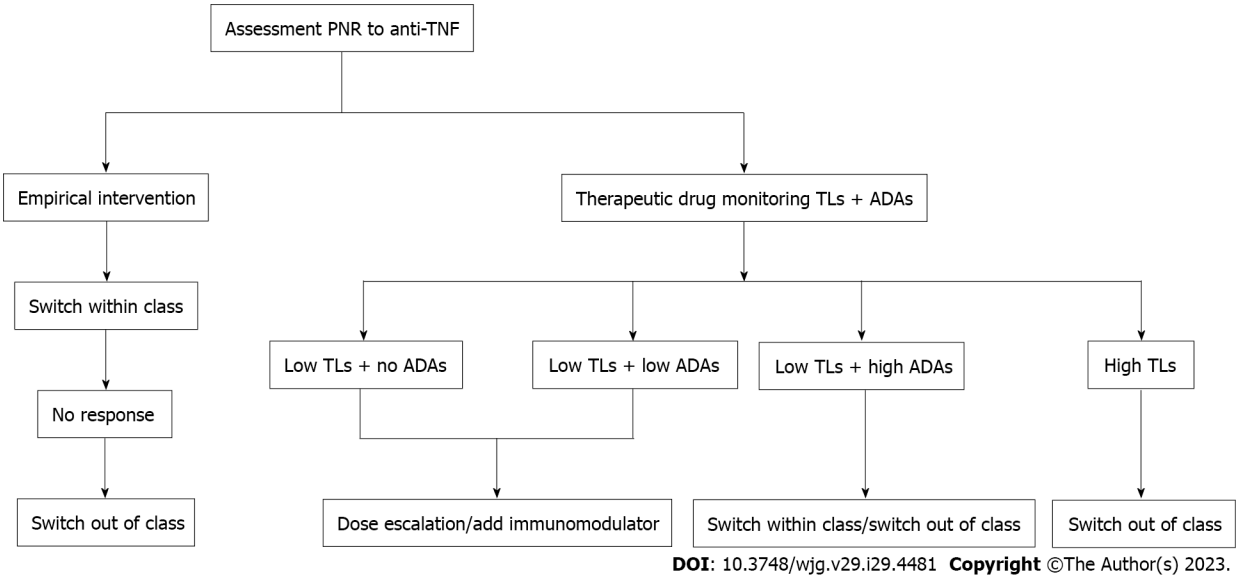

Figure 1 Flow diagram for management of primary nonresponse to tumor necrosis factor antagonists. PNR: Primary nonresponse; TNF: Tumor necrosis factor; TL: Trough level; ADA: Antidrug antibody.

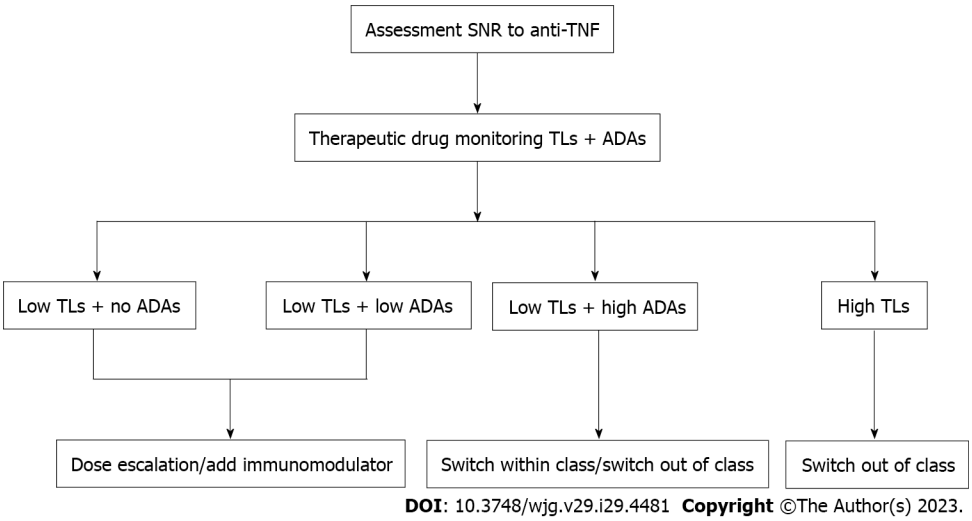

Figure 2 Flow diagram for management of secondary nonresponse to tumor necrosis factor antagonists. SNR: Secondary nonresponse; TNF: Tumor necrosis factor; TL: Trough level; ADA: Antidrug antibody.

benefited from treatment with a novel agent. One study involving 128 CD patients who had failed previous anti-TNF therapy reported that the corticosteroid-free clinical response rates of vedolizumab and ustekinumab treatment at weeks 12, 24, and 52 were 22.7%, 29.7%, 26.8% and 27.1%, 42.4%, 45.9% respectively[162]. Furthermore, propensity score matching concluded that patients who failed anti-TNF therapy benefited more from ustekinumab than vedolizumab[162].

CONCLUSION

IBD is incurable, and anti-TNF therapy plays an important role in IBD. Although existing studies have found that previous surgical history, disease manifestations, drug concentrations, ADAs, serum albumin, ANCA, p-ANCA, ANA, *etc.* have potential predictive effects, to date, there are no practically available indicators that can predict response to TNF antagonists in patients with IBD. Further research is needed to verify the accuracy of existing predictors or discover new biomarkers to achieve personalized treatment for patients with IBD.

TDM forms the core of an optimal strategy for treating IBD. It is recommended to optimize the dose or add immunomodulators when patients with low TLs and no or low titer ADAs. For nonresponders with low TLs and high titer ADAs, switching to another TNF antagonist or biologic agent with a different mechanism can be suggested. When TLs are sufficient, patients can consider switching to another biological agent. In the future, more large randomized

controlled trials are needed to investigate the efficacy of different next-step therapies for IBD patients who do not respond to anti-TNF.

FOOTNOTES

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