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Review

Evaluation of anti-TNF therapeutic response in patients with inflammatory bowel disease: Current and novel biomarkers

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ABSTRACT

Neutralizing tumour necrosis factor (TNF) antibodies have been widely used to treat inflammatory bowel disease (IBD) in the clinical practice. In this review, the principal biomarker analysis revealed that faecal calprotectin, C-reactive protein, serum or mucosal concentrations of anti-TNF monoclonal antibodies (mAbs) and antibodies to anti-TNF mAbs are commonly used as current biomarkers in the evaluation of anti-TNF therapeutic efficacy. However, mucosal cytokine transcripts. microRNAs, proteomics and faecal and mucosal gut microbiota profile and mucosal histological features are reported to be novel candidates of biomarkers with high clinical utility in the evaluation of anti-TNF therapeutic efficacy in patients with IBD. Therefore, a robust validation of novel promising biomarkers and comparison studies between current used and novel biomarkers are urgently required to improve their value in the evaluation of therapeutic efficacy and optimization of personalized medicine and identification of IBD candidates for anti-TNF therapy in future clinical practice.

1. Introduction

It is widely known that inflammatory bowel disease (IBD), principal types include Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic inflammatory disorders that mainly affect the gastrointestinal tract. Although the aetiology for IBD remains to be fully identified, accumulative evidence has strongly suggested that environmental factors, genetic predisposition, and dysregulated immune response are strongly associated with the development of IBD [1–3].

Clinically, the goals of IBD treatment are to induce and maintain disease remission and mucosal healing, and then improve the patient's quality of life. Tumour necrosis factor (TNF)-α is a proinflammatory cytokine and plays an essential role in the induction and maintenance of inflammation in the intestine [4]. As a result of this, block of TNF signal by anti-TNF monoclonal antibodies (mAbs) becomes a main therapeutic strategy for severe steroid refractory or dependant IBD patients today [4]. The evaluation of therapeutic efficacy in IBD patients with anti-TNF mAbs is extremely important for optimise therapeutic strategy [5]. Clinically, there is currently no single "gold standard" approach to assess anti-TNF therapeutic efficacy in patients with either CD or UC. Instead, it is made based on a combination of disease activity index, endoscopic observation with histological examination and biomarkers in IBD patients with anti-TNF treatment [6]. In addition, laboratory biomarkers provide a reproducibly quantifiable tool for the evaluation of disease status and therapeutic efficacy in IBD patients. Therefore, the discovery of reliable biomarkers would be extremely useful in the clinical practice and adds a great help to assess therapeutic efficacy, minimize side-effects, and optimize personalized medicine and strategy for identifying IBD patients who will benefit from anti-TNF therapy [7,8].

In this study, we conducted a review that focus on current and novel biomarkers in the context of biological therapies against TNF- in patients with IBD.

2. A brief looking back the role of TNF-alpha in the pathogenesis of IBD

TNF-α is a pleotropic cytokine with a potential proinflammatory capacity and has been recognized as a triggering cytokine in the induction of colorectal inflammation and involved in the pathogenesis of IBD [4] (see Fig. 1). Today, anti-TNF mAbs have been widely introduced to treat severe steroid refractory or dependant IBD patients in clinical practice. Clinical evidence showed that anti-TNF therapy result in an improved clinical success including a rapid

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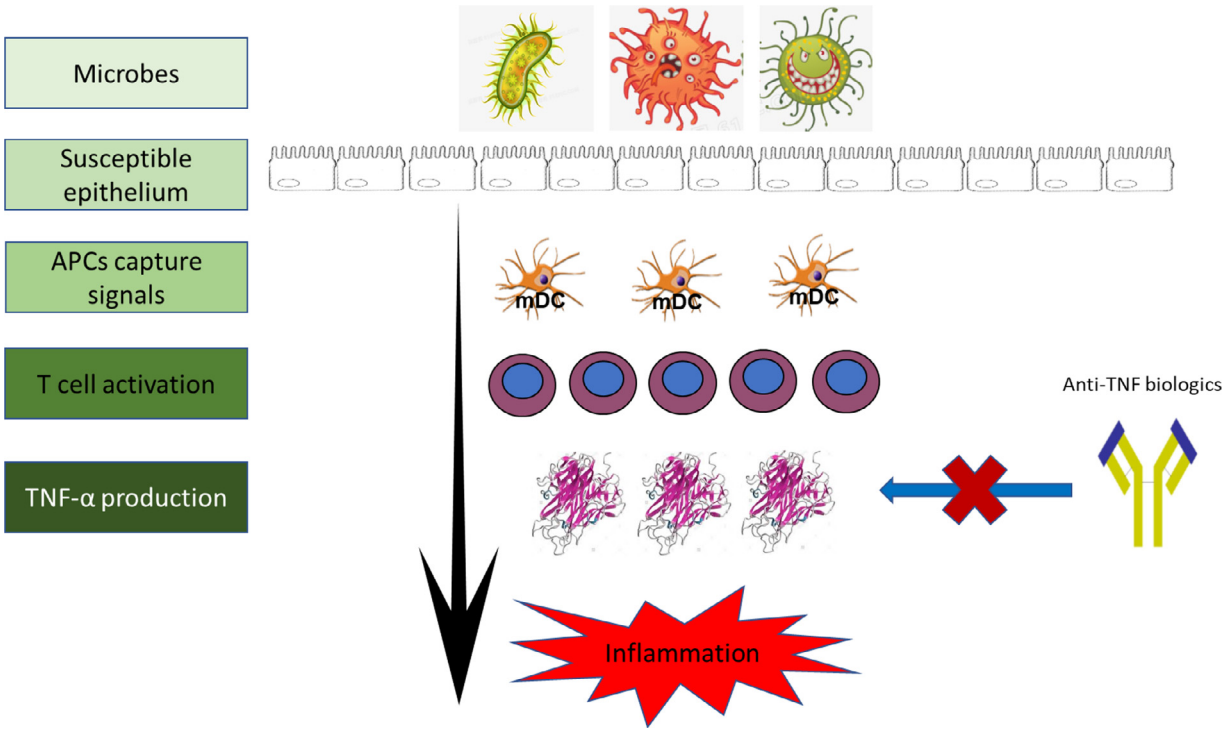

Fig. 1. Schematic summary of TNF-α's role and anti-TNF therapy in the pathogenesis of IBD.
Current data suggested that TNF-α plays a central role in the pathogenesis of IBD, and block of TNF-α signal by anti-TNF mAbs could significantly suppress inflammation and improve mucosal healing.

disease remission, a high rate of mucosal healing, and improved quality of life in ~ 60% of IBD patients. However, clinical studies reported that 20~40% of IBD patients did not respond to anti-TNF-α induction therapy, and ~50% of primary response IBD patients may subsequently loss of response to anti-TNF-α maintaining therapy after induction period [9]. Moreover, anti-TNF-α bioagents are very expensive and have several site effects. Therefore, how to evaluate therapeutic response and identify IBD patients who will benefit from anti-TNF therapy becomes important [8,9].

3. Current commonly used biomarkers in the evaluation of anti-TNF therapeutic response in patients with IBD

Researchers have previously identified multiple biomarkers such as faecal calprotectin (FC), C-reactive protein (CRP), levels of anti-TNF-α agent level and anti-drug antibody to provide reproducible, quantitative tools to assess disease severity and status, and therapeutic efficacy in patients with IBD (see Fig. 2).

3.1. FC

Clinical results revealed that significantly reduced FC level might predict disease remission and mucosal healing in patients with IBD who received various therapies including anti-TNF mAbs [10]. Studies showed that the levels of FC were well correlated with endoscopic scores of disease activity in IBD patients who received anti-TNF mAbs [11,12]. Further studies reported that a high level of pre-treatment baseline FC could predicate a high rate of nonresponse [13] and a lower rate of clinical remission or mucosal healing in IBD patients undergoing anti-TNF therapy [14,15]. Colombel et al. showed that FC concentration is a reliable biomarker to predict treatment failure and decision to escalate in CD patients with adalimumab treatment [16]. Increased CRP concentration could show a slightly lower predicating significance than FC concentration. Increased concentration of FC could significantly influence the decision to escalate after CD patients received adalimumab treatment at different week-points [16].

3.2. Serum levels of CRP

The importance of CRP in anti-TNF induction therapy has been intensively studied. Two clinical studies reported that a high baseline concentration of CRP was associated with a reduced rate of clinical remission and response to anti-TNF mAbs in steroid refractory or moderate-to-severe UC patients [17,18]. Normalization of CRP levels at week 14 could predict rates of maintained response or remission in CD patients with IFX maintenance therapy [19]. Acute severe ulcerative colitis (ASUC) is a clinical emergency condition that needs a prompt therapeutic intervention [20]. Choy et al. reported that the CRP/albumin ratio following IFX salvage could predict the therapeutic response and identify who at high risk of colectomy in patients with ASUC [21].

3.3. Serum levels of anti-TNF mAbs

The effective level of anti-TNF mAbs can be reflected in the level of drugs in the blood. In a systematic review with meta-analysis, Moore et al. [22] found that a trough threshold of IFX during maintenance ($> 2\ \mu g/ml$) was associated with a greater probability of remission and mucosal healing in IBD patients with IFX therapy [22]. Similarly, a high trough serum level of adalimumab could predicate a better long-term clinical outcome in CD patients [23,24]. In contrast to above findings, Hinojosa et al. [25] reported that low serum levels of adalimumab were correlated with loss of clinical and endoscopic response and low rate of mucosal healing in IBD patients with either adalimumab induction or maintenance therapies.

3.4. Anti-drug antibody

Considerable evidence has shown that the administration of anti-TNF mAbs into human body may induce the production of anti-drug

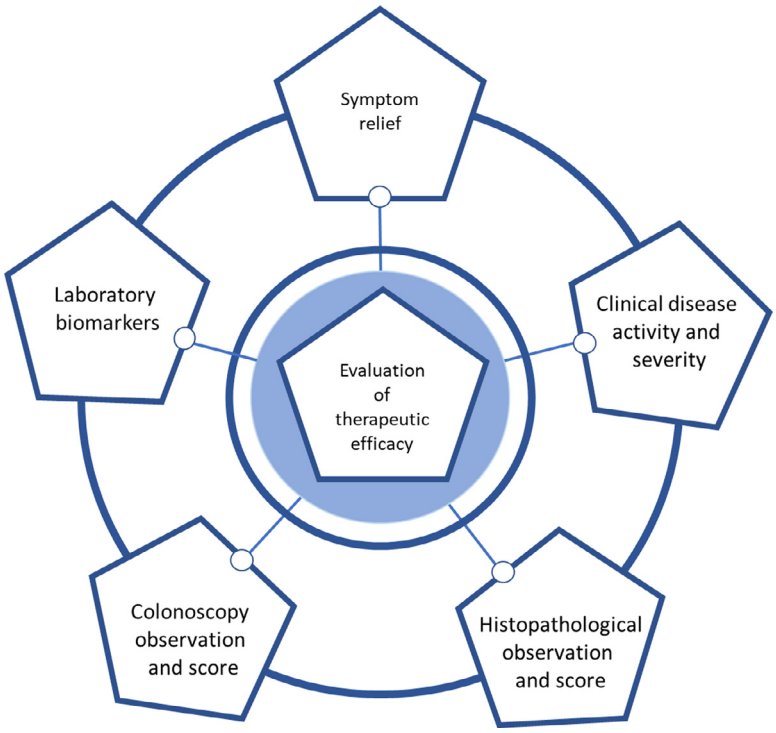

Fig. 2. Schematic summary of the current approaches used in the evaluation of different therapeutic efficacy in patients with IBD.

Current approaches used in the evaluation of anti-TNF therapy in patients with IBD are based on multiple clinical parameters e.g., symptom relief, changes of severity evaluated by clinical disease activity and severity index, colonoscopy evaluation with histological examination and laboratory biomarkers.

antibody, and levels of anti-drug antibody are associated with both short and long-term response to anti-TNF mAbs in IBD patients [26,27].

Casteele et al. [28] revealed that a cut-off anti-drug antibody value <3.15 U/mL was correlated with disease remission in CD patients with IFX therapy. Moreover, Brandse et al. [29] underlined that higher serum concentrations of anti-drug antibody in IBD patients with anti-TNF therapy may predicate a low quality of life and more complications. In addition, Kharlamovaa et al. showed that measuring drug and anti-drug antibody concentrations in IBD patients with anti-TNF treatment could help to identify anti-drug antibody positive IBD patients, which could lead to a more personalized and efficient treatment regime [30]. The drug-tolerant assay method enabled to detect anti-drug antibody earlier and regardless of drug level at time of sampling [30]. Further studies showed that the detective rate of anti-drug antibody in the drug-tolerant assay was much higher than that in the drug-sensitive assay (63% vs. 21%) [31], which allows a better follow-up of anti-drug antibody concentration changes and observation of true transient versus persistent anti-drug antibody in IBD patients with anti-TNF therapy.

Current biomarkers used in the evaluation of anti-TNF therapeutic efficacy in IBD patients are summarized in Table 1 and Fig. 2.

4. Novel putative biomarkers

The specificity of current biomarkers likes CRP are relatively low; in addition, the sensitivity of these biomarkers between patients with CD and UC are different, which limits their clinical values in the evaluation of anti-TNF therapeutic efficacy in patients with IBD. Moreover, the expression levels of those biomarkers in IBD patients with anti-TNF therapy are not always consistent with changes of disease activity and the rate of mucosal healing after treatment. Therefore, development and identification of novel biomarkers to promote personalised treatment of IBD patients with anti-TNF therapy is needed. Which could better identify patients whose IBD is refractory to the anti-TNF therapy, help clinicians to prevent unnecessary anti-TNF-α therapy, accelerate the process of providing effective for each patient.

4.1. Mucosal transcript landscape

4.1.1. TNF-α

Anti-TNF mAbs could significantly reduce the expression level of TNF-α and suppress the inflammation, therefore the changed mucosal TNF-α transcript level might be used as a promising biomarker to assess the anti-TNF efficacy. More recently, we have validated a correlation between mucosal TNF-α transcript levels and response to anti-TNF mAbs in UC [7]. Validation data demonstrated that baseline mucosal TNF-α transcript level was a better biomarker with a high-test reliability for the prediction of clinical outcomes than other clinical parameters e.g., calprotectin, the UC disease activity index (UCDAI) score, Mayo endoscopic score in patients with UC [7].

Consequently, we evaluated whether the mucosal levels of TNF-α transcript after IFX treatment in patients with UC could predicate the therapeutic response. We found that the mucosal TNF-α transcript level, in responders to IFX therapy, was significantly reduced, in which a reduced mucosal TNF-α transcript level was well correlated to the disease remission and mucosal healing rate examined by colonoscopy observation in both UC and CD responders with anti-TNF introduction therapy [32–34]. Furthermore, normalization of mucosal TNF-α transcript levels could predicate a good long-term disease remission in UC responders with discontinuing anti-TNF therapy [35].

4.1.2. IL-17A

TH17 signature cytokine IL-17A has been repeatedly shown to be a valuable candidate biomarker to assess anti-TNF efficacy in patients with IBD. Our data showed that UC patients with a higher mucosal IL-17A transcript level tended to have a higher rate of disease remission in response to three IFX infusions, showing a predicate value in UC

Table 1
Significance of commonly used current biomarkers in the evaluation of anti-TNF therapeutic efficacy in patients with IBD in the clinical practice.

Biomarker	Decreased or normalized in CD			Decreased or normalized in UC		
	Response	Remission	Mucosal healing	Response	Remission	Mucosal healing
Faecal calprotectin	+ [13]	+ [79]	+ [11]	+ [79]	+ [79]	+ [12]
CRP	+ [75, 80]	+ [81]	+ [82]	+ [83]	+ [19]	+ [82]
Serum levels of anti-TNF drugs	+ [22, 25, 84, 85]	+ [22-24, 28]	+ [22, 25]	+ [86]	+ [86]	+ [87]
Anti-drug antibody	+ [88, 89]	+ [28, 90]	+ [89]	+ [88]	+ [91]	+ [89]

(reference ID].

patients received IFX induction therapy [36]. Nevertheless, decreased mucosal IL-17A transcript level was associated with complete mucosal healing defined by colonoscopy examination in CD patients received adalimumab treatment [33], and normalized mucosal IL-17A transcript level after IFX therapy appeared to predicate a long-term disease remission in patients with CD [34].

4.1.3. IL-7 receptor (IL-7R)

Belarif et al. [37] reported that increased mucosal IL-7R transcript levels were associated with non-responders of severe CD and UC patients to either immunosuppressive/corticosteroid, anti-TNF, or anti-$\alpha 4\beta 7$ therapies. High expression of both IL7R and IL-7R signalling signature in the colon before treatment was closely associated with nonresponse rate to anti-TNF therapy in patients with IBD. Their findings suggest that an overexpression of mucosal IL-7R correlated strongly to failure of anti-TNF therapy in patients with CD and UC. Its value as a biomarker candidate remains to be validated.

4.1.4. Cytokine oncostatin M (OSM) and its receptor (OSMR)

Cytokine OSM belongs to IL-6 subfamily and can be produced by several types of immune and stromal cells. More recently, Kim et al. [38] reported that high mucosal levels of both OSM and its receptor OSMR were strongly associated with the inflammation degree and disease severity in patients with IBD. Furthermore, anti-TNF-resistant IBD mice lacking OSM developed less inflammation and colitis than wild-type mice [38]. Genetic deletion or pharmacological blockade of OSM could significantly attenuate the process of colitis. In patients with IBD, a high expression level of OSM was associated with the failure of anti-TNF (IFX and golimumab) therapies [38]. Therefore, OSM might be considered as a biomarker candidate in the evaluation of anti-TNF therapeutic efficacy in patients with IBD [39].

4.1.5. Other cytokines

Our data demonstrated that in addition to decreased TNF mRNA level, IFX therapy in patients with UC also induced a decreased mRNA levels of interferon (IFN)-γ in inflamed mucosa [32]. Mavragani et al. [40] have reported that levels of type I and II IFN genes in the serum could predict the response to IFX in patients with IBD. Responders tended to have significant decreased level of both types of interferon [40]. Their studies confirmed that both Types I and II IFN gene can be the candidates of biomarker for IFX therapy.

4.2. Triggering receptor expressed on myeloid cells 1 (TREM1)

Studies showed that TREM-1 was involved in the development of inflammation and anti-TNFα responsiveness mechanism, and levels of TREM-1 in peripheral blood and inflamed mucosa were a potential biomarker of anti-TNF therapeutic efficacy in patients with IBD [41,42]. Gaujoux et al. [42] reported baseline serum TREM-1 (sTREM1) concentration may predicate anti-TNF response with very high accuracy in patients with CD, responders had a higher level of TREM-1 than non-responders. In inflamed mucosa, TREM1 expression level was also decreased in IFX responders [42]. However, Verstockt et al. observed a opposite connection between sTREM-1 level and mucosal healing. CD patients with anti-TNF therapy (adalimumab and infliximab) who achieved mucosal healing after 6 months tended to have a lower baseline sTREM-1 levels than those non-responders [41]. Recently, they further showed that low sTREM1 level could predict anti-TNF response in both CD and UC [43]. Such discrepancy between two results might potentially be attributed to differences in several aspects e.g., sample size, definition standards of response and different ethnicity [41]. Thus, whether the expression level of sTREM-1 could be an accurate biomarker for the evaluation of anti-TNF response remains to be validated in well-designed studies with large sample size.

4.3. Faecal and mucosal microbiota profile

Faecal microbiota was a rich source of biomarkers that were associated with intestinal inflammation [44]. Magnusson et al. [45] reported that the gut microbiota profile between responders and non-responders was different. Responders tended to have a lower dysbiosis indexes and a higher abundance of Faecalibacterium prausnitzii than non-responders at baseline. In addition, an increased abundance of Faecalibacterium prausnitzii was observed in responders during the IFX/adalimumab induction therapy [45]. Therefore, this finding might discriminate responders from non-responders at baseline. The metabolomic analyses of faecal samples showed that metabolite exchange was significantly associated with later clinical remission in patients with IBD who received anti-TNF therapy [44]. Vatn and European colleagues [46] reported that differences were observed for some bacterial markers, but they did not find a statistical significance between responders and non-responders in IBD patients with anti-TNF therapy. Dovrolis et al. [47] found that the populations of several bacterial genera in IBD patients were dramatically decreased after IFX therapy regardless of response. Their study further revealed that IFX treatment could significantly impact the gut microbial composition and the inflamed tissue transcriptome in IBD patients. In which, enterotypes at baseline correlates with transcriptome changes and could differentiate IFX responders versus non-responders and predicts anti-TNF response in patients with IBD [47]. Other studies confirmed that altered gut microbiota profile could reflect the rate of biotherapy response in patients with CD [48]. More recently, Wang et al. [49] examine the changed faecal microbiota profile in paediatric CD patients with anti-TNF therapy. They found that IFX in paediatric CDs could increase the bile salt hydrolases-producing bacteria, higher abundances of Methylobacterium, Sphingomonas, Staphylococcus, and Streptococcus were associated with a higher rate of sustained response in these patients with IFX therapy [49]. In a systematic review with 8 anti-TNF studies in patients with IBD, Estevinho et al. [50] indicated that the microbiomes of faecal or colon samples taken from IBD patients, in response to anti-TNF therapies, showed a decreased abundance of Escherichia and Enterococcus bacteria, but increased abundance of short-chain fatty acid-producing bacteria. In addition, higher microbial diversity at baseline or throughout treatment was associated with response to anti-TNF therapy [50].

4.4. MicroRNAs

MicroRNAs (miRNAs) are small, non-coding RNAs and are involved in the proinflammatory cytokine production and inflammation process as seen in IBD. Thus, circulating and faecal miRNAs have been considered as novel biomarker candidates that predict therapeutic response in patients with IBD [51]. For example, Batra et al. validated that the expression of seven miRNAs showed in remarkable changes after treatment in responders but not in non-responders in a small cohort of paediatric IBD with diverse treatments including anti-TNF mAbs [52]. However, a Greek group evaluated the association of miRNA polymorphisms with anti-TNF treatment response [53] did not detect any correlations between studied miRNA (miR-146 rs2910164, miR-196a rs11614913, miR-221 rs113054794 and miR-224 rs188519172) polymorphisms and patients' response to anti-TNF mAbs in 107 CDs. Therefore, the profile of serum or mucosa miRNAs as promise biomarkers in analysing the therapeutic response to anti-TNF mAbs in IBD patients remains to be investigated in future clinical practice.

4.5. Proteomics

The interaction between environmental factors and susceptible genes will inevitably result in a significant alteration of proteome profile in both serum and inflamed mucosa of IBD, which has been recently considered as the potential diagnostic and differentiate biomarkers for IBD [54]. For instance, Meuwis et al. reported that 4 serum proteins (platelet aggregation factor 4, haptoglobin a2, fibrinopeptide A, and myeloid-related protein 8) were associated with acute-phase inflammation and tended to be high sensitivity and specificity diagnostic biomarkers in patients with IBD [55]. Zhang et al. [56] reported that serum proteomic profiling may have a diagnostic value in differentiating IBD from intestinal tuberculosis. Starr et al. [57] showed that a panel of five proteins as candidate biomarkers that could distinguish patients with paediatric IBD from controls, and a panel of 12 proteins that enable differentiation between CD and UC [57]. Furthermore, Drobin et al. [58] have identified that 13 serum proteins were associated with cytokine signalling, immune-metabolic regulation, and immune cell activation in IBD patients.

Changed inflammation-related proteomic profiling could also be biomarker candidates in the evaluation of therapeutic response in IBD. Medina-Medina et al. [59] identified that 17 proteins regulated by acetylation had a predicting value for primary response to anti-TNF therapy and 4 proteins were potential biomarkers of loss of response in 54 CD patients. D'Haens et al. [60] recently developed a validation test to identify remission in CD patients with biologicals, based on serum levels of 13 proteins (ANG1, ANG2, CRP, SAA1, IL-7, EMMPRIN, MMP1, MMP2, MMP3, MMP9, TGFA, CEACAM1, and VCAM1) combined with the endoscopic healing index analysis. Their validation results showed that this test could accurately identify remission in CD patients, which were comparable to measurement of FC and higher than measurement of serum CRP [60]. Pierre et al. [61] identified that protein biomarker candidates could be distinctly classified as biomarkers associated with the risk of short-term and biomarkers associated with mid/long-term relapse in CD patients with IFX biological treatment, which related to different pathophysiological processes. Their results might help the clinicians to select the protein biomarker candidates for the evaluation of short-term and mid/long-term relapse in response to anti-TNF mAbs. However, Telesco et al. [62] reported that the specificity of a panel of 13 candidate biomarkers at gene levels in predicating mucosal healing response to golimumab treatment in patients with UC was low and not sufficient for the clinical utility.

4.6. Genomic

Susceptibility loci in IBD can be identified [63], the value of different genomic biomarkers such as functional polymorphisms in the relevant genes encoding in predicating response to TNF therapy in patients with IBD has been evaluated [64,65]. Since the target of anti-TNF mAbs is on TNF, the functional polymorphisms for TNF and TNF receptor superfamily have attracted much attention and researched [63,64]. Studies revealed that polymorphisms in cytokine pathways (IL-1B, IL-6, IFN-gamma, TNFRSF1A, NLRP3, IL1RN, IL-18, and JAK2), the NFκB pathway (TLR2, TLR4 and NFKBIA) were closely associated with response to anti-TNF therapy in patients with IBD [64,66]. Polymorphisms in encoding many other genes such as HLA-DQA1*05 have also been reported to be associated with response to anti-TNF therapy [67].

Recently, the development of genomic-relevant serological antibodies in patients with IBD has been reported. Degenhardti et al. [68] showed that the tested serological antibodies anti-GP2 IgA and IgG were associated with CD and had a high discriminatory capability for CD versus UC. In addition, a genome wide association study of antibody expression in their cohort could identify distinct loci associated with levels of anti-GP2 isoform beta IgG and IgA, many of which are known susceptibility loci for IBD [68]. However, their significance in the evaluation of anti-TNF efficacy in CD verse UC has not been studied. Finally, biomarkers might also play a key role in differentiating paediatric- from adult-onset IBD. For example, genome-wide association study (GWAS) has revealed the single-nucleotide polymorphism differences in the polygenic architecture between paediatric- and adult-onset IBD [69]. Which could be the potential genetic biomarkers to study the role and significance of accumulated rare and deleterious variants in affected paediatric- and adult-onset.

4.7. Other new biomarkers

The therapeutic response to anti-TNF mAbs may also induce changes of mucosal histology. We found that densities of T lymphocytes and macrophages were significantly decreased in UC patients with healed mucosa after IFX introduction treatment [32]. Li et al. [70] reported that both UC and CD patients with IFX therapy showed a sustained decreased population of regulatory T cells (Tregs) in peripheral blood and downregulated expression level of FoxP3 (a marker for Tregs) transcript in inflamed mucosa, particularly in UC and CD responders. However, as many immune cell and new subsets of lymphocytes such as TH9 and TH22 have been identified in the colorectal mucosa [71], their exact role in the pathogenesis of IBD and therapeutics remains unclear.

More recently, Osterman et al. [72] reported that ileal microvillar length has a significance to predict the therapeutic response to ustekinumab (mAbs to IL-12 and IL-23) and Vedolizumab (mAbs to integrin) in patients with CD. However, the predicative value of ileal microvillar length in IBD patients with anti-TNF mAbs remains to be investigated. Andreou et al. [73] showed that serum B-cell activating factor (BAF) concentration at baseline in CD response to IFX was higher than CD non-response to IFX. Which was associated with its polymorphisms. Importantly, serum BAF concentration in CD responders was remarkably reduced after IFX [73]. Their findings suggest that serum BAF might have a predicating significance for anti-TNF therapy. Reports indicated that low serum albumin levels could predicate a worse response to IFX or golimumab in patients with UC [18,74].

For the convenience for readers, we have summarized selected novel biomarkers in Table 2.

5. Combination, validation and comparison studies between current and novel biomarker in the evaluation of anti-TNF therapeutic response in IBD

The use and significance of different biomarkers in the clinical practice might be varied. Some biomarkers such as genomic, RNA and protein levels, and FC concentration have been frequently used

Table 2
Novel putative biomarkers in the evaluation of anti-TNF therapeutic efficacy in patients with IBD.

Biomarker	Decreased or normalized in CD			Decreased or normalized in UC		
	Response	Remission	Mucosal healing	Response	Remission	Mucosal healing
Mucosal transcripts						
TNF-α	+ [33, 34]	+ [33, 34]	+ [33, 34]	+ [35]	+ [35]	+ [35]
IL-17A	+ [34]	+ [34]	+ [34]	+ [33, 36]	+ [33, 36]	+ [33, 36]
OSM	+ [38, 39]	+ [38, 39]		+ [38, 39]	+ [38, 39]	
IL-7R	+ [37]			+ [37]		
TREM1	+ [41, 43]			+ [41, 43]		
miRNAs	+ [52, 53]			+ [52]		
Faecal and mucosal microbiota profile	+ [44, 46, 48, 49]			+ [44–46]		
Proteomics	+ [59, 76]					
Genomic	+ [63, 64]			+ [63, 64]		

TNF-α: tumour necrosis factor-α; IL-17A: interleukin-17A; miRNAS: MicroRNAs; OSM: Oncostatin M; IL-7R: interleukin-7 receptor; TREM1: Triggering receptor expressed on myeloid cells 1.
(reference ID).

to assess pre-treatment non-response to anti-TNF mAbs in patients with CD [16,65]. However, the level of drugs and ADA are often applied to the monitoring of anti-TNF therapy. Mucosal TNF transcript is a biomarker that not only help in evaluation of therapeutic response, but also help to identify the candidates who should prior to the administration and personation of anti-TNF mAbs in patients with UC [7]. Moreover, the accuracy and power of individual biomarker in the evaluation of therapeutic response in patients with IBD might be low. One of strategies to improve the power of biomarkers in clinic is to use the combination of different biomarkers in the evaluation of anti-TNF therapeutic response in patients with IBD [6]. Roblin et al. [75] reported that CRP levels, together with IFX trough levels and anti-drug antibody levels were associated with the rate of loss response to infliximab in patients with IBD. However, how to optimally group these different biomarkers for clinical use is a particular future task.

Vatn et al. [46] have compared faecal microbiota profile with other inflammatory biomarkers such as CRP and faecal calprotectin in patients with IBD, they observed a strong correlation between the degree of dysbiosis and the faecal calprotectin levels. Alterations in microbiota composition have previously been associated with response to anti-TNF therapy [45]. However, they could not validate such correlation between changed microbiota and anti-TNF therapeutic response [46]. More recently, our group have validated the value of mucosal TNF transcript as a reliable biomarker in the evaluation of anti-TNF therapeutic response in patients with UC [7]. We were able to show that baseline mucosal TNF-α transcript level was a better biomarker than other clinical parameters e.g., calprotectin, the UC disease activity index (UCDAI) score, Mayo endoscopic score in patients with UC [7]. Meuwis et al. [76] validated that changed serum proteins could predict the therapeutic response to anti-TNF in a small cohort of CD patients. Haberman et al. validated that a subset of severity genes and changed microbiota profile are associated with response to anti-TNF mAbs in adult UCs [77]. However, the sensitivity and specificity of most of them require validation studies on a larger cohort of patients (see Summarized in Fig. 3). Therefore, validation of current and novel biomarkers in well-designed studies with large patient size should be considered in the future. In addition, whether one biomarker is better than another biomarker in reflecting disease activity change is important for its use in the evaluation of

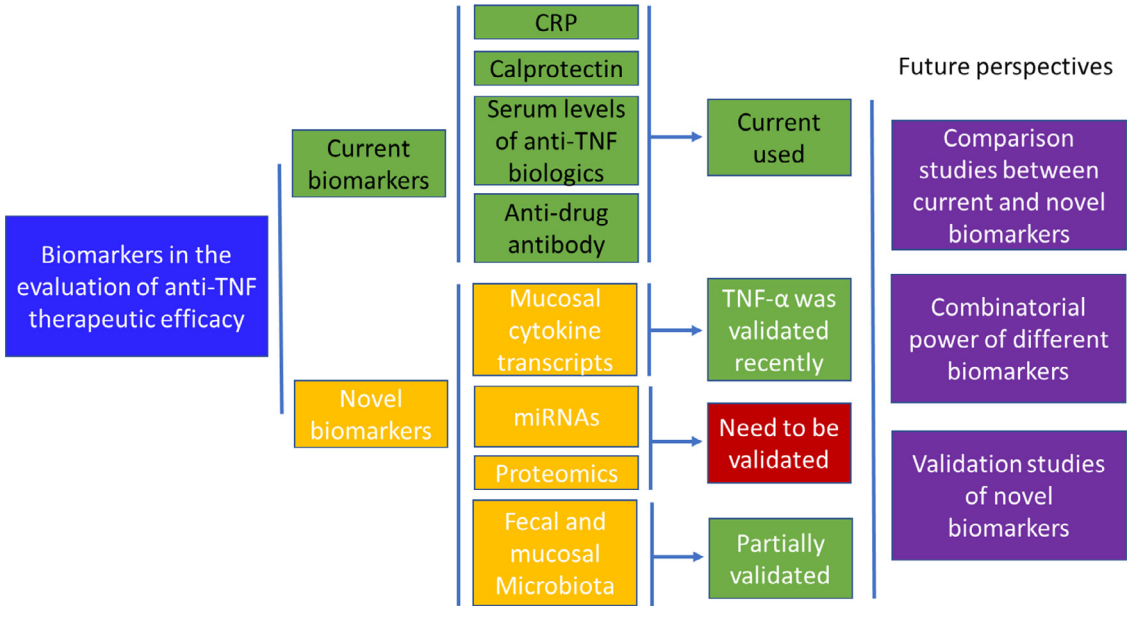

Fig. 3. Schematic summary of the statues of current and novel laboratory biomarkers used in the evaluation of anti-TNF therapy in patients with IBD
Many laboratory factors have been used as biomarkers in the evaluation of anti-TNF therapeutic response. However, the sensitivity and specificity of most of them have not been well validated in clinical studies with a larger sample size. Future comparison studies between current and novel biomarkers and the combination power of different biomarkers in clinic in the evaluation of anti-TNF therapeutic response in patients with IBD are waiting to be conducted.

therapeutic response in patients with IBD. To the best of our knowledge, high-quality comparison studies between commonly used current and novel biomarkers are waiting to be conducted. These works are extremely important for the selection and development of ideal biomarkers, optimization of personal medicine and strategy for identifying IBD patients who will benefit from anti-TNF therapy in the future clinical practice.

6. Limitations of this review

Due to the high number of biomarkers and publications in biomarker research field, we focused this review only on commonly used and selected novel biomarkers for the evaluation of anti-TNF therapeutic efficacy in patients with IBD. We could have missed some promising novel biomarkers. Future reviews could be extended to include these biomarkers in the evaluation of anti-TNF efficacy when the data is sufficient. Furthermore, the accuracy and potential value for these novel biomarkers in the evaluation of response to anti-TNF therapy in IBD patients need to be validated in large sample size cohorts of IBD patients. Finally, because of sample size, anti-TNF mAbs and methodological heterogeneity of included studies, we did not conduct a formal assessment of quality and risk of bias of included studies and a meta-analysis for individual biomarkers was not carried out in this review.

7. Conclusions

Anti-TNF strategy has been widely used and shows a significant benefit in the management of severe steroid refractory or dependant IBD patients. How to find reliable laboratory biomarkers may significantly help the evaluation, improvement and personalization of anti-TNF therapy in the clinical practice. Most biomarkers seem to reflect a generalized inflammation, are not IBD specific. Therefore, their usage and clinical significance in IBD patients with different types of anti-TNF mAbs are non-different.

Many new biomarkers are reported. However, most of them reflect a generalized inflammation, are not CD or UC specific. Therefore, the inflammatory biomarkers usually cannot differentiate CD and UC. One of the main works in the future is to validate these novel biomarkers in well-designed studies with large size of IBD patients. Furthermore, comparison studies between current and novel biomarkers are necessary, which may help the clinicians to select reliable biomarkers, better evaluate efficacy and personalize medicine of anti-TNF therapy in the future clinical practice.

8. Outstanding questions

The importance of biomarkers in the evaluation of therapeutic efficacy in patients with IBD has been intensively studied. Current analysis provides new insights and challenges to optimize personal anti-TNF strategy (precision medicine) in patients with IBD.

8.1. Optimize the use of different biomarker for clinical practice

Can we classify the laboratory biomarkers into categories such as surveillance of disease activity, monitoring therapeutic response and predicating prognosis [78]?

8.2. Biomarkers in the candidate selection prior to for the administration of anti-TNF mAbs

Some biomarkers such as mucosal TNF transcript could predicate the response rate to anti-TNF mAbs [34]. Should we measure the levels of the biomarker before we decide to prescribe anti-TNF mAbs to a patient? Should those patients with a high level of the biomarker be in the priority of consideration for anti-TNF therapy?

8.3. Optimizing dose and duration of anti-TNF mAbs

The levels of some biomarkers such as FC and serum CRP could predicate the failure rate in IBD patients with anti-TNF therapy [16]. How to identify a correlation between the dose/duration of anti-TNF mAbs and the biomarker levels?

To improve the accuracy and power of individual biomarker in the clinic, one of strategies is to combinate different biomarkers in the evaluation of anti-TNF therapeutic response in patients with IBD. However, how to optimally group different biomarkers for clinical use remains to be investigated.

8.4. Search strategy and selection criteria

A literature research was electronically carried out in academic databases PubMed, MEDLINE and Google scholar by the authors using the search terms “biomarker”, “inflammatory bowel diseases”, “ulcerative colitis”, “Crohn’s disease”, “anti-TNF treatment”, “efficacy”, “predicators”, “C-reactive protein”, “calprotectin”, "infliximab level", "anti-infliximab", "adalimumab level" and "anti-adalimumab". After screening the abstracts, relevant publications from appropriate papers added as additional literature sources.

We used the following eligibility criteria to include publications in this systematic review (2): (1) article written in English and full-text available; (2) only studies performed in humans; (3) individual patient information; (4) studies only published as abstract or not in English were excluded.

The electronic literature search resulted in a total of 2651 abstracts (2641 in English from MEDLINE, PUBMED and Google scholar, 10 full-text publications in English by cross-reference search), latest search date: 31st of May 2020. Of which 91 full-text publications were finally included for analysis after excluding publications not meeting the selection criteria.

Contributors

GC had the idea for this systematic review and performed the electronic search for literatures, QF, ZL and RG performed literature selection, data extraction and analysis. JF joined the data analysis and discussion. All the listed authors contributed to this manuscript in writing and final approvement.

Declaration of Competing Interest

The authors declare no conflicts of interests.

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