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Review

Precision medicine and drug optimization in adult inflammatory bowel disease patients

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***Abstract*:** Inflammatory bowel diseases (IBD) encompass two main entities including ulcerative colitis and Crohn's disease. Although having a common global pathophysiological mechanism, IBD patients are characterized by a significant interindividual heterogeneity and may differ by their disease type, disease locations, disease behaviours, disease manifestations, disease course as well as treatment needs. Indeed, although the therapeutic armamentarium for these diseases has expanded rapidly in recent years, a proportion of patients remains with a suboptimal response to medical treatment due to primary non-response, secondary loss of response or intolerance to currently available drugs. Identifying, prior to treatment initiation, which patients are likely to respond to a specific drug would improve the disease management, avoid unnecessary side effects and reduce the healthcare expenses. Precision medicine classifies individuals into subpopulations according to clinical and molecular characteristics with the objective to tailor preventative and therapeutic interventions to the characteristics of each patient. Interventions would thus be performed only on those who will benefit, sparing side effects and expense for those who will not. This review aims to summarize clinical factors, biomarkers (genetic, transcriptomic, proteomic, metabolic, radiomic or from the microbiota) and tools that could predict disease progression to guide towards a step-up or top-down strategy. Predictive factors of response or non-response to treatment will then be reviewed, followed by a discussion about the optimal dose of drug required for patients. The time at which these treatments should be administered (or rather can be stopped in case of a deep remission or in the aftermath of a surgery) will also be addressed. IBD remain biologically complex, with multifactorial etiopathology, clinical heterogeneity as well as temporal and therapeutic variabilities, which makes precision medicine especially challenging in this area. Although applied for many years in oncology, it remains an unmet medical need in IBD.

Keywords: drug optimization, inflammatory bowel disease, precision medicine

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Introduction

Inflammatory bowel diseases (IBD) are chronic and recurrent inflammatory disorders of the gastrointestinal tract, which encompass two main entities including ulcerative colitis (UC) and Crohn's disease (CD).[1] The pathogenesis of IBD is not fully understood but the most commonly accepted hypothesis is an inappropriate gut mucosal immune response towards the constituents of the gut microbiota which cross an impaired epithelial barrier, in genetically predisposed individuals and under the influence of environmental factors.[2–4] Although having a common global pathophysiological mechanism, patients are characterized by a significant inter-individual heterogeneity.[1] IBD patients may differ by their IBD type, disease locations, disease behaviours (inflammatory, structuring, penetrating), disease manifestations [including the presence or absence of extraintestinal manifestations (EIMs)], disease course and evolution as well as treatment needs.[5–9]

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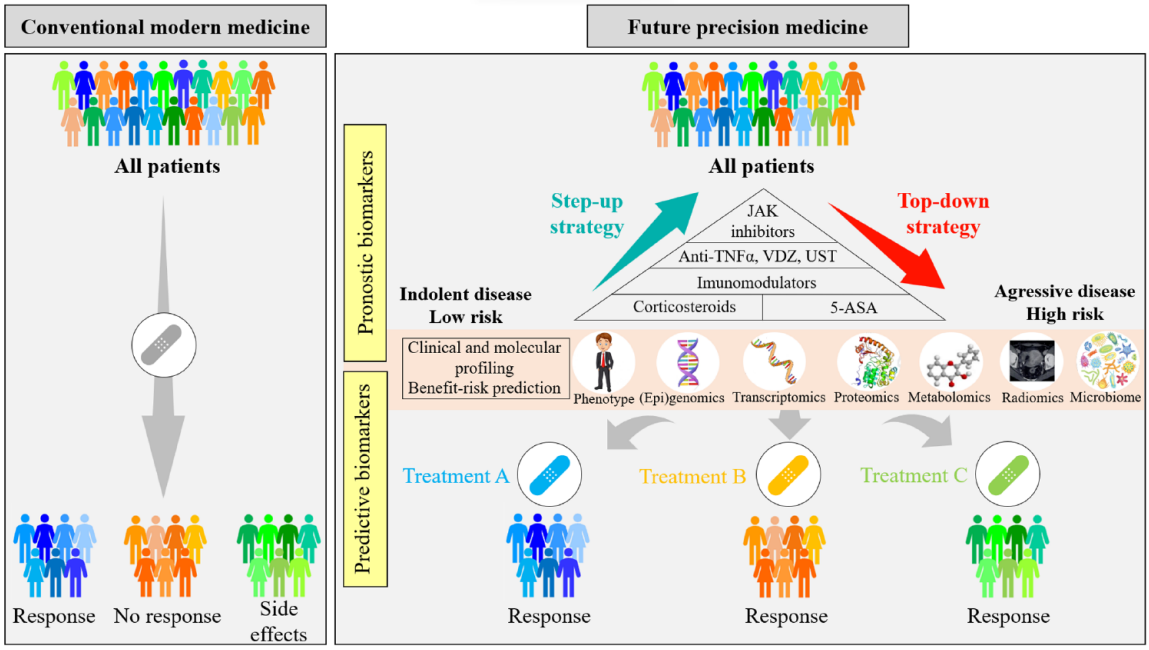

Figure 1. Concept of precision medicine.
Currently, our treatment approach is more the one shown in the left of the figure, where the same treatments are given to all patients. But with this 'one-size-fits-all' approach, some patients will show a clinical response, some will not and some may develop side effects. Using clinical factors and biomarkers (genetic, transcriptomic, proteomic, metabolomic, radiomic and microbiota) as well as predictive tools, precision medicine towards which there is a desire to evolve (on the right-hand side of the figure), could allow stratification of patients into high-risk patients, who would require a top-down strategy, and low-risk patients, for whom a step-up strategy would be more appropriate. It would also predict the response to treatment, allowing the administration of a certain type of drug only on those who will benefit, sparing side effects and expense for those who will not.
5-ASA, 5-aminosalicylic acid; JAK, Janus kinase; TNF-α, tumour-necrosis factor α; UST, ustekinumab; VDZ, vedolizumab.

These patients require a continuous monitoring and treatment to manage the disease. Unfortunately, despite currently available options, a proportion of patients experience a suboptimal response to these costly therapies [due to primary non-response (PNR), secondary loss of response (SLR) or intolerance], justifying multiple sequences of these or a recourse to surgery.[10–13] As a consequence, IBD, whose prevalence continues to increase worldwide,[14] have a significant economic impact on healthcare systems and create a considerable financial burden.[15,16] There is a need to change our disease management and shift our 'reactive' approach, where cares are driven by complications, for a 'proactive' approach, more accurate, aiming to prevent disease consequences.[17] Directly administering the most effective treatment, with a limited risk of side effects, to each patient, would improve the quality of life of these patients (by reducing the number of flares-up, the development of complications, as well as the emotional impact related to treatment failure[17]) and reduce costs for healthcare systems.[16,18]

Precision medicine is based on the classification of individuals into subpopulations according to their clinical and molecular characteristics (using biomarkers), to tailor preventative and therapeutic interventions to the characteristics of each patient (Figure 1).[5,18,19] Interventions would thus be performed only on those who will benefit, sparing side effects and expense for those who will not.[5,19] Although often confused, precision medicine is slightly different from personalized medicine, which refers to treatments tailored towards single individuals (rather than subgroups based on risk/characteristics stratification).[5,19] While the concept of precision medicine has been applied for longer in oncology [e.g. the benefit from a monoclonal antibody targeting human epidermal growth factor receptor 2

(HER2) (trastuzumab) for patients with HER2+ breast cancer[20]], it remains an unmet medical need in IBD.[21] IBD are biologically complex diseases, with a multifactorial etiopathology, characterized by patients and clinical heterogeneity as well as temporal and therapeutic variability, which make precision medicine especially challenging in this area.[5]

This review aims to summarize clinical factors, biomarkers (genetic, transcriptomic, proteomic, metabolic, radiomic or from the microbiota) and tools identified as predictors of (1) disease progression (and severity), (2) treatment response and (3) optimal dose of drug for a particular patient. The time at which these treatments should be administered (or rather can be stopped in case of a deep remission or in the aftermath of a surgery) will also be addressed. These data should help the clinician to choose the right strategy, the right treatment and the right dose at the right time for the right patient.[17,22]

Stratifying IBD patients at diagnosis: Predictors of disease course

A first important point in the management of patients is the identification of their risk of disease progression or severity.[23] If gastroenterologists historically used clinical predictors to help tailor the strategy, we have progressively moved to the use of biomarkers.[17] Whether in UC or CD, genome-wide association studies (GWASs) were used to identify genetic variations associated with the risk of colectomy for medically refractory UC or those that could influence prognosis in CD.[24–26] Haritunians *et al.*[25] showed that a risk score based on the combination of 46 single nucleotide polymorphisms (SNPs) should provide a useful adjunct to clinical parameters to predict the natural UC history. They also reported that the major histocompatibility complex (MHC) and *TNFSF15* (*TL1A*) could contribute to severe UC.[25] The HLA-DRB1 polymorphism seems also to be associated with a more complicated disease in UC (including pancolic disease and increased risk of colectomy).[5,27] In CD, Lee *et al.* identified four SNPs associated with poor prognosis using GWAS, including rs5929166, rs9279411, rs147856773, rs75764599 corresponding to the *XACT*, MHC, *FOXO3* and *IGFBP1–IGFBP3* candidate genes, respectively. *NOD2* polymorphism appears to also be associated with more complicated disease course[28,29], *ATG16L1* (risk allele rs2241880) seems to be associated with perianal involvement.[5,30] Regarding transcriptomics, on a cohort of newly diagnosed paediatric CD patients, Kugathasan *et al.* demonstrated that the upregulation of ileal genes controlling extracellular matrix production at diagnosis was associated with the occurrence of stricturing disease in a risk model including age, race, disease location and antimicrobial serologies (RISK study).[31] The implementation of this gene signature improved the specificity of this promising prediction model, which should be tested and validated on adult cohorts.[24,31]

Metabolomics can also be used to predict disease outcome. Analysing the total plasma N-glycomes of 2635 IBD patients by mass spectrometry, it has been shown that in addition to being able to discern UC and CD patients, some glycosylation patterns, such as the decrease in IgG-related galactosylation, were associated with disease progression, the need for a more potent medication and surgery.[32] Recently, Shubhakar *et al.*[33] investigated the composite serum N-glycomic biomarker to predict future disease course in a cohort of 244 newly diagnosed IBD patients. Assessing also these biomarkers on an independent replication cohort, they demonstrated that serum N-glycan biomarkers had the ability to predict the risk of treatment escalation from a first-line treatment to biologics or surgery.[33] Low plasma histidine level has also been suggested to be associated with poorer disease course.[34–36]

Finally, the radiomics, or biomarkers based on imaging, can also help to assess the disease prognosis.[24] An initial scan can show underlying bowel damage resulting from long-term inflammation.[24] This CD-related bowel damage can be assessed by the Lémann index which uses clinical, endoscopic and magnetic resonance enterography (MRE) data.[24,37–39] Liu *et al.* showed that Lémann index at diagnosis could predict the risk of surgery in the first year after CD diagnosis.[24,37–39] In another prospective study, Fiorino *et al.*[40] evaluated the ability of the Lémann index and the Magnetic Resonance Index of Activity (MaRIA) score to predict disease progression in CD. They reported that

Lémann index was independent risk factor for intestinal surgery and CD-related hospitalization during patient follow-up, while the MaRIA score was not associated with a worse outcome.[40] Again, using the MRE, it has recently been demonstrated that the risk of progressing to surgery within 5 years was more common in patients with restricted diffusion, a greater degree of upstream dilation from stricture, the presence of complex fistula, a perienteric oedema and a fibrofatty proliferation.[41] Longer bowel involvement and an increased bowel wall thickness are other factors associated with the risk of surgery.[24,41,42] Finally, the METRIC-EF study (a multicentre, non-randomized, single-arm, prospective study) which is currently underway aims to identify MRE features, present at diagnosis, in a cohort of newly diagnosed adult CD patients, and which could improve the prediction of disabling CD within 5 years of follow-up.[43] Ultrasound (US) could be used to predict disease course as well. On a cohort of 225 ileal and/or colonic CD patients, Allocca *et al.* set up a non-invasive quantitative US-based score (bowel US score). Bowel US score greater than 3.52 (considering bowel wall thickness and vascularization changes) and the presence of at least one disease complication (stricture, fistula, abscess) at baseline bowel US (as well as faecal calprotectin value of 250 μg/g or greater at baseline and male sex) were independent predictors of a worse outcome (including the need for treatment change or steroids, hospitalization or surgery) throughout the 12-month period.[44] The sonographic lesion index for CD (SLIC), based on the use of the small intestine contrast ultrasonography, allowed us to classify patients and identify those most at risk of having surgery within 1 year.[45] This index includes the following parameters: bowel wall thickness, lumen diameter, lesion length, number of lesion sites, presence of fistula, mesenteric adipose tissue alteration, abscess and lymph nodes.[45] More specifically, patients with a bowel wall thickness >7 mm at US had a higher risk of surgery over a short period.[46]

Factors present at diagnosis and shown to be associated with a poor disease outcome in CD patients or with the risk of colectomy in UC patients are listed in Table 1. However, these factors were identified retrospectively and have been found to be associated with disease outcome but are not necessarily predictive of it and lack of validation to truly predict the disease progression risk and correctly guide treatment decisions to date.[5,21,47,48] While there are no sufficiently reliable markers to dictate disease management, several scores, incorporating a combination of factors, have been developed to predict the specific outcome of the patient's disease.[49–51] One of the best validated clinical-biological tools to date is PROSPECT or Personalised Risk and Outcome Prediction Tool, a web-based tool developed by Siegel *et al.*[51] which allows us to display individualized risks for developing CD complications, based on disease location (small bowel, left colonic disease, perianal disease), serologic markers [anti-Saccharomyces cerevisiae antibody (ASCA), anti-flagellin (CBir1), perinuclear anti-neutrophil cytoplasmic antibody (pANCA)], the *NOD2* frameshift mutation, and an interaction term between perianal disease and ASCA. More recently, a team has demonstrated that a transcriptional signature in CD8 T cells can predict disease course both in UC and CD.[52,53] As the need for cell separation and microarray-based gene expression analysis made it difficult to translate to clinical practice, they developed, optimized and independently validated a whole 17-gene quantitative polymerase chain reaction (qPCR)-based classifier that is able to reliably predict prognosis in CD and UC patients from diagnosis without the need for cell separation.[54] This first validated prognostic biomarker is currently being assessed in the 'Predicting outcomes for Crohn's disease using a molecular biomarker' (PROFILE) trial.[55] If its clinical utility is demonstrated, this would represent a major step towards precision medicine in IBD.[55] Another purely blood-based predictive tool may also emerge from the Nordic IBD treatment strategy trial (NORDTREAT), which investigates prognostic serum protein profile (derived from the IBD character and Swedish Inception Cohort).[56]

Finally, the disease course can also be characterized by the occurrence of EIMs which can also influence the therapeutic strategy. Both in UC and CD, elevated pANCA levels have been identified as predictor of the occurrence of uveitis and erythema nodosum.[101] Other molecular arguments have also been incriminated. HLA-B27-positive IBD patients may have a greater risk of developing an ankylosing spondylitis.[101] Carriers

Table 1. Parameters associated with unfavourable disease course at diagnosis including stricturing and penetrating disease in CD and colectomy in UC (except for acute severe UC).

Prognostic factors	Factors associated with complicated disease in CD (penetrating, fistulizing disease, need for surgery)	Factors associated with the risk of colectomy in UC (except for severe acute UC)
Environmental	Smoking[57–60]	
Clinical	- Male gender[61] - Age of diagnosis <40 years[62,63] - Nausea and vomiting or abdominal pain on presentation[60] - Ileocolonic and small bowel disease location[57,60,62] - Upper gastrointestinal involvement[62] - Perianal disease at diagnosis[57,62,63] - Stricturing or penetrating behaviour at diagnosis[64] - Need for steroid at initial presentation[57,62,63] - Early use of azathioprine or anti-TNF[57]	- Male gender[65,66] - Younger age at diagnosis[48,50,66] - Baseline stool frequency[67] - Progression from proctitis/left-sided to extensive colitis, extent of disease[50,66,68–70] - Need for systemic steroids[50,66] or ever use of corticosteroid[69] - Need for cyclosporine[66] - Family history of UC[25] - Arthritis[67] - Pyoderma gangrenosum[67] - Primary sclerosing cholangitis[71] - Treating 'high-risk' patients with medications other than anti-TNF therapy during the first 6 months after diagnosis[67]
Biological/ serological	- Low haemoglobin and haematocrit levels[72] - Neutrophils count[60] - Circulating antibodies against bacterial antigens (including anti-I2, anti-ompC, anti-Saccaromyces cerevisiae IgG antibody, perinuclear antineutrophil cytoplasmic antibodies, anti-CBir1 flagellin, anti-mannobioside carbohydrate IgG antibody, anti-chitobioside carbohydrate IgA antibody, anti-laminarin IgA)[73–78] - Extracellular matrix molecules (fibronectin, collagen propeptides, laminin)[79] - Growth factors (YKL-40, bFGF)[80,81] - Faecal calprotectin[82]	- High baseline C-reactive protein[50,66,83] - High erythrocyte sedimentation rate[50,66] - Anaemia[65,67] - Low serum albumin level (proposed cut-off : 2.45 g/dL) [4] - High anti-αvβ6 measured in serum samples[85]
Endoscopic	- Severe endoscopic appearances with deep mucosal ulceration[48,86]	
Histological		- Presence of histological inflammation in the endoscopically uninflamed mucosa[87]
Genetic	- *NOD2/CARD15*[88] (SNP: rs2066847)[89–91] - *IRGM* polymoprhism[92] - *MHC* (SNP: rs77005575)[93] - *FOXO3* (SNP: rs147856773)[26] - *XACT* (SNP: rs5929166)[26] - *IGFBP1* (SNP: rs75764599)[26] - Major histocompatibility complex region stretching from the HLA-B to HLA-DR genes (rs9279411)[26] rs2241880 polymorphism of ATG16L1[94] - *MMP3*[95] - Increased amount of rick alleles for *IBD5, DLG5, ATG16L1* and *IL23R*[96–98]	- A risk scoring system (based on the combination of 46 SNPs), identified by GWAS analyses and provided suggestive association at the TNFSF15 (TL1A) locus[25] - *HLA-DRB1*0103* allele[27]
Transcriptomic (from intestinal biopsies)		- Gene expression from rectal biopsies with following clusters: RGS14, *MRPL20*, PTK2B, *TNFRSF4*, TNFRSF18, *CDC42SE2* upregulation and *CISD1, EDN3, RORC and PLA2R1* downregulation[99]
Transcriptomic blood (from whole blood)	- CD8+ T-cell transcriptional profiles: elevated expression of genes involved in antigen-dependent T-cell responses, including signalling initiated by both IL-7 and TCR ligation pathways (associated with the need for treatment escalation or surgery (or both) over time in both CD and UC)[53]	
Metabolomics	- Serum N-Glycomic Biomarkers[33] - The decrease of IgG-related galactosylation[32] - Serum N-glycan biomarkers[33]	- Serum N-glycomic biomarkers[33] - The decrease in IgG-related galactosylation[32] - Serum N-glycan biomarkers[33]
Radiomics	Using MRE: - Lémann index at diagnosis[37,40] - Longer bowel involvement[41,42] - Increased bowel wall thickness[41,42] - Restricted diffusion[41] - Greater degree of upstream dilation from stricture[41] - The presence of complex fistula[41] - A perienteric oedema[41] - Fibrofatty proliferation[41] Using US: - Bowel US score greater than 3.52[44] - Presence of at least 1 disease complication (stricture, fistula, abscess) at baseline bowel US[44] - Patients classified in class E and D using sonographic lesion index for CD[45] - Bowel wall thickness >7 mm[46]	CT scan: - Mural stratification[100] - Number of positive findings using bowel wall thickening, stranding and hyperenhancement as well as mural stratification, mesenteric hyperaemia and proximal dilation[100]

bFGF, basic fibroblast growth factor; CD, Crohn's disease; GWAS, genome-wide association study; IL, interleukin; SNP, single nucleotide polymorphism; TCR, T-cell receptor; TNF, tumour necrosis factor; UC, ulcerative colitis; US, ultrasound; YKL-40, chitinase 3-like 1.

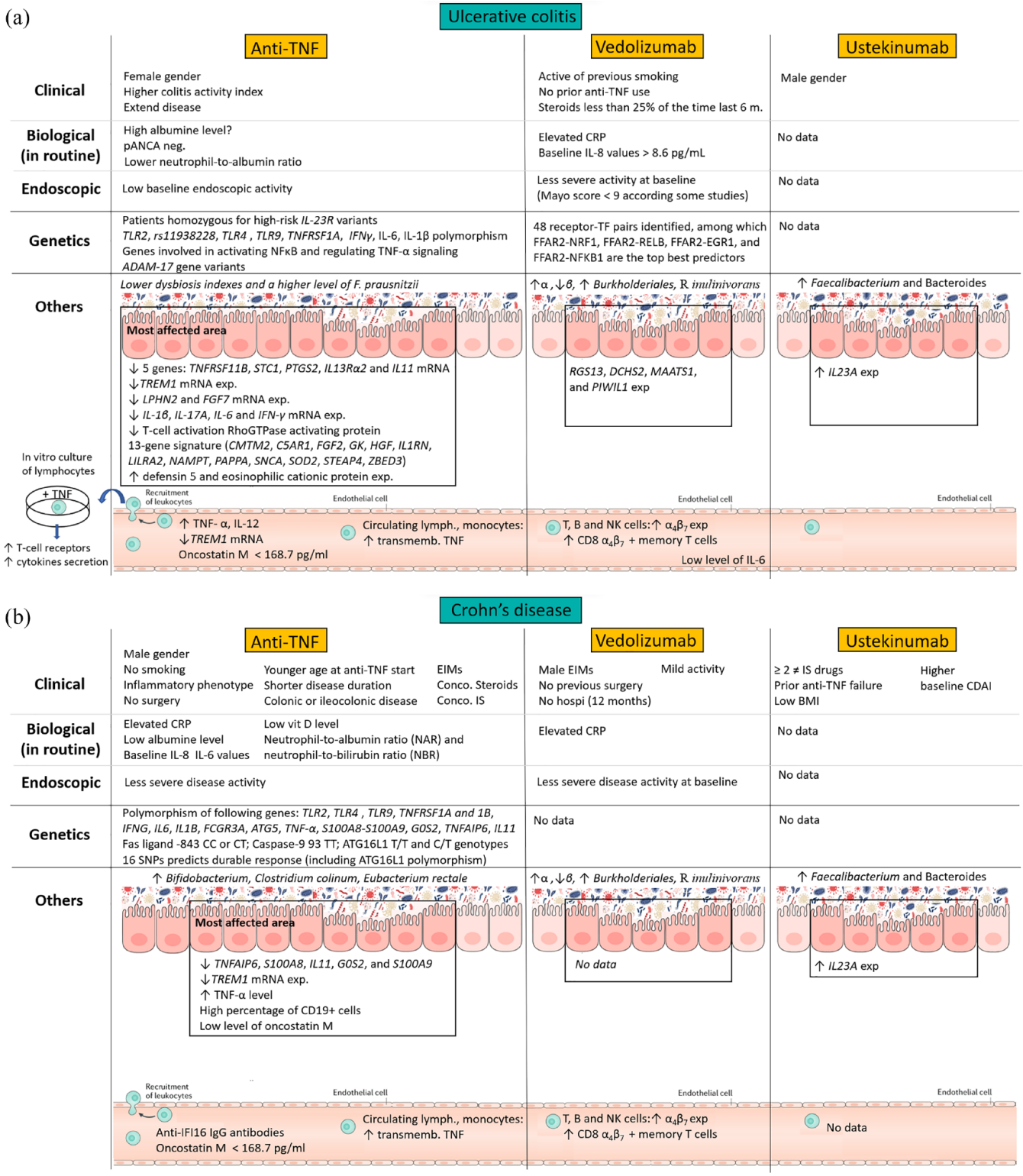

Figure 2. Predictive factors of response to anti-TNF, vedolizumab and ustekinumab in UC (a) and CD (b) patients.
ANCA, anti-neutrophil cytoplasmic antibody; BMI, body mass index; CRP, C-reactive protein; EIM, extraintestinal manifestation; IL, interleukin; IS, immunosuppressor; NK, natural killer; SNP, single nucleotide polymorphism; TLR, toll-like receptor; TNF, tumour necrosis factor; TREM, triggering receptor expressed on myeloid cells 1.

of the mutant allele for IL23R SNP had a significantly higher probability of developing EIMs ($p < 0.05$)[102] and in UC, the HLA-DRB1*0103 allele is associated with the development of EIMs.[27] These elements could be important to take into consideration, as they could guide the clinician to institute, for example, directly a treatment potentially acting on these EIMs.

Choosing the appropriate treatment

Predictors of treatment response

In recent years, our better understanding of the pathophysiological mechanisms underlying IBD has contributed to expand the therapeutic armamentarium.[103] Current therapies include 5-aminosalicylic acids (5-ASA), corticosteroids, immunomodulators (such as azathioprine, 6-mercaptopurine, methotrexate and cyclosporine), anti-tumour necrosis factor (TNF) agents (including infliximab, adalimumab, certolizumab pegol for CD, golimumab for UC), an anti-integrin $\alpha_4\beta_7$ inhibiting lymphocytes trafficking from the blood into the gut (vedolizumab), an anti-interleukin (IL)–12/23 p40-subunit (ustekinumab) and small molecule Janus kinase (JAK) inhibitors (such as tofacitinib and recently filgotinib in UC). Identifying, prior to treatment initiation, which patients are likely to respond to a specific drug (or even the optimal therapeutic sequence or combination) would improve the disease management and clinical outcomes.[23] Beside clinical and biological factors already used in current practice, there is a whole series of biomarkers (including genetic, transcriptomic, proteomic, metabolomic, radiomic and from microbiota) previously explored that could predict response or non-response to these therapies. Predictive factors of treatment response in UC and CD are summarized in Figure 2(a) and (b), respectively (and detailed in Tables 2 and 3).

Genomics. Genetic polymorphism could influence the response to treatment by a series of mechanisms including drug clearance or immunogenicity and have the advantage of not changing over time. There are therefore several reasons to believe that SNP could be potential biomarkers to predict response to treatment, maybe to identify slow responders from early complete responders and to help selecting the best therapy for each individual patient.[139,202] In a systematic review including 15 studies, Bek *et al.*[139] attempted to

Table 2. Predictors of response to biologic and small molecule drugs at baseline in adult UC patients (except for severe acute UC).[104–107]

		Factors	Predict						Predict the absence of			Predict	
			Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy	Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
Corticosteroids	C/B/E/H	Disease severity[108]		W12 CSF										Yes
		Normal stool frequency at baseline[108]				M6				M3				
		Lower UC activity index[111]						Yes	Yes		M3			
		History of 5-ASA topical product use[108]				M6							Yes	
		Proteo												
5-ASA	C/B/E/H	Older age[116]						M12					1 year	
		Lower UC activity index[111]						Yes	Yes				1 year	
		Glucocorticoid use before prescription[116]						M3					Yes	

		Factors	Predict						Predict the absence of			Predict	
			Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy	Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
		Extensive UC[109]												
		Weight loss[110]								M3				
		Serum PR3-ANCA positivity[112]												
		Anaemia at diagnosis[113]												
		Initial requirement of total parenteral nutrition[113]												
		Colonic mucosal hypereosinophilia[114]								M1				
		Higher MMP-7 expression[115]								M3				
		Male gender[117]												
		Short disease duration[117]												
		Left-sided or extensive colitis at diagnosis[118]												

(Continued)

Table 2. (Continued)

		Predict								Predict the absence of			Predict	
		Factors	Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy	Factors	Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
										Number of co-morbid illnesses[116]					
										Hospitalization for a gastrointestinal condition[116]					
										Initial haemoglobin level <10.5 g/dL[118]				Yes	
										Higher C-reactive protein-to-albumin ratio[119]	M3				
										Higher C-reactive protein-to-lymphocyte ratio[119]	M3				
Thiopurines	C/B/E/H	Older age[120]				LT				Younger age at IBD diagnosis[121]			W16		
		Lower WBC or neutrophils count[120]; WBC was less than 5×10^9 292						Yes		Male gender[121]			W16		
		Higher mean Cell volume[120]								Concomitant systemic steroid administration[122]				Yes	
		TPMT activity level <15.3 U/mL blood[123]	M4							TPMT activity >35 pmol/h/mgHb[124]		M6			
	Genetics	c.94C>A variant on ITPA[125]	M12							SNP AOX1 (the product of which activates the essential cofactor for aldehyde oxidase and xanthine oxidase/dehydrogenase) c.3404A>G (Asn1135Ser, rs55754655)[124]	M3				
										GSTM1 deletion[126]	M3				
MTX	C/B/E/H	Younger age at diagnosis[127]						Yes							
		Longer duration between diagnosis and methotrexate initiation[127]						Yes							
	Other									Nomogram developed by Wang *et al.* with age at diagnosis and sex as predictors[127]					Yes
ANTI-TNF	C/B/E/H	Female gender[128]		1 year					Yes	Ex-smoker status[129]	M6				
		Lichtiger clinical activity index score ⩾ 9[128]; higher colitis activity index before anti-TNF therapy[130]	W14	W6						History of CMV colitis within 3 months prior to anti-TNF treatment[131]	Induction				

(Continued)

Table 2. (Continued)

	Factors	Predict							Factors	Predict the absence of			Predict	
		Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy		Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
	Extend disease[132]	LT-FU							Prior calcineurin inhibitors use[128]		W61y			
	Concomitant immunomodulator[128]		W6 1 year						Absence of concomitant immunosuppressant therapy					Yes
	Higher serum albumin level[133]	W8							pANCA+/ASCA-[134]	W10				
	Lower albumin[135]	LT							Severe disease (Mayo score ⩾11 points) at the initiation of anti-TNF[131]; Severe Mayo score[129]	Induction M6				
	Lower neutrophil-to-albumin ratio[136]	W12							Haemoglobin ⩽9.4 g/dL at initiation[137]	M18				
	pANCA sero-negativity[130]	W14												
	Non-severe endoscopic finding at baseline[133]		W8											
	Lower UCEIS bleeding[138]	W8												
Genetics	Patients homozygous for high-risk *IL-23R* variants[130]	W14							In a dominant model, the homozygous variant genotype of TLR2 > (rs4696480) and both the homozygous and the heterozygous variant genotypes of *TLR2* C > A (rs11938228), *LY96* (MD-2) – 1625 C>G (rs11465996), *CD14* – 159G > A (rs2569190), *TNFAIP3* (A20) C > G (rs6927172), *IL1RN* T > C (rs4251961) and *IL17A* 197G > A (rs2275913)[139,140]	W22				
	In a dominant model, both the homozygous and the heterozygous variant genotype of *TLR4* G>A (rs5030728)[139,140]	W22							In a dominant model, the heterozygous genotype of *TNFA* – 238G > A (rs361525) and both the homozygous and the heterozygous variant genotypes of *TLR4* T > C (rs1554973)[139,140]	W22				
	In a dominant model, both the homozygous and the heterozygous variant genotypes of *IL1B* – 3737G>A (rs4848306)[139,140]	W22							In a recessive model, the homozygous variant genotype of *TLR2* C > A (rs11938228) and the homozygous variant genotype of *TLR2* A > T (rs4696480)[139,140]	W22				

(Continued)

Table 2. (Continued)

	Factors	Predict							Factors	Predict the absence of			Predict	
		Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy		Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
	In a dominant model, the homozygous and the heterozygous variant genotypes of *IL6* – 6331T > C (rs10499563)[139,140]	W22							In a recessive model, the homozygous variant genotype of *TLR9* 1174G > A (rs352139) and the homozygous variant genotype of *IL17A* 197G > A (rs2275913)[139,140]	W22				
	In a dominant model, homozygous variant genotype of *TNFRSF1A* – 609G > T (rs4149570)[139,140]	W22							The combined homozygous and the heterozygous variant genotypes of IL12B –10993 G > C (rs3212217)[141]	W22				
	In a dominant model, the heterozygous genotypes of *TLR9* – 1486T > C (rs187084)[139,140]	W22												
	In a dominant model, the heterozygous genotypes of *MAP3K14* T > C (rs7222094)[139,140]	W22												
	In a dominant model, both the homozygous and the heterozygous variant genotypes of *TLR2* 597T > C (rs3804099), *LY96* (MD-2) –1625 C > G (rs11465996), *IL1B* – 3737G > A (rs4848306) and *IFNG* 874T > A (rs2430561)[139,140]	W22												
	In a recessive model, the homozygous variant genotype of *TLR2* 597T > C (rs3804099)[139,140]	W22												
	In a recessive model, the homozygous variant genotype of *TLR4* G > A (rs5030728)[139,140]	W22												
	In a recessive model, the homozygous variant genotype of *TNFRSF1A* – 609G > T (rs4149570)[139,140]	W22												
	The combined homozygous and the heterozygous variant genotypes of IL18-607 C4A (rs1946518)[141]	W22												
	The homozygous variant genotype of IL12B-10993 G > C (rs3212217) and the combined homozygous and the heterozygous variant genotypes of NLRP3 29940 C > G (rs10754558)[141]	W22												

(Continued)

Table 2. (Continued)

	Factors	Predict							Factors	Predict the absence of			Predict	
		Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy		Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
Transcriptomics	A downregulation of a combination of 5 genes (and proteins encoded): *TNFRSF11B* (osteoprotegerin), *STC1* (stanniocalcin-(1), *PTGS2* (prostaglandin-endoperoxide synthase (2), *IL13Ralpha2* (interleukin 13 receptor alpha 2) and *IL11* (interleukin 11) in intestinal biopsies[142]				W8	W8			High pre-treatment level of oncostatin M in the gut[143]; A higher expression of OSM and OSMR in the intestine[144]		M2; M4			
	LPHN2 and *FGF7* expression levels were significantly lower at baseline in intestinal biopsies[145]				W52	W52			Higher mucosal mRNA expression of *IL-1β*, *IL-17A*, *IL-6* and *IFN-γ*[146]	W14				
	A 13-gene signature (*CMTM2, C5AR1, FGF2, GK, HGF, IL1RN, LILRA2, NAMPT, PAPPA, SNCA, SOD2, STEAP4, ZBED3*)[147]				W6				Lower pre-treatment mucosal expression of Th1 transcription factor – *Tbet* and higher expression of Th17-*Rorc*[148]			W12 W54		
	Downregulation of mucosal *TREM1* mRNA expression levels at baseline[149]				W10				Upregulation of blood gene expression of the triggering receptor expressed on myeloid Cells 1 (*TREM-1*) and chemokine receptor type 2 (*CCR2*) – chemokine ligand 7 (*CCL7*) – axes[150]	W14		W14		
	Downregulation of T-Cell activation RhoGTPase activating protein on colon biopsies[151]					W30 (response)								
	Lower mucosal mRNA expression of IL-1β, IL-17A, IL-6 and IFN-γ[146,152]	W14												
	Downregulation of whole blood *TREM1* mRNA expression levels at baseline[149]				W10									
	Panel including ACTN1, CXCL6, LAMA4, EMILIN1, CRIP2, CXCL13 and MAPKAPK2[153]				Resp W12									

(Continued)

Table 2. (Continued)

			Predict								Predict the absence of			Predict	
		Factors	Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy	Factors	Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
	Proteomics	Higher levels of defensine 5 (DEF5, gene name = DEFA5), eosinophil cationic protein (ECP, gene name = RNASE3)[154]	W12 or W14							Higher levels of cathelicidin antimicrobial peptide (CATH, gene name = CAMP), *IL-12*, *IL-17A* and *TNF* before treatment start[154]	W12 W14				
		Higher transmembrane TNF-α in circulating lymphocytes and monocytes[155]			W14	W14				Elevated innate but not adaptive immune responses[156]	M3				
		Stronger suppression of T-Cell surface receptor expression and cytokine secretion from blood Cells cultured *in vitro*[157]	W12or 14							Higher frequency of pre-treatment plasma Cells abundance (assessed by CD138+ immunochemistry staining) in colon biopsies[150]	W14				
		Serum elevated level of TNF-α and IL-12[158]		W6						Serum elevated level of IL-8, IL-2, IL-5, IL-1β and IFN-γ[158]		W6			
		Low oncostatin M levels in serum (proposed threshold <168.7 pg/mL)[34,68]				W54				Higher IL-13 and lower IL-15 level[159]	W10				
										ACTBL2 (Q562R1), MBL2 (P11226), BPI (P17213), EIF3D (O15371) and CR1 (P17927)[160]	W14				
	Radiomics	Visceral adipose tissue volume ⩾3000cm^3[,161]	M12							CT: visceral adipose tissue volume ⩾3000 cm^3[,161]	M12				
										CT: visceral fat index ⩾ 0.67[161]					M6 M12
	Microb.	Lower dysbiosis indexes and a higher level of *F. prausnitzii*[154]	W12 W14												
VEDOLIZUMAB	C/B/E/H	Mild disease activity (partial Mayo score < 5, Simple Clinical Colitis Activity Index < 6 or mild disease as defined by PGA) on treatment onset[162,163]		W14						Articular EIM[164]		W54			
		Active or previous smoking[165]		W14						Mayo score > 9 at baseline[166,167]		W14 CSF			
		No prior anti-TNF use[165,168,169]		W14 W54						High baseline UC-PRO2[164]		W54			

(Continued)

Table 2. (Continued)

		Predict								Predict the absence of			Predict	
	Factors	Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy	Factors	Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
	Prior steroids less than 25% of the time in the last 6 months[169]		W54						Concomitant steroid use at the time of induction[318322]		W54 CSF		Yes	
	Elevated baseline CRP > 0.8 mg/L at induction[170]; higher CRP at baseline[163]	W14	W14						Corticosteroid-refractory disease[164]		W54			
	Baseline IL-8 values >8.6 pg/mL[171]	M12							Anti-TNF refractory disease[164]		W54			
									Previous anti-TNF exposure[172,173]	W6	W26			
									Elevated CRP at induction[163]; CRP greater than 20 mg/L[166]		W14		Yes	
									Leucocyte count > 9000 × 10^9/L at baseline[167]		W54 CSF			
									Low serum 25(OH)D[174]				Yes	
Genetics	Using a diffusion-based signalling model which is mainly focused on the T-Cell receptor signalling network – 48 receptor-TF pairs identified, among which *FFAR2-NRF1*, FFAR2-RELB, *FFAR2-EGR1* and *FFAR2-NFKB1* are the top best predictors[175]	W6 W12 W52												
Transc.	Expression of *RGS13, DCHS2, MAATS1* and *PIWIL1* in colon tissue predicts endoscopic remission in VDZ treated patients[176]				W14									
Proteo.	Higher than α4β7 expression on T, B and natural killer Cells[177]	180 days							Higher circulating levels of IL-6[178]	W14				
	Higher baseline CD8 $\alpha_4\beta_7$ + memory T Cells[179]	W14		W14	W14									
Microb.	Higher α-diversity and lower β-diversity; *R. inulinivorans* and Burkholderiales were more Abundant[180]		W14											

(Continued)

Table 2. (Continued)

		Factors	Predict							Factors	Predict the absence of			Predict	
			Clinical response	Clinical remission	Biologic	Endoscopic	Histologic	Treatment persistence	Survival without colectomy		Clinical response	Clinical remission	Mucosal healing	Treatment discontinuation	Colectomy
	Other									Score ⩽ 26 at clinical decision support tool[181]		W26 CSF			
USTEKINUMAB	C/B/E/H	Male gender[182]						W16		Partial mayo score > 6[183]		W12 W16			
										History of both exposure to anti-TNF and vedolizumab therapies[183]		W12 W16			
										High CRP at baseline[184]		W16			
	Transc.									Lower mucosal expression of IL-23A (IL-23p19)[144]		M2 M4			
	Microb.	The presence of an abundance of two operational taxonomic units affiliated with *Faecalibacterium* and Bacteroides at baseline (using 16S rRNA gene sequencing)[185]		W16											
TOFACITINIB	C/B/E/H	Older age[186]		W52						Oral corticosteroid use[186]		W52			
		Partial Mayo score < 2[186]		W52						Higher CRP at baseline[186]		W52			
		Endoscopic subscore at baseline < 2[186]		W52											

Factors and biomarkers, present at baseline (before initiation of treatment), that have been shown (in multivariate analysis) their ability to predict the achievement or non-achievement of the end point (and the associated timing).
Ab, antibody; ASCA, anti-Saccharomyces cerevisiae antibody; ANCA, anti-neutrophil cytoplasmic antibodies; C/B/E/H, clinical, biological, endoscopic and histological predictive factors; CMV, cytomegalovirus; CRP, C-reactive protein; CSA, Cyclosporin-A; CSF, corticosteroids-free; EIMs, extraintestinal manifestation; IFN, interferon γ; IFX, infliximab; IL, interleukin; Is, immunosuppressant; MTX, methotrexate; NF-κβ, nuclear factor-kappa B; PRO, patient-reported outcome; RNA, ribonucleic acid; TLR, toll-like receptor; TNF, tumour necrosis factor; Transc., transcriptomics; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; VDZ, vedolizumab; WBC, white blood Cell.
Clinical, biological, endoscopic and histological predictive factors are in purple, genetic factors are in the light orange colour, transcriptomic factors are in blue, proteomic factors in green, radiomic factors in grey, factors from the microbiota in yellow and the other factors are in dark orange.

Table 3. Predictors of response or non-response to biologics and small molecule drugs at baseline in adult CD patients (for luminal disease).[104–107]

			Predict								Predict the absence of				Predict	
		Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery	Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
Thiopurine	C/B/E/H	Colonic disease[120]		M6						Male gender[121]				W16		
		Concomitant oral 5-ASA therapy[122]						LT		Younger age at IBD diagnosis[121]				W16		
		Non-fistulizing, non-stricturing disease[122]						LT		TPMT activity > 35 pmol/h/mgHb[124]		M6				
		WBC was less than 5×10^{9}[120]						Yes		Concomitant systemic steroid administration[122]					Yes	
										Stricturing disease[187]						Yes
										Ileal and ileocolonic location[187]						Yes
	Genetics	c.94C > A variant on ITPA[125]								SNP AOX1 (the product of which activates the essential cofactor for aldehyde oxidase and xanthine oxidase/dehydrogenase) c.3404A > G (Asn1135Ser, rs55754655)[124]	M3					
MTX	Clinical	Younger age at diagnosis[127]						Yes								
		Exclusive upper gastrointestinal tract disease[127]						Yes								
ANTI-TNF	C/B/E/H	Male gender[188,189]		W14						More advanced age at anti-TNF initiation (age ⩾ 65 years for some)[190,191]	M3					
		No smoking[192]		M6						Smoking[193–196]	W4 M3	M3			Yes	
		Shorter disease duration (less than 3 years for somes)[196–201]	W12 W26	W26 W52 W56				Yes		Longer disease duration[202,203]	M3					
		Non-stricturing non-penetrating behaviour[192]		M6						Isolated ileal disease[191]	M3					Yes
		Colonic disease[188,191,195,204]	W4	W14						Previous surgery[190,191,205]	M3					
		Younger age at anti-TNF initiation[201,204]	W4	W26						BMI < 18.5[190]	M3					
		EIMs[206]		W26	W26	W26				Severe disease activity at induction, baseline HBI score[196]					Yes	
		Hospitalization within 12 months before baseline[206]		W26	W26	W26				Stricturing disease behaviour[187,203]	M3					Yes

(Continued)

Table 3. (Continued)

		Predict								Predict the absence of					
	Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery	Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
	Concomitant steroids[206]		W26	W26	W26				Penetrating disease behaviour[187]						Yes
	Use of immunosuppressive drug[191,194,197,203,204,206–208]	W4 W10 M3	W24 W26 W52	W26	W26		Yes		Faecal calprotectin level (>863 µg/g for some) at initiation[196,209]	M3				Yes	
	Absence of prior anti-TNF therapy[201]		W4						Higher CRP level, >15 mg/dL[210]	M3					
	Previous surgical resection[196,197]		W24 W52				Yes		Low albumin[196]					Yes	
	No previous CD-related surgical resection[201,206]		W4 W26		W26		Yes		Low haematocrit[196]					Yes	
	Elevated CRP level (greater than twice the upper limit of the normal range for somes)[203,208]	W4 W10 M3													
	Low serum albumin concentration at baseline[196]						Yes								
	Haematocrit (every 10% increase in haematocrit increases the probability that a patient will maintain remission)[196]						Yes								
	Low vitamin D level[211]		W14												
	Neutrophil-to-albumin ratio and neutrophil-to-bilirubin ratio (NBR)[212]	Induction		M12											
	Baseline IL-8 values >8.6 pg/mL and baseline IL-6 values >1.6 pg/mL[171]	M12													
Genetics	In a dominant model, homozygous variant genotype of *TNFRSF1A* –609G > T (rs4149570)[139,140]	W22							16 SNPs predicts durable response (including *ATG16L1* polymorphism)[202]		M3				
	In a dominant model, homozygous and heterozygous genotype of *TLR4* G > A (rs5030728)[139,140]	W22							In a dominant model, the heterozygous genotype of *TNFA* –238G > A (rs361525) and both the homozygous and the heterozygous variant genotypes of *TLR2* C > A (rs11938228), *TLR4* T > C (rs1554973) and *TNFAIP3* (A20) C > G (rs6927172)[139,140]	W22					

(Continued)

Table 3. (Continued)

	Predict							Predict the absence of				Predict	
Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery	Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
In a dominant model, both the homozygous and the heterozygous variant genotypes of *TLR2* 597T > C (rs3804099), *TLR2* C > T (rs1816702), *LY96* (MD-2) – 1625 C > G (rs11465996), *IFNG* 874T > A (rs2430561)[139,140]	W22							In a recessive model, the homozygous variant genotypes of *TLR4* G > A (rs5030728)[139,140]	W22					
In a dominant model, the heterozygous genotypes of *TLR9* –1486T > C (rs187084)[139,140]	W22							In a recessive model, the homozygous variant genotypes of *TLR9* 1174G > A (rs352139)[139,140]	W22					
In a dominant model, the heterozygous genotypes of *MAP3K14* T > C (rs7222094)[139,140]	W22							In a recessive model, the homozygous variant genotype of *IL17A* 197G > A (rs2275913)[139,140]	W22					
In a dominant model, both the homozygous and the heterozygous variant genotypes of *IL1B* –3737G > A (rs4848306) and *IL6* –6331T > C (rs10499563)[139,140]	W22							Haplotype rs1061624_A-rs3397_T of TNFRSF1B gene[213]	W10					
In a recessive model, the homozygous variant genotype of *TNFRSF1A* –609G > T (rs4149570)[139,140]	W22							CD patients with one or two rare TNFR1 alleles[214]			W4 W8			
In a recessive model, the homozygous variant genotype of *TLR2* 597T > C (rs3804099)[139,140]	W22							Fas ligand 843TT genotype[204]	W4					
ATG16L1 (rs10210302) CT or TT genotype[139,140]			W12 W20 W30					IBD5 locus homozygous mutant genotype[215]	W4					
PTGER4 (rs10512734) GG genotype[139,216]	W12 W30							Several other SNPs including CARD11, IL1R1, IL1R2, IL18 receptor complex[202]	M3					
CASP9 (rs4645983) TT genotype or T allele[139,216]	W12							High activity of TLR5[141]	W22					

(Continued)

Table 3. (Continued)

	Factors	Predict							Factors	Predict the absence of				Predict	
		Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery		Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
	IL27 (rs8049439) CT or TT genotype[139,216]	W4		W4					Expansion of IL-23 receptor bearing TNFR2+ *T* Cells is associated with molecular resistance to anti-TNF[217]	W12					
	C11orf30 (rs7927894) CC genotype[139,216]	W12		W12 W20					SNP of TNF receptor superfamily 1A (rs767455)[218]	W4					
	CCNY (rs12777960) CC genotype[139,216]	W4		W20											
	NR1I2 (rs3814057) CC genotype or C allele[139,216]			W30											
	IL13 (rs1295686) AA genotype[139,216]	W20 W30													
	FCGR3A-158V/V genotype[208,219,220]	W10		W2 W6 W8 W10											
	Fas ligand –843 CC or CT genotype (compared to Fas ligand 843TT genotype)[204]	W4													
	Caspase-9 93 TT genotype in luminal CD (compared to CC and CT genotype)[204]	W4													
	The homozygous variant genotype of IL12B – 10993 G > C (rs3212217) and the combined homozygous and the heterozygous variant genotypes of NLRP3 29940 C > G (rs10754558)[141]	W22													
	S100A8-S100A9, G0S2, TNFAIP6 and *IL11* gene expression profile[221]	W10													
	TNFRSF1B polymorphism (rs1061622)[222]	W10													
	SNPs rs9373839 and rs510432 in *ATG5* gene[223]	W30													
	Allele C and genotypes CC and CT of the rs1130864 in the *CRP* gene[223]	W30													
	TNF-α polymorphisms (rs1568885 and rs1813443)[224]				W12 W20										

(Continued)

Table 3. (Continued)

		Predict								Predict the absence of				Predict	
	Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery	Factors	Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
Transcr.	*TNFAIP6*, *S100A8*, *IL11*, *G0S2* and *S100A9* genes[225]	M3							High pre-treatment level of oncostatin M in the gut[143]; A higher expression of OSM and OSMR in the intestine[144]		M2 M4				
	Downregulation of mucosal or whole blood *TREM1* mRNA expression levels at baseline[149]				W24				Upregulation of blood gene expression of the triggering receptor expressed on myeloid Cells 1 (TREM-1) and chemokine receptor type 2 (CCR2)- chemokine ligand 7 (CCL7)–axes[150]	W14			W14		
	Panel including ACTN1, CXCL6, LAMA4, EMILIN1, CRIP2, CXCL13 and MAPKAPK2[153]				Resp W12										
Proteomics	Low oncostatin M levels in serum (proposed threshold <168.7 pg/mL)[226,227]				W54				Treg frequency and serum TGF-β1 levels were significantly higher[228]	M3					
	High percentage of CD19+ Cells in the inflamed intestinal mucosa predict response to infliximab[229]	M3							Higher level of serum TNF-α[230]	M3					
	Higher transmembrane TNF-α in circulating lymphocytes and monocytes[155]			W14	W14				Higher platelet aggregation factor 4 (PF4) expression[231]	W4		W4			
									Higher frequency of pre-treatment plasma Cells abundance (assessed by CD138 + IHC staining) in colon biopsies[150]	W14					
									Increased expression of IL-13R[232]				Y1		
Radiomics	Visceral adipose tissue volume 1500–2999 cm^3[3,161]	M12							Visceral adipose tissue volume ⩾3000 cm^3[3,161]	M12					
	A small bowel stricture length of <12 cm[233]	W24							Visceral fat index ⩾ 0.67[161]						M6
	A maximal small bowel diameter proximal to stricture(s) of 18–29 mm[233]	W24							DW-MRE: apparent diffusion coefficient $< 1 \times 10^{-3}$ mm^2/s[234]					M12	

(Continued)

Table 3. (Continued)

		Factors	Predict							Factors	Predict the absence of				Predict	
			Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery		Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
		A marked enhancement on delayed phase[233]	W24							MRE : presence of creeping fat[235]					LT	
		The absence of a fistula[233]	W24							Nomogram based on a MRI-based radiomic index able to detect change in iron metabolism developed by Feng *et al.*[236]					SLR W24	
		Clinical radiomics nomogram (combining disease duration and a CTE-based radiomics signature) developed by Zhu *et al.* [237]				W26				Radiomic nomogram with 8 radiographic features developed by Chen *et al.* [238]						
	Microb.	Increase in *Clostridiales* relative abundance[239]	W30													
	Others	High number of mTNF-positive Cells in the colon after spread of fluorescent anti-TNF Ab topically onto the diseased mucosa and used of endoscopic confocal laser endomicroscopy to detect and quantify mTNF-bearing mucosal Cells[240]	W12													
		Presence of GIMAT module[241]		M6 CSF						Absence of GIMAT module[241]		M6				
										IL-6-based nomogram[242]	W14					
										Bioelectrical impedance analysis-based nomogram construction[238]						SLR W54
VEDOLIZUMAB	C/B/E/H	No history of EIMs[165]		W14						Smoking history[243]		Y1				
		No previous surgery[163]		W14						Higher disease activity at baseline (HBI score > 10 for some)[163,166,167,243]		W14 Y1		Y1		
		No hospitalization in the past 12 months[165]		W14						Active perianal disease[243]		Y1				
		Elevated baseline CRP[163,166,170]		W14						Concomitant steroid use at time of induction[163,166,167]		W14 W54			Yes	
		Mild disease activity at baseline,[163] low HBI score[162,165,168]		W14						Previous surgery[163]					Yes	
										Prior anti-TNF use[243]		Y1		Y1		
										Elevated baseline CRP[170]	W14	W14				
										The presence of anaemia at induction[163]					Yes	
										Low serum 25(OH)D[174]					Yes	

(Continued)

Table 3. (Continued)

		Factors	Predict							Factors	Predict the absence of				Predict	
			Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery		Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
	Epigen.	Novel 25- and 23-feature panels of epigenetic biomarkers. CpGs of interest implicated genes involved in endothelial Cell–Cell adhesion and integrin-dependent T-Cell homing[244]	LT		LT	LT										
	Proteo.									Higher soluble CD40 ligand (sCD40 L) level[178]	W14					
										Higher circulating levels of IL-6[178]	W14					
	Microb.	Higher α-diversity and lower β-diversity; *R. inulinivorans* and Burkholderiales were more abundant[180]		W14												
	Other	High number of $\alpha_4\beta_7$-positive Cells in the colon after spread of fluorescent Ab topically onto the diseased mucosa and used endoscopic confocal laser endomicroscopy to detect and quantify $\alpha_4\beta_7$-positive Cells[245]	LT		LT			Yes								
USTEKINUMAB	C/B/E/H	History of 2 or more different immunosuppressive drugs[246]	LT							Younger age[247]		W8				
		Prior anti-TNF primary failure (*versus* secondary failure or intolerance)[248]	Short-term							Smoking[247]		W56				
		Lower body weight[249]	W8							History of intestinal resection[246]					Yes	
		Higher baseline CDAI[249]	W8							Proximal disease location or L4[247]		W8				

(Continued)

Table 3. (Continued)

	Factors	Predict							Factors	Predict the absence of			Predict	
		Clinical response	Clinical remission	Biological end point	Endoscopic remission	Histologic	Treatment persistence	Survival without surgery		Clinical response	Clinical remission	Biological end point	Endoscopic remission	Treatment discontinuation	Surgery
									Perianal involvement[247]		W8				
									Age <17years at diagnosis[247]		W56				
									Corticosteroid dependency[247]			W16			
									Stricturing/penetrating phenotype[247]			W16			
	Trans.								Lower mucosal expression of IL-23A (IL-23p19)[144]			M2 M4			
	Microb.	Significantly higher α-diversity; more abundance of *Faecalibacterium* and Bacteroides[185]	W6						Higher levels of *Faecalibacterium* and *Escherichia/Shigella*[185]	W6					
		Lower abundance of *Escherichia* and *Shigella*[185]	W6												

Factors and biomarkers, present at baseline (before initiation of treatment), that have been shown (in multivariate analysis) their ability to predict the achievement or non-achievement of the end point (and the associated timing).
Ab, antibody; ANCA, anti-neutrophil cytoplasmic antibodies; BMI, body mass index; C/B/E/H, clinical, biological, endoscopical and histological predictive factors; CDAI, Crohn disease activity index; CRP, C-reactive protein; CTE, computed-tomography enterography; EIMs, extraintestinal manifestation; Epigen., epigenetic; HBI, Harvey–Bradshaw index; IFN, interferon γ; IFX, infliximab; IL, interleukin; LT, long term; Microb., microbiote; M, month; MRE, magnetic resonance enterography; NF-κβ, nuclear factor-kappa B; Proteo., proteomic; RNA, ribonucleic acid; SLR, secondary loss of response; TLR, toll-like receptor; TNF, tumour necrosis factor; Trans., transcriptomics; VDZ, vedolizumab; Y, year; W, week.
Clinical, biological, endoscopic and histological predictive factors are in purple, genetic factors are in the light orange colour, transcriptomic factors are in blue, proteomic factors in green, radiomic factors in grey, factors from the microbiota in yellow and the other factors are in dark orange.

identify potential genetic markers to predict anti-TNF response in UC and CD patients. They highlighted that genes involved in the innate immune response such as recognition of bacterial components and cytokine pathways could be important for the response to anti-TNF.[139] Indeed, toll-like receptor (TLR) 4 (rs55030728), FC fragments of IgG receptor IIIa (*FCGR3A*, rs396991), tumour necrosis factor receptor superfamily 1A (*TNFRS1A*, rs4149570), interferon-gamma (*IFN*γ, rs2439561), IL-6 (*IL-6*, rs10499563) and interleukin-1B (*IL-1B*, rs4848306) polymorphism were associated with improved anti-TNF response in IBD.[139] TLR2 (rs3804099) and TLR9 (rs352139) SNPs were, on the contrary, associated with a poorer response.[139] A number of genes among the 200 susceptibility genes identified in IBD population were also studied to see whether it could predict the response to biological.[104,250–252] Although being the strongest susceptibility gene identified for CD,[89] NOD2/CARD15 polymorphism was not found to be a good predictor of response to infliximab or adalimumab in CD patients.[104,253] In contrast, variants in IL-23R, another IBD susceptibility gene, seem to be associated with the response to anti-TNF.[130] Homozygous carriers of IBD risk-increasing IL23R variants (rs1004819, rs2201841, rs10889677, rs11209032 and rs1495965) were more likely to respond to infliximab therapy than homozygous carriers of IBD risk-decreasing IL23R variants (rs7517847, rs10489629, rs11465804 and rs1343151).[130] IL-23 receptors are highly expressed on the surface of Th17 cells and are important for the differentiation of these cells producing TNF-α, which could explain links between IL23R genotype and response to anti-TNF.[130] However, only a minority of IBD patients are homozygous for these IL23R variants, making the use of IL23R genotyping for predicting response to infliximab limited in clinical practice.[130] Hlavaty *et al.*[204] have also reported that polymorphisms in apoptosis genes (Fas ligand and caspase-9 gene) could influence response to infliximab in luminal and fistulizing CD. Patients with a Fas ligand −843 CC/CT genotype and caspase-9 93 TT genotype have a higher rate of clinical response to infliximab than those with Fas ligand −843 TT genotype and caspase-9 93 CC and CT genotype, respectively.[204] Unfortunately, these findings are not systematically found from one study to another. It was indeed demonstrated on a prospective cohort of 121 CD patients that patients with a Fas ligand CC genotype being a non-responder were fourfold higher as compared to a TC or TT genotype[254]

While some studies have shown that models combining genetic and clinical variables were superior to a model including only clinical variables to predict PNR to anti-TNF,[21,202] other studies found that the addition of genetic markers did not provide any benefit to these predictive models.[190] To date, few and weak genetic biomarkers were identified to predict response to treatment. These are sometimes not reproducible and are associated with polymorphisms rarely present in the population, which makes their use in clinical practice limited.[139] Furthermore, the expression of these potential genes could be influenced by environmental factors (or the exposome). These can act by modulating the epigenome, which are poorly considered in studies looking for genes associated with treatment response, and deserved to be taken into consideration.[255] The genome sequencing for SNP identification in IBD patients is not currently considered to bring sufficient benefit to justify the associated costs.[256]

Transcriptomics. If the study of genomics has not allowed to find sufficiently robust genetic markers to predict response to anti-TNF to date, transcriptomics is another science that could bring complementary data. Transcriptomic studies can be performed on intestinal mucosa biopsies or on blood samples. By analysing the mRNA expression profiles of colonic mucosal biopsies from UC patients enrolled in the Active Ulcerative Colitis Trial 1 (ACT1), Toedter *et al.* found an expression difference of genes involved in the Th1, Th2 and Th17 pathways between responders and non-responders to infliximab.[151] Similarly, Arijs *et al.*[142] compared the pre-treatment colonic mucosal biopsy-derived mRNA expression between responders and non-responders to provide a predictive response signature for infliximab treatment in UC. They found that the downregulation of a combination of five genes (*TNFRSF11B, STC1, PTGS2, IL13Ralpha2* and *IL11*) predicted the response to infliximab at weeks 4–8 with 89% of accuracy.[142] A few years later, still in UC patients, but for golimumab this time, baseline gene expression signature was studied to see whether it could be used to predict patients which would achieve mucosal healing, clinical response and clinical remission at weeks 6 and 30 of this anti-TNF.[147] A 13-gene signature (*CMTM2,*

C5AR1, FGF2, GK, HGF, IL1RN, LILRA2, NAMPT, PAPPA, SNCA, SOD2, STEAP4, ZBED3) was also highlighted to predict mucosal healing at week 6 (note that this was not significant in predicting clinical remission or response).[147] For CD patients, the same group (Arijs *et al.* and colleagues) therefore investigated whether they could identify a mucosal gene panel allowing reliable prediction of response to infliximab. The top five differentially expressed genes at baseline (*TNFAIP6, S100A8, IL11, G0S2* and *S100A9*) allowed to distinguish responders from non-responders to anti-TNF with an overall accuracy of 100% in patients with colonic involvement.[225] Although these studies demonstrated that transcriptional profiles could be useful to predict anti-TNF response, no overlap was found between the identified genes.[23] Finally, a study performed on 48 UC patients showed that non-responders have a more severe proinflammatory cytokine profile with higher *IL-1*β, *IL-17A, IL-6* and *IFN-*γ mucosal mRNA expression,[146] but these results were not unanimous and other studies reported that higher gene expression levels of *IL-17A* and *IFN-*γ were significantly associated with remission after infliximab.[152]

Because of their identified role in the IBD pathophysiology, the role of more specific biomarkers has been investigated. The oncostatin M (*OSM*), a cytokine belonging to the IL-6 cytokine family, whose expression is increased in inflammatory intestinal tissues, would seem to be an inflammatory amplifier and driver of disease chronicity by promoting chemokines, cytokines and adhesion-factor production by intestinal stromal cells.[143] It was demonstrated on an analysis including two cohorts from phase III clinical trials of infliximab and golimumab (more than 200 UC and CD patients), that high baseline expression of *OSM* was strongly associated with anti-TNF failure.[143] Other mucosal biomarkers have also been suggested but with less robust data. The downregulation of the T-cell activation RhoGTPase activating protein or of the triggering receptor expressed on myeloid cells 1 (*TREM1*) mRNA expression levels at baseline was indeed associated with better chance of responding to anti-TNF.[149,151] The upregulation of this latter marker (*TREM1*) in whole blood was also found to be rather predictive of non-response to anti-TNF, as well as the upregulation of chemokine receptor type 2 (CCR2)-chemokine ligand 7 (CCL7).[149,150] Peripheral blood markers have the advantage of being more easily accessible and associated with less patient discomfort, making them very attractive targets for the future.[23]

Although less widely studied than to predict response to anti-TNF, mucosal gene expression has also been used to attempt to predict response to anti-integrins or to anti-IL12/IL-23. Similar to what they did to try to identify genes that predict response to infliximab in patients with UC and CD, Arijs *et al.* analysed mucosal gene expression in UC patients treated by vedolizumab. However, no gene has been identified as predictive of vedolizumab response by comparing the pre-treatment array profiles of responders with non-responders.[145] In contrast, Verstock *et al.* identified, in a cohort of 31 IBD patients, four genes (*RGS13, DCHS2, MAATS1* and *PIWIL1*) whose baseline expression levels in colon tissues could predict endoscopic remission with vedolizumab.[176] Preliminary data were also available for etrolizumab, another anti-integrin targeting the β_7 subunit of the heterodimeric integrins $\alpha_4\beta_7$ and $\alpha_E\beta_7$, before the development was stopped.[257] The presence of increase levels of granzyme a (*GZMA*) and integrin αE gene mRNAs in colon tissues of UC patients could have allowed IBD specialists to identify patients who are more likely to respond to this treatment.[258,259] Finally, for ustekinumab, Nishioka *et al.*[144] have recently demonstrated that higher mucosal *IL23A* expression predicts the response to ustekinumab in both UC and CD patients.

History has unfortunately shown that biomarkers found in one cohort were not necessarily found in another.[147] They must also be interpreted with caution because some are simply associated with response to treatment but are not necessarily predictive of it (a remark also applicable to other types of markers).[56] To date, all these highlighted biomarkers need therefore to be validated on independent cohorts before being implemented in clinical practice.

Proteomics and proteins expression. Transcriptomics does not take into account post-translational modifications and does not always allow to have information on the functional repercussions of the mRNA observed changes.[23] To this end, the proteomic or other tools of protein quantification, including immunohistochemistry and flow

cytometry, could give more precise indications on how cell function could be impacted and with it, the response to different IBD treatments.[23]

A proteomic analysis performed on mucosal biopsies of 56 biologic-naïve UC patients showed that anti-TNF responders and non-responders had differential pattern expressions of anti-microbial peptide AMP and cytokines.[154] Patients responders have higher levels of defensin-5α, eosinophil cationic protein in mucosa, whereas non-responders have higher levels of cathelicidin antimicrobial peptide, IL-12, IL-17A at baseline.[154] Proteomic analyses can also be carried on the blood. A study performed in 47 infliximab-naïve IBD patients showed that patients with a response to infliximab at week 14 had higher transmembrane TNF-α (tmTNF-α) in their circulating lymphocytes and monocytes.[155] Studies are not unanimous regarding the role of TNF-α serum levels in predicting response to anti-TNF. While some have suggested that a higher basal level of TNF-α may be predictive of response to infliximab in UC patients,[158] another study demonstrated that a higher level of serum TNF-α before treatment initiation was associated with lack of response to anti-TNF.[230] Locally in the mucosa, high mucosal TNF-α levels before treatment might instead be associated with a better response to anti-TNF in CD patients.[260] This discrepancy can be explained by the fact that, in humans, the abundance of proteins (such as cytokines) is subject to large genetic variations and that individual differences in abundance do not always reflect individual differences in biological activity.[158] Indeed, for the same level of cytokines, the activity of these may be different and the underlying cytokines composition may also differ.[158] It may therefore be more interesting to study a coordinated (matrix-evaluated) cytokine response rather than the level of a single cytokine to predict response to treatment.[158] Using seven cytokines (TNF-α, IL-12, IL-8, IL-2, IL-5, IL1-β and IFN-γ), Obraztsov *et al.*[158] proposed a model allowing to classify patients into responders and non-responders with a sensitivity of 84.2% and a specificity of 93.3%. Increases in other cytokines were also associated with a lack of response, but with the same limitation. It was thus demonstrated in 20 CD patients that those not responding to anti-TNF had a higher frequency of Treg (assessed by flow cytometry) in pre-treatment and transforming growth factor (TGF)−β1 level [assessed by enzyme-linked immunosorbent assay (ELISA)].[228]

Some teams have also tried to use proteomic or proteins expression data to try to predict the response to IBD therapies other than anti-TNFs. By analysing immunophenotyping of peripheral blood mononuclear cells and expression of $\alpha_4\beta_7$ integrin on lymphocytes from 26 IBD patients, Boden *et al.*[177] sought to identify biomarkers associated with response to vedolizumab. They found that $\alpha_4\beta_7$ expression on multiple subsets of T, B and natural killer (NK) cells was higher in responders than in non-responders prior to treatment administration.[177] Another study using multiplex ELISA to quantified 47 preselected plasma proteins in blood samples of 28 anti-TNF refractory IBD patients prior to initiation of vedolizumab demonstrated that higher IL-6 and soluble CD-40 ligand circulating level could predict non-response to vedolizumab (only in UC patients for CD-40 ligand) while higher levels of osteocalcin could predict response.[178] Osteocalcin (a marker of bone formation), although increased in responders compared to non-responders, appears to be of limited value in predicting response to vedolizumab and guiding treatment choice. Indeed, the high level of bone formation may only reflect relative bone sparing in patients with less severe disease or less long-standing inflammation.[178] In contrast, IL-6 levels may be more informative. As previously mentioned, high levels of IL-6 have also been described in patients refractory to anti-TNF drugs, suggesting that IL-6 may play a role in non-TNF mediated inflammation.[146,178,261] These data suggest that patients with higher IL-6 signalling would benefit from therapy other than anti-TNF or vedolizumab.[145,178] For ustekinumab, Creyns *et al.*[262] demonstrated, in 46 anti-TNF and vedolizumab refractory CD patients, that responders had lower baseline level of innate lymphoid cells expressing transcription factors/cytokines present in Th1 cells (also known as ILC1s cells) while non-responders had higher rates. Finally, a series of anti-IL23 drugs will probably reach the market in the near future.[103] For these therapies, baseline serum concentration of IL-22 (an upstream regulator of IL-23) could be used to predict response to treatment at week 8. Indeed, patients with an IL-22 concentration greater than or equal to 15.6 pg/mL were more likely to respond to anti-IL23p19.[263]

Similar to what was observed with transcriptomics, these studies describing potential biomarkers are encouraging but have generally been observed in small cohorts and need to be validated in larger cohorts before being applied in clinical practice.[23]

Metabolomics. Metabolomics could also help in predicting the response to biotherapies.[36] In a prospective longitudinal cohort study enrolling 76 CD patients, Ding *et al.*[264] demonstrated that a range of metabolic biomarkers may contribute to prediction of response to anti-TNF therapy in CD patients. Primary non-responders tended to have modification of serum lipids (higher level of ceramide and sphingomyelin) as well as serum and faecal bile acids changes (higher levels of circulating primary unconjugated bile acids as well as higher levels of bile acids conjugated to sulphate, taurine and glycine in faeces).[264] In contrast, anti-TNF responders had a higher histidine levels in faeces and serum as well as a higher urinary cysteine level and the ROC analysis demonstrated a good model for predicting anti-TNF response for this latter.[264] Faecal metabolites' profiles could also provide some answers. For example, butyrate and substrates involved in butyrate synthesis (e.g. acetaldehyde) have been identified as predictive metabolites of clinical remission following biologic therapy.[36,265] The presence of these metabolites in the stool is influenced by the microbiota, which can, of course, also be used in precision medicine.

Radiomics. A few studies have evaluated the ability of imaging-based biomarkers to predict, at diagnosis, the response to specific treatments. Rimola *et al.*[235] showed that CD patients with creeping fat or ileal lesions at pre-treatment MRE were unlikely to heal severe inflammation on a long term under anti-TNFα treatment. Some criteria assessed in MRE could also help predict which CD patients with symptomatic ileal stenosis are likely to respond to anti-TNF therapy.[233] In the CREOLE study, CD patients with four criteria or more (including MRE ones) among the following (the use of an immunomodulator, the presence of obstructive symptoms for <5 weeks, a Crohn disease obstructive score >4, a small bowel stricture length of <12 cm, a maximal small bowel diameter proximal to stricture(s) of 18–29 mm, a marked enhancement on delayed phase and absence of a fistula) were considered to be likely to respond to adalimumab.[233] The presence of an apparent diffusion coefficient $<1\times10^{-3}$ mm^2/s assessed by diffusion-weighted MRE could also predict response to anti-TNF in CD patients with stricture.[234] A team also looked at the ability of visceral adipose tissue volume and visceral fat index (visceral: subcutaneous adipose tissue ratio; VFI), assessed by computed tomography scans, to predict clinical response and C-reactive protein (CRP) reduction in response to anti-TNFα initiation.[161] IBD patients with visceral adipose tissue volume of 1500–2999 cm^3 were most likely to response and to have a mean CRP reduction at 12 months (compared with those with a volume $\geqslant$3000 cm^3).[161] In contrast, patients with VFI $\geqslant 0.67$ were significantly more likely to undergo surgery at 6 and 12 months compared with those with VFI < 0.33.[161] Finally, nomograms based on radiomics were established to predict mucosal healing or SLR with infliximab in CD patients.[236–238] Zhu *et al.*[237] indeed attempted to predict mucosal healing in biologic-naïve CD patients treated with infliximab using clinical factors and radiomics features. Their clinical radiomics nomogram combined disease duration and a computed tomography enterography (CTE)-based radiomics signature at baseline and performed well to predict mucosal healing in CD patients after 26 weeks of infliximab treatment.[237] Feng *et al.*[236] also established and validated a nomogram based on an MRI-based radiomic index able to detect change in iron metabolism to identify CD patients at risk of SLR to infliximab. Chen *et al.*[238] also developed a radiomic nomogram with eight radiographic features to predict loss of response to infliximab in CD patients.

Microbiome. Playing a key role in the initiation and propagation of intestinal inflammation in IBD, and modifying in response to IBD treatments, the gut microbiome could also be used to predict attenuation of inflammation in response to biologic treatments.[266–270] While for anti-TNF, the presence of a more diverse microbiome at baseline was not predictive of treatment response,[269,271] it was, however, associated with clinical remission with vedolizumab (and even predictive for this treatment) and ustekinumab.[180,185] More specifically, it has been shown by several studies that disturbances in the taxa that typically produce short-chain fatty acids (SCFA) were associated with conventional and biologics treatment failures.[272,273] Indeed, studies have shown that patients more likely to achieve clinical remission with anti-TNF seem to have

greater abundance of species producing butyrate prior treatment initiation such as *Clostridium citroneae or Agathobaculum butyricproduces*.[266,274] Consistent with these data, it has been demonstrated that the abundance of another SCFAs producers, *F. prausnitzii*, tended to be higher in anti-TNF responders than in non-responders at baseline,[154] but this association was not found in all studies.[266] The same is true for patients treated by vedolizumab, for whom, a greater abundance of other SCFAs producers species at baseline, *Roseburia inulinivorans* and *Burkholderiales*, was also predictive of remission at week 14.[180] The same authors highlighted the importance of predictive models incorporating both clinical and microbiome data (such as vedoNet, a network algorithm) in predicting clinical remission.[180] Finally, a study investigated the association between faecal microbiota composition and response to ustekinumab in 232 anti-TNF refractory CD patients (from phase 2 CERTIFI study).[185] *Faecalibacterium* and *Bacteroides* species were significantly more abundant at baseline in subjects who were in remission 6 weeks after ustekinumab treatment than those who were not,[185] while *Escherichia* or *Shigella* were lower.[185]

The use of microbiota as predictors of response is made difficult by the fact that the identified disturbance in microbiota may be the reflect of the inflammatory burden or any other confounding factors, including environmental ones.[21] For some, microbiota may be a better biomarker for predicting response to gut-specific therapies, such as vedolizumab, than systemic therapies such as anti-TNF.[180] Lee *et al.*[266] pointed that the association between microbiome and clinical or endoscopic outcomes was stronger for week 14 than for week 52, suggesting that microbiome may have a greater impact on short-term outcomes. Studies systematically comparing the evolution of microbial profiling with the clinical course in response to a specific treatment would help identify the optimal prediction window of the microbiome for individual clinical outcomes.[266]

Others and visualization tools. The use of confocal laser endomicroscopy with the topically application of fluorescent antibodies (targeting anti-TNF or $\alpha_4\beta_7$ integrin) directly onto the disease mucosae allows the detection and quantification of mTNF-bearing or $\alpha_4\beta_7$-positive mucosal cells and to predict response to anti-TNF and to vedolizumab, respectively.[240,245] These findings need to be validated in independent larger multicentre cohorts but the use of these fluorescent antibodies in relapsing patients for whom an endoscopy is performed prior to a treatment change would allow us to measure the amount of molecules that is targeted by a particular therapy and could guide the therapeutic strategy.[21] In 2019, Martin *et al.*[241] showed, using single-cell analysis of ileal inflamed tissues from CD patients, that the presence of GIMAT module at diagnosis was correlated with failure to achieve durable CS-free remission upon anti-TNF therapy. The GIMAT organization refers to a unique cellular module with IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells and stromal cells and is driven by a unique MNP-dependent cytokine/chemokine network.[241]

Some have created clinical decision support tools (CDST) to predict outcomes of treatment with vedolizumab in UC and CD patients.[181] In UC patients, using the absence of exposure to an anti-TNF (+3 points), disease duration of 2 years or more (+3 points), baseline endoscopic activity (moderate *versus* severe) (+2 points) and baseline albumin concentration (+0.65 points per 1 g/L), they could determine, on a validation cohort, with a high sensitivity (93%), that patients with a score of 26 points or less did not respond to vedolizumab.[181] Patients with a score of 27–32 points or 33 points or more had intermediate and high probability of vedolizumab response (corticosteroid-free remission at week 26), respectively.[181] Similarly, a scoring system has been developed and validated to identify CD patients most likely to respond to 26 weeks of vedolizumab treatment.[173] The following factors were used: previous anti-TNF treatment (+3 points), absence of prior bowel surgery (+2 points), absence of prior fistulizing disease (+2 points), baseline level of albumin (+0.4 points per g/L) and baseline concentration of CRP (reduction of 0.5 points for values between 3.0 and 10.0 mg/L and 3.0 points for values >10.0 mg/L).[173] The cut-off value of $\leqslant 13$ points allowed us to identify, with a good sensitivity, CD patients most likely to respond.[173]

Other visualization tools, such as nomogram, or machine learning related to artificial intelligence, have also been applied to guide drug use in IBD. Nomogram is a graphical representation of a mathematical formula (or of an algorithm) in which are incorporated several predictors models as continuous variables to predict an end point

and facilitates patient management-related decisions by providing superior individualized disease-related risk estimations.[275] These are based on traditional statistical methods, such as multivariable logistic regression and Cox proportional hazards analysis.[275] Nomograms based on radiomics have been presented above. Nomograms were developed, from IBD Bioresourse (United Kingdom), to predict surgery for IBD patients initially treated with methotrexate in monotherapy.[127] For UC, sex and age at diagnosis were predictors in the nomogram.[127] For CD, gender, treatment era, tolerance, lesion site, perianal involvement, disease behaviour and biologics requirements were in the nomogram.[127] Using multiple logistic regression, Chen *et al.*[242] found that disease behaviour, body mass index (BMI), CRP and IL-6 levels before infliximab initiation were predictive factors of PNR to infliximab at week 14 in CD patients and developed and validated an IL-6 nomogram. Finally, a nomogram based on bioelectrical impedance analysis indexes (based on body composition parameters) and laboratory markers (haemoglobin, albumin, serum iron) could predict SLR to infliximab in bio-naïve CD patients at 54 weeks.[238] Other nomograms have been proposed to predict response to treatment but were based on factors other than those present at baseline.[276]

Machine learning belongs to the field of artificial intelligence and refers to the ability of computers to learn to make decisions or detect patterns from data, without explicitly being programmed.[277] Several machine learning predictive models have already been suggested such as (1) a machine learning algorithm to predict clinical remission with thiopurines[278]; (2) a machine learning to predict non-durable response to anti-TNF therapy in CD patients using transcriptome imputed from genotypes[279]; (3) a machine learning to identify, in CD patients, predictive factors of remission and drug durability with ustekinumab[280]; or (4) a machine learning gene expression to predict response to ustekinumab in CD patients.[281]

Prediction of side effects. If in precision medicine, biomarkers can be used to predict response to treatment, they can also predict the occurrence of side effects. Some IBD patients (more frequently UC patients) can develop fever and a worsening of diarrhoea under mesalamine.[282] After conducting GWASs followed by a meta-analysis on two independent pharmacogenetic Japanese IBD cohorts (MENDEL and Tohoku), Suzuki *et al.* identified a significant association between rs144384547 (upstream of RGS17) and these adverse reactions called 'mesalamine allergies'.[282] In addition, using the GWAS results, they suggest a polygenic risk score and established a combined genetic/clinical prediction model, which yielded a higher area under the curve than polygenic risk score or clinical factors alone (area under the curve, 0.89; sensitivity, 71.4%; specificity, 90.8%).[282] Patients with *N*-acetyltranferase 2 (*NAT2*) gene polymorphism (in particular slow metabolizer allele) have a higher risk to develop salazosulfapyridine (a 5-ASA metabolized to sulfapyridine and mesalamine) dose-related adverse effects (NAT2 playing a role in sulfapyridine metabolism).[283,284] The prediction of the risk of life-threatening myelosuppression induced by thiopurine medications using thiopurine methyltransferase (TPMT) measurement is used for several years.[285] The measurement of TPMT activity allows us to adjust the thiopurine dose to avoid this type of side effects and could be superior to genotype to predict the risk of their occurence.[285,286] More recently, Yang *et al.* found that nudix hydrolase 15 NUDT15 polymorphisms (SNP: rs116855232) were also associated with the onset of myelosuppression induced by thiopurine in a cohort of South Korean patients.[287] A few years later, the achievement of an exome-wide association study in European patients affected and unaffected by thiopurine-induced myelosuppression allowed us to confirm that carriage of any three coding NUDT15 variants was associated with an increased risk of myelosuppression.[288] Similarly, HLA-DQA1-HLA-DRB1 (rs2647087) polymorphism has been associated with the risk of thiopurine-induced pancreatitis[289,290], HLA-DRB1*03:01 with the risk 5-ASA-induced nephrotoxicity[291] and HLA-DQA1*05 variant with the risk of development of antibodies to both infliximab and adalimumab.[292,293] Still regarding thiopurine, tobacco and GSTM1-null genotype were risk factors for thiopurines-induced adverse events such as myelosuppression, hepatotoxicity and pancreatitis.[294] Regarding methotrexate, the presence of the methylenetetrahydrofolate reductase (MTHFR) 1298C mutation could be associated with a risk of the occurrence of side effects with methotrexate in IBD patients.[295,296] Another team reported that the presence of HLA-DQ2 risk haplotypes more than doubled the risk of anti-drug antibody (ADA) formation in patients with

immune-mediated inflammatory diseases.[297] Finally, Steenholdt *et al.*[222] have also shown that the carriage of the minor allele of FASLG, rs76110 increased the risk of severe infusion reactions. The realization of a panel of SNP-based genetic tests before the administration of a treatment could possibly identify patients at risk of side effects and guide the treatment, but would nevertheless require a cost–benefit analysis.[21]

The appropriate dose and drug optimization

Once the treatment is chosen, it is usually initiated by the IBD specialist at the standard dose with the goal of achieving the therapeutic objective individually defined for each patient (including clinical response/remission, endoscopic response/remission, biomedical remission, mucosal healing, transmural healing or even histological remission).[298–300] However, patients' blood drug levels can be influenced by a variety of factors, differing from one patient to another, including genetic, gender, patient's age and BMI, inflammatory burden (extent and severity of disease), serum albumin, the presence or absence of a concomitant immunomodulator and the presence of ADAs.[301–305] The therapeutic drug monitoring (TDM) is therefore an integral part of precision medicine.[306–308]

Drug dose of immunosuppressors such as azathioprine and 6-mercaptopurine can be monitored and adjusted for different patients, stratified into distinct subgroups. Thiopurines are prodrugs which need to be activated to form 6-thioguanine nucleotide (6-TGNs) which are the major active metabolites (incorporated into the DNA in place of guanine nucleotides to exert its effect). However, all thiopurines are not converted into 6-TGN and TPMT acts as a shield against toxic effects of these drugs by converting part of these into inactive metabolites. Patients with reduced TPMT activity are exposed to a higher level of 6-TGNs and thus a higher risk of toxic adverse events. As there is an important interindividual variation in TPMT activity, TPMT genotype/phenotype is generally determined when thiopurines are initiated.[309] Approximately 0.3% of patients have two loss-of-function alleles of the *TPMT* gene and have low or undetectable TPMT activity (homozygous deficient or poor metabolizers) while approximately 10% of patients have one loss-of-function TPMT allele leading to intermediate TPMT activity (heterozygous deficient or intermediate metabolizers).[309] Individuals with homozygous deficiency required 10% or less of the standard thiopurine dose while it is generally recommended to adjust the dose on tolerability in intermediate metabolizers patients.[309] In the absence of clinical response, metabolites (6-TGN and 6-MMP) can be measured to assess whether this is due to a pharmacogenetic resistance (low level of 6-TGN and high level of 6-MMP), to a refractory disease (high level of active metabolite 6-TGN and of 6-MMP) or due to a poor adherence or insufficient dosage (low level of 6-TGN and 6-MMP).[295] In the latter case, the dose of thiopurine may be increased to obtain a level of 6-TGN $>$ 230–260 pmol/8×10^8 red blood cells, which has been shown to be associated with a significant therapeutic response.[310,311] Pharmacodynamic markers such as Rac1/pSTAT3 expression in leukocytes could have an added clinical value for prediction of therapeutic effectiveness in combination with TDM and could be integrated into clinical practice in the future.[312] Levels of methotrexate and 7-hydroxymethotrexate (its metabolite) have a short half-time (5–8 h) and are not widely used to monitor methotrexate efficacy and toxicity.[295,313,314] Red blood cell methotrexate polyglutamates' (RBC MTXGlu1–5) levels, which correlate with disease activity in rheumatoid arthritis, were not correlated with efficacy in CD, but the concentration of red blood cells MTXGlu4&5 was higher in patients experiencing adverse effects.[315] It is not currently used in clinical practice in IBD. Finally, some authors recommend a reduced methotrexate dose in case of elevated liver tests at baseline, but there are no societal recommendations for monitoring and prevent hepatotoxicity with methotrexate.[316]

The measure of biologic serum concentration and the level of ADAs, allows to adjust drug dose on an individual basis, to optimize the concentration of the drug in the patient's blood and maximize therapeutic benefits.[301,304] Indeed, numerous studies have shown that lower drug concentration was associated with higher rates of biologic failure.[105,193,299,317–319] For example, among many others, the PANTS study or Personalized anti-TNF therapy in Crohn's disease study, including bio-naïve CD patients with active luminal disease (955 infliximab-treated and 655 adalimumab-treated), demonstrated that PNR was associated with low biologics trough levels at week 14.[293] Based on the studies available in the literature, according to the biologic and the disease (UC and CD separately), Table 4 resumes, for the

different objective therapeutic outcomes already studied, the biologic concentration thresholds (at different time points) associated with its achievement.[298–300] In addition to serum anti-TNF levels, more recent studies show that mucosal and stool anti-TNF levels might also be good indicators of future treatment outcomes.[320–323] In a single-centre prospective study enrolling 25 CD patients, Yoshihara *et al.* reported that patients with low-drug levels in the noninflamed tissues had a significantly lower sustained response rate than patients with high-drug levels and that tissue anti-TNF concentration could be useful for the therapeutic monitoring of these patients.[320] Brandse *et al.* showed that high faecal concentrations of infliximab after the first day of treatment (median concentration, 5.01 µg/mL) in severe UC patients was associated with the absence of a clinical response at week 2.[321] Judit Szántó *et al.* suggested that the anti-TNF faecal loss might be associated with a decreased drug mucosal accumulation and that this faecal dosage could be a good indicator of tissue concentrations of anti-TNF agents.[322] The usefulness of these tissue and faecal anti-TNF levels to predict treatment response deserves to be further investigated and may provide additional support for precision medicine in IBD.

Two TDM strategies have been proposed in IBD: the proactive monitoring and the reactive one (which is supported by most guidelines and statements up to date).[324] Routine proactive monitoring is used in patients with quiescent disease in two situations. First, it allows the proactive optimization of the drug level, through dose titration, to achieve a target threshold concentration and prevent the occurrence of SLR or the development of ADAs due to too low drug level.[324] Second, proactive monitoring can be used in patients in clinical remission before anti-TNF de-escalation or discontinuation (see below).[347] In contrast, reactive TDM is used in patients with active disease who do not respond to treatment to

Table 4. Therapeutic outcomes and associated biologic trough level, suggested trough concentration and predictive factors of the response to drug optimization for biologics and small molecules.[298,306,324]

		Therapeutic outcomes and associated biologic trough level	Suggested trough concentration for adults (µg/mL)	Predictive factors of the response to drug optimization
Thiopurines		**Clinical response** 6-TGN > 230–260 pmol/8 × 10^8 RBC[310]	Maintenance phase: 6-TGN > 230–260 pmol/8 × 10^8 RBC[310]	–
Methotrexate		Not recommended due to the lack of valid data[295]	Not recommended due to the lack of valid data[295]	–
Infliximab	UC	**W8 – Mayo endoscopic subscore ⩽1** Week 2: ⩾18.6 µg/mL; week 6: ⩾10.6 µg/mL and week 8: ⩾34.9 µg/mL[300] **W30 – Clinical response** Week 14: >5.1 µg/mL[319] **W30 – Mayo endoscopic subscore ⩽1** Week 14: ⩾5.1 µg/mL and week 30: ⩾2.3 µg/mL[300] **W30 – Mayo endoscopic = 0** Week 14: ⩾6.7 µg/mL and week 30: ⩾3.8 µg/mL[300]	Induction phase (week 2): ⩾25[325] Induction phase (week 6): ⩾15[325] (⩾25 for mucosal healing) Post-induction phase (week 14) ⩾ 5[325] or ⩾7[307] Maintenance phase: ⩾3[307] or ⩾5[306,326] (>7 for mucosal healing)	**For dose doubling to 10 mg/kg every 8 weeks:** - Immunomodulator concomitantly to optimization[327]
	CD	**W12 – Endoscopic remission** Week 2: >23.1 µg/mL and week 6: >10.0 µg/mL[328] **W14 – Complete perianal fistula response** Week 6: >13.9 µg/mL and week 14: >4.8 µg/mL[329] **W54 – Clinical response** Week 14: ⩾3.5 µg/mL[299] **W54 – Clinical remission** Week 14: >7 µg/mL[293] **Mucosal healing** >5 µg/mL[330]		**For interval shortening to 5 mg/kg every 4 weeks:** - Changes in serum trough levels of infliximab during treatment intensification[331] **For dose doubling to 10 mg/kg every 8 weeks:** - Infliximab trough level ⩾1 µg/mL before optimization[332] - Interleukin 6 level ⩽2.41 pg/mL before optimization[332] - Albumin level ⩾3.8 g/dL before optimization[332]

(Continued)

Table 4. (Continued)

		Therapeutic outcomes and associated biologic trough level	Suggested trough concentration for adults (µg/mL)	Predictive factors of the response to drug optimization
Adalimumab	UC	**Mucosal healing** >4.9 µg/mL[330]	Induction phase (week 4): ⩾7[307] or ⩾7.5[325] Maintenance phase: ⩾5[307] or ⩾7.5[306,325,326] (>7 for mucosal healing)	**For interval shortening to weekly injection:** - Short-term clinical benefit to adalimumab initiation could predicts successful dose escalation[333]
	CD	**W54 – Clinical remission** Week 14: >12 µg/mL[293] **Mucosal healing** >4.9 µg/mL[334] >7.1 µg/mL[330]		**For interval shortening to weekly injection:** - Normal CRP at dose intensification[335]
Certolizumab pegol	CD	**W6 – Clinical response** Week 6: >31.8 µg/mL[336] **W26 – CDAI ⩽ 150 and faecal calprotectin <250 µg/g** Week 6: >36.1 µg/mL[336] **W26 – Clinical response** Week 12: >14.8 µg/mL[336]	Induction phase (week 6) ⩾ 32[307] Maintenance phase: between ⩾15 and ⩾20[306,307,326]	No data
Golimumab	UC	**W6 – Clinical response** Week 2: >8.9 µg/mL and week 6: >2.5 µg/mL[337]	Induction phase (week 6) ⩾ 2.5[307] Maintenance phase ⩾ 1[307]	No data
Vedolizumab	UC	**W6 – Clinical remission** Week 6: >37.5 µg/mL[338] **W14 – Clinical response** Week 2: >28.9 µg/mL; week 6: >20.8 µg/mL and week 14: >12.6 µg/mL[339] **W14 – Mucosal healing** Week 14: >17 µg/mL[339] **Vedolizumab persistence (1 year)** Week 6:>16.55 µg/mL[340]	Induction phase (week 2) ⩾ 28[307] Induction phase (week 6) > 20[308] (⩾18.5–35.2)[338] Maintenance phase (week 14 and beyond) > 12[308] (⩾12–13.6) • Clinical response > 12.6[339] • Mucosal healing > 17[339]	**For interval shortening to every 4 weeks:** - Low CRP at the time of intensification[341] - Response at week 12[341] - Early changes in the pharmacokinetic profile of vedolizumab-treated patients (from baseline and month 3 after dose optimization)[342]
	CD	**W6 – Clinical remission** Week 6: >33.3 µg/mL[168] **W6 – Biomedical remission** Week 2: >35.2 µg/mL[339]		**For interval shortening to every 4 weeks:** - Low CRP at the time of intensification[341] - Response at week 12[341] - Early changes in the pharmacokinetic profile of vedolizumab-treated patients (from baseline and month 3 after dose optimization)[342]
Ustekinumab	UC	No data	Induction phase (week 8): >4[308] Post-induction ⩾ 3.5[307] Maintenance phase (week 16 and beyond): >2[308]	No data
	CD	**W8 – Clinical remission** Week 8: >3.3 µg/mL[343] **W8 – Biological remission** Week 8: >7.2 µg/mL[325]		**For interval shortening to every 4 weeks:** - Older age at time of dose escalation was significantly associated with biological remission[344] - Loss of response to ustekinumab (*versus* incomplete response)[345] - Duration of ustekinumab therapy before dose intensification[345] **For interval shortening to every 4 or 6 weeks:** - Absence of perianal disease, opioid use at the time of intensification[346]
Tofacitinib				No data

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; HBI, Harvey–Bradshaw Index; UC, ulcerative colitis; w, week.

clarify the cause of the PNR or SLR.[306] PNR or SLR can be explained by various mechanisms including a pharmacodynamic failure or a pharmacokinetic failure, and this latter can be immune mediated or not.[306] In pharmacodynamic failure, IBD patients did not respond despite optimal drug trough concentrations. In this case, inflammatory mediators driving the disease are not blocked by the particular drug and these patients are unlikely to response to other drugs of the same class and a shift to another drug class should be considered.[306] In the case of immune-mediated pharmacokinetic failure, patients have low or undetectable trough concentration and the presence of ADAs. In case of low neutralizing ADAs (<8 µg/mL or <10 U/mL for infliximab), anti-TNF can be optimized, being administered at short intervals and/or increase dose and the use of a concomitant immunosuppressive medication.[307] In the case of high levels of ADAs (>8 µg/mL or >10 U/mL for infliximab), either a switch within drug class using combination therapy with an immunomodulator or a monotherapy with proactive TDM or a change of drug class should be considered.[307,348] Finally, in non-immune-mediated pharmacokinetic failure, IBD patients do not respond adequately to treatment in a context of subtherapeutic trough concentrations and absence of antidrug antibodies.[306] This situation is usually due to rapid clearance of the drug (often due to a high inflammatory burden) and these patients may benefit from a dose increase.[306]

While these drug optimizations generally recapture the control of inflammation, a certain percentage of patients does not respond to these dose escalations. Identifying the predictive factors of non-response to these dose escalations would save time for the patient, avoiding a double dose for no therapeutic benefit and would also reduce the related costs for society. Predictive factors of a response to drug optimization for each molecule and disease are shown in Table 4.

Predictors of response or lack of response to anti-TNF dose escalation appear to be poorly studied. The increase in anti-TNF levels following treatment intensification was reasonably associated with improved clinical outcomes.[331] The place of trough levels of anti-TNF at the time of intensification as a prognostic factor for success is not unanimous. For some, the response to optimization does not depend on the trough level at the time of optimization,[349] while others have found that a certain threshold could influence the response.[332] The presence of an immunomodulator concomitantly to dose doubling,[327] a short-term clinical benefit to anti-TNF at initiation,[333] a normal CRP,[335] an albumin level ⩾3.8 g/dL[332] and IL-6 level ⩽2.41 pg/mL at dose intensification[332] seemed to be predictive of the response to it. In a retrospective multi-centric study, the predictors of infliximab dose doubling failure in UC patients were the absence of the introduction of an immunomodulator concomitantly to dose doubling, a partial Ulcerative Colitis Disease Activity Index (UCDAI) >6, a CRP level >10 mg/L, a leucocyte count >8000/mm³ and a haemoglobin level <12.5 g/dL.[327]

For vedolizumab (for both UC and CD), a low CRP at the time of intensification, an early change in the pharmacokinetic profile of vedolizumab-treated patients (from baseline and month three after dose optimization) and a response at week 12 (which predict long-term response) were the predictive factors of a response to drug optimization.[341,342] In addition to these individual factors, CDST described above also allowed us to identify patients who may benefit from interval shortening.[181,350] For UC patients, they reported that only the low (CDST score, 26 points or less) and intermediate (CDST score, 27–32 points) probability groups benefitted from interval shortening of vedolizumab administration, in case of lack of response.[181] For CD, using the different variables such as no prior bowel surgery (+2 points), no prior TNF-antagonist therapy (+3 points), no prior fistulizing disease (+2 points), baseline albumin (+0.4 points per g/L), baseline CRP (−0.5 points if 3.0–10.0 mg/L; −3 points if >10 mg/L), they found that patients with >19 points did not benefit from shortening of infusion intervals.[350] For ustekinumab, older age at time of dose escalation,[344] duration of ustekinumab therapy prior dose intensification[345] and loss of response to ustekinumab (versus incomplete response)[345] were predictive of a response to dose escalation in CD patients. The presence of perianal disease, Harvey–Bradshaw Index (HBI), corticosteroid and opioid use were, however, associated with ustekinumab failure after dose intensification.[346] Factors that predict which UC patients will benefit from dose escalation with ustekinumab, tofacitinib or filgotinib have not been studied to our knowledge at this time.

However, there are still a number of barriers to the use of TDM in daily clinical practice such as the time between samplings and results, the lack of consensus on the optimal drug concentration, and the interpretation of ADAs titres among different assays.[351] Despite several negative prospective randomized trials on proactive TDM,[352,353] it is not certain that proactive TDM should be abandoned and its place deserves to be further studied. Clarification of the usefulness of TDM with biologics other than anti-TNFs is needed, and pharmacogenetic and pharmacokinetic modelling dashboards should be used for specifying the dose to be administered to each patient.[351]

Strategy in the context of precision medicine

IBD patients can have a markedly variable disease course and the stratification of these patients into low-risk and high-risk patients as well as response to previous treatment allow the IBD specialist to choose between a step-up or a top-down type therapeutic strategy, respectively (Figure 1).[23,207,354,355] In the step-up approach, medication is reactively escalated in response to disease flares, while in the top-down one, the most potent therapies (included biologics) are used from the outset.[23,207,354,355] Correct stratification of patients into low risk and high risk allows us to reduce exposure to unnecessary costly biologics in the low-risk population and to improve disease outcome in the high-risk population, respectively.[23,207,354,355]

Timing for treatment de-escalation or discontinuation and identification of patients for whom this is feasible

If precision medicine can provide guidance for dose escalation, it can also provide guidance for de-escalation. Indeed, in certain circumstances, patients can be spared (at least temporarily) from biological treatment, such as in the case of a deep remission or after a surgery that has cleared the disease. Identifying patients at very low risk of relapse in either situation could save patients from unnecessary biological therapies (at least for a period of time). Certain factors, present before thiopurines withdrawal in patients in remission, have been identified as being associated with increased risk of relapse, such as male sex and short duration of therapy with thiopurines.[356] The STORI study aimed to identify predictive factors of clinical relapse in 115 CD patients who discontinued the anti-TNFα while they were in sustain remission (clinical, biologic and endoscopic) and were followed prospectively.[347] Male sex, the absence of surgical resection, leukocyte counts $>6.0 \times 10^9$/L, and levels of haemoglobin $\leqslant 14.5$ g/L, CRP $\geqslant 5.0$ mg/L, and faecal calprotectin $\geqslant 300$ µg/g were the factors that exposed to the risk of relapse.[347] Patients with no more than two of these risk factors (approximately 29% of the study population) had a 15% risk of relapse within 1 year.[347] Pharmacokinetic parameters could also be used to make the decision to stop treatment or not. Indeed, patients with a detectable level of anti-TNF at the time of discontinuation, relapsed more frequently than those with low or undetectable levels.[357] This is due to the fact that in these patients, stable deep remission for some time was not dependent on anti-TNF treatment, which may then be stopped.[357] Consistent with these data, in STORI, infliximab trough level above 4.5 µg/mL was predictive of relapse, suggesting that, in contrast, in these patients, remission is maintained by a certain level of anti-TNF, which needs to be maintained.[347] In addition to these factors and markers that are more accessible in clinical practice, other more specific biomarkers could be identified. Using STORI cohort, a proteomic study allowed us to identify distinct biomarker candidates associated with the risk of short-term (15 proteins) and mid/long-term (17 proteins) relapse.[358] On another proteomic study (performed on the same cohort), studying 92 immune-related proteins by proximity extension assay in serum of CD patients stopping infliximab, it has been demonstrated that patients with short-term and mid/long-term clinical relapse have distinct blood protein profiles.[359] Patients with mid/long-term clinical relapse had a high serum level of proteins mainly expressed in lymphocytes, a low serum level of anti-inflammatory effectors and cellular junction proteins.[359] Patients with short-term clinical relapse had rather a high serum level of pro-inflammatory effectors and a low or high serum level of proteins mainly expressed in antigen presenting cells.[359] The SPARE study, a multicentre, open-label, randomized controlled trial performed in 64 hospitals in 7 countries in Europe and Australia also studied the factors associated with time to relapse.[360] Adult CD patients in steroid-free clinical remission for more than 6 months, on combination therapy of infliximab and immunosuppressant therapy for

at least 8 months were randomly assigned (1:1:1) to continue combination therapy (combination group), discontinue infliximab (infliximab withdrawal group) or discontinue immunosuppressant therapy (immunosuppressant withdrawal group).[360] Factors associated with time to relapse were as follows: infliximab withdrawal group (*versus* the combination group and *versus* the immunosuppressant withdrawal group), young age at diagnosis (<17 years), hsCRP at baseline (1.0 mg/l of hsCRP inducing a 0.1 increment of HR), faecal calprotectin higher than 300 µg/g at baseline, Crohn's Disease Endoscopic Index of Severity (CDEIS) at baseline (1.0 point of CDEIS inducing a 0.1 increment of hazard ratio or HR). In patients who discontinued infliximab, only a 6-TGN at baseline higher than 300 pmol per 8×10^8 red blood cells was associated with relapse.[360] In a 10-year follow-up study including UC patients with moderate to severe disease, it has been demonstrated that mucosal TNF copies/µg mRNA < 10,000 at anti-TNF discontinuation predicted long-term remission, biological free remission and lower risk of colectomy.[361] Another study showed that it was possible to identify IBD patients who appeared quiescent but were not in histological remission and who were, consequently, at risk of relapse using serum samples multiomics approach.[34,36] By using a model combining three proteins (IL-10, glial cell line-derived neurotrophic factor, and the T-cell surface CD8 alpha chain) and 4 metabolites (propionyl-l-carnitine, carnitine, sarcosine and sorbitol), the authors were able to predict the risk of relapse at 2 years.[36,362] Still using metabolomics, Hisamatsu *et al.* demonstrated, in a cohort of 369 patients with quiescent UC, that a decreased histidine plasma level predicts the risk of relapse within a 1-year period.[34] The gut microbiota composition of patients prospectively included in the STORI study (33 CD patients) was investigated to determine the impact of dysbiosis in CD relapse. Lower levels of firmicutes, *Faecalibacterium prausnitzii, C. coccoides* and bacteroides in the faecal samples predicted relapse.[363]

Some biomarkers may also help predict the risk of relapse following surgery and could help to more accurately identify those patients who require postoperative IBD treatment *versus* those who could be spared at least temporarily.[364–374] However, these are numerous and could be the subject of a separate review.

Challenges to overcome and future directions

Although many biomarkers and factors have been identified, the number of cases of such data being applicable or having been applied in clinical practice remains very small and key challenges remain.[277] First, to identify prognosis and predictive factors or biomarkers, large well-characterized longitudinal prospective cohorts are needed (to capture small but important clinical subgroups).[18] Ideally, they should include patients at inception, and age-specific cohort (adult, paediatric, very early-onset IBD) but also ethnic-minority specific cohorts should be built.[18] Some cohorts are being set up and should provide interesting data in the next few years (such as PANTS and IBD Bioresource for genomics, PROFILE trial for transcriptomics, Collaborative IBD Biomarker Research Initiative or COLLIBRI for proteomics, PRoteomic Evaluation and Discovery in an IBD Cohort of Tri-service Subjects or PREdICCt for proteomics and metabolomics, IBD response for metabolomic and microbiome as well as multi-omics projects such as RISK cohort and IBD Multiomics database).[56,375] Once a large cohort is available, it is necessary to determine which tissue is most likely to provide information in terms of medicine precision (because, in IBD, there is no equivalent of the tumour for oncology). Do they have to come from whole blood or from intestinal biopsies? Should they involve all the cells present in the selected tissue or only one cell type? These are questions to which we do not have any precise answer yet. Once the matrix from which these biomarkers are to be collected is chosen, it would then be necessary to see how to standardize and harmonize the sample collection, the measurement of the data, and to define reference thresholds for each identified factor.[18,21,376] The next step is to find the ideal prognostic and predictive biomarker, which must meet several characteristics to be implemented in clinical practice.[21] They should ideally be available at diagnosis to allow greater flexibility in preventive and therapeutic intervention, should be obtained in a minimally invasive way, rapid and reproducible, simple to interpret, accurate for what they aim to predict.[17,21,377] Then, improvement in patient outcome and cost-effectiveness should be evaluated.[18] Some technological improvements are also needed to advance in precision medicine. New advanced technologies such as single-cell multimodal omics in epithelial or immunes cells are also being developed.[378]

Indeed, there is a growing need for a 'multi-omic' approach, with the collection of diverse data type from different sources and to integrate them, rather than continuing to search on single factors at a single moment.[277] Therefore, tools are needed to integrate and interpret these data, such as machine learning-based algorithms or systems biology-based tools and it remains to be seen how these complex data can be translated into clinical practice.[277,379]

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Sophie Vieujean: Writing – original draft; Writing – review & editing.

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The data underlying this article are available in the article.

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