REVIEW

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Biomarkers in Inflammatory Bowel Diseases: Predicting the Indication and the Effect of Biologics

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ABSTRACT

Crohn's disease and ulcerative colitis, the two most common inflammatory bowel diseases (IBD), are characterized by chronic relapsing inflammation. Although recent progress regarding the therapeutic approach to these diseases has been made in the development of biologic therapies, not every patient responds well, resulting in a high percentage of ineffectiveness. Even though the immunological cascades range between the current pharmacological agents for IBD treatment and the constant research for more possible pharmacological targets, a lot of progress still needs to be made regarding the correct therapeutical choice for each individual patient. Therefore, it is still important to find proper, inexpensive, and measurable biomarkers, in order to be able to assess the efficacy of these therapies, to make personalized choices, as well as to avoid potential adverse drug reactions and side effects. The biomarkers that are available in the present vary; metabolic, microbial, cytokine-related, genetic, disease-specific and drug-specific. This review presents the existing biological agents for IBD and focuses both on the cascades affected by each biologic agent and on the different markers that have been found to be indicative of their effectiveness.

Key words: inflammatory bowel diseases – IBD – biologics – biomarkers – anti-TNF – anti-integrin – anti-IL12/23.

Abbreviations: CCL: chemokine (C-C motif) ligand; CCR: chemokine receptor; CD: Crohn's disease; CRP: C reactive protein; CXCL: chemokine (C-X-C motif) ligand; IBD: inflammatory bowel diseases; Ig: Immunoglobulin; IL: interleukin; JAK: Janus kinase; MAdCAM-1: mucosal addressin cell adhesion molecule-1; MMP: matrix metalloproteinase; OSM: oncostatin M; SNP: single nucleotide polymorphism; Th1: type 1 T helper; TLR: Toll like receptor; TNF: tumor necrosis factor; Tregs: regulatory T cells; UC: ulcerative colitis; VCAM-1: vascular cell adhesion protein 1.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), two idiopathic chronic diseases characterized by mucosal intestinal inflammation, are the most common inflammatory bowel diseases (IBD), affecting both children and adults [1]. Although there is a hereditary predisposition, epigenetics, environmental factors, nutritional and lifestyle habits, as well as the interactions between the microbiome and a genetically susceptible person widely contribute to the development and course of these diseases [2].

The aim of IBD therapies is a sustained repression of the inflammatory activity in the intestinal tract. Biologics focus directly on altering the key pathways of inflammation, targeting cytokines, their receptors, and some pivotal adhesion molecules [3], and have increased the quality of patients' lives and reduced the risk of disease-related complications, including bowel damage, risk of colonic dysplasia, surgery and hospitalization [4]. Nonetheless, a significant number of patients do not respond or relapse during the treatment of IBD. In addition, the expenses for the initial year of disease exceed 4 million Euros, with biological therapy accounted for 25% in Western European CD patients [5]. Therefore, there is an extensive need to expand therapeutic options and to find biomarkers for personalized therapies, on the basis of the exact underlying immunopathophysiological mechanisms causing the disease [6].

The importance of good clinical biomarkers, which could be indicators of a biological process offering measurable, quantitative, quality, low-cost, and quick results, is becoming

more and more obvious [7]. In this review, we aimed to describe the current therapies for IBD, focusing on biologics, and to discuss the importance of the existing biomarkers, as well as new possible indicators of the disease activity and the treatments' courses. Furthermore, we also describe the exact mechanisms and the immunological pathways that could be targeted in order to maximize the efficacy of IBD therapeutical approaches.

CURRENT THERAPEUTIC APPROACHES INVOVING BIOLOGICS

Treatment for both CD and UC includes aminosalicylates, corticosteroids, immunomodulators, Janus kinase (JAK) inhibitors, and biologics, meaning monoclonal antibodies targeting tumor necrosis factor-α (anti-TNF-α), interleukin-12/23 (anti-IL-12/23), or integrins (anti-integrin) [8].

The use of biologics has highly impacted the therapeutic options as well as the quality of life of IBD patients, and although they were recently developed, they have become more and more popular. Expanding the current knowledge by decoding the wide variety and exact mechanisms of action and downward interactions that are involved, could provide a better insight in IBD among other inflammatory conditions.

Anti-TNF Agents

Tumor necrosis factor-α is a proinflammatory cytokine, having both a transmembrane (tmTNF-α) and a soluble form (sTNF-α), and it is implicated in a variety of cell pathways, such as homeostasis, inflammation, differentiation, proliferation, apoptosis and necrosis [9, 10]. Anti-TNF drugs were the first biologics used to treat the disease, as they can regulate the elevated protein and mRNA expression levels of TNF-α-related proinflammatory cascades in IBD patients [11].

Currently there are several different anti-TNF agents, including infliximab, a chimeric immunoglobulin (Ig) G1 antibody with a murine sequence [12], Adalimumab, a fully humanized antibody being produced using Chinese Hamster Ovary (CHO) cell [13], certolizumab pegol, a PEGylated humanized Fab0 fragment of an anti-TNFα antibody [14], and golimumab, a fully human monoclonal IgG1 antibody that binds to both the soluble and transmembranic precursor forms of TNF-a cytokine [15].

Despite achieving long term remission in up to 70% of responding IBD patients [16], anti-TNF agents seem effective in just about 65% of the total patients prescribed [17]. They can also be associated with risks [18, 19]. Therefore, it is needed to quantitatively identify their effectiveness, and adjust the dosage or altogether switch to a different medication class, whenever necessary and as soon as possible. Up until now, several different biomarkers have been identified to possibly predict failure or success of anti-TNF therapies (Table I) and will be further analyzed in the following paragraphs [12, 20-43].

Anti-integrin Therapy

Integrins are a family of adhesion receptors, contributing to various major cellular pathway cascades due to their ability to interact with both extracellular and cytoplasmic ligands and transmit signals [44]. In particular, the interactions between α4β7-integrins on the surface of T leukocytes and their ligands, mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on the gut endothelium play a major role in the pathogenesis of IBD, providing an alternative pharmacological target [45]. Natalizumab and Vedolizumab, the approved anti-integrin therapeutic regiments for IBD, target those aforementioned mechanisms and reduce the migration of T leukocytes to the inflamed regions of the gut [46, 47]. Promising results are emerging from clinical trials involving new anti-integrin therapies, for instance the anti-MAdCAM-1 antibody ontamalimab, which is safe, well tolerated, and proven efficient up to 16 weeks [48], and the α4-antagonist AJM300, which is also safe and well tolerated, and needs further investigation in order to confirm its efficacy [49].

Natalizumab (Tysabri®) is an intravenously administrated biologic agent, specifically an a4 integrin blocker that inhibits inflammation by blocking leucocyte migration to the gut via integrin α4β7 and integrin α4β1 interactions with the endothelial receptors vascular cell adhesion molecule 1 (VCAM-1) and MAdCAM-1 respectively [50, 51].

Vedolizumab is a monoclonal IgG1 antibody, a humanized version of the act-1 murine antibody, that binds to α4β7 integrin, interrupts its interactions with MAdCAM-1, and thus reduces inflammation by preventing lymphocyte translocation into the gut [4, 52].

In this context, biomarkers that could predict the failure or success of any possible anti-integrin therapy are required. Although there is not much information, as opposed to anti-TNF biomarkers, there are still several biomarkers (Table II) that will be further discussed during the following paragraphs [38, 53-75].

Anti-IL-12/23 Therapy

IL-12 and IL-23 are dimer proteins that have a common subunit, p40, and p35 or p19 respectively [76]. Crohn's disease was mainly attributed to type 1 T helper (Th1)-mediated cascades, and UC to Th2 [77], but since the importance of Th17 interactions for IBD progression was recognized [78], these new therapies specifically targeting the IL-12/23 cascade were developed.

The only antibody against IL-12/23 used for IBD treatment so far is ustekinumab, which was approved by FDA in 2016 for moderate to severe CD [79] and moderate to severe UC [80]. It is shown to be highly effective and safe, even as a second or third-line treatment after the failure of other biologics [81]. Regarding its mechanism of action, this agent can recognize and block the p40 subunit present in both IL-12 and IL-23 [82], so the cytokines cannot bind to their receptor IL-12Rβ1 and cannot cause a Th1 and/or Th17 subsequent immune response [83]. New IBD drugs under clinical studies include the IL-23 inhibitor brazikumab (formerly MEDI2070) that suppresses the transcription of IL-12 and IL-23 and can reduce inflammatory markers and lead to remission up until week 24 in CD patients [84], and mirikizumab, guselkumab and risankizumab, which target the IL-23 subunit p19, which prove to be safe, well tolerated and more effective than placebo [85-88].

Although there is just one biological agent against IL-12/23 that has been approved for IBD so far, possible biomarkers predicting its effect have been emerging increasingly (Table III) and will be discussed throughout the following paragraphs [89-100].

Table I. Various types of biomarkers which could indicate anti-TNF failure or success

Type of Biomarker	Biomarker	Details	Reference
Clinical	Disease location	Colonic involvement in CD is associated with higher response and wound healing rates	[20-22]
	Disease sub-phenotypes	Inflammatory CD (B1) patients respond better to Infliximab	[12]
	Fistulae location	Patients with perianal fistulae respond better	[23]
Metabolic	Vitamin D	Low levels or complete deficiency correlate with treatment failure	[24-26]
	Albumin	Low levels might indicate therapy ineffectiveness	[27]
	CRP levels	Elevated levels in CD might indicate ineffectiveness	[28, 29]
	Fecal calprotectin	High levels are associated with non-response	[30]
Immunogenicity	Anti-drug antibody production	High levels might indicate loss of response	[31, 32]
	Matrix metalloproteinase 3	High levels might suggest early nonresponse	[33]
Microbiota	Microbiota's composition	It provides crucial information regarding the treatment course and efficacy	[34, 35]
Pro-Inflammatory Cytokines	Oncostatin M and its receptor, OSMR	High mucosal expression is associated with lack of response	[36]
	CCL2	Low levels are correlated with primary non-response in CD	[29]
	IL-6	High levels are associated with primary non-response	[37, 38]
	IL-8 and TNF-α	High levels are associated with better response	[38]
	IL-7 and its receptor, IL-7R	High levels are associated with lack of response	[39]
	IL13RA2 mRNA levels	High levels are associated with lack of response	[40]
Genetic	*TLR8, HCK* and *FCGR2A* genes	Differentially expressed in anti-TNF non-responders	[41]
	AHR, DAXX, DENND1B, DTNBP1, RHCG, SYNGAP1 genes	SNPs in these genes are correlated with anti-TNF non-response	[42]
	O*PG, STC1, PTGS2, IL13RA2, IL-11* genes	These genes were differentially expressed in UC patients who responded	[43]

AHR: aryl hydrocarbon receptor; CCL2: chemokine (C-C motif) ligand 2; CD: Crohn's disease; CRP: C reactive protein; DAXX: death domain associated protein; DENND1B: DENN domain containing 1B; DTNBP1: dystrobrevin binding protein 1; FCGR2A: Fc Gamma Receptor IIa; HCK: hemopoetic cell kinase; IL-: interleukin-; IL12RA2: interleukin 13 receptor subunit alpha 2; OPG: osteoprotegerin; PTGS2: prostaglandin-endoperoxide Synthase 2; RHCG: Rh family C glycoprotein; SNP: single nucleotide polymorphism; STC1: stanniocalcin 1; SYNGAP1: synaptic Ras GTPase activating protein 1; TLR8: toll-like receptor 8; TNF-α: tumor necrosis factor alpha.

EXISTING BIOMARKERS IN IBD

Biomarkers Regarding IBD Diagnosis, Susceptibility and Prognosis

Biomarkers contribute not only to a more precise diagnosis [101], but they can also provide indications to the progression of the disease and/or the effectiveness of the treatment and/or some possible side-effects [7]. Widely used serum markers could also be used as biomarkers for IBD, providing crucial information regarding the disease course. For instance, physicians could be using the levels of serum amyloid A, IL-6, IL-8 and Eotaxin-1 among other inflammatory cytokines [102, 103], the ratio of neutrophils to lymphocytes [104] and the ratio of albumin to globulin [105] as an indication of the disease severity.

The interactions between the gut and the microbiota are involved in the pathophysiology of a wide variety of diseases, including IBD [106]. Although there is not a normal gut microbiome, the gut's health depends on the symbiosis of the co-existing microbiota and the human host, and alterations of the diversity and/or abundance of those populations can be highly indicative of IBD severity and treatment response or lack thereof [107-109], while infections with known pathogens such as *Salmonella enterica* [110] and *Clostridium difficile* [111] can severely worsen the disease course.

Researchers are now focusing more and more on serum microRNAs, which are found to be indicative of both distinguishing between CD and UC and could shed some insight into disease severity [112-114]. Due to GWAS studies over 240 IBD related genetic loci [6] regarding CD or UC diagnosis, susceptibility, prognosis and therapy response have been identified, including but not limited to programmed death-ligand 1 (*PD-L1*) [115], mannose-binding lectin (*MBL2*) [116], autophagy related 16 like 1 (*ATG16L1*) [117], *CD74* [118], nucleotide-binding oligomerization domain-containing protein 2 *NOD2/CARD15* [119], *IGRM* [120], *IL23R* [121].

Biomarkers Regarding Biologic Therapies

Since there are several different options in biologics, clinicians often come to the dilemma of what type of biologic to administrate and to whom. As already mentioned, each biologic has a different effect, suppresses a different molecular pathway, and furthermore, each patient is unique and different. Therefore, there is a crucial need for biomarkers that would predict the response and efficacy to treatment, as well as, the progress of the disease (Table IV), and these could include clinical, metabolic, immunogenicity, microbiota, pro-inflammatory and genetic factors (Figs. 1 and 2).

Table II. Various types of biomarkers which could indicate anti-integrin failure or success

Type of Biomarker	Biomarker	Details	Reference
Clinical	Previous treatment with anti-TNF	Poorer response to anti-integrin therapy	[53-57]
	Disease location	UC patients with less extensive inflammation and distal/left localization of the colitis, as well as CD patients with isolated colitis non involving the small intestine, show better outcomes to Vedolizumab treatment	[57, 58]
Metabolic	Serum calprotectin	High levels are associated with non-response	[59]
	CRP levels	Normal CRP levels and high Vedolizumab levels are associated with better response	[60-66]
Microbiota	*Roseburia inulinivorans and Burkholderiales* species	More abundant in patients who achieved remission	[67]
Pro-inflammatory cytokines	α4β7+ Tregs and Th1 Cells	Increase of these cells is associated with lack of endoscopic response to Vedolizumab	[68]
	CXCL1, IL-22 and IL-23	High serum levels are associated with primary non-response to Vedolizumab	[38, 68]
	CCL19, IL-6, IL17A and TNF-α	Low serum levels are associated with primary non-response to Vedolizumab	[38, 68]
	OSM	Higher expression in the colon mucosa of CD patients correlates with lack of Vedolizumab response	[69, 70]
	α4β7, MAdCAM-1, VCAM-1 and ICAM-1	Decreased serum levels of α4β7, MAdCAM-1, VCAM-1 and ICAM-1 are associated with remission in UC, while CD patients' remission is associated with higher serum levels of VCAM-1 and ICAM-1. Undetectable MAdCAM-1 is associated with remission in both CD and UC	[71-74]
Genetic	α4β7 expression	Higher expression on T lymphocytes has been associated with better response to Vedolizumab	[61]
	21 differentially expressed genes	Responders had a unique differentially expressed gene signature	[75]

CCL19: chemokine (C-C motif) ligand 19; CD: Crohn's disease; CRP: C reactive protein; CXCL1: chemokine (C-X-C motif) ligand 1; ICAM-1: intercellular adhesion molecule 1; IL-: interleukin-; MAdCAM-1: mucosal addressin cell adhesion molecule-1; OSM: oncostatin M; Th1: Type 1 T helper; TNF-: tumor necrosis factor-; Tregs: regulatory T cells; UC: ulcerative colitis; VCAM-1: vascular cell adhesion protein 1.

Clinical Factors that Influence Biologic Therapy's Success

Like every other treatment, anti-TNF therapy's success is highly influenced by earlier diagnosis, the disease's severity, and the patients themselves, with the early use of any biological therapy to be connected to a better clinical outcome [124-126]. Despite sharing similar qualities, some drugs in the same category can cause different therapeutic results and have different effectiveness, which depends on each individual patient. Even though only a percentage of patients respond to anti-TNF agents, discontinuation of the treatment can reversibly lead to relapse of the disease in CD, while it is most common in UC patients [127].

The patient's weight might be a contributing factor to their response to adalimumab and infliximab, as it changes the therapeutic dosage needed [122, 123], while the data correlating the patient's age and their response to anti-TNF agents are conflicting in between studies [27]. More specifically, pediatric UC seems to be more diverse, both in its severity and response to therapy, and needs further cohort studies [128] and switching from infliximab to adalimumab [129] or preferably vedolizumab [130, 131] has been proven more effective. On the other hand, pediatric CD appears more aggressive, urging the need for earlier escalation to biologic therapy with frequent therapeutic drug monitoring to ensure response, which is

Table III. Various types of biomarkers which could indicate anti-IL-12/-23 failure or success

Type of Biomarker	Biomarker	Details	Reference
Clinical	Patient's age	Better responses to younger patients	[89]
	Disease Location	Less effective in CD patients with ileal disease	[20]
	Smoking	Lowers efficacy for both UC and CD patients	[80, 89]
	Weight	Lower weight is associated with better outcome	[80]
Metabolic	CRP and fecal calprotectin levels	Low levels at the first few weeks of administration may predict efficacy	[90-92]
Immunogenicity	Previous treatment with anti-TNF	Better response when switching to Ustekinumab, but poorer if multiple different anti-TNF agents have been tried	[92-96]
Microbiota	*Escherichia, Shigella and Faecalibacterium*	Higher populations are associated with remission maintenance	[97, 98]
Pro-Inflammatory Cytokines	IL-6 and IL-22	High serum levels are associated with response to ustekinumab	[38, 99, 100]

CD: Crohn's disease; CRP: C reactive protein; IL-: interleukin-; TNF-: tumor necrosis factor-; UC: ulcerative colitis.

Table IV. Various biomarkers which could indicate the failure or success of the different biologic agents

Effect	Biomarker	Biologic	Reference
Course and efficacy of treatment	Microbiota's composition	Anti-TNF, anti-integrin, anti-IL12/23	[34]
	Patient weight, differentially expressed *OPG, STC1, PTGS2, IL13RA2* and *IL-11* genes	Anti-TNF	[43, 122, 123]
Higher response rates	Inflammatory CD (B1), colonic involvement in CD, perianal fistulae, ↑IL-8 and TNF-α levels	Anti-TNF	[12, 23, 38]
	UC patients with less extensive inflammation and distal/left localization of the colitis, CD patients with isolated colitis non involving the small intestine, normal CRP levels with ↑Vedolizumab levels, ↑serum levels of VCAM-1 and ICAM-1 in CD patients, ↓serum levels of α4β7, MAdCAM-1, VCAM-1 and ICAM-1 in UC patients,↑α4β7 expression on T lymphocytes, *Roseburia inulinivorans* and *Burkholderiales* species,21 differentially expressed genes	Anti-integrin	[57, 58, 60-67, 71-75]
	↓Patient's Age and weight, ↓CRP and fecal calprotectin levels, previous anti-TNF treatment (not multiple agents), ↑*Escherichia*, *Shigella* and *Faecalibacterium* populations, ↑serum IL-6 and IL-22 levels	Anti-IL12/23	[38, 80, 81, 89-100]
Lack/Loss of response	Stricturing CD (B2), ↑levels of anti-drug antibody production, ↑fecal calprotectin or CRP levels, ↓levels or complete deficiency of vitamin D or albumin, ↑mucosal expression of oncostatin M and its Receptor, ↑IL-7 and its receptor levels, ↑IL13RA2 mRNA levels, ↑MMP3 and IL-6 levels, ↓CCL2 levels, SNPs in *AHR, DAXX, DENND1B, DTNBP1, RHCG* and *SYNGAP1*, differentially expressed *TLR8, HCK* and *FCGR2A* genes	Anti-TNF	[24-33, 36, 39-42]
	Previous Treatment with anti-TNF, ↑serum and/or fecal Calprotectin levels, ↑CXCL1, IL-22 and IL-23 levels, ↓OSM in the colon mucosa of CD patients, ↓serum CCL19, IL-6, IL17A and TNF-α levels, ↑α4β7+ Tregs and Th1 Cells	Anti-integrin	[30, 38, 53-57, 59, 68-70]
	Patients with ileal CD disease, smoking, ↑fecal calprotectin levels	Anti-IL12/23	[20, 30, 80, 89]

AHR: aryl hydrocarbon receptor; CCL19: chemokine (C-C motif) ligand 19; CD: Crohn's disease; CRP: C reactive protein; CXCL1: chemokine (C-X-C motif) ligand 1; DAXX: death domain associated protein; DENND1B: DENN domain containing 1B; DTNBP1: dystrobrevin binding protein 1; FCGR2A: Fc gamma receptor IIa; HCK: hemopoetic cell kinase; ICAM-1: intercellular adhesion molecule 1; IL-: interleukin-; IL-: interleukin-; IL12RA2: interleukin 13 receptor subunit alpha 2; MAdCAM-1: mucosal addressin cell adhesion molecule-1; MMP3: matrix metalloproteinase 3; OPG: osteoprotegerin; PTGS2: Prostaglandin-endoperoxide synhase 2; RHCG: Rh family C glycoprotein; SNP: single nucleotide polymorphism; STC1: stanniocalcin 1; SYNGAP1: synaptic Ras GTPase activating protein 1; Th1: T helper 1; TLR8: toll-like receptor 8; TNF-: tumor necrosis factor-; Tregs: regulatory T cells; UC: ulcerative colitis; VCAM-1: vascular cell adhesion protein 1.

ultimately quite efficient [132-134]. Primary non-response to anti-TNF therapy is also common within CD patients who were older when diagnosed, started anti-TNF treatment in a later stage of the disease and are smokers [135].

Unlike anti-TNF treatment, vedolizumab response is better among elder people [136], while ustekinumab has shown better responses when prescribed to younger patients [89]. Smoking has been demonstrated to lower ustekinumab efficacy in UC and CD patients [80, 89], while both CD and UC patients with lower weight have a better outcome [80]. In addition, white females are more prone to respond to ustekinumab treatment [137-139], even though male patients, especially anti-TNF naive ones, maintain remission for longer [140].

Crohn's disease location could also predict anti-TNF efficacy, since colonic involvement is associated with higher response and wound healing rates than ileal disease [20-22]. Ulcerative colitis patients with less extensive inflammation and distal/left localization of the colitis, as well as CD patients with isolated colitis, non-involving the small intestine, show better outcomes to vedolizumab treatment [57, 58]. Ustekinumab also seems less effective for CD patients with ileal disease, although it was helpful to patients with both ileal and colonic involvement [20, 137, 141].

Regarding CD sub-phenotypes, patients with inflammatory phenotype (B1) respond better to infliximab [12], while patients with stricturing disease (B2) correlate with long term lack of response [142]. In patients with penetrating CD (B3), the response to anti-TNF depends on the type of fistulae; in patients with perianal fistulae both adalimumab and infliximab seem effective [23], with therapeutic drug monitoring levels being indicative of the response [143-146], while in patients with non-perianal fistulae, surgery seems to be unavoidable [147].

There has always been speculation about the efficiency of forfeiting one biologic for another. Although vedolizumab is an efficient first line agent for the induction and maintenance treatment of both CD and UC [148, 149], especially after lack of response to immunosuppressants [150, 151], it is worth mentioning that various studies confirm that patients who were previously treated with an anti-TNF agent seem to respond poorer to vedolizumab than anti-TNF naïve patients [53, 55, 56]. This response could be attributed to the presence of circulating exosomes produced by previous exposure to anti-TNF therapy that led to the blockage of vedolizumab from binding to its targets [152]. Switching to ustekinumab due to previous nonresponse to anti-TNF therapy is beneficial [81,

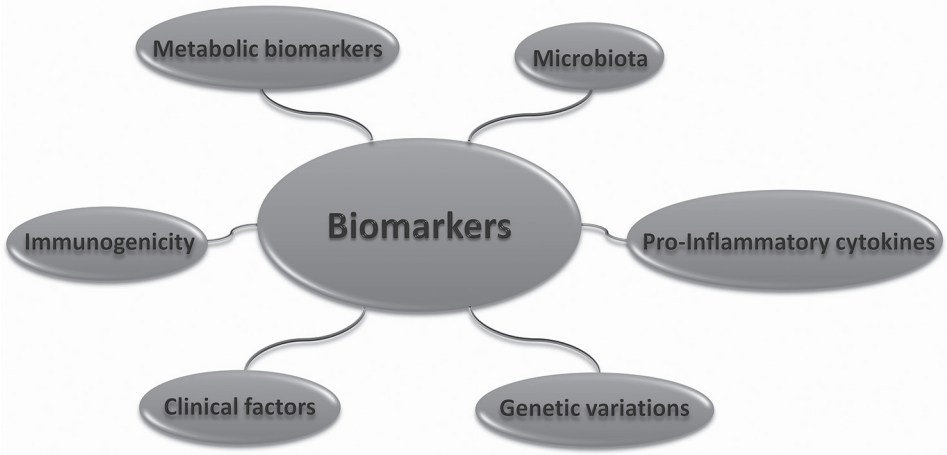

Fig. 1. Different factors that could be possible biomarkers regarding the biologic agents for inflammatory bowel diseases' treatment.

92-94], and sometimes proven more effective than switching to vedolizumab [153, 154]. However, after multiple anti-TNF agents and when used later in the disease's course, ustekinumab results in loss of response long term too [95, 96]. It should be noted that the frequency of infections and adverse effects caused by ustekinumab are also low [155].

Metabolic Biomarkers

Common metabolic pathways seem to be affected by the same mechanisms causing IBD, thus, some known markers should be considered as possible therapeutic indicators. It is shown that measuring serum and fecal bile acids and lipids, histidine, and urinary cysteine could predict the response to anti-TNF therapy [34]. Low levels or complete deficiency of vitamin D seem to also correlate with failure to anti-TNF treatment [24-26], probably due to lower IL-6, IL-8 and IL-12 levels [156].

While it needs to be further investigated, low serum albumin levels could also foreshadow the ineffectiveness of anti-TNF therapy [27], whereas C reactive protein (CRP) levels' suitability as an anti-TNF therapy biomarker is more complicated. More specifically, on the one hand CRP levels were found elevated in CD patients [27] and remained elevated even after infliximab treatment in non-responders [28, 29], providing promising evidence of lack of anti-TNF response. On the other hand, other research teams found that CRP serum levels were reduced in UC patients, which could be attributed to either response to anti-TNF therapy, or just to the presence of inflammation [27, 157, 158].

Measuring both the drug and anti-drug antibody levels, in combination with serum CRP levels [159] or serum and fecal S100 calprotectin and S100A12 [30, 160, 161], which are known and widely used inflammatory markers, seems to provide a more accurate estimate of the patients' anti-TNF response. In fact, fecal calprotectin level monitoring is low-cost, easy, reproducible, and reliable [162], and appears to be more predictive of treatment efficacy, remission and/or disease relapse than CRP and disease markers in both CD and UC patients, regardless of the treatment used [163, 164].

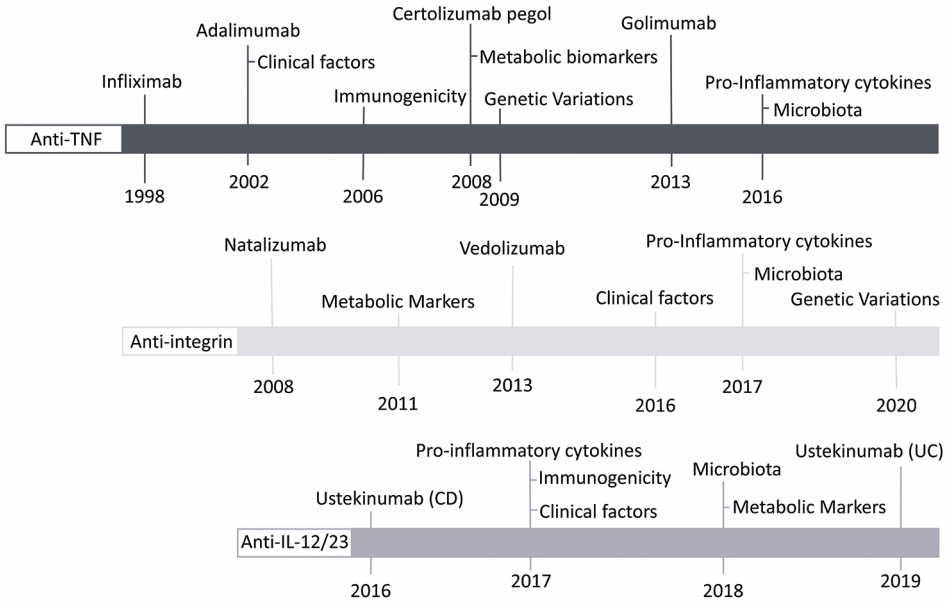

Fig. 2. The significant milestones of biologic agents' approvals and biomarker discovery.

Serum calprotectin levels are also indicative of vedolizumab response, future loss of it, as well as complete lack thereof [59]. Low CRP and fecal calprotectin levels were noticed as soon as the first few weeks of ustekinumab administration [90-92], proving the patients' response by reduced inflammatory markers.

Higher serum levels of vedolizumab during induction and maintenance treatment, combined with normal CRP levels, have also been associated with better response [60, 61, 63-66]. Therapeutic drug monitoring is also necessary to improve both vedolizumab and ustekinumab efficacy, since its serum levels are highly dependent on the dosage used, and higher maintenance concentrations correlate with better patients' response [91, 165, 166].

Apart from the aforementioned markers found in blood or in feces, biogenic amines in urine could also serve as possible biomarkers and should be further researched. It was recently observed that patients with CD, who were previously administrated with azathioprine, had significantly decreased levels of serotonin and norepinephrine, and increased levels of histamine and spermidine [167].

Immunogenicity as a Possible Biomarker

In order to develop useful and accurate treatment strategies, it is required to quantify the immunogenicity and efficacy as well as the loss of response and possible side effects of these drugs. Firstly, the presence of different auto-antibodies has been proposed to help diagnose between CD and UC [27, 168], and the levels of such anti-nuclear antibodies should also be measured before starting anti-TNF treatment, since elevated levels might benefit anti-TNF antibody production and ultimately lead to lack of response to therapy [26, 27]. It is worth mentioning that higher serum drug levels may correlate with endoscopic healing; however, they do not always correspond adequately [169].

Loss of response to anti-TNF therapy can also be attributed to high anti-drug antibody production, and thus increased drug clearance [31, 32]. Serum and fecal drug level and/or anti-drug antibodies' measurements, as identified for loss of responsiveness to infliximab [159, 170], are suggested as possible markers of the anti-TNF therapy efficacy. Higher levels of matrix metalloproteinase 3 (MMP3) also correspond to early nonresponse to infliximab, since this protein cleaves the drug, and thus increasing its clearance [33]. It is worth mentioning that despite being just recently FDA approved, ustekinumab has shown a lack of neutralizing antibodies [91, 92] making it a safe and effective IBD therapeutic factor with fewer adverse effects.

Microbiota and its Role as a Biomarker

The abundance of the microbial species cohabiting the human gastrointestinal tract have been highly implicated with its "normal" function, as well as a wide range of diseases. Not only does the composition of the microorganisms differ between the intestinal tract of healthy individuals and the distinct subphenotypes UC and CD patients [171], but it can also provide crucial information regarding the course and efficacy of the biological treatment [34, 35]. Recently, the correlation between the abundance and diversity of the gut microflora and the progress of IBD has become more apparent [172, 173] and checking the microbiota abundance can be an easy early predictor of response [174, 175]. For example, patients who responded to anti-TNF therapy had a plethora of microbes belonging to the genera *Faecalibacterium, Roseburia*, or *Clostridium* [176, 177].

One study demonstrated that a genetic defect in utilizing tryptophan is crucial to UC development, due to its effects in intestinal microbiota [178]. Not only did anti-TNF therapy enrich the different ratios between the microbial populations, which were limited before treatment and resemble more the non IBD individuals' composition after, but also the production of butyrate and its substrates was induced within remitters [179]. Although the individual taxa did not seem to directly affect anti-TNF therapy response [179], their metabolites influenced it [180, 181].

Regarding ustekinumab, responders who also maintained remission appeared to have higher populations of the species *Escherichia*, *Shigella* and *Faecalibacterium* [97, 98, 165]. Ananthakrishnan et al. [67] showed that patients with CD, who were administrated vedolizumab and achieved remission at 14 weeks of treatment, had two bacteria species, *Roseburia inulinivorans* and *Burkholderiales*, that were significantly more abundant than in patients who did not achieve remission.

Pro-inflammatory Cytokines and Chemokines as Biomarkers

The presence of active inflammation in IBD is a concerning factor that usually worsens the patients' quality of life. The variety of the circulating immunological cells and the transcellular signals they receive and secrete, can importantly affect the course of IBD, creating an ideal environment for both the structural cells of the gut and the microbiota. The importance of the ratio of the different populations of T cells during IBD is often highlighted. It was already distinctive between the UC and CD patients [77] and it could further provide information about the course of IBD and the effectiveness of treatment, since the lack of endoscopic response to vedolizumab is accompanied by a greater increase in circulating α4β7+ regulatory T cells (Tregs) and Th1 cells [68]. Vedolizumab responders show higher α4β7 expression on their T lymphocytes prior to treatment [61], possibly suggesting a predisposition to better respond to the cascade involving this agent.

Mucosal expression of oncostatin M (OSM) and its receptor OSMR was found to be increased in patients prior to treatment, and it was correlated with acute inflammation and lack of response to anti-TNF therapy in IBD patients treated both with infliximab and golimumab [36, 69, 70]. Increased expression of the triggering receptor expressed on myeloid cells 1 (TREM-1) in gut mucosa and by inflamed macrophages and of chemokine receptor type 2 (CCR2) chemokine ligand 7 (CCL7) by inflamed macrophages were other factors associated with anti-TNF lack of response alongside OSM [40, 182]. In addition, higher expression of OSM in the colon mucosa of CD patients correlates with the lack of vedolizumab response [69, 70].

The stimulation of the Toll like receptors (TLRs) as well as their differentiated expression can affect the innate immune responses of IBD patients [183], suggesting that their downward cascades are involved both in the disease

progression, as well as the therapeutic effectiveness. Indeed, it was recently shown on peripheral blood mononuclear cells (PBMCs) of UC responders that TLR-mediated cytokines TNF, IL-1β, IL-6 and IL-10, included in the innate immunity responses cascades, are higher compared to non-responders, despite anti-TNF therapy [184].

Higher serum IL-6 levels, as well as genes involved in its downward pathway, could predict primary non response to infliximab [37, 38], while responders also present higher IL-8 and TNF-α levels [38]. Serum IL-6 and IL-22 levels could provide new insights in ustekinumab efficacy as well, since they were higher among responders [38, 99, 100]. The serum levels of IFN-γ are also conversely corresponding to ustekinumab efficacy [185].

IL-7 and its receptor's (IL-7R) early expression could not only offer a biomarker, since it is highly associated with lack of response to anti-TNF therapy [39], but also suggest a novel therapeutic pathway to target. Serum IL-9, an indicator of severe CD, is downregulated by infliximab, and therefore its levels could be used to predict its efficacy [186]. The IL-23 receptor IL13RA2 mRNA levels, a downstream modulator of TNF pathway, as well as TNF mRNA levels itself, are also overexpressed in UC and CD patients in whom anti-TNF treatment fails to induce mucosal healing [40, 187].

In another study by Li et al. [29], UC patients who responded to anti-TNF treatment showed lower expression of IL-1β, IL-6, IL-17A and IFN-γ, higher MMP3, as already mentioned, and lower CCL2 serum levels, which were also correlated with primary non response to infliximab in CD patients. In contrast, Magnusson et al. [188] showed that UC patients who responded to infliximab had lower CCL2, as well as CD14, CD16 and tenascin C monocyte expression. Furthermore, increased expression of IL-22, IL-23 and decreased of chemokine (C-X-C motif) ligand (CXCL) 8 (IL-8), CCL13, CCL19, CCL20, CCL28, IL-6, IL17A and TNF-α serum levels have been associated with response to vedolizumab therapy in CD patients and so have decreased granulocyte-colony stimulating factor (G-CSF) and IL-7 levels in UC patients, with inconclusive results regarding CXCL1 levels between the research teams [38, 68, 166, 189].

High pre-treatment mucosal expression of α4β7 as well as its receptor could benefit vedolizumab treatment's efficacy [61, 190]. Ulcerative colitis patients' remission after Vedolizumab treatment correlated with increased α4β7 and decreased MAdCAM-1, VCAM-1, intercellular adhesion molecule 1 (ICAM-1) and TNF serum levels [71, 72], while in CD patients, remission was accompanied by higher serum levels of VCAM-1 and ICAM-1 [73]. Lack of detectable MAdCAM-1 serum levels was observed during remission in both CD and UC patients [74].

Genetic Variations as Biomarkers

Using DNA polymorphisms as biomarkers could be highly beneficial, since DNA is stable and easily obtainable from blood, sputum, urine, endoscopic biopsies and/or stool samples, before, during and after treatment [191]. The use of artificial intelligence is becoming more and more necessary, as large databases are being developed that can provide quick and inexpensive insight regarding both patients' diagnosis and course of treatment [192]. The genetic polymorphism *HLADQA1*05* is making IBD patients prone to develop anti-TNF-drug antibodies and subsequently loss of response to anti-TNF treatment [193, 194].

According to bioinformatics researches, some genes (*CCR1, CD86, CCL4, TLR1, TLR4, TLR8, HCK, FCGR2A*) included in the TLR and FcγR signaling pathway are differentially expressed and common in anti-TNF therapy of non-responders, with the last three ones being able to be used as blood biomarkers [41]. There are single nucleotide polymorphisms (SNPs) present in the genes: aryl hydrocarbon receptor (*AHR*), death domain associated protein (*DAXX*), DENN domain containing 1B (*DENND1B*), dystrobrevin binding protein 1 (*DTNBP1*), Rh family C glycoprotein (*RHCG*) and synaptic Ras GTPase activating protein 1 (*SYNGAP1*) correlating with anti-TNF non-response [42], and it is worth mentioning that those genes are known between IBD susceptibility genes [195]. Regarding poor infliximab response, it can be attributed to increased expression of proinflammatory IL-1β, due to the C allele present in the SNP rs1143634 in CD patients [196]. According to gene expression studies in mucosal biopsies, osteoprotegerin (*OPG*), stanniocalcin-1 (*STC1*), prostaglandin-endoperoxide synthase 2 (*PTGS2*), interleukin 13 receptor alpha 2 (*IL13RA2*), and IL-11 are also differentially expressed genes in UC patients responding to infliximab treatment [43].

Lack of response to anti-integrin agents correlated with *IL1B+/LYZ+* myeloid cells in UC patients [136]. The higher expression of α4β1 integrin on peripheral blood CD4+ T cells could also predict vedolizumab response due to higher adhesion affinity [197]. *PIWIL1, MAATS1, RGS13*, and *DCHS2* genes baseline expression in colon tissues is an indicator of response to vedolizumab [153]. In another recent study, Gazouli et al. [75] reported 21 differentially expressed genes among patients with UC, who responded or not to Vedolizumab treatment. Most of these 21 genes referred to differentially expressed chemokines, and further analysis revealed dysregulated pathways in non-responders that were associated mainly with inflammatory processes [75].

More insight was provided in a series of IL-12–IL-23 pathway genes as well, which affect the progress of CD, with key genes being variants in *JAK2, STAT3, TYK2, IL10RA, IL12RB1*, and *IL12B* [198-202]. Those genes, the proteins they express, and their downward intra- and transcellular targets involved, should be considered as probable indicators of effectiveness and adverse effects. However, there are so far no conclusive genetic biomarkers tying ustekinumab response to any hereditary predisposition.

CONCLUSIONS

The approval of the first anti-TNF agent was over two decades ago, and since then several different biologics for the treatment of IBD were gradually developed. As the therapeutic choices multiplied, a need emerged for accurate biomarkers to indicate the best course of treatment for each individual patient, and therefore more studies started focusing on biomarker discovery.

Biomarkers should predict the response and efficacy to treatment and/or indicate the disease's progress, and may

include clinical, metabolic, immunogenicity, microbiota, pro-inflammatory and genetic factors. There is much information on biomarkers predicting the efficacy of anti-TNF, as it was the first and most researched biologic agent, while biomarkers associated with anti-integrin or anti-IL-12/23 therapies are still under the researchers' microscope. In conclusion, biomarkers predicting the response rates of each biologic, though highly needed, are not yet adequately evaluated and more studies are required in order to lead to an easy-to-evaluate and cost-effective biomarker with a high accuracy.

Conflicts of interest: None to declare.

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