World Journal of Gastrointestinal Pathophysiology

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4291/wjgp.v5.i3.293

World J Gastrointest Pathophysiol 2014 August 15; 5(3): 293-303
ISSN 2150-5330 (online)

REVIEW

Predictors of response to anti-tumor necrosis factor therapy in ulcerative colitis

Evanthia Zampeli, Michalis Gizis, Spyros I Siakavellas, Giorgos Bamias

Evanthia Zampeli, Gastroenterology Department, Alexandra General Hospital, 11528 Athens, Greece
Michalis Gizis, Spyros I Siakavellas, Giorgos Bamias, Academic Department of Gastroenterology, Ethnikon and Kapodistriakon University of Athens, Laikon Hospital, 15235 Athens, Greece
Author contributions: Zampeli E, Gizis M and Siakavellas SI reviewed the literature; Zampeli E, Gizis M, Siakavellas SI and Bamias G analyzed the data; Zampeli E and Bamias G designed the structure of the review; Zampeli E and Bamias G wrote the paper.
Correspondence to: Giorgos Bamias, Consultant in Gastroenterology, Academic Department of Gastroenterology, Ethnikon and Kapodistriakon University of Athens, 17 Agiou Thoma st., 15235 Athens, Greece. gbamias@gmail.com
Telephone: +30-21-06456504 Fax: +30-21-07791839
Received: January 4, 2014 Revised: March 7, 2014
Accepted: June 10, 2014
Published online: August 15, 2014

Abstract

Ulcerative colitis (UC) is an immune-mediated, chronic inflammatory disease of the large intestine. Its course is characterized by flares of acute inflammation and periods of low-grade chronic inflammatory activity or remission. Monoclonal antibodies against tumor necrosis factor (anti-TNF) are part of the therapeutic armamentarium and are used in cases of moderate to severe UC that is refractory to conventional treatment with corticosteroids and/or immunosuppressants. Therapeutic response to these agents is not uniform and a large percentage of patients either fail to improve (primary non-response) or lose response after a period of improvement (secondary non-response/loss of response). In addition, the use of anti-TNF agents has been related to uncommon but potentially serious adverse effects that preclude their administration or lead to their discontinuation. Finally, use of these medications is associated with a considerable cost for the health system. The identification of parameters that may predict response to anti-TNF drugs in UC would help to better select for patients with a high probability to respond and minimize risk and costs for those who will not respond. Analysis of the major clinical trials and the accumulated experience with the use of anti-TNF drugs in UC has resulted to the report of such prognostic factors. Included are clinical and epidemiological characteristics, laboratory markers, endoscopic indicators and molecular (immunological/genetic) signatures. Such predictive parameters of long-term outcomes may either be present at the commencement of treatment or determined during the early period of therapy. Validation of these prognostic markers in large cohorts of patients with variable characteristics will facilitate their introduction into clinical practice and the best selection of UC patients who will benefit from anti-TNF therapy.

Key words: Ulcerative colitis; Infliximab; Adalimumab; Anti-tumor necrosis factor; Predictors of response; Personalized treatment

Core tip: The use of anti-tumor necrosis factor (TNF) monoclonal antibodies for the treatment of ulcerative colitis has been associated with high rates of primary and secondary non-response, important safety issues and considerable cost. Selection of patients with the highest probability to response to anti-TNF treatment would overcome these problems. Analysis of the pivotal trials and accumulated experience from clinical practice has led to the identification of certain prognostic factors for favorable or adverse outcomes. These include clinical and epidemiological parameters, biological markers of inflammation, endoscopic findings, molecular signatures and pharmacological factors. Incorporation of such predictors into the current therapeutic protocols may lead to the optimization of anti-TNF treatment in ulcerative colitis.

Zampeli E, Gizis M, Siakavellas SI, Bamias G. Predictors of

response to anti-tumor necrosis factor therapy in ulcerative colitis. *World J Gastrointest Pathophysiol* 2014; 5(3): 293-303 Available from: URL: http://www.wjgnet.com/2150-5330/full/v5/i3/293.htm DOI: http://dx.doi.org/10.4291/wjgp.v5.i3.293

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon, which affects almost 0.1% of the Western population[1]. Its natural history is dominated by chronic, relapsing intestinal inflammation, extra-intestinal involvement, and the development of long-term complications, which lead a considerable percentage of patients to colectomy.

Treatment for UC has been traditionally aimed against controlling acute and chronic inflammation[2]. Conventional therapy consists of 5-aminosalicylic acid (5-ASA) compounds, whereas more severe cases are handled with steroids during the acute phase and immunosuppressants (thiopurines) as the maintenance regimen. Despite the proven efficacy of these drugs, a significant number of patients do not accomplish durable remission and/or experience side effects. Furthermore, there has been a change in the therapeutic goals in UC in recent years. Traditionally, such goals have been considered the achievement of clinical remission and the avoidance of colectomy. Nowadays, however, it has become clear that treatment should include the complete elimination of active inflammation in the colon without long-term use of corticosteroids. In this context, mucosal healing and deep remission which both indicate the absence of endoscopically and biologically (*i.e.,* serological and/or fecal inflammatory markers) evident inflammation may be the ultimate endpoint. The accomplishment of such demanding endpoints has been linked to better long-term outcomes including colectomy and cancer prevention[3].

In recent years, treatment of UC has been revolutionized by the therapeutic application of monoclonal antibodies against tumor necrosis factor (TNF) as these agents offer effective long-term treatment for the most difficult cases.

ANTI-TNF TREATMENT IN UC

There are currently three monoclonal antibodies against human TNF that are licensed for the treatment of UC, infliximab (IFX), adalimumab (ADA), and Golimumab[4]. The data regarding Golimumab are limited. Therefore, our review will focus on IFX and ADA. IFX is a chimeric mouse/human IgG1 antibody that is administered intravenously. On the other hand, ADA is a humanized IgG1 antibody administered as subcutaneous injection. The two clinical scenarios for anti-TNF therapy in UC are: firstly, outpatient cases with moderate to severe UC who are refractory or intolerant to first-line treatment; and, secondly, patients with acute severe disease refractory to intravenous steroids[4]. In regards to the latter scenario, data exist only for IFX.

Recent clinical trials have established the efficacy of anti-TNF treatment in UC. In the two pivotal IFX trials, ACT 1/2, the primary short-term (8 wk) response of moderate to severe UC to IFX has been reported to be 65.5%/69.4% for clinical response and 33.9%/39% for remission, respectively (dose regimen 5 mg/kg at 0-2-6)[5]. Among patients who responded to the induction regimen nearly 50% maintained their response at week 30. Similarly, in the definitive clinical trial (ULTRA) for ADA, short-term response at week 8 was achieved in nearly 50% of patients, whereas long-term remission rate at week 52 was 17%[6].

Despite these encouraging results, the use of anti-TNF monoclonal antibodies is compromised in clinical practice by certain issues of efficacy and safety. Anti-TNF failure is an intriguing issue as it may be attributed to both disease characteristics and the drugs' interference with the immune system. Primary non-response is characterized by lack of response to induction therapy. The incidence ranges between 20%-40% for both anti-TNF agents. Switching to another drug is common practice, with a success rate of more than 50%[7,8]. On the other hand, loss of response is defined as the recurrence of the patient's symptoms following successful induction of remission. In the case of CD it has been estimated between 23%-46%[9], whereas no solid data exists for UC. It is believed that immunogenicity underlies secondary failure, as antibodies against anti-TNF drugs and reduced trough levels have been implicated in the majority of studies[10-12]. Optimization of treatment (dose increase and/or shortening of the administration interval) leads to recovery of response in 60%-90% of patients[10].

The use of anti-TNF has also been associated with safety concerns. Among the most fearful ones are: severe infectious including reactivation of latent tuberculosis, neurological manifestations and risk of neoplasia. In addition, infusion reactions and delayed hypersensitivity to IFX occurred in 10% and 1% of patients, respectively, in the ACT trials. The most significant side effects are probably associated with long-term administration and combination with other immunomodulatory medications. It should be noted that in the ACT and ULTRA studies there were no differences between active drug and placebo.

Taken together, it is currently evident that fine-tuning of the use of anti-TNF therapy in UC is required. The ultimate goal should be to achieve maximum efficacy with a minimum risk for side effects. When therapeutic strategies are designed the following parameters should be taken into consideration: (1) the patients who receive anti-TNF therapy are the ones with the most difficult-to-treat disease; (2) the drugs' efficiencies are far from perfect with high rates of primary and secondary failures; (3) the potential for serious side effects especially with chronic use; and (4) the high cost of these medications. One significant way to address these problems and optimize the clinical use of anti-TNF agents would be

Table 1 Prognostic indicators of response to anti-tumor necrosis factor treatment in ulcerative colitis

At initiation of treatment	During treatment
Clinical and epidemiological parameters	
Severity of the disease	Early clinical response
Younger age	
Duration of colitis < 3 yr	
Extensive colitis	
Laboratory indicators	
CRP	Low CRP at week 12
Hemoglobin	Drop of serum CRP
Serum albumin	Fecal calprotectin
Immunological and genetic markers	
p-ANCA	Gene expression profiling
Pre-treatment mucosal TNF-α expression	Percentages of regulatory T cells
Mucosal expression of IL-17 and IFN-γ	
Genetic polymorphisms	
Endoscopic findings	
	Mucosal healing
Treatment-related factors	
Pharmacological history	Number of IFX infusions
Exposure to immunosuppressants	Co-administration of immunosuppressants
Response to prior treatment with infliximab	Escalation of anti-TNF therapy
	IFX trough levels
	Antibodies against anti-TNF

CRP: C-reactive protein; p-ANCA: Perinuclear antineutrophil cytoplasmatic antibodies; TNF:Tumor necrosis factor; IL: Interleukin; INF: Interferon; IFX: Infliximab.

to carefully select patients in whom there is decreased probability for primary or secondary non-response. Such an approach will ensure that the patients who receive the medications are those who will most probably benefit. As almost ten years have passed since the initial application of anti-TNF therapies in UC, analyses of the pivotal clinical trials and accumulation of clinical experience has allowed the identification of such factors that signify a better response to these treatments (Tables 1 and 2). It is the purpose of the current review to summarize information regarding prognostic markers for response to anti-TNF monoclonal antibodies in patients with UC.

PREDICTORS OF RESPONSE

Prognostic factors at the initiation of anti-TNF treatment

Clinical and epidemiological parameters: Several studies have looked into the effect that the severity of the UC episode may have on the response to anti-TNF administration. In a study by Jürgens *et al*[13], 90 UC outpatients were treated with IFX and followed for 14 wk. Disease activity was quantified by use of the Colitis Activity Index (CAI). Nearly half of the patients achieved early remission at week 14. Overall, the mean CAI dropped from 10.4 points at baseline to 5.0 at week 14 ($P < 0.001$). The authors reported a significant positive association between UC activity and response to treatment with IFX. It should be noted, however, that only a small number of severe cases were included in this study.

In a second report, 191 UC patients who received at least one infusion of IFX between 2000 and 2009 were analyzed with the aim to identify predictors of response[14]. Mean follow-up was 18 mo. Failure outcomes included primary-non response, dose-escalation, colectomy and hospitalization, which were noted in 22%, 45%, 19% and 36% of patients, respectively. In contrast to the study by Jurgens, administration of IFX for the indication of acute severe colitis was associated with a 3-fold risk for unfavorable outcome.

Park *et al*[15] studied 89 Korean patients with moderate to severe UC who were treated with IFX. Following induction, 59 patients exhibited clinical response at week 8 (66.3%). None had a colectomy within one year, in contrast to 11/30 of those who did not respond. Predictors of primary non-response to the drug were the severity of the disease before initiation as well as prior cytomegalovirus (CMV) infection of the colon. Patients with a pre-treatment Mayo score ⩾ 11 had an increased risk of colectomy (OR = 5.05, $P = 0.007$).

Analysis of the large clinical trials ACT 1 and 2- offers additional information regarding prognostic factors for colectomy (*i.e.,* failure of IFX) in patients with moderate to severe UC[16]. As reported by Sandborn *et al*[16], 630 patients who participated in the ACT trials had a complete follow-up for colectomy. A baseline Mayo score of ⩾ 10 strongly increased the risk for colectomy (HR = 1.84, $P = 0.01$).

Prognostic indicators for response to ADA in UC have also been reported recently. A placebo controlled trial of ADA for UC patients with refractory disease who were naïve to biologics evaluated the short-term efficacy of the drug[17]. At week 8, 18.5% were in remission ($P = 0.031$ *vs* placebo). Study analysis identified a trend towards less efficacy in cases of more severe disease at baseline. Patients with Mayo score ⩾ 10, CRP ⩾ 10 mg/L and extensive disease responded less favorably

Table 2 Clinical trials that reported prognostic indicators for response to anti- tumor necrosis factor treatment in Ulcerative Colitis

Ref.	Type of study	No. of patients	Anti-TNF drug	Response endpoints	Predictor of response
Arijs *et al*[26]	Cohort		IFX	Endoscopic and histological healing	Mucosal gene expression signature
Armuzzi *et al*[31]	Retrospective	88 (78.4% IFX experienced)	ADA	Clinical remission (4-54 wk)	Short-term clinical remission Low CRP at week 12 (remission at week 54) [1]*Previous immunosupressant use (lower long-term remission rates)*
Armuzzi *et al*[27]	Prospective	126	IFX	Steroid–free clinical remission Mucosal healing Colectomy (12 mo)	Thiopurine-naïve status Combination treatment CRP drop to normal
Ben–Horin *et al*[10]	Retrospective	62 (CD/UC)	IFX	Loss or response	[1]*Low trough levels* *Anti-infliximab antibodies*
Cesarini *et al*[39]	Retrospective	41 (secondary loss of response)	IFX	Clinical remission Colectomy–free (52 wk)	Rapid clinical response to optimization
Colombel *et al*[3]	Prospective (ACT trials)	728	IFX	Clinical remission Clinical response Colectomy	Mucosal healing at week 8 (predictive of long-term outcome)
De Vos *et al*[32]	Prospective	53	IFX	Mayo clinical score Endoscopic remission	Fecal Calprotectin
Fasanmade *et al*[23]	Retrospective	728	IFX	Trough levels Clinical response	[1]*Serum albumin concentration*
Ferrante *et al*[21]	Cohort	121	IFX	Colectomy-free survival (33 mo)	Short term clinical response CRP > 5 mg/L [1]*Previous iv treatment with steroids/cyclosporin*
Ferrante *et al*[18]	Cohort	100	IFX	Early clinical response	Younger age pANCA-/ACSA+
Garcia-Bosch *et al*[28]	Retrospective	48	ADA	Clinical response (partial Mayo score) Colectomy (week 54)	Response to prior treatment with infliximab Early response to adalimumab
Gonzalez-Lama *et al*[20]	Retrospective	47	IFX	Clinical response Steroid-free remission Colectomy	[1]*Disease extent*
Gustavsson *et al*[35]	Placebo controlled trial	45	IFX	Colectomy (3 yr f-up)	Mucosal healing at 3 mo
Jakobovits *et al*[19]	Retrospective	30	IFX (not standard induction regimen 0-2-6)	Colectomy	[1]*Younger age at diagnosis*
Jürgens *et al*[13]	Retrospective	90	IFX	Clinical response Clinical remission (week 14)	CAI-disease activity ANCA seronegativity IL23R genotype
Lee *et al*[22]	Retrospective	134	IFX	Clinical response Clinical remission	Haemoglobin > 11.5 CRP > 3 Immunomodulator-naïve status Response at week 2 Mucosal healing
Kohn *et al*[36]	Open label	83 severe colitis	IFX	Colectomy/Death > 2 mo after first infusion (median f-up 23 mo)	[1]*Single infusion*
Li *et al*[34]	Prospective?	17 24	IFX	CRP Clinical response Endoscopic healing	Changes in percentages of Foxp3(+) Tregs (mucosal and systemic)
McDermott *et al*[30]	Retrospective	23 (86% infliximab experienced)	ADA	Failure (discontinuation of ADA) Colectomy (follow-up 22 mo)	[1]*Short–term failure (increased risk for colectomy)*
Olsen *et al*[24]	Retrospective	59	IFX	UCDAI	Mucosal TNF-a mRNA expression
Oussalah *et al*[14]	Retrospective	191	IFX (≥1 infusion)	Primary non-response Colectomy Infliximab optimization Hospitalization (median 18 mo)	[1]*Indication for acute severe colitis* *Hb ⩽ 9.4 g/dL* *Non-response*
Park *et al*[15]	Retrospective	89	IFX	Clinical response Clinical remission Colectomy	[1]*Mayo score ⩾ 11)* *CMV infection (within prior 3 mo)*
Reinisch *et al*[17]	Prospective (ULTRA 1)	390 (anti-TNF naïve)	ADA	Clinical remission at week 8	[1]*Mayo score ⩾ 10* *CRP = 10 mg/L*
Rismo *et al*[25]	Prospective	74	IFX	UCDAI	Mucosal gene expression signature (Th1 and Th17 related cytokines)

Rostholder *et al*[38]	Retrospective observational	56	IFX	Clinical remission	Escalation of infliximab therapy
Sandborn *et al*[16]	Prospective (ACT1&2)	630	IFX	Colectomy (54 wk)	[1]*Concomitant steroids* *CRP ⩾ 2 mg/dL* *Disease duration < 3 yr* *Mayo ⩾ 10*
Seow *et al*[40]	Cohort	115	IFX	Clinical remission Endoscopic improvement Colectomy	Trough levels
Steenholdt *et al*[41]	Retrospective	106 (CD/UC)	IFX	Loss of response	[1]*Trough levels* *Anti-infliximab antibodies*
Taxonera *et al*[29]	Retrospective	30 (IFX experienced)	ADA	Clinical response at week12 Colectomy (follow-up 48 wk)	Short–term response at week-12 (Associated with less withdrawal and colectomy rates)
Toedter *et al*[33]	Prospective (ACT-1)	48	IFX	Clinical response	Mucosal gene expression signature

[1]Italics correspond to prognostic factors for adverse outcome. IFX: Infliximab; ADA: Adalimumab; UCDAI: Ulcerative colitis disease activity index; HACA: Human anti-chimeric antibodies; CRP: C-reactive protein.

to ADA in the short-term. It should be noted, however, that these parameters did not strongly affect the result and their consideration as predictive factors must be cautious.

In all, the majority of studies appear to support the notion that severe UC demonstrates a less favorable response to treatment with anti-TNF monoclonal antibodies. From the pure clinical standpoint, the best candidate for anti-TNF administration may be an outpatient with moderate to severe UC but not severe disease requiring hospitalization, as defined by the criteria of Truelove and Witts.

In addition to disease severity, other clinical parameters may also affect the response to anti-TNF in UC. Ferrante *et al*[18] studied a cohort of 100 UC patients who were treated with IFX. More than half had extensive disease, were on immunosuppressants and received a single infusion as opposed to the standard induction scheme. Early clinical response was accomplished in 65% of patients. Younger age was associated with a higher percentage of early clinical response (responders: median age 35.7 years *vs* non-responders: 41.6, $P = 0.049$). Different results were obtained by Jakobovits *et al*[19] who reviewed the records of 30 patients with refractory UC who had received a single IFX infusion over the period 2000-2006. Half of the patients underwent colectomy over a median follow-up period of 140 d. In this cohort, younger age at diagnosis correlated with increased risk of surgery (colectomy: mean age 27.5 years *vs* non-colectomy 38.7 years, $P = 0.016$). In contrast, the indication before starting IFX was not relevant to colectomy rates. The number of patients in this study was too small for definitive conclusions to be drawn. In the analysis of the ACT trials duration of colitis ⩽ 3 years strongly increased the risk for colectomy (hazard ratio = 0.36, $P < 0.001$, respectively)[16]. Finally, disease extent may also affect response to treatment. Gonzalez-Lama *et al*[20] studied 47 UC patients who were treated with IFX and were followed for a mean duration of 8 mo. Pre-treatment predictive factors were sought: extent of the disease was the only factor that was related to higher response rates to IFX ($P = 0.02$). Extensive colitis appeared to respond less favorably in the short term in the aforementioned study of ADA as well[17].

Laboratory indicators: Among the various laboratory biomarkers of inflammation, C-reactive protein (CRP) has been the most extensively applied to clinical practice. The association between CRP and inflammatory activity in UC has not been equally strong as it is for Crohn's disease. Nevertheless, its relevance increases when cases of severe UC are studied. As these are the patients that usually require administration of anti-TNF agents, the predictive value of CRP for treatment efficacy/failure may be increased in this population. Ferrante *et al*[21] reported on a cohort of 121 UC outpatients treated with IFX and followed for a median of 33 mo. Eighty-one patients (67%) exhibited short-term response and 21 (17%) underwent colectomy. A value of pre-treatment CRP ⩾ 5 mg/L was an independent predictor for colectomy (HR = 14.5, $P = 0.006$). Similar results were presented in a study of 134 Korean patients with UC who had received at least one infusion of IFX[22]. At week 8, 87% and 45% achieved response and remission, respectively. A pre-treatment CRP ⩾ 3 mg/dL was predictive of clinical remission at week 8 (OR = 4.77, $P = 0.01$). The association between elevated CRP and less favorable response to anti-TNF was also confirmed in the analysis of the ACT trials[16]. A baseline CRP ⩾ 2 mg/L was significantly associated with increased colectomy risk (HR = 1.73, $P = 0.04$). Of note, several studies found an association between elevated CRP and colectomy[21]. Therefore, increased CRP may represent a strong marker of inflammation that requires potent treatment and will respond optimally to anti-TNF. Alternatively, CRP may be an indicator of refractory disease.

In the previous Korean study, high pre-treatment hemoglobin **w**as also a predictor of good response to IFX[22]. Baseline haemoglobin of ⩾ 11.5 g/dL was associated with higher probability for remission at week 8 (OR = 4.47, $P = 0008$). This is in accordance with the study by Oussalah[14] who reported that pre-treatment hemo-

globin ≤ 9.4 g/dL predicted primary non-response to IFX (OR = 4.35). This occurred in 22% of 191 treated patients who were included in the study. According to Truelove criteria low hemoglobin is an indicator of severe disease, which increases the risk of non-response to IFX. High pre-treatment hemoglobulin may reflect the presence of milder disease that responds better to anti-TNF treatment.

Serum albumin concentration may also have prognostic value. A study by Fasanmade *et al*[23] focused on the association between serum IFX and albumin concentration. Data from 728 patients who participated in two clinical trials were analyzed. A value of serum albumin that was outside the normal range was directly related to trough IFX levels and clinical response. Patients with low serum albumin had reduced IFX concentration and worse clinical outcomes. This correlation may reflect a common clearance pathway for albumin and anti-TNF antibodies that belong to the IgG class of immunoglobulins. In all, measurement of albumin before commencement of treatment may serve as a predictive marker of the drug's pharmacokinetics.

Immunological and genetic markers: In recent years significant advances have taken place in our understanding of the immunopathogenesis of UC. In addition, genome wide association studies have discovered polymorphisms which confer susceptibility to or protect from developing UC. These studies led to the identification of several immunological markers with may serve as indicators of disease activity and severity. The possibility that such markers may also serve as predictors of response to treatment, in particular to therapy with anti-TNF monoclonal antibodies, has been increasingly explored.

One of the classical immunological markers that are associated with UC is the presence of perinuclear antineutrophil cytoplasmatic antibodies (p-ANCA). In two recent studies absence of this marker was strongly associated with better response to IFX. In a retrospective study of 90 patients who were evaluated up to week 14 on scheduled IFX infusions, negativity for p-ANCA (along with disease severity and IL23R genotype) was predictive of IFX efficacy[13]. Similar results were obtained in the study by Ferrante *et al*[18]. The authors followed 100 UC patients treated with IFX (84 patients received a single infusion). ANCA seronegativity served as predictor of good response. Notably, a serological phenotype of ANCA+/ASCA- status was particularly correlated with lower rates of response ($P = 0.049$).

During acute flares of UC an abundance of inflammatory mediators are upregulated at the intestinal mucosa and can be detected at both the mRNA and the protein level, whereas, anti-inflammatory treatment is paralleled by a decrease or even disappearance of these markers. Therefore, such markers may hold predictive value for the response to anti-TNF treatment. A first obvious target has been TNF itself. Olsen *et al*[24] looked for predictive factors of response to induction treatment (weeks 0, 2, 6) with IFX in a cohort of 59 patients with moderate to severe disease. The outcome was assessed based on UC disease activity index (UCDAI). Among various parameters elevated pre-treatment mucosal TNF-a expression was the only independent predictive factor of clinical and endoscopic remission ($P = 0.01$ and $P = 0.003$, OR = 2.5 and 4.8, respectively).

UC-related intestinal inflammation has been characterized by upregulation of several components of the major adaptive immunity pathways (Th1, Th2, Th17). A recent study looked at the expression of the pivotal Th1 (IFN-γ) and Th17 (IL-17) cytokines before and after treatment with IFX[25]. Mucosal cytokine profile was determined by PCR and confirmed by immunohistochemistry in biopsies of 74 UC patients. Efficacy was evaluated after 3 infusions and was based on UCDAI. High pre-treatment mucosal expression of IL-17 and IFN-γ significantly correlated with remission after induction therapy (OR = 5.4, $P = 0.013$ and OR = 5.5, $P = 0.011$, respectively).

In a much broader approach, Arijs *et al*[26] performed a gene-array study in mRNA from colonic mucosal biopsies obtained from UC patients who received induction therapy with IFX. Analysis of the arrays revealed genes that were differentially expressed among responders and non-responders. Genes that showed a highly differential expression were osteoprotegerin, stanniocalcin-1, prostaglandin-endoperoxide synthase 2, interleukin 13 receptor alpha-2 and interleukin 11. The sensitivity and specificity in predicting response to IFX based on this gene profiling was 95% and 85%, respectively.

The effect of genetic polymorphisms to response to treatment remains unknown. In the aforementioned study by Jurgens the effect of UC-associated, IL-23R variants on the efficacy of IFX was reported[13]. In this study of 90 patients, homozygosity for the IBD-risk-increasing IL23R variants was associated with higher probability to respond to IFX than homozygosity for IBD-risk-decreasing IL23R variants (74.1% *vs* 34.6%; $P = 0.001$).

Treatment-related factors: Several studies have shown that the pharmacological history plays an important role in the response to anti-TNF treatment. In the study by Ferrante *et al*[21], 121 UC patients received IFX and were followed-up for a median of 33 mo. Colectomy was performed in 21 patients (21%). Previous *iv* treatment with steroids and/or cyclosporine significantly increased the risk for colectomy (HR = 2.4, $P = 0.033$). A similar association was seen in the study by Oussalah *et al*[14]. Previous use of cyclosporine was a positive predictive factor for colectomy (hazard ratio = 2.53). Finally, in the analysis of the colectomy rates in the context of the ACT-trials patients who were on steroids when IFX was started had an increased risk for surgery (HR = 1.84, $P = 0.01$)[16]. However, caution is required for the interpretation of these associations, which should take into consideration the severity of the disease. Indeed, in all of these studies

more severe disease was associated to adverse outcomes and less favorable response to anti-TNF. Therefore, the use of *iv* steroids and/or cyclosporine may simply reflect severe disease.

The association between exposure to immunosuppressants and efficacy of anti-TNF therapy merits special attention. Converging lines of evidence indicate that immunosuppressant-naïve patients respond better to anti-TNF. The efficacy of IFX was evaluated in a cohort of 126 steroid-dependent patients[27]. Approximately half of the patients achieved steroid-free remission, whereas mucosal healing at 12 mo was accomplished in one third. Thiopurine-naïve status was positively associated to steroid-free remission as well as mucosal healing at 12 mo (HR = 2.8 and OR = 3.6, respectively). In the aforementioned Korean study[22] immunomodulator-naïve status was an independent predictors for early clinical remission (OR = 4.89, $P = 0.01$). This consistent finding is in agreement with the growing evidence regarding earlier introduction of biologics in patients with moderate disease, as patients who never received thiopurines may had suffered a shorter disease course.

Finally, for patients who receive ADA as a second anti-TNF monoclonal antibody, the treatment efficacy is affected by the response to prior treatment with IFX. This was shown in a recent retrospective study that evaluated the clinical response and colectomy rate in a cohort of 48 UC patients treated with ADA[28]. The majority (81.3%) was previously exposed to IFX. Early response to ADA at week 12 was significantly more frequent in patients who achieved remission on prior treatment with IFX ($P = 0.01$).

Prognostic factors during anti-TNF treatment

Several recent studies have provided evidence to support the notion that patients with early response to anti-TNF (*i.e.,* within 3 mo) are the ones who will also benefit in the long-term. Early response was defined by a variety of clinical and biological markers in these publications.

Clinical parameters: A Spanish study evaluated the efficacy of ADA in 48 UC patients who were followed-up to week 54[28]. In this cohort the only predictive factor for colectomy was the absence of early clinical response, which was determined by partial Mayo score at week 12 (colectomy: 14.7% *vs* no colectomy: 42.9%, $P = 0.035$).

These results were replicated in a cohort of 121 UC outpatients[21] Eighty-one patients initially responded to IFX with 2/3 maintaining clinical response throughout follow-up. Twenty-one patients ended up with colectomy after a median follow-up of 33 mo. No predictors for durable response were identified. Colectomy on the other hand strongly correlated with early non-response to IFX (HR = 10.8, $P < 0.001$).

In the study by Lee *et al*[22], 45% of 134 patients with UC who received at least a single IFX infusion, achieved remission at week 8. Short-term remission rates were higher in patients who responded very early, at week 2 (OR = 20.54, $P = 0.006$).

The value of ADA in 30 UC patients who had failed IFX was studied retrospectively[29]. Response and remission rates were assessed at weeks 4 and 12 and colectomy rates over a mean follow-up of 48 mo. In the long-term 50% were still on ADA and 20% underwent colectomy. The risk of surgery was higher for patients who did not achieve response at week 12 ($P = 0.001$).

Similarly, Mc Dermott *et al*[30] studied 23 patients who received ADA induction and maintenance treatment. Of note, 86% had previously failed IFX. Discontinuation of ADA over a follow-up period of 22 mo was the primary endpoint and occurred in 70% of patients. Colectomy-free survival at 24 mo was 59%. The only factor associated with increased risk for surgery was the absence of early response to ADA. Among patients who underwent colectomy, 55% had failed ADA at week 12.

Armuzzi *et al*[31] evaluated the short- and long-term effects of ADA in 88 UC patients out of whom 78% had previously received IFX. The rates of clinical remission increased from 17% to 43% at weeks 4 and 54, respectively. Interestingly, achievement of early remission as well as low CRP at week 12 predicted remission at week 54 (OR = 4.17 and 2.63, respectively).

Laboratory indicators: The same conclusion regarding the predictive value of early response was obtained when laboratory markers of inflammation were studied. We already mentioned the predictive value of low CRP at week 12 in the study by Arnuzzi[31]. In another publication from the same group regarding 126 steroid-dependent patients who received IFX[27] drop of serum CRP value to normal after the induction-regimen predicted steroid-free remission and mucosal healing at 12 mo (HR = 4.6, OR = 6.0, respectively). Similar results were reported in a study that used fecal calprotectin as an inflammatory marker. Serial weekly measurements of fecal calprotectin were performed in a cohort of 53 patients who received IFX[32]. Two thirds of patients achieved endoscopic remission at week 10, whereas the median calprotectin level significantly drop from baseline ($P < 0.001$). Early reduction of calprotectin at week 2 predicted endoscopic remission. At week 10, clinical and endoscopic remission strongly correlated to fecal calprotectin concentration.

Immunological markers: Early post-IFX changes of the mucosal and peripheral immunophenotype of UC patients showed strong correlation with clinical response to the drug. Toedter *et al*[33] studied 113 colonic biopsies from 48 patients who participated in the ACT-1 trial. Biopsies were taken before and after treatment with IFX up to week 30. Gene expression profiling was performed. The investigators were able to identify certain genes that demonstrated significant alterations in patients that responded to treatment with IFX but not in non-responders.

In a study that included both Crohn's and UC, the

effect of IFX on the percentages of regulatory T cells (Treg) was investigated[34]. Flow cytometry, PCR and immunohistochemistry were applied to quantify the expression of Forkhead box protein3 (Foxp3)-positive T cells in both peripheral blood samples and mucosal biopsies before and after IFX treatment. Responders to IFX were characterized by significantly increased numbers of CD4(+) CD25(+) Foxp3(+)Treg and CD4(+) CD25(-) Foxp3(+) Tregs in blood ($P < 0.05$) and a significant down-regulation in the tissue ($P < 0.001$). The duration of clinical response to IFX correlated to a sustainable peripheral increase of Foxp3 (+) Treg cells.

Although such individual molecular characterization is far from being clinically applicable, it shows that personalized therapy which will be based on the particular immunophenotype may guide the therapeutic approach in the future.

Endoscopic findings: In recent years, mucosal healing (*i.e.,* the disappearance of visible active inflammatory lesions in endoscopy) has emerged as a definitive endpoint in the natural history of UC and an indispensable therapeutic target both in clinical trials and "real-life" practice. This is because mucosal healing has been shown to be associated with sustained long-term remission in patients with UC[3].

In the pivotal ACT trials endoscopic evaluations were performed at various time points and mucosal healing was defined as Mayo subscore of 0 (normal) or 1 (mild). Early endoscopic improvement at week 8 was associated to improved clinical outcomes[3]. Accordingly, low endoscopy subscores at week 8 predicted reduced risk of colectomy through week 54 ($P = 0.0004$) as well as higher remission and steroid-free remission rates ($P < 0.0001$).

A single IFX infusion or placebo was administered to 45 patients with acute, steroid-refractory UC[35]. Three years later the beneficial effect of the drug persisted as less patients in the IFX group underwent operation (50% *vs* 76%, $P = 0.012$). Endoscopic remission at month 3 strongly predicted a reduced long-term risk for colectomy ($P = 0.02$).

Mucosal healing was also a positive predictive factor for long-term remission in the study by Lee *et al*[22]. A variety of predictors for short-term outcome were identified whereas the only parameter associated with sustained long-term benefit was endoscopic remission (OR = 4.66, $P = 0.04$).

Treatment-related factors: The number of IFX infusions was associated with improved sustained response to anti-TNF treatment. Kohn *et al*[36] studied the effect of IFX treatment in 83 patients with severe steroid-refractory UC.Patients received ⩾ 1 infusions and were followed for a median of 23 mo. Twelve out of 83 patients (15%) had a colectomy within 2 mo. The risk for a prime adverse event was significantly higher among patients who received a single IFX infusion as opposed to those who were given two or more doses (OR = 9.53, $P = 0.001$).

The combined administration with immunosuppressants appears to have an advantage in comparison to single IFX therapy. This was shown in the study by Armuzzi *et al*[27]. In this cohort of 126 steroid-dependent UC patients combination treatment with IFX and thiopurines was a predictor of steroid-free remission (HR = 2.2). In another prospective trial Panaccione studied 231 patients with moderate disease who were biologics-naïve and had not received azathioprine over the 3 mo before enrollment. Patients were offered IFX monotherapy, azathioprine monotherapy or combination treatment. Steroid-free remission at week 16 was significantly more common in the combination arm of the study ($P < 0.05$ compared to both monotherapies)[37].

The need for escalation of anti-TNF therapy is also a poor prognostic factor for long-term outcome. In a cohort of 56 patients with moderate colitis who were treated with IFX, 89% proceeded to maintenance treatment[38]. During a mean follow-up of 38 mo, clinical remission was achieved in 36% of patients at 12 mo, whereas 54% required escalation of treatment. Intensification of IFX treatment was a negative predictive factor of remission at 12 mo ($P = 0.01$). In accordance, colectomy was performed more often in the "escalation" group (33% *vs* 21%).

In a related study, Cesarini *et al*[39] showed that rapid response to escalation treatment has a favorable effect on long-term outcome. They studied the records of 41 UC patients with loss of response to IFX who were treated with either dose doubling or interval shortening. The primary outcome was rapid response which was evaluated at the follow-up visit after treatment escalation. Remission and colectomy were evaluated by week 52. The majority (90%) responded rapidly and 46% achieved rapid remission. Only 4 patients (9.8%) underwent colectomy by week 52. The main predictor for avoidance of colectomy was initial response to intensification treatment ($P = 0.002$).

Recent developments emphasize the importance of serum trough levels of IFX and ADA and the formation of antibodies against anti-TNF monoclonal antibodies for the pharmacokinetics as well as the therapeutic efficacy of these drugs. In a study of 115 UC patients on maintenance treatment, clinical outcomes were associated to IFX trough levels[40]. Detectable drug in serum predicted clinical remission and endoscopic improvement at week 54 ($P < 0.001$ for both parameters). Reduced trough levels correlated with increased risk of colectomy in this cohort ($P < 0.001$). Interestingly, antibody-status was not predictive of response to IFX treatment.

Steenholdt *et al*[41] retrospectively studied 106 IBD patients on IFX, who either maintained or lost their response. Significantly higher IFX levels and lower antibodies titer were measured in patients with sustained response to IFX ($P < 0.0001$). Moreover, the authors suggested threshold values for the two parameters to ac-

curately predict and/or explain loss of response to IFX.

Similarly, Ben-Horin *et al*[10] tested the samples of 62 mixed IBD patients for anti- IFX antibodies and serum trough levels. Low trough levels and high antibodies titer were found in 83% of patients with loss of response and in 8% of patients who maintained remission ($P < 0.001$).

Critique of available markers

As the number of UC patients who have been exposed to anti-TNF monoclonal antibodies steadily increases, more factors will be reported that may be associated with better or worse response to these medications. Before, however, their use is recommended for the selection of patients in clinical practice, careful analysis of the specifics of each marker should be performed and inherent problems with the interpretation of the results from clinical trials should be kept in mind.

Clinical markers have the advantage to be readily available and identifiable in a straightforward fashion. They are easy to use, replicable, non-invasive and, overall, convenient for use in clinical practice. Caution, however, is needed when data from clinical trials are analyzed as the definition of a certain parameter may vary between different studies. In particular, clinical response and remission may be related to a variety of activity scoring systems or arbitrarily defined clinical criteria. In addition, the time point in which a certain clinical marker is reported is of pivotal significance. This is so because UC is a lifelong condition and, therefore, only time points with significant length are relevant to a true remission. Criticism also occurs regarding RCTs in the means that they may not always include patients that reflect 'real-life' IBD populations[42].

Endoscopic markers such as mucosal healing are of significance as recent studies have shown that they are indeed associated with better disease outcomes. It should be noted, however, that the major clinical trials have defined mucosal healing as Endoscopy Mayo score of 0 or 1. Whether the latter score truly represents absolute and complete elimination of inflammation is questionable. In addition, such markers require the performance of an invasive procedure (colonoscopy) soon after the commencement of treatment ($\leqslant$ 3 mo), which may not be easily acceptable from a patient, in particular when clinical remission has taken place.

Serological markers such as CRP are also easy to obtain. Nevertheless, there has not been good correlation between CRP and clinical activity of UC with the exception of severe cases. In addition, its prognostic value has only been reported in a minority of trials, given the fact that CRP is usually determined in every case of UC. Fecal calprotectin is a good indicator of ongoing acute (neutrophilic) inflammation in the colon. However, no studies have indicated that the magnitude of pre-treatment fecal calprotectin predicts the response to anti-TNF. In addition, the measurement of fecal calprotectin is not widely applied in practice and technical issues exist regarding the standardization of methodology. It should be noted, however, that both serum CRP and fecal calprotectin may be more useful when their short-term change in response to anti-TNF is considered rather that their absolute pre-treatment values.

Immunological and genetic markers are important as they hold promise for individualized therapy based on the specific characteristics of each individual patient. The major drawbacks for the application of such markers are technical challenges and lack of replication for most results. An additional problem is the redundancy of the immunological pathways that underlie inflammation in UC. Therefore, a single marker may not be sufficient enough to cover the whole mechanism of injury. Similarly, UC is a polygenetic trait and single gene polymorphisms do not usually lead to the manifestation of the disease phenotype. Nonetheless, as additional biological drugs will become available for the treatment of UC, selection of patients according to the predominant immunogenetic pathway may become the most cost-effective approach.

CONCLUSION

Currently, no single marker fulfils all criteria for being an appropriate prognostic indicator for response to anti-TNF treatment in UC. The ideal predictor should be clearly defined, simple and easy to obtain, as well as of repetitive association between different trials. Alternatively, a predictive model which includes clinical, laboratory and even genetic and/or immunological parameters may be more difficult to develop but more accurate in its predictive value. In that context, and whilst our experience with anti-TNF therapy in UC expands, it is important to continue the search for optimal predictive factors of response or failure. Each of the proposed prognostic parameters should be validated in large populations of patients and across clinical trials of different ethnicities. Eventually, personalized treatment may be the best, safest and most cost-effective strategy in diseases with such a complex pathogenetic background.

REFERENCES

1 **Ordás I**, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. *Lancet* 2012; **380**: 1606-1619 [PMID: 22914296 DOI: 10.1016/S0140-6736(12)60150-0]

2 **Dignass A**, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, D'Haens G, D'Hoore A, Mantzaris G, Novacek G, Oresland T, Reinisch W, Sans M, Stange E, Vermeire S, Travis S, Van Assche G. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012; **6**: 991-1030 [PMID: 23040451 DOI: 10.1016/j.crohns.2012.09.002]

3 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID:

21723220 DOI: 10.1053/j.gastro.2011.06.054]
4 **Blonski W**, Buchner AM, Lichtenstein GR. Treatment of ulcerative colitis. *Curr Opin Gastroenterol* 2014; **30**: 84-96 [PMID: 24285003 DOI: 10.1097/MOG.0000000000000031]
5 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095]
6 **Sandborn WJ**, van Assche G, Reinisch W, Colombel JF, D' Haens G, Wolf DC, Kron M, Tighe MB, Lazar A, Thakkar RB. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257-65.e1-3 [PMID: 22062358 DOI: 10.1053/j.gastro.2011.10.032]
7 **Ho GT**, Smith L, Aitken S, Lee HM, Ting T, Fennell J, Lees CW, Palmer KR, Penman ID, Shand AG, Arnott ID, Satsangi J. The use of adalimumab in the management of refractory Crohn's disease. *Aliment Pharmacol Ther* 2008; **27**: 308-315 [PMID: 18081730]
8 **Swaminath A**, Ullman T, Rosen M, Mayer L, Lichtiger S, Abreu MT. Early clinical experience with adalimumab in treatment of inflammatory bowel disease with infliximab-treated and naïve patients. *Aliment Pharmacol Ther* 2009; **29**: 273-278 [PMID: 19006540 DOI: 10.1111/j.1365-2036.2008.03878.x]
9 **Siegel CA**, Melmed GY. Predicting response to Anti-TNF Agents for the treatment of crohn's disease. *Therap Adv Gastroenterol* 2009; **2**: 245-251 [PMID: 21180547 DOI: 10.1177/1756283X09336364]
10 **Ben-Horin S**, Yavzori M, Katz L, Kopylov U, Picard O, Fudim E, Coscas D, Bar-Meir S, Goldstein I, Chowers Y. The immunogenic part of infliximab is the F(ab')2, but measuring antibodies to the intact infliximab molecule is more clinically useful. *Gut* 2011; **60**: 41-48 [PMID: 20519742 DOI: 10.1136/gut.2009.201533]
11 **Maser EA**, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1248-1254 [PMID: 16931170]
12 **Karmiris K**, Paintaud G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, Van Assche G, Vermeire S, Rutgeerts P. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology* 2009; **137**: 1628-1640 [PMID: 19664627 DOI: 10.1053/j.gastro.2009.07.062]
13 **Jürgens M**, Laubender RP, Hartl F, Weidinger M, Seiderer J, Wagner J, Wetzke M, Beigel F, Pfennig S, Stallhofer J, Schnitzler F, Tillack C, Lohse P, Göke B, Glas J, Ochsenkühn T, Brand S. Disease activity, ANCA, and IL23R genotype status determine early response to infliximab in patients with ulcerative colitis. *Am J Gastroenterol* 2010; **105**: 1811-1819 [PMID: 20197757 DOI: 10.1038/ajg.2010.95]
14 **Oussalah A**, Evesque L, Laharie D, Roblin X, Boschetti G, Nancey S, Filippi J, Flourié B, Hebuterne X, Bigard MA, Peyrin-Biroulet L. A multicenter experience with infliximab for ulcerative colitis: outcomes and predictors of response, optimization, colectomy, and hospitalization. *Am J Gastroenterol* 2010; **105**: 2617-2625 [PMID: 20736936 DOI: 10.1038/ajg.2010.345]
15 **Park SH**, Yang SK, Hong SM, Park SK, Kim JW, Lee HJ, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Severe disease activity and cytomegalovirus colitis are predictive of a nonresponse to infliximab in patients with ulcerative colitis. *Dig Dis Sci* 2013; **58**: 3592-3599 [PMID: 23979435 DOI: 10.1007/s10620-013-2828-1]
16 **Sandborn WJ**, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137**: 1250-160; quiz 1520 [PMID: 19596014 DOI: 10.1053/j.gastro.2009.06.061]
17 **Reinisch W**, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60**: 780-787 [PMID: 21209123 DOI: 10.1136/gut.2010.221127]
18 **Ferrante M**, Vermeire S, Katsanos KH, Noman M, Van Assche G, Schnitzler F, Arijs I, De Hertogh G, Hoffman I, Geboes JK, Rutgeerts P. Predictors of early response to infliximab in patients with ulcerative colitis. *Inflamm Bowel Dis* 2007; **13**: 123-128 [PMID: 17206703]
19 **Jakobovits SL**, Jewell DP, Travis SP. Infliximab for the treatment of ulcerative colitis: outcomes in Oxford from 2000 to 2006. *Aliment Pharmacol Ther* 2007; **25**: 1055-1060 [PMID: 17439506]
20 **Gonzalez-Lama Y**, Fernandez-Blanco I, Lopez-SanRoman A, Taxonera C, Casis B, Tabernero S, Bermejo F, Martinez-Silva F, Mendoza JL, Martinez-Montiel P, Carneros JA, Sanchez F, Maté J, Gisbert JP. Open-label infliximab therapy in ulcerative colitis: a multicenter survey of results and predictors of response. *Hepatogastroenterology* 2008; **55**: 1609-1614 [PMID: 19102352]
21 **Ferrante M**, Vermeire S, Fidder H, Schnitzler F, Noman M, Van Assche G, De Hertogh G, Hoffman I, D'Hoore A, Van Steen K, Geboes K, Penninckx F, Rutgeerts P. Long-term outcome after infliximab for refractory ulcerative colitis. *J Crohns Colitis* 2008; **2**: 219-225 [PMID: 21172214 DOI: 10.1016/j.crohns.2008.03.004]
22 **Lee KM**, Jeen YT, Cho JY, Lee CK, Koo JS, Park DI, Im JP, Park SJ, Kim YS, Kim TO, Lee SH, Jang BI, Kim JW, Park YS, Kim ES, Choi CH, Kim HJ. Efficacy, safety, and predictors of response to infliximab therapy for ulcerative colitis: a Korean multicenter retrospective study. *J Gastroenterol Hepatol* 2013; **28**: 1829-1833 [PMID: 23829336 DOI: 10.1111/jgh.12324]
23 **Fasanmade AA**, Adedokun OJ, Olson A, Strauss R, Davis HM. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. *Int J Clin Pharmacol Ther* 2010; **48**: 297-308 [PMID: 20420786]
24 **Olsen T**, Goll R, Cui G, Christiansen I, Florholmen J. TNF-alpha gene expression in colorectal mucosa as a predictor of remission after induction therapy with infliximab in ulcerative colitis. *Cytokine* 2009; **46**: 222-227 [PMID: 19286392 DOI: 10.1016/j.cyto.2009.02.001]
25 **Rismo R**, Olsen T, Cui G, Christiansen I, Florholmen J, Goll R. Mucosal cytokine gene expression profiles as biomarkers of response to infliximab in ulcerative colitis. *Scand J Gastroenterol* 2012; **47**: 538-547 [PMID: 22486187 DOI: 10.3109/00365521.2012.667146]
26 **Arijs I**, Li K, Toedter G, Quintens R, Van Lommel L, Van Steen K, Leemans P, De Hertogh G, Lemaire K, Ferrante M, Schnitzler F, Thorrez L, Ma K, Song XY, Marano C, Van Assche G, Vermeire S, Geboes K, Schuit F, Baribaud F, Rutgeerts P. Mucosal gene signatures to predict response to infliximab in patients with ulcerative colitis. *Gut* 2009; **58**: 1612-1619 [PMID: 19700435 DOI: 10.1136/gut.2009.178665]
27 **Armuzzi A**, Pugliese D, Danese S, Rizzo G, Felice C, Marzo M, Andrisani G, Fiorino G, Sociale O, Papa A, De Vitis I, Rapaccini GL, Guidi L. Infliximab in steroid-dependent ulcerative colitis: effectiveness and predictors of clinical and endoscopic remission. *Inflamm Bowel Dis* 2013; **19**: 1065-1072 [PMID: 23448790 DOI: 10.1097/MIB.0b013e3182802909]
28 **García-Bosch O**, Gisbert JP, Cañas-Ventura A, Merino O,

Cabriada JL, García-Sánchez V, Gutiérrez A, Nos P, Peñalva M, Hinojosa J, García-Planella E, Muñoz F, Calvet X, Panés J. Observational study on the efficacy of adalimumab for the treatment of ulcerative colitis and predictors of outcome. *J Crohns Colitis* 2013; **7**: 717-722 [PMID: 23142005 DOI: 10.1016/j.crohns.2012.10.004]

29 **Taxonera C**, Estellés J, Fernández-Blanco I, Merino O, Marín-Jiménez I, Barreiro-de Acosta M, Saro C, García-Sánchez V, Gento E, Bastida G, Gisbert JP, Vera I, Martinez-Montiel P, Garcia-Morán S, Sánchez MC, Mendoza JL. Adalimumab induction and maintenance therapy for patients with ulcerative colitis previously treated with infliximab. *Aliment Pharmacol Ther* 2011; **33**: 340-348 [PMID: 21133961 DOI: 10.1111/j.1365-2036.2010.04531.x]

30 **McDermott E**, Murphy S, Keegan D, O'Donoghue D, Mulcahy H, Doherty G. Efficacy of Adalimumab as a long term maintenance therapy in ulcerative colitis. *J Crohns Colitis* 2013; **7**: 150-153 [PMID: 22520592 DOI: 10.1016/j.crohns.2012.03.016]

31 **Armuzzi A**, Biancone L, Daperno M, Coli A, Pugliese D, Annese V, Aratari A, Ardizzone S, Balestrieri P, Bossa F, Cappello M, Castiglione F, Cicala M, Danese S, D'Incà R, Dulbecco P, Feliciangeli G, Fries W, Genise S, Gionchetti P, Gozzi S, Kohn A, Lorenzetti R, Milla M, Onali S, Orlando A, Papparella LG, Renna S, Ricci C, Rizzello F, Sostegni R, Guidi L, Papi C. Adalimumab in active ulcerative colitis: a "real-life" observational study. *Dig Liver Dis* 2013; **45**: 738-743 [PMID: 23683530 DOI: 10.1016/j.dld.2013.03.018]

32 **De Vos M**, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, Franchimont D, Moreels T, Staessen D, Terriere L, Vander Cruyssen B, Louis E. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naïve patients with ulcerative colitis. *J Crohns Colitis* 2012; **6**: 557-562 [PMID: 22398050 DOI: 10.1016/j.crohns.2011.11.002]

33 **Toedter G**, Li K, Marano C, Ma K, Sague S, Huang CC, Song XY, Rutgeerts P, Baribaud F. Gene expression profiling and response signatures associated with differential responses to infliximab treatment in ulcerative colitis. *Am J Gastroenterol* 2011; **106**: 1272-1280 [PMID: 21448149 DOI: 10.1038/ajg.2011.83]

34 **Li Z**, Arijs I, De Hertogh G, Vermeire S, Noman M, Bullens D, Coorevits L, Sagaert X, Schuit F, Rutgeerts P, Ceuppens JL, Van Assche G. Reciprocal changes of Foxp3 expression in blood and intestinal mucosa in IBD patients responding to infliximab. *Inflamm Bowel Dis* 2010; **16**: 1299-1310 [PMID: 20196149 DOI: 10.1002/ibd.21229]

35 **Gustavsson A**, Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, Vilien M, Ström M, Verbaan H, Hellström PM, Magnuson A, Halfvarson J, Tysk C. Clinical trial: colectomy after rescue therapy in ulcerative colitis - 3-year follow-up of the Swedish-Danish controlled infliximab study. *Aliment Pharmacol Ther* 2010; **32**: 984-989 [PMID: 20937043 DOI: 10.1111/j.1365-2036.2010.04435.x]

36 **Kohn A**, Daperno M, Armuzzi A, Cappello M, Biancone L, Orlando A, Viscido A, Annese V, Riegler G, Meucci G, Marrollo M, Sostegni R, Gasbarrini A, Peralta S, Prantera C. Infliximab in severe ulcerative colitis: short-term results of different infusion regimens and long-term follow-up. *Aliment Pharmacol Ther* 2007; **26**: 747-756 [PMID: 17697208]

37 **Panaccione R,** Sandborn WJ, Gordon G. Infliximab, azathioprine, or infliximab azathioprine for treatment of moderate to severe ulcerative colitis: The UC SUCCESS trial. *J Crohns Colitis* 2011; **5**: 2

38 **Rostholder E**, Ahmed A, Cheifetz AS, Moss AC. Outcomes after escalation of infliximab therapy in ambulatory patients with moderately active ulcerative colitis. *Aliment Pharmacol Ther* 2012; **35**: 562-567 [PMID: 22239070 DOI: 10.1111/j.1365-2036.2011.04986.x]

39 **Cesarini M**, Katsanos K, Papamichael K, Ellul P, Lakatos PL, Caprioli F, Kopylov U, Tsianos E, Mantzaris GJ, Ben-Horin S, Danese S, Fiorino G. Dose optimization is effective in ulcerative colitis patients losing response to infliximab: a collaborative multicentre retrospective study. *Dig Liver Dis* 2014; **46**: 135-139 [PMID: 24246151 DOI: 10.1016/j.dld.2013.10.007]

40 **Seow CH**, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut* 2010; **59**: 49-54 [PMID: 19651627 DOI: 10.1136/gut.2009.183095]

41 **Steenholdt C**, Bendtzen K, Brynskov J, Thomsen OØ, Ainsworth MA. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand J Gastroenterol* 2011; **46**: 310-318 [PMID: 21087119 DOI: 10.3109/00365521.2010.536254]

42 **Ha C**, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. *Clin Gastroenterol Hepatol* 2012; **10**: 1002-1007; quiz e78 [PMID: 22343692 DOI: 10.1016/j.cgh.2012.02.004]

P- Reviewer: Akiho H, Zoller M **S- Editor**: Wen LL
L- Editor: A **E- Editor:** Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com