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Predictive value of blood concentration of biologics on endoscopic inactivity in inflammatory bowel disease: A systematic review

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Abstract

BACKGROUND

Although blood concentration of biologics is an important composition of disease management in inflammatory bowel disease (IBD) patients, complexity and uncertainty of biological management encourage many disputes in predicting the outcome of IBD patients through blood concentration of biologics.

AIM

To verify the predictive value of blood concentration of biologics on endoscopic inactivity in IBD patients under different situations.

METHODS

We searched PubMed/MEDLINE, Embase, and Web of Science up to May 2020 and identified IBD patients as the research cohort as well as the correlations between blood concentration of biologics and endoscopic inactivity in IBD patients as the research direction.

RESULTS

A total of 23 articles with 30 clinical studies and 1939 IBD patients were included. The predictive cut-off value of blood concentration of infliximab on mucosal healing should be 2.7-10.6 µg/mL in IBD. Blood concentration of infliximab reaching 5.0-12.7 µg/mL or more increased the probability of fistula healing/closure in perianal fistulizing Crohn's disease. Blood concentration of adalimumab reaching 7.2-16.2 µg/mL or more could predict mucosal healing in IBD. The predictive cut-off value of blood concentration of adalimumab on fistula healing/closure should be 5.9-9.8 µg/mL in perianal fistulizing Crohn's disease.

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Blood concentration of vedolizumab surpassing 25.0 µg/mL indicated mucosal healing in ulcerative colitis patients under maintenance therapy and the predictive cut-off value of blood concentration on mucosal healing or endoscopic remission under induction therapy in IBD could be 8.0-28.9 µg/mL.

CONCLUSION

Blood concentration of biologics should not be utilized to predict endoscopic inactivity of IBD independently due to discrepancies in clinical studies, whereas conducting therapeutic drug monitoring intensively contributes to precise therapy.

Key Words: Inflammatory bowel disease; Biological blood concentration; Endoscopic inactivity; Infliximab; Adalimumab; Vedolizumab

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Core Tip: Deep remission is considered the primary endpoint of biological therapy in inflammatory bowel disease. However, it is still difficult to determine or predict whether inflammatory bowel disease (IBD) patients achieve deep remission or not. Although endoscopic examinations are widely accepted by gastroenterologists as the golden standard in evaluating disease states, the majority of IBD patients reject frequent invasive examinations. Hence, new methods for early prediction of therapeutic outcomes in IBD patients on biologics are brought forward by gastroenterologists. Blood concentration of biologics, one of the major monitoring indicators during biological therapy, exhibits enormous tendency to correlate with outcomes of IBD patients. Nonetheless, blood concentration of biologics is not a substitute for endoscopic examinations in detecting deep lesions. By contrast, the combination of blood concentration of biologics and endoscopic examinations is conducive to enhancing the accuracy of outcome prediction.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a class of chronic and unspecific inflammatory intestinal diseases induced by immune-mediated disorder, which mainly destroys intestinal structure and impairs the intestinal function. The involvement of large intestinal mucosa, frequent spreading of inflammation to the whole digestive tract, and invasion of the mucosal muscular layer of the intestine may distinguish CD from UC.

Previously, the therapeutic goal for IBD focuses on the management of symptoms only, but changing the course of the disease is recognized as the therapeutic goal currently. Therefore, based on the traditional top-down therapy, several clinical trials have put forward two novel therapeutic strategies of accelerating top-down therapy and implementing step-up therapy in the early stage, during which biological management remains crucial^[1-3]. Different responses of IBD patients to the same biologic due to individual variations and increment of biological therapy failure over time are still a nodus in the treatment. Monitoring blood concentration of biologics is regarded as the significant part of biological management, which assists in estimating the therapeutic effects in IBD patients sufficiently^[4].

Endoscopic mucosal healing is considered the major therapeutic goal in IBD patients and it has been verified in several clinical trials, which showed that endoscopic healing is beneficial in decreasing the hospitalization rate, surgical risk, cancerous rate, and so on. Endoscopy remains the golden standard for mucosal healing evaluation, and is advantageous in reflecting gastrointestinal lesions directly

and disadvantageous due to its poor compliance, high cost, painful procedure, and subjective discrepancies in outcome evaluation among different physicians^[5-9]. Hence, biomarkers that can temporarily substitute endoscopy or assist endoscopy in evaluating the prognosis of IBD have been focused on by current research studies^[10,11]. Similar to the specific inflammatory biomarkers in IBD, blood concentration of biologics published in a series of clinical trials has the ability to predict the prognosis of IBD in patients under biological therapy, especially remission and relapse^[4]. This review lays emphasis on the predictive value of blood concentration of biologics on endoscopic inactivity in IBD patients.

MATERIALS AND METHODS

Literature search

We searched PubMed/MEDLINE, Embase, and Web of Science till March 2020 for studies that met the following inclusion criteria: (1) Study cohorts containing adults or children diagnosed with IBD; (2) Studies that reported the definition of endoscopic inactivity outcome, and the therapeutic target of study cohort endoscopic inactivity; and (3) Studies that evaluated the correlation between biological blood concentration and endoscopic inactivity outcome and identified the best cut off values of blood concentration of biologics in predicting the endoscopic outcome. Studies were identified using the following key words: "UC", "Ulcerative colitis", "CD", "Crohn's disease", "IBD", "Inflammatory bowel disease", "IFX", "Infliximab", "ADA", "Adalimumab", "VDZ", "Vedolizumab", "anti-TNF- α drug", "anti-TNF- α agent", "anti-TNF α therapy", "anti-TNF α treatment", "Serum level", "Trough level", "Serum concentration", "Trough concentration", "Endoscopic remission", "Mucosal healing", "Histological healing", "Histological remission", "Endoscopic inactivity", and "Endoscopic healing". Literature search focused on full-texts and references of each article were carefully checked. Additionally, the literature search was not limited by country, language, and published date. First, two authors (Rong Huang and Xue-Hui Qiao) deleted repetitive studies according to the search results. Second, they included studies based on the inclusion criteria, after rigorous screening of the titles, abstracts, and key words of studies. Any disagreements during the screening process were judged by the third author (Ke-Fang Jiang).

Data extraction

The data collected from each study included author, year, and study type, and the data was divided into three major segments. The first part involves collection and systematic analysis of data including diagnosis, age, disease course, smoking, disease severity, disease location, previous medical therapy, previous surgery, previous biological therapy, and so on. The second part involves collection and systematic analysis of data that are relevant to biological management, including biological type, course of the research, therapeutic stage, injection dose, injection frequency, injection time, and so on. The third part includes collection and systematic analysis of data relevant to the predictive value of blood concentrations of biologics on endoscopic inactivity outcome, including the best predictive cut off values of blood concentration of biologics, sensitivity, specificity, positive predictive value, negative predictive value, area under the curve, the definition of endoscopic inactivity, and the number of patients achieving endoscopic inactivity.

RESULTS

Literature selection

Three researchers identified a total of 1086 studies based on the inclusion criteria. Of these, 455 duplicates or irrelevant studies or studies that did not report the original data were removed. Moreover, 604 studies were excluded after finishing rigorous check of the inclusion criteria, abstract, and key words. Additionally, another four studies were deleted due to the lack of best cut-off values of blood concentration after carefully reviewing the full-texts. Finally, 23 studies involving 30 clinical studies and 1939 IBD patients were included in the study. Two studies concentrated on pediatric CD, whereas the major study design and consequences were approximated to adults. Eight studies have focused on IBD patients and 15 studies distinguished CD patients from UC patients in study cohorts. The flow chart of study selection process is shown

in **Figure 1** and the demographics and disease characteristics of study cohorts are shown in **Tables 1** and **2**.

Quality of literature

The Newcastle-Ottawa Scale (NOS) was adopted to evaluate the quality of studies included in this study. NOS mainly contains eight aspects: “The representativeness of the exposed cohorts”, “the selective methods of unexposed cohorts”, “identification of exposure”, “the verification of concerned results absent in the start of study”, “the comparability of cohorts based on design and analysis”, “sufficient evaluation of study results”, “long follow-up period after obtaining the study results”, and “long follow-up period of cohorts”. Quality evaluation of studies has ruled out two aspects by considering “the selection methods of unexposed cohorts” and “the comparability of cohorts based on design and analysis” that are irrelevant to the study. One star is assigned if the literature achieved any one of the six items and the highest point that can be achieved is six stars. However, the literature with not less than five stars is defined as high quality study. Nineteen studies^[12-30] were considered as low quality and four studies^[31-34] were considered as high quality (**Table 3**).

Biological management

Several discrepancies existed in the biological management put forwarded by different studies. Twenty-three studies showed clear records of biological type^[12-34]; eleven studies involved adalimumab (ADA)^[12,16,18-20,24,26-30], thirteen involved infliximab (IFX)^[12,14,15,17,18,21-24,27,28,31,32], and four involved vedolizumab (VDZ)^[13,25,33,34]. El-Matary *et al*^[32] have failed to publish IFX therapeutic stage, nine studies referred to ADA maintenance therapy^[12,16,18,19,24,26,27,29,30], three referred to ADA induction therapy^[18,20,28], ten referred to IFX maintenance therapy^[12,14,15,17,18,21,22,24,27,31], four referred to IFX induction therapy^[18,23,28,31], three referred to VDZ induction therapy^[13,33,34], and four referred to VDZ maintenance therapy^[13,25,33,34]. Thirteen studies had the course of research^[12-15,19,20,23,24,28,29,31,33,34]. The injection dose of ADA induction therapy recorded in the studies was 160 mg at week 0, 80 mg at week 2, and 40 mg at week 6^[18,20,28]. ADA maintenance therapy adopted an injection dose of 40 mg every other week or 40 mg every week^[16,18,19,24,27,29,30]. Injection dose of IFX induction therapy was 5 mg/kg at weeks 0, 2, and 6 in the published studies^[18,31]. Nonetheless, the injection dose of IFX maintenance therapy varied in different studies. The standard dose of IFX maintenance therapy was 5 mg/kg every 8 wk whereas the interval time of injection was shortened to 6 wk or the dose of injection was strengthened to 7.5 mg/kg or 10 mg/kg in some patients^[14,15,18,21,24,27,31]. Three studies recorded the injection dose of VDZ induction therapy as 300 mg at weeks 0, 2, and 6^[13,33,34], while Dreesen *et al*^[13] have implemented another VDZ injection dose of 300 mg at week 10 due to a low response rate. Injection dose of VDZ maintenance therapy adopted 300 mg every 4 wk or every 8 wk from week 14^[13,25,33,34] (**Table 4**).

Endoscopic scores and definition of endoscopic inactivity

The definition of endoscopic inactivity varied in different studies. Ten studies did not utilize a standard criterion for endoscopic inactivity evaluation of CD or UC^[13,14,24,26,27,29-32,34]. The definition of fistula healing/closure in three studies of perianal fistulizing Crohn's disease (pfCD) mainly concentrated on physical examination^[24,27,32], and only Strik *et al*^[27] utilized magnetic resonance imaging (MRI) examination to evaluate the endpoint with no detailed description. Seven studies have defined mucosal healing as a lack of inflammation or disappearance of ulcerations under endoscopy instead of endoscopic scoring systems^[13,14,26,29-31,34]. Seventeen studies involved endoscopic scoring systems for outcome evaluation of CD or UC^[12,13,15-23,25,26,28,31,33,34]. Four studies defined mucosal healing of CD as a Simple Endoscopic Score for Crohn's Disease (SES-CD) < 3^[12,17,28] or SES-CD of 0^[17] and endoscopic remission of CD as an SES-CD ≤ 4^[33], Dreesen *et al*^[31] selected a Crohn's Disease Endoscopic Index of Severity (CDEIS) < 3 to define endoscopic remission, and Morita *et al*^[19] and Imaeda *et al*^[15] selected a modified Rutgeerts' score of 0 (no lesions or scar) or 1 (5 aphthous lesions) to define mucosal healing. Three studies selected a Rutgeerts' score of < 2 to define mucosal healing of CD in postoperative setting^[12,16,21]. Ten studies defined mucosal healing of UC as a Mayo Endoscopic Score (MES) ≤ 1^[12,13,16,20,22,23,26,28,33,34], Morita *et al*^[18] utilized an Ulcerative Colitis Endoscopic Index of Severity (UCEIS) ≤ 1 (the bleeding descriptor and the erosions and ulcers descriptor were both 0, and the vascular pattern descriptor was 0 or 1) to define mucosal healing. Considering the inconsistency between intestinal inflammation under endoscopy and clinical symptoms, Hanžel *et al*^[33] have included clinical remission and endoscopic

Table 1 Disease phenotype of study cohort

Ref.	CD, Location, <i>n</i> (%)			CD, Behavior, <i>n</i> (%)					UC, Location, <i>n</i> (%)				
	Ileal	Colonic	Ileocolonic	UGT	Inflammatory	Stricturing	Fistulizing	Perianal	Penetrating	Extensive	Left-side	Pancolitis	Proctitis
Chaparro <i>et al</i> ^[12] , 2018	49 (38.6)	25 (19.7)	52 (40.9)	4 (3.1)	67 (52.8)	34 (26.8)	26 (20.5)	85 (66.9)		39 (30.7)	16 (12.6)		
Ungar <i>et al</i> ^[28] , 2016	31 (27.9)	26 (23.4)	54 (48.6)		49 (44.1)	28 (25.2)			34 (30.6)		16 (14.4)	17 (15.3)	
Yarur <i>et al</i> ^[29] , 2016	16 (27.9)	9 (15.6)	14 (24.1)	3 (5.2)		29 (50.0)		20 (34.4)	11 (19.0)		1 (14.3)	6 (86.7)	0
Roblin <i>et al</i> ^[26] , 2014	13 (59.1)	4 (18.2)	5 (22.7)			4 (18.2)			4 (18.2)	14 (77.8)	4 (18.2)		
Morita <i>et al</i> ^[18] , 2016											19 (29.7)	45 (70.3)	
Morita <i>et al</i> ^[19] , 2016	14 (33.3)	4 (9.5)	24 (57.1)			50.0			6 (14.3)				
Strik <i>et al</i> ^[27] , 2019													9 (13.6)
Plevris <i>et al</i> ^[24] , 2020	11 (17.2)	26 (40.6)	27 (42.2)			11 (17.2)			16 (25.0)				
Zittan <i>et al</i> ^[30] , 2016	12 (20.0)	14 (23.3)	34 (56.7)						18 (30.0)				
Juncadella <i>et al</i> ^[16] , 2018	20 (27.8)	13 (18.1)	39 (54.2)	3 (4.2)		10 (13.9)		32 (44.4)	29 (40.3)	10 (38.5)	16 (61.5)		
Papamichael <i>et al</i> ^[23] , 2016												63 (62.4)	
Papamichael <i>et al</i> ^[20] , 2017										20 (46.5)			
Papamichael <i>et al</i> ^[22] , 2018												29 (51.8)	
Feng <i>et al</i> ^[14] , 2019	15 (10.6)	6 (4.3)	120 (85.1)			29 (20.6)			15 (10.6)				
Papamichael <i>et al</i> ^[21] , 2018	20 (18.3)	25 (22.9)	59 (54.1)	5 (4.6)		18 (16.4)			38 (34.5)				
Dreesen <i>et al</i> ^[31] , 2020													
Imaeda <i>et al</i> ^[15] , 2014	14 (31.1)	4 (8.9)	27 (60.0)			16 (35.6)			4 (8.9)				
El-Matary <i>et al</i> ^[32] , 2019	5 (8.5)	17 (28.8)	27 (45.8)	10 (16.9)									
Kang <i>et al</i> ^[17] , 2019	8 (7.6)	6 (5.7)	91 (86.7)	70 (66.7)		18 (17.1)			3 (2.9)				
Hanzel <i>et al</i> ^[33] , 2019	0	4 (14.3)	24 (8.6)	6 (2.1)				4 (14.3)		16 (69.6)	7 (30.4)		
Dreesen <i>et al</i> ^[13] , 2018													
Pouillon <i>et al</i> ^[25] , 2019											13 (41.9)	15 (48.4)	3 (9.7)
Yacoub <i>et al</i> ^[34] , 2018	14(35.9)	6 (15.4)	19 (48.7)			11 (28.2)			6 (15.4)	27 (62.8)	15 (34.9)		1 (2.3)

UGT: Upper gastroenterological tract; CD: Crohn's disease; UC: Ulcerative colitis.

remission into the primary endpoint. Additionally, five studies defined primary endpoint as histological healing or histological remission^[16,21,22,25,29], whereas only Pouillon *et al.*^[25] have defined histological healing of UC as a Nancy Histological Index ≤ 1 rather than subjective description (Table 5 and Figure 2).

Predictive value of blood concentration of biologics on endoscopic inactivity

Study cohorts of inflammatory bowel disease: In the study by Ungar *et al.*^[28], IBD patients under IFX or ADA induction therapy had a 80%-90% probability of mucosal healing satisfying an IFX serum level ranging from 6 $\mu\text{g/mL}$ to 10 $\mu\text{g/mL}$ or ADA serum level ranging from 8-12 $\mu\text{g/mL}$. The combination of IFX serum level at week 2 during treatment and clinical symptoms demonstrated a great effect on the prognostic prediction as well as the meaningful option and evaluation of IFX continual or transformational or intensive therapy^[35]. A cross-sectional study of IBD patients under IFX or ADA therapy using stable doses for at least 6 mo suggested the best cut off values of 3.4 $\mu\text{g/mL}$ and 7.2 $\mu\text{g/mL}$ of IFX and ADA trough levels in predicting mucosal healing, respectively^[12]. Specifically, the ADA serum level that surpasses 7.5 $\mu\text{g/mL}$ or 7.8 $\mu\text{g/mL}$ was found to be predictive of mucosal healing or histological healing with a 61%-62% sensitivity and 83%-95% specificity in IBD patients under maintenance therapy^[29]. Inversely, the possibility of the absence of mucosal healing was increased dramatically with an ADA trough level of lower than 4.9 $\mu\text{g/mL}$ ^[26]. VDZ would be a better choice if anti-TNF- α agents failed to terminate inflammatory activity of IBD. Hanžel *et al.*^[33] have demonstrated that vedolizumab trough level (VTL) ≥ 8.0 $\mu\text{g/mL}$ at week 22 or VTL ≥ 22.0 $\mu\text{g/mL}$ at week 6 assisted in moderately predicting IBD remission (endoscopic remission and clinical remission) within the first year of VDZ treatment with a sensitivity and specificity of more than 70%.

Study cohorts of ulcerative colitis: In the study by Papamichael *et al.*^[23], IFX serum levels exceeding 15 $\mu\text{g/mL}$ at week 6 or 2.1 $\mu\text{g/mL}$ at week 14 during induction therapy in UC patients were shown to act as independent factors that affect the short term mucosal healing as defined by MES ≤ 1 from week 10 to week 14. Moreover, IFX trough level of more than 7.5 $\mu\text{g/mL}$ or 10.5 $\mu\text{g/mL}$ acts as a good predictor of endoscopic healing with a 77% sensitivity and 62% specificity or histological healing with a 54% sensitivity and 78% specificity, respectively, under maintenance therapy^[22]. However, Morita *et al.*^[18] held the view that IFX trough level of ≥ 2.7 $\mu\text{g/mL}$ and ADA trough level of ≥ 10.3 $\mu\text{g/mL}$ were both capable of predicting UCEIS ≤ 1 with a sensitivity and specificity exceeding 80% among UC patients under maintenance therapy. Differently, Juncadella *et al.*^[16] have considered ADA serum level exceeding 16.2 $\mu\text{g/mL}$ as a good predictor of MES ≤ 1 with an 85% sensitivity and histological healing with a 100% sensitivity. However, under induction stage of therapy, ADA serum level of more than 9.4 $\mu\text{g/mL}$ could predict short-term mucosal healing at weeks 8-14 with a 67% sensitivity and 77% specificity. Dreesen *et al.*^[13] have confirmed that VTL ≥ 28.9 $\mu\text{g/mL}$ at week 2 and VTL ≥ 13.9 $\mu\text{g/mL}$ at week 14 showed a moderate sensitivity and low specificity to predict MES ≤ 1 at week 14. Another study in UC patients under induction therapy with VDZ considered that VTL surpassed 18.0 $\mu\text{g/mL}$ at week 6 predicted MES ≤ 1 in the first year treatment with a 100% sensitivity and 75% specificity^[34]. Pouillon *et al.*^[25] have discovered that UC patients under maintenance therapy with VDZ had VTL ≥ 25.0 $\mu\text{g/mL}$, which showed a significant possibility of achieving histological healing (Nancy Histological Index ≤ 1).

Study cohorts of Crohn's disease: The follow-up study of CD patients during the first year therapy of IFX demonstrated that IFX trough level exceeding 23.1 mg/L at week 2 or 10.0 mg/L at week 6 had a high sensitivity and low specificity in predicting endoscopic remission, which was defined as CDEIS < 3 or absence of ulcerations at week 12^[31]. IFX serum levels of more than 4.85 $\mu\text{g/mL}$ at week 14 and 2.85 $\mu\text{g/mL}$ at week 30 could assist in moderately predicting the complete absence of any sign of the ulceration in CD^[14]. Nonetheless, Papamichael *et al.*^[21] have verified that IFX serum level of ≥ 10 $\mu\text{g/mL}$ might not be a good predictor of endoscopic remission or histological remission under maintenance stage with a low sensitivity and specificity. The study on CD patients with stable IFX or ADA infusions for at least 6 mo showed that IFX trough level of ≥ 4.0 $\mu\text{g/mL}$ ^[15] or ADA ≥ 7.9 $\mu\text{g/mL}$ ^[19] assisted in moderately predicting the modified Rutgeerts' Scoring System Score of ≤ 1 . Similarly, a 91% sensitivity and 76% specificity acts as the predictive value of ADA trough level of ≥ 8.14 $\mu\text{g/mL}$ on complete absence of ulceration in CD patients^[30]. However, Juncadella *et al.*^[16] have suggested that ADA serum level of 12 $\mu\text{g/mL}$ or more, much higher than trough level, assisted in predicting endoscopic remission or histological healing with a

Table 2 Demographics of study cohorts in inflammatory bowel disease

Ref.	Diagnostic	Biological	Number	Female, <i>n</i> (%)	Smoking, <i>n</i> (%)	Previous surgery, <i>n</i> (%)	Previous biological therapy, <i>n</i> (%)	Concomitant medications				
								CS, <i>n</i> (%)	IMMs, <i>n</i> (%)	5-ASA, <i>n</i> (%)	Surgical intervention, <i>n</i> (%)	Enteral nutrition, <i>n</i> (%)
Chaparro <i>et al</i> ^[12] , 2018	IBD	ADA/IFX	182	90 (49.5)	50 (27.5)	49 (26.9)	48 (26.4)		63 (34.6)			
Ungar <i>et al</i> ^[28] , 2016	IBD	ADA/IFX	145	64 (44.1)	19 (13.1)	33 (22.8)	37 (25.5)	27 (18.6)	79 (54.5)			
Yarur <i>et al</i> ^[29] , 2016	IBD	ADA	66	27 (40.9)	6 (9.1)		42 (63.6)	14 (21.2)	21 (31.2)			
Roblin <i>et al</i> ^[26] , 2014	IBD	ADA	40	22 (55)					5 (12.5)			
Morita <i>et al</i> ^[18] , 2016	UC	ADA/IFX	64	25 (39.1)			4 (6.3)	50 (78.1)	34 (53.1)	48 (75.0)		
Morita <i>et al</i> ^[19] , 2016	CD	ADA	42	15 (35.7)		18 (42.9)	15 (35.7)	5 (11.9)	24 (57.1)	30 (71.4)		
Strik <i>et al</i> ^[27] , 2019	PfCD	ADA	19	9 (47.4)	5 (26.3)		9 (47.4)				4 (21.1)	
Plevris <i>et al</i> ^[24] , 2020	PfCD	ADA	35	17 (48.6)	3 (8.6)		21 (60.0)		15 (42.9)			
Zittan <i>et al</i> ^[30] , 2016	CD	ADA	60	31 (51.7)	9 (15.0)		36 (60.0)	Total of concomitant therapy: 18 (30.0)				
Papamichael <i>et al</i> ^[20] , 2017	UC	ADA	43	20 (46.5)	4/35 (11.4)		38 (88.4)	12 (27.9)	7 (16.3)			
Juncadella <i>et al</i> ^[16] , 2018	IBD	ADA	98	60 (61.2)	34 (34.7)	28/72 (38.9)			26 (26.5)			
Feng <i>et al</i> ^[14] , 2019	CD	IFX	141	51 (36.2)	5 (3.5)	22 (15.6)	8 (5.7)		20 (14.2)			
Papamichael <i>et al</i> ^[22] , 2018	UC	IFX	56	24 (42.9)	11 (19.6)				18 (32.1)			
Papamichael <i>et al</i> ^[21] , 2018	CD	IFX	110	51 (46.4)	19 (17.3)	20 (18.2)	8 (7.3)		28 (25.5)			
Strik <i>et al</i> ^[27] , 2019	PfCD	IFX	47	29 (61.7)	7 (14.9)		15 (31.9)				13 (27.7)	
Plevris <i>et al</i> ^[24] , 2020	PfCD	IFX	29	11 (37.9)	4 (13.8)		1 (3.4)		17 (58.6)			
Papamichael <i>et al</i> ^[23] , 2016	UC	IFX	101	37 (36.6)	12 (12.0)		5 (4.9)	36 (35.6)	49 (48.5)			
Dreesen <i>et al</i> ^[31] , 2020	CD	IFX	116	68 (58.6)								
Imaeda <i>et al</i> ^[15] , 2014	CD	IFX	45	12 (26.7)				8 (17.8)	15 (33.3)	33 (73.3)		
El-Matary <i>et al</i> ^[32] , 2019	PCD	IFX	52	21 (40.4)				33 (63.5)	AZA 17 (32.7); MTX 30 (57.7)	7 (13.5)	15 (28.8)	10 (19.2)

Kang <i>et al</i> ^[17] , 2019	PCD	IFX	105	31 (29.5)		6 (5.7)	6 (5.7)	95 (90.5)	
Dreesen <i>et al</i> ^[13] , 2018	IBD	VDZ	179	106 (59.2)	32 (17.9)	153 (85.5)	73 (40.8)	20 (11.2)	
Yacoub <i>et al</i> ^[34] , 2018	IBD	VDZ	82	44 (53.7)	18 (22.0)	67 (78.0)	6 (7.3)	13 (15.9)	14 (17.1)
Hanzel <i>et al</i> ^[33] , 2019	IBD	VDZ	51	19 (37.3)	10 (19.6)	43 (84.3)	20 (39.2)	6 (11.8)	
Pouillon <i>et al</i> ^[25] , 2019	UC	VDZ	31	13 (41.9)	7 (22.6)	28 (90.3)	12 (38.7)	7 (22.6)	14 (45.2)

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IFX: Infliximab; ADA: Adalimumab; VDZ: Vedolizumab; PFCD: Perianal fistula Crohn's disease; CS: Corticosteroid; IMM: Immunosuppressor; 5-ASA: 5-amino salicylic acid.

low specificity or sensitivity, respectively. IFX trough level surpassing 5 µg/mL had maximum possible opportunity to assist pediatric CD patients in attaining mucosal healing under maintenance therapy^[17]. In CD patients under induction therapy, VDZ trough level of ≥ 18.0 µg/mL at week 6 predicted mucosal healing in the first year of treatment with an 80% sensitivity and 63% specificity^[34]. VDZ trough level of ≥ 13.6 µg/mL at week 22 predicted mucosal healing with a 69% sensitivity and 71% specificity^[13]. Although these two studies^[13,34] did not adopt standard tools to evaluate mucosal healing, the former^[34] utilized MRI to evaluate intestinal inflammation.

Study cohorts of perianal fistulating Crohn's disease: Yarur *et al*^[36] have confirmed that the possibility of fistula healing would rise substantially among pfCD patients if the optimal trough level of IFX was increased to 10 µg/mL or more at week 4, while a minor change is needed in the optimal trough levels of IFX more than 20 µg/mL. Plevris *et al*^[24] have demonstrated that pfCD patients under maintenance therapy attaining an IFX trough level > 7.1 µg/mL and ADA trough level > 9.8 µg/mL were highly probable to achieve fistula healing and an IFX trough level of over 7.1 µg/mL and an ADA trough level of over 6.8 µg/mL were the best serum levels in predicting the fistula closure. Strik *et al*^[27] have suggested that IFX ≥ 5.0 µg/mL or ADA ≥ 5.9 µg/mL acts as a good predictor of fistula closure in pfCD patients. When compared to adults, pediatric pfCD patients should be cured with a higher IFX serum level for deeper remission. Moreover, the correlation between IFX trough level at week 24 and fistula healing in pediatric pfCD patients has been verified and the IFX trough level with an increment to more than 12.7 µg/mL increases the possibilities of fistula healing at week 24^[32].

Table 3 Quality of articles

Ref.	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6
Chaparro <i>et al</i> ^[12] , 2018	★			★		
Ungar <i>et al</i> ^[28] , 2016	★			★		
Yarur <i>et al</i> ^[29] , 2016	★	★		★		
Roblin <i>et al</i> ^[26] , 2014	★			★		
Morita <i>et al</i> ^[18] , 2016	★	★		★		
Morita <i>et al</i> ^[19] , 2016	★	★		★		
Strik <i>et al</i> ^[27] , 2019	★	★		★		
Plevris <i>et al</i> ^[24] , 2020	★	★		★		
Zittan <i>et al</i> ^[30] , 2016	★	★		★		
Juncadella <i>et al</i> ^[16] , 2018	★	★		★		
Papamichael <i>et al</i> ^[23] , 2016	★	★	★	★		
Papamichael <i>et al</i> ^[20] , 2017	★	★	★	★		
Papamichael <i>et al</i> ^[22] , 2018	★		★	★		
Feng <i>et al</i> ^[14] , 2019	★	★	★	★		
Papamichael <i>et al</i> ^[21] , 2018	★	★		★		
Dreesen <i>et al</i> ^[31] , 2020	★	★	★	★	★	★
Imaeda <i>et al</i> ^[15] , 2014	★	★		★		
El-Matary <i>et al</i> ^[32] , 2019	★	★	★	★	★	★
Kang <i>et al</i> ^[17] , 2019	★			★		
Hanzel <i>et al</i> ^[33] , 2019	★	★	★	★	★	★
Dreesen <i>et al</i> ^[13] , 2018	★	★		★		
Pouillon <i>et al</i> ^[25] , 2019	★	★		★		
Yacoub <i>et al</i> ^[34] , 2018	★	★	★	★	★	★

Item 1: The representativeness of the exposed cohorts; Item 2: Identification of exposure; Item 3: The verification of concerned results absent in the start of study; Item 4: The sufficient evaluation of study results; Item 5: Follow-up is long enough after study results take place; and Item 6: Follow-up of cohorts is long enough. ★: Contents of the literature in line with the item.

DISCUSSION

Pharmacological mechanism and clinical efficacy of biologics in IBD

Anti-TNF- α antagonists contain three anti-TNF- α biologics with integrated IgG1 antibody (IFX, ADA, and GOI), Certolizumab with fragment Fab modified by polyethylene glycol, and Etanercept with TNF- α extracellular domain including Receptor2/IgG1-Fc fusion protein^[37-40]. As a matter of fact, the efficacy of inducing clinical or endoscopic remission in IBD is merely realized by the three anti-TNF- α biologics with integrated IgG1 antibody instead of Certolizumab or Etanercept. Anti-TNF- α biologics regulate immune response and maintain intestinal status by preventing TNF- α from inducing mucosal inflammation^[41]. In IBD subtypes, IFX has better ability to induce mucosal healing of UC than ADA and is similar to that of ADA in inducing mucosal healing of CD^[42].

VDZ is an integrin antagonist that combines with $\alpha 4\beta 7$ integrin expressed on the surface of lymphocytes or monocytes. The crucial mechanism of intestinal lymphocyte migration to the intestinal mucosal layer attributes to the integration of $\alpha 4\beta 7$ integrin and mucous membrane addressing cell adhesion molecule-1 expressed in the

Table 4 Biologic management in inflammatory bowel disease patients

Ref.	Biology	Diagnosis, n	Therapeutic stage	Therapeutic course	Injection dose	Injection frequency
Chaparro <i>et al</i> ^[12] , 2018	ADA	IBD 94	Maintenance	At least 6 mo	/	/
Ungar <i>et al</i> ^[28] , 2016	IFX	IBD 88	Maintenance	At least 6 mo	/	/
Yarur <i>et al</i> ^[29] , 2016	ADA	IBD 67	Induction	Less than 1 mo	/	/
Roblin <i>et al</i> ^[26] , 2014	IFX	IBD 78	Induction	Less than 2 mo	/	/
Chaparro <i>et al</i> ^[12] , 2018	ADA	IBD 66	Maintenance	At least 12 wk	160 mg, 80 mg, 40 mg	Induction: 160 mg at week 0 and 80 mg at week 2; Maintenance: 2 weekly (47 patients), weekly (19 patients)
Ungar <i>et al</i> ^[28] , 2016	ADA	IBD 40	Maintenance	/	/	2 weekly or weekly
Morita <i>et al</i> ^[18] , 2016	ADA	UC 33	Induction and Maintenance	/	160 mg, 80 mg, 40 mg	160 mg at week 0, 80 mg at week 2, and 40 mg 2 weekly
	IFX	UC 31	Induction and maintenance	/	5 mg/kg	At weeks 0, 2, 6 and 8 weekly later
Morita <i>et al</i> ^[19] , 2016	ADA	CD 42	Maintenance	At least 6 mo	40 mg	2 weekly
Strik <i>et al</i> ^[27] , 2019	ADA	PfCD 19	Maintenance	/	40 mg	2 weekly (11 patients), Weekly (8 patients)
	IFX	PfCD 47	Maintenance	/	5 mg/kg, 10 mg/kg	5 mg/kg 8 weekly (27 patients), 5 mg/kg 6 weekly (10 patients); 5 mg/kg 4 weekly (3 patients), 10 mg/kg 8 weekly (4 patients); 10 mg/kg 6 weekly (2 patients), 10 mg/kg 4 weekly (1 patients)
Plevris <i>et al</i> ^[24] , 2020	ADA	PfCD 35	Maintenance	At least 24 wk	40 mg	Weekly (17 patients), Fortnightly (18 patients)
	IFX	PfCD 29	Maintenance	At least 24 wk	5 mg/kg, 10 mg/kg	5 mg/kg 8 weekly (16 patients), 5 mg/kg 6 weekly (7 patients); 10 mg/kg 8 weekly (3 patients), 10 mg/kg 6 weekly (3 patients)
Zittan <i>et al</i> ^[30] , 2016	ADA	CD 60	Maintenance	/	40 mg or not	40 mg (53 patients), other than 40 mg (7 patients); 2 weekly (35 patients), other than 2 weekly (25 patients)
Juncadella <i>et al</i> ^[16] , 2018	ADA	IBD 98	Maintenance	/	40 mg or not	40 mg 2 weekly (59 patients), other than 40 mg 2 weekly (36 patients)
Papamichael <i>et al</i> ^[20] , 2017	ADA	UC 43	Induction	14 wk	160 mg, 80 mg, 40 mg	160 mg at week 0, 80 mg at week 2, 40 mg 2 weekly or weekly from week 4, or 80 mg 2 weekly or weekly from week 4
Feng <i>et al</i> ^[14] , 2019	IFX	CD 141	Maintenance	At least 14 wk	5 mg/kg	5 mg/kg at weeks 0, 2, 6 and thereafter every 8 wk during the study period (week 30)
Papamichael <i>et al</i> ^[22] , 2018	IFX	UC 56	Maintenance	/	/	/
Papamichael <i>et al</i> ^[21] , 2018	IFX	CD 110	Maintenance	/	5 mg/kg or not	5 mg/kg 8 weekly (63 patients), other than 5 mg/kg 8 weekly (47 patients)
Papamichael <i>et al</i> ^[23] , 2016	IFX	UC 101	Induction	14 wk	/	/
Dreesen <i>et al</i> ^[31] , 2020	IFX	CD 116	Induction and maintenance	54 wk	5 mg/kg	Induction: 5 mg/kg at week 0, 2, 6; Maintenance: 5 mg/kg, 7.5 mg/kg, or 10 mg/kg at week 14 and later
Imaeda <i>et al</i> ^[15] , 2014	IFX	CD 45	Maintenance	At least 6 mo	5 mg/kg, 10 mg/kg	5 mg/kg 8 weekly (37 patients), 10 mg/kg 8 weekly (8 patients)
El-Matary <i>et al</i> ^[32] , 2019	IFX	PfCD 52	/	/	5 mg/kg or more	5 mg/kg/dose, often rounded up to the nearest 100 mg at weeks 0, 2, 6; Dose 4 was received at a median time interval following the third dose
Kang <i>et al</i> ^[17] , 2019	IFX	PCD 105	Maintenance	/	/	/
Hanzel <i>et al</i> ^[33]	VDZ	IBD 51	Induction and	54 wk	300 mg	Induction: At weeks 0, 2, 6, 10; Maintenance: 4 weekly or 8

2019			maintenance			weekly from week 14 onwards
Dreesen <i>et al</i> ^[13] , 2018	VDZ	UC 66; CD 113	Induction and maintenance	22 wk	300 mg	Induction: At weeks 0, 2, 6 (179 IBD patients), At week 10 (102 CD patients); Maintenance: 8 weekly (162 IBD patients), 4 weekly (4 UC and 13 CD patients)
Pouillon <i>et al</i> ^[25] , 2019	VDZ	UC 31	Maintenance	/	300 mg	8 weekly (19 samples) or 4 weekly (16 samples)
Yacoub <i>et al</i> ^[34] , 2018	VDZ	CD 39; UC43	Induction and maintenance	52 wk	300 mg	Induction: At weeks 0, 2, 6; Maintenance: 4 weekly or 8 weekly from week 14 onwards

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; IFX: Infliximab; ADA: Adalimumab; VDZ: Vedolizumab; PFCD: Perianal fistula Crohn's disease.

gastrointestinal endotheliocytes. The mechanism of VDZ mainly involves inhibition of T lymphocytes from migrating and aggregation in the mucosal layer^[43]. Recently, another viewpoint highlights the regulation of innate immunity and the interference of monocytes migrating and aggregating in the mucosal layer is considered the major mechanism of VDZ^[44]. A meta-analysis including nine real-world studies verified the effectiveness of VDZ for IBD accompanied with adequate security^[45]. Endoscopic healing, radiographic healing, and histological healing are achieved in IBD patients in long-time therapy of VDZ, whereas the risk of atypical hyperplasia also increases^[46-48].

Effect of endpoint definition on blood concentration

MES is the most extensively used scoring system to evaluate disease severity of UC, and contains four grades, including no lesions (0), mild (1), moderate (2), and severe (3). Mucosal healing is normally defined as MES ≤ 1. However, it is a remarkable fact that UC patients with MES = 1 had extensive mucosal inflammation and higher probability of clinical relapse and colectomy in the future than UC patients with MES = 0^[49,50]. What's more, even in UC patients with MES = 0, 30.4% had abnormal mucosal pattern and 73.9% had abnormal vascular pattern on high definition colonoscopy^[51]. Similarly, 41.8% and 4.6% were classified as LCI-B (redness with visible vessels) and LCI-C (redness without visible vessels) based on color imaging^[52]. Recently, UCEIS consisting of three major indicators (vascular pattern, bleeding, and erosions and ulcers) is divided into eight grades (0-8), and verifies the changes of symptoms and mucosal lesions more accurately than MES^[53,54]. Considering that histological inflammation invisible under colonoscopy might persistently exist in UC patients with endoscopic mucosal healing, histopathological detection contributes to the direct reflection of mucosal microinflammation. Based on the histologic scoring system, histological healing is defined as Geboes score < 2 or Robarts Histological Index < 3 or Nancy Histological Index ≤ 1, but these histologic scoring systems should be simplified and verified again^[50].

Different from UC, the definition of mucosal healing in CD is more complex due to extensive and deep lesions. CDEIS is the gold-standard for endoscopic mucosal healing in CD, and it consists of four major segments (deep ulcerations, superficial ulcerations, surface involved by ulcerations, and surface involved by disease). As SES-CD involves the same evaluative contents similar to that of CDEIS and is highly correlated with CDEIS, SES-CD has become more popular than CDEIS^[55]. Nevertheless, both CDEIS and SES-CD focused only on colorectal lesion evaluation and ignored ileal lesions evaluation^[56]. Hence, the modified Rutgeerts' Scoring System that paid much attention to mucosal lesions has been proposed in evaluating ileal lesions^[57]. Capsule endoscopy and balloon-assisted endoscopy accompanied with the Lewis score system are utilized to evaluate small intestinal lesions while the Rutgeerts' scoring system is applied in CD patients with colectomy only. Therefore, definitions of primary endpoints involving only one endoscopic scoring system are unable to evaluate inflammation in CD completely. Additionally, different from mucosal lesions of UC, intestinal lesions of CD tend to invade the submucosa or muscular layer deeply or swollen lymph nodes so that deep healing has been proposed to be a part of expected outcome in CD.

In fact, by considering the segmental and transmural inflammation of the intestine in CD, diagnostic imaging tests have been put forwarded for detecting deep lesions whereas histological detection is not recommended due to tiny and shallow biopsies, especially in pfCD. Currently, gastroenterologists have opted deep remission as fistula healing or fistula closure under endoscopic examination or other radiological examinations to be the primary endpoint of pfCD^[58]. T2-weighted MRI with fat-

Table 5 Correlation between endoscopic outcome and biologic blood concentration

Ref.	Patients	Definition of primary endpoint	Biology	Cut-off value	Clinical outcome (Yes/Not)	SE	SP	PPV	NPV	AUC
Chaparro <i>et al</i> ^[12] , 2018	IBD	Mucosal healing: (1) CD: SES-CD < 3; (2) UC: MES ≤ 1; and (3) CD in Postoperative setting: Rutgeerts < 2	ADA	7.2 µg/mL (TL)	Mucosal healing (35/59)	0.65	0.56	0.46	0.72	0.60
			IFX	3.4 µg/mL (TL)	Mucosal healing (58/30)	0.60	0.60	0.73	0.42	0.63
Ungar <i>et al</i> ^[28] , 2016	IBD	Mucosal healing: (1) CD: SES-CD < 3; (2) UC: MES ≤ 1	ADA	7.1 µg/mL (SL)	Mucosal healing	0.32	0.85	0.51	0.72	0.70
			IFX	6 µg/mL (SL)	Mucosal healing	0.39	0.85	0.70	0.62	0.75
Yarur <i>et al</i> ^[29] , 2016	IBD	Mucosal healing: Lack of any inflammatory findings in the intestinal mucosa	ADA	7.8 µg/mL (SL)	Mucosal healing (19/47)	0.61	0.95			0.76
		Histological healing: Lack of histologic inflammation on biopsies obtained during colonoscopy	ADA	7.5 µg/mL (SL)	Histological healing (20/46)	0.62	0.83			0.73
Roblin <i>et al</i> ^[26] , 2014	IBD	Mucosal healing: (1) CD: Disappearance of all ulcerations; (2) UC: MES < 2	ADA	4.9 µg/mL (TL)	Absence of mucosal healing (16/24)	0.66	0.85	0.88	0.51	0.77
Morita <i>et al</i> ^[18] , 2016	UC	Mucosal healing: UCEIS: The bleeding descriptor and the erosions and ulcers descriptor were both 0, and the vascular pattern descriptor was 0 or 1	ADA	10.3 µg/mL (TL)	Mucosal healing (Absence)	0.82	0.80			0.87
			IFX	2.7 µg/mL (TL)	Mucosal healing (11/20)	0.83	0.89			0.93
Morita <i>et al</i> ^[19] , 2016	CD	Mucosal healing: Endoscopic score based on the modified Rutgeerts' scoring system: 0 (No lesions or scar) or 1 (≤ 5 apthous lesions)	ADA	7.90 µg/mL (TL)	Mucosal healing (14/28)	0.69	0.86			0.79
Strik <i>et al</i> ^[27] , 2019	PfCD	Fistula closure: Absence of active drainage at gentle finger compression and/or fistula healing on magnetic resonance imaging	ADA	5.9 µg/mL (SL)	Fistula closure (13/6)					0.89
			IFX	5.0 µg/mL (TL)	Fistula closure (32/15)					0.92
Plevris <i>et al</i> ^[24] , 2020	PfCD	Perianal fistula healing: No spontaneous discharge or no discharge on palpation in the absence of seton drainage; Perianal fistula closure: Absence of an external skin opening	ADA	9.8 µg/mL (TL)	Fistula closure (15/20)	0.93	0.75			0.86
			ADA	6.8 µg/mL (TL)	Fistula healing (21/14)	1.00	0.79			0.90
			IFX	7.1 µg/mL (TL)	Fistula healing (18/11)	0.78	1.00			0.93
			IFX	7.1 µg/mL (TL)	Fistula closure (13/16)	0.64	1.00			0.97
Zittan <i>et al</i> ^[30] , 2016	CD	Mucosal healing: Absence of any ulceration in all ileocolonic segments	ADA	8.14 µg/mL (TL)	Mucosal healing (35/25)	0.91	0.76	0.84	0.86	
Juncadella <i>et al</i> ^[16] , 2018	CD	Endoscopic remission: Absence of a mucosal break for CD, a Rutgeerts score of ≤ 1 for CD with ileocolonic resection, a Mayo endoscopic score of ≤ 1 for UC. Histological healing: Absence of any sign of active inflammation including erosions, abscesses, or neutrophil infiltration	ADA	12 µg/mL (SL)	Endoscopic remission (20/25)	0.80	0.68			
			ADA	12.2 µg/mL (SL)	Histological healing (13/28)	0.57	0.85			
	UC		ADA	16.2 µg/mL	Endoscopic remission (7/20)	0.85	0.61			

Hanzel <i>et al</i> ^[33] , 2019	IBD	Endoscopic remission: (1) CD: SES-CD ≤ 4 ; (2) UC: MES ≤ 1 ; Clinical remission: (1) CD: mean daily stool frequency of ≤ 1.5 , abdominal pain ≤ 1 ; (2) UC: a rectal bleeding score of 0, a stool frequency score of ≤ 1	VDZ	22.0 $\mu\text{g}/\text{mL}$ week 6 (TL)	Combined Remission (Endoscopic Remission AND Clinical Remission) within the first year of treatment (16/35)	0.77	0.73	0.72	0.88	0.73
			VDZ	8.0 $\mu\text{g}/\text{mL}$ week 22 (TL)		0.79	0.75	0.65	0.86	0.82
Dreesen <i>et al</i> ^[13] , 2018	UC	Mucosal healing: MES ≤ 1	VDZ	28.9 $\mu\text{g}/\text{mL}$ week 2 (TL)	Mucosal healing at week 14 (32/22)	0.73	0.62	0.59	0.75	0.70
			VDZ	13.9 $\mu\text{g}/\text{mL}$ week 14 (TL)	Mucosal Healing at week 14 (32/22)	0.85	0.54	0.48	0.88	0.72
	CD	Mucosal healing: Complete absence of ulcerations	VDZ	13.6 $\mu\text{g}/\text{mL}$ week 22 (TL)	Mucosal healing at week 22 (10/33)	0.69	0.71	0.83	0.52	0.70
Pouillon <i>et al</i> ^[25] , 2019	UC	Histological healing: Nancy Histological Index ≤ 1	VDZ	25.0 $\mu\text{g}/\text{mL}$ (TL)	Histological healing (18/17)	0.77	0.71	0.74	0.75	0.75
Yacoub <i>et al</i> ^[34] , 2018	CD	Mucosal healing: (1) Absence of any ulcerations during endoscopy; (2) The absence of significant intestinal inflammation on MRI	VDZ	18.0 $\mu\text{g}/\text{mL}$ week 6 (TL)	Mucosal healing within the first year of treatment (18/21)	0.80	0.63	0.73	0.71	0.70
	UC	Mucosal healing: (1) MES ≤ 1 ; (2) The absence of significant intestinal inflammation on MRI	VDZ	18.0 $\mu\text{g}/\text{mL}$ week 6 (TL)	Mucosal healing within the first year of treatment (24/19)	1.00	0.75	0.88	1.00	0.75

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; PCD: pediatric Crohn's disease; IFX: Infliximab; ADA: Adalimumab; VDZ: Vedolizumab; SE: Sensitivity; SP: Specificity; PPV: Positive prospective value; NPV: Negative prospective value; AUC: Area under the curve; SL: Serum level; TL: Trough level.

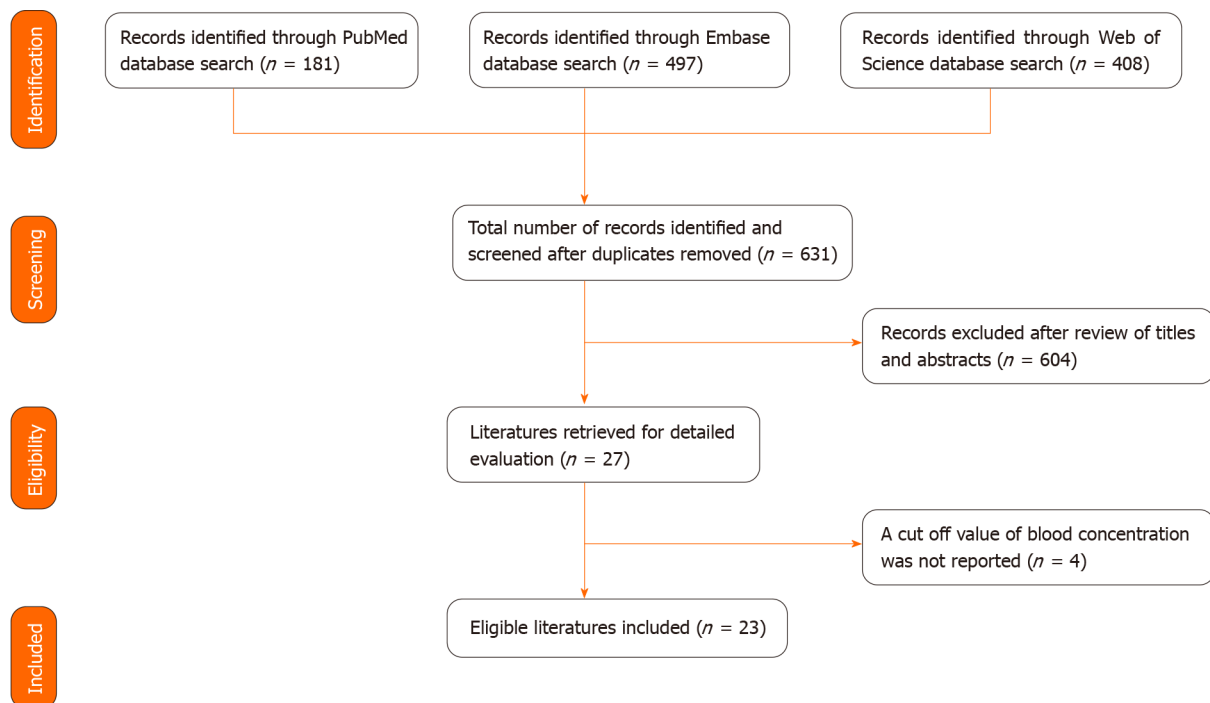


Figure 1 Literature selection.

suppression is considered the gold-standard for fistula imaging and an MRI-based score is currently available for defining disease activity^[59]. Thomassin *et al*^[60] have defined MRI healing as the disappearance of T2 hyperintensity and contrast enhancement after gadolinium injection. Nonetheless, the re-opening of “closed”

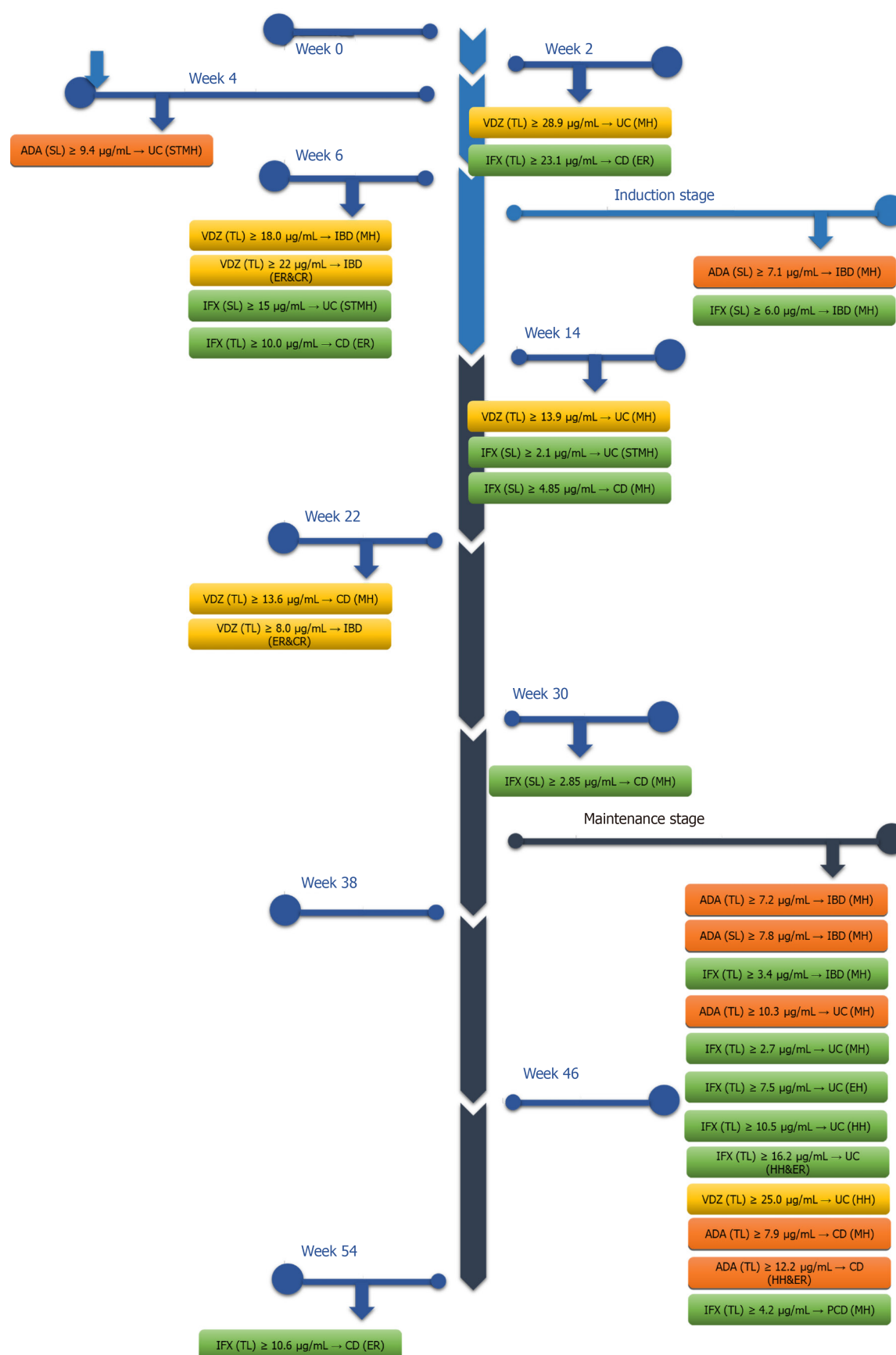


Figure 2 Target of blood concentration during different therapeutic stages of biologics. IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; PCD: Pediatric Crohn's disease; IFX: Infliximab; ADA: Adalimumab; VDZ: Vedolizumab; MH: Mucosal healing; HH: Histological healing; EH: Endoscopic healing; ER: Endoscopic remission; CR: Clinical remission; STMH: Short term mucosal healing; SL: Serum level; TL: Trough level.

fistula tracts occurred more frequently in pfCD patients, which was diagnosed as fistula healing by MRI after the discontinuation of IFX maintenance therapy^[61]. On one hand, radiologists without adequate experience in detecting perianal fistula and MRI itself were unable to discover activity around the anus, thus leading to inaccurate estimate of MRI. According to a recent review, examination under anaesthesia combined with MRI or endoanal ultrasound increased the accuracy of pfCD diagnosis to 100%^[62]. On the other hand, half of pfCD patients relapse within 5 years after anti-TNF- α discontinuation.

Effect of biologic optimization on blood concentration

There is enormous discrepancy in the biological management of IBD patients due to complicated disease phenotypes and variable individual genes that contribute to the effect of blood concentration analysis. Above all, different timings for testing have been a major impact in analyzing optimal levels for biologic blood concentration that decreases with time and the incidence of biologic antibody that increases with time. Second, the primary or secondary onset of loss of response is universal in IBD patients under biological maintenance therapy, while dose optimization of biologics or shortening the interval time of injection contributes to regaining of response to biologics. Paul *et al*^[63] have verified that optimization of therapeutic dose of IFX could enhance IFX serum level and Δ IFX serum level of $> 0.5 \mu\text{g/mL}$ was confirmed as the only factor of IBD mucosal healing. Third, there is a growing tendency to combine biologics with other immune suppressants in medicine therapy for IBD with a high ratio of non-responders during biologic management, especially AZA or 6-mercaptopurine (6-MP). AZA is the precursor of 6-MP. 6-thioinosine 5'-mono-phosphate is a substance that is produced in the body as 6-MP is metabolized, ultimately producing 6-thioguanine nucleotides (6-TGN) and 6-methylthiopurine ribonucleotide through metabolism^[64,65]. The clinical efficacy is dominated by adequate doses of 6-TGN, while myelosuppression is triggered by excessive doses of 6-TGN^[66,67]. However, AZA or 6-MP in some CD patients produces 6-methylthiopurine ribonucleotide due to hepatotoxicity in preference to 6-TGN, resulting in the accumulation of hepatic toxin and suspension of this maintenance therapy finally. Yarur *et al*^[68] have considered 6-TGN concentration of $\geq 125 \text{ pmol}/8 \times 10^8$ red blood cells could assist IFX in facilitating mucosal healing of CD *via* increasing the blood concentration of IFX to more than $8.3 \mu\text{g/mL}$. However, Yacoub *et al*^[34] have demonstrated that the addition of immunosuppressants could neither enhance the blood concentration of VDZ nor improve the probability of deep remission in IBD patients by VDZ management because of low immunogenicity of VDZ^[69]. Last but not the least, this review included study cohorts of VDZ, which mainly contained IBD patients previously exposed to anti-TNF- α agents or with inadequate response to anti-TNF- α agents that is considered one of the vital factors resulting in low blood concentration or failure of VDZ induction therapy^[70,71].

Effect of patient demographics and characteristics on blood concentration

The demographics and characteristics of patients with IBD are another key point that impacts the biologic blood concentration. Above all, CD patients with perianal fistula require higher biologic blood concentrations than CD patients with luminal activity in order to achieve deep remission. Yarur *et al*^[72] have discovered that the anti-TNF-to-TNF ratio in tissues remained higher in uninflammatory areas than in severely inflammatory areas as well as higher rate of serum to tissue drug level mismatch in patients with active disease than in those with remission. Hence, it can be postulated that obstruction of biologics to penetrate into the inflamed tissues surrounding the perianal fistula accounted for higher biological blood concentration as needed by pfCD patients^[4,72]. Regrettably, the evidence of biological blood concentration on penetration, stenosis, or perianal disease besides fistula still requires in-depth research. Second, the morbidity associated with pediatric IBD has significantly increased in recent years and the efficacy of biologics on deep remission has also been verified. Nonetheless, Kelsen *et al*^[73] showed a downward trend in the maintenance efficacy of IFX in children less than 5 years old. Third, smoking or duration of disease increases the probability of biological treatment failure or disease relapse after suspension of biologics, but according to Bond *et al*^[74], neither smoking nor duration of disease showed an association with categorical trough levels of IFX or ADA, whereas the body mass index tended to decrease the trough level of ADA^[74-76]. Last but not the least, females might be an adverse factor of IBD disease progression as estrogen signaling might play a role in local immune response and maintenance of epithelial homeostasis in a gender- and age-dependent manner^[77]. Moreover, it has been confirmed that sex discrepancy influences the therapeutic target of pfCD when considering higher

incidence of perianal fistula and less therapeutic effect in females than in males^[36,78,79].

CONCLUSION

In conclusion, several aspects of optimal serum levels demanded by IBD under biologic agents require deep investigation in the future. First, whether the discrepancy of optimal serum level in complicated phenotype or simple phenotype exists or not should be investigated. Second, how much maintenance time and serum levels of biologic agents are still needed to prevent IBD from disease flare after identification of deep remission. Furthermore, the achievement of deep remission in the prognosis of IBD patients should be evaluated in the future during the induction phase by combining with the serum level of biologics and patient characteristics. Finally, non-responders of IBD patients in the initial phase of biological treatment are considered appropriate to optimize the serum levels tentatively by increasing the injection dose, shortening the interval time of injection, or converting the type of biologics. Also the variation in serum levels during optimization period of biological therapy should be emphasized on therapeutic drug monitoring.

ARTICLE HIGHLIGHTS

Research background

Blood concentration has been proved to be an important predictor of outcomes in inflammatory bowel disease (IBD) patients during biological therapy. It has also been acknowledged that disparate therapeutic targets correspond to specific blood concentrations. The greater the therapeutic expectation required by IBD patients, the higher the value of blood concentration suggested by IBD specialists.

Research motivation

Given the invasive, painful, and expensive examinations, such as endoscopy, for disease evaluation in IBD patients, identification of biologic blood concentration for predicting endoscopic inactivity in IBD patients may contribute to better, less painful, less risky, less expensive treatments.

Research objectives

To identify the predictive value of biologic blood concentration on endoscopic inactivity in IBD patients and explore factors relevant to predictive value.

Research methods

A comprehensive search target was utilized to search PubMed/MEDLINE, Embase, and Web of Science systematically. Two authors screened and extracted the literature according to the inclusion and exclusion criteria. The quality of the included literature was assessed using the Newcastle Ottawa Scale. Authors assisted by a biostatistician extracted, synthesized, and reviewed the data in accordance with the research topic.

Research results

A total of 23 articles with 30 clinical studies and 1939 IBD patients were included. All studies verified the correlation between biologic blood concentration and endoscopic inactivity in IBD patients. Thirteen studies focused on infliximab and demonstrated that blood concentration reaching 4.0-10.6 µg/mL could predict the mucosal healing in Crohn's disease (CD) patients while ulcerative colitis (UC) patients with a blood concentration higher than 2.7-10.5 µg/mL were more likely to achieve mucosal healing under maintenance therapy. Whereas infliximab blood concentration of perianal fistulizing Crohn's disease (pfCD) patients reaching 5.0-12.7 µg/mL or more increased the probability of mucosal healing. Eleven studies focused on adalimumab and indicated that blood concentration reaching 7.2-16.2 µg/mL or more could predict mucosal healing in IBD patients while patients with a blood concentration lower than 4.9 µg/mL showed no mucosal healing under maintenance therapy. What's more, the predictive cut off value of adalimumab blood concentration on fistula healing/closed should be 5.9-9.8 µg/mL in pfCD. Four studies focused on vedolizumab and verified that blood concentration surpassing 25.0 µg/mL indicated mucosal healing in UC patients under maintenance therapy and the predictive cut off value of blood

concentration on mucosal healing or endoscopic remission under induction therapy in IBD could be 8.0-28.9 µg/mL. However, different studies had several discrepancies in the disease phenotype and demographics of study cohorts as well as the therapeutic stage, therapeutic course, injection dose, and injection frequency of biologic management. In addition, the definition of primary endpoints was not consistent in all studies. Fifteen studies considered mucosal healing as the main endpoint, three studies including pCD patients adopted fistula healing/closure, and four adopted endoscopic remission alone or in combination with clinical remission as the main endpoint. Additionally, five studies identified the desirable endpoint as histological healing or histological remission.

Research conclusions

Considering the discrepancies in study design, study cohort, and biological management among different clinical studies, the best predictive cut-offs of biologic blood concentration on endoscopic inactivity published in 23 studies varied and the biological blood concentration might not be an appropriate predictor of endoscopic inactivity in IBD patients currently.

Research perspectives

In view of the fact that conduction of intensive monitoring for biological management plays a vital role in precise treatment of IBD patients, much larger and more stringent prospective studies are warranted to provide the best predictive cut-offs for biologic blood concentration as acknowledged globally in allusion to different types of IBD patients for distinguishing endoscopic inactivity from endoscopic activity.

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