REVIEW

Clinical Predictive Factors of Response to Biologics in IBD

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Abstract

Background: Growing insights into complex molecular pathways involved in the pathogenesis of inflammatory bowel diseases (IBD) have led to advent of new treatment options. Currently, there are three classes of biological agents approved for the treatment of IBD: anti-tumor necrosis factor agents (anti-TNFs), vedolizumab (VDZ) and ustekinumab. Each of these molecules have different targets in the inflammatory process, inhibiting specific mediators. Since the therapeutic options tend to increase and become more and more variate, it would be important to establish predictive markers of response to choose the best therapeutic option for the most suitable patient. Nowadays, the concept of „personalized medicine" which means selecting the right drug for the right person at the right time based on the characterization of an individual's phenotype and genotype seems to be more reasonable and tends to replace the strategy "one drug suits all" that we used for many years.
Aim: To present the currently available data regarding the clinical predictors of response not only to anti-TNFs, but also to VDZ and ustekinumab.
Methods: A literature search was performed in PubMed to identify publications reporting on predictive factors of response to biologic therapy in patients with IBD, using pre-defined keywords. We selected RCTs, observational studies, reviews and meta-analyses.
Results: For anti-TNF agents most of the evaluated factors have not proved to be accurate enough as to enter daily clinical practice as a decisive tool to enable an individualized therapeutic approach. Factors identified as potential predictors include disease behavior/ phenotype, disease severity, CRP, prior anti-TNF exposure, but the results were variable and sometimes conflicting. For VDZ, even more discouraging results were obtained, with only few factors (disease severity and prior anti-TNF exposure) showing limited value. Regarding ustekinumab, no predicting factor has been reported yet to be helpful in clinical practice.
Conclusion: Current scientific results cannot establish a single biomarker that fulfills all criteria for being an appropriate prognostic indicator for response to any biological treatment in IBD. Further research is needed to identify new and more reliable predictors or to better evaluate the existing ones.

Keywords: IBD, predictive factors of response, anti-TNFs, VDZ, ustekinumab.

Abstract

Noile descoperiri în ceea ce privește procesele moleculare complexe implicate în patogeneza bolilor inflamatorii intestinale (BII) au condus la apariția unor noi opțiuni terapeutice. În prezent, sunt aprobate în tratamentul BII trei clase de agenți biologici: anticorpi anti-factor de necroză tumorală (anti-TNF), vedolizumab (VDZ) și ustekinumab, fiecare acționând în diferite etape (inhibțnd diferiți mediatori ai inflamației) ale procesului inflamator. Creșterea numărului și diversificarea opțiunilor terapeutice a impus necesitatea stabilirii unor factori predictivi pentru răspunsul la o anumită terapie, pentru un anumit pacient. Astfel, conceptul de „medicină personalizată" (alegerea medicamentului

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potrivit pentru pacientul potrivit) tinde să înlocuiască treptat conceptul „același medicament pentru toti" pe care l-am folosit mult timp.
Scop: Prezentarea ultimelor date referitoare la identificarea unor factori predictivi de răspuns la terapia biologică, atât anti-TNF, cât și cele mai recent introduse în practică, VDZ și ustekinumab.
Metoda: Am efectuat o căutare în literatura de specialitate pe platforma PubMed, încercând să identificăm publicațiile legate de subiectul abordat, utilizând cuvinte-cheie prestabilite. Au fost selectate spre analiză RCT-uri, studii observaționale, review-uri și meta-analize.
Rezultate: Pentru anti-TNFs, majoritatea factorilor evaluați nu au arătat o acuratețe și eficiență suficiente pentru a putea fi utilizați ca instrument în selecția unei terapii personalizate. Potențialii factori predictivi includ fenotipul bolii, severitatea, nivelul proteinei C reactive (PCR), expunerea anterioară la anti-TNF.
Pentru VDZ, rezultatele au fost și mai puțin încurajatoare, cu numai doi factori (severitatea bolii și expunerea anterioară la anti-TNF) identificați, și aceștia cu valoare limitată. În ceea ce privește ustekinumabul, nu a fost identificat niciun factor predictiv, util în practică.
Concluzii: Datele științifice actuale nu sunt suficiente pentru a identifica și stabili un singur biomarker care să îndeplinească rolul de factor prognostic pentru răspuns la orice agent biologic utilizat în tratamentul BII.

Cuvinte-cheie: BII, factori predictivi de ră.spuns, anti-TNF, VDZ, ustekinumab.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, immune-mediated disease of the gastrointestinal tract with two main entities: Crohn's disease (CD) and ulcerative colitis (UC). These are relapsing, progressive conditions characterized by mucosal inflammation and epithelial injury causing a lifelong morbidity with a major impact on an individual's quality of life. Therefore, there is an urgent need for establishing an effective and safe treatment, with rapid and persistent response.

Growing insights into complex molecular pathways involved in the pathogenesis of IBD have led to advent of new targeted therapies, which selectively inhibit crucial mediators of the inflammatory process[1].

The first class of biological therapies approved for the treatment of IBD patients were anti-tumor necrosis factor (anti-TNF) agents, which includes the chimeric monoclonal antibody infliximab, the monoclonal human antibody adalimumab, corresponding infliximab and adalimumab biosimilars, the fully human monoclonal antibody golimumab, and the PEGylated humanized Fab' fragment certolizumab pegol[1]. Their use decreased the need for steroid therapy, promotes mucosal healing, reduces hospitalizations and surgeries and therefore dramatically improves the quality of life of IBD patients[2]. However, treatment failures are not uncommon with anti-TNFs. Only approximately two thirds of the IBD patients treated with anti-TNF drugs have an initial response to therapy[2] and 30%-50% of them will lose response in the course of treatment[2].

Recently, two new biological drugs that target different inflammatory pathways have been approved for IBD – an anti-**α**4**β**7integrin inhibitor - vedolizumab (VDZ) and an anti-IL-12/IL-23p40 antibody – ustekinumab. These molecules appear to have a more favorable safety and tolerance profile. They provide alternative options to anti-TNF therapy in the treatment of moderate to severe forms of IBD[3]. However, similar to anti-TNF agents, a significant number of patients do not respond to these drugs; response rates for VDZ range between 49%-64% in CD and 43%-57% in UC, with an about 20% rate of loss of response during maintenance therapy; for ustekinumab, the response rates were around 84% and about one-third of patients developed loss of response during maintenance[3].

Since the aforementioned biologic medications do not have a universal response, are associated with rare, but serious side effects and have a high cost, it would be important to establish predictive markers of response to identify the subgroup of IBD patients who selectively respond to different targeted therapies. Moreover, a particular patient might respond to a particular drug or drug combination with different inflammatory mechanisms being involved in the pathogenesis of IBD.

Nowadays, the concept of „personalized medicine" which means selecting the right drug for the right person at the right time based on the characterization of an individual's phenotype and genotype seems to be more reasonable and tends to replace the strategy „one drug suits all" that we used for many years.

Current data demonstrate that response to biological therapy may be influenced by many

factors that consist of disease-related and clinical characteristics, biochemical markers, blood and stool derived parameters, pharmacogenomics, microbial, and metabolic factors, as well as local mucosal factors[1].

The purpose of this review is to present the currently available data regarding the clinical predictors of response not only to anti-TNFs, but also to VDZ and ustekinumab.

A literature search was performed in PubMed to identify publications reporting on predictive factors of response to biologic therapy in patients with IBD, using key words: IBD, anti-TNF, IFX, AZA, VDZ, ustekinumab, predictive factors of response. Articles selected for this review included RCTs, observational studies, reviews and meta-analyses. References from these papers were also reviewed.

Clinical predictors of response to biologics

To obtain a more concise and clear presentation, we categorized the clinical predictive factors as follows: ***(1)*** patient related factors; ***(2)*** disease related factors; ***(3)*** inflammatory biomarkers; ***(4)*** prior anti-TNF exposure or prior therapies.

(1) Patient related factors

Age, Gender, Weight, Smoking

Data regarding association between **age** and response to biological therapy **(**either anti-TNF, or vedolizumab or ustekinumab**)** are inconsistent, multiple studies showing opposite results. For anti-TNF agents, mainly including infliximab, younger age at initiation of therapy has been implied to predict better primary response in some trials[1,4], no relationship could be established in some others[1,5] and opposite conclusions, showing that older age is associated with a higher probability of response were reported in a recent review[2,6]. Similarly, for vedolizumab, subgroup analysis of GEMINI 2 trial showed higher clinical remission rates in younger patients, while other studies concluded that age has no impact on the therapeutic response[3,7-10]. For ustekinumab, subgroup analyses in the UNITI trials found that younger age is associated with better response, while other studies[3,11-14] could not establish any correlation.

Gender is another potential predictive factor that has been evaluated, but the results are inconsistent, similarly to those regarding age. Therefore, for anti-TNFs, most available data indicated no relation at all, although there is one study that suggests a better outcome in male CD [1,15] patients and others that suggest a favorable response in female UC patients[1, 16,17]. Same results have been described when using vedolizumab and ustekinumab, with most trials showing no reliable relation between gender and therapeutic response[1,11-14].

Weight have been evaluated as a predictive marker mainly in anti-TNF treated patients. Pooled analysis of individual participant data from clinical trials of infliximab[1,18] did not demonstrate that obesity led to worse therapeutic response. Possibly, this finding can simply reflect the weight-based dosing of infliximab. On the other hand, PANTS study (a prospective observational UK-wide study, published in 2019, which investigates the factors associated with anti-TNF treatment failure in anti-TNF naïve patients with active luminal CD) showed that a higher body-mass index at baseline is associated with primary non-response in patients treated with adalimumab; it is suggested that obesity is independently correlated with low drug concentrations, causing a lack of response; and also, it is associated with immunogenicity to adalimumab. The authors suggested that dose optimization may improve/change these results[5]. In summary, obesity (or low weight) does not seem to have a clear impact on response to anti-TNF therapy[2].

Smoking is a well-known worse prognostic factor for CD; smokers with CD have a more complicated disease course than non-smokers and discontinuation led to better outcomes[1]. However, studies evaluating the association between smoking and response to treatment have not come to a clear conclusion; two meta-analyses that evaluated the role of smoking habit in the treatment response of CD patients concluded that there was no effect of tobacco smoking on the efficacy of infliximab and the relative risk of non-response was not significantly different in smokers. The first, published in 2009, found no effect of tobacco smoking on the efficacy of infliximab in CD patients[2,19]. The second meta-analysis, published in 2015, also concluded that the relative risk of non-response was not significantly different in smokers[2,20]. The PANTS study found that smoking at baseline was associated with poorer outcomes at week 14 (primary non-response) for IFX on univariable analyses, and at week 54, for both anti-TNFs (IFX and ADA) on univariable analyses and only for ADA on multivariable analyses. The authors observed that cigarette smoking was independently associated with an increased risk of immunogenicity to IFX, thus explaining the poorer

and less durable anti-TNF response in patients with CD who smoke than in non-smokers[5]. Regarding the response to VDZ, the VICTORY consortium cohort reported that patients with smoking history were less likely to achieve clinical remission[1,7]. However, the association between smoking habit and response to vedolizumab has not been confirmed by most of the studies[2, 8-10]. Several retrospective studies have assessed the role of smoking status in predicting the response to ustekinumab and no clear correlation could be found.

***(2)* Disease related factors**

Studies carried out so far evaluating disease-related predictors of response to biologic treatments in IBD have come to variate and inconsistent results.

In anti-TNFs treated patients post-hoc analyses of large phase 3 clinical trials have demonstrated that shorter disease **duration** predicts a higher responsiveness to anti-TNF drugs. In the CHARM study, remission rates with ADA approached 60% in patients who had been diagnosed with CD for up to 2 years compared with 40% ($p < 0.05$) in those with a longer duration of disease[21, 22]. In UC, the available data could not find the same correlation; on the contrary, there are some studies that suggest that patients with longer disease duration tend to respond better to anti-TNF agents[2, 23].

Disease **location/extension** has been described as a potential predictive factor in CD, but not in UC. Several cohort studies indicated better short-term and sustained clinical response to anti-TNF therapy in isolated colonic than in ileal CD[1]. In UC disease extension has not been correlated with a consistent pattern of response in most of the studies[2, 16, 24-27]. Disease **behavior** seems to significantly influence response to anti-TNFs in CD. Thus, an inflammatory phenotype (Montreal classification B1) is associated with better short and long-term response in comparison to stenosing(B2) or fistulizing disease (B3)[1, 28, 29].

Disease **severity** was demonstrated as a predictive factor especially in UC. A less severe disease has higher chances of achieving short and long-term response and lower colectomy rates[1, 16, 30].

Disease **activity** at baseline seems to be an independent predictor of response to **VDZ** in both UC and CD (3). In subgroup analyses of GEMINI 1 and 2 trials, baseline Mayo score < 9 and CDAI score ≤ 330 were associated with higher clinical remission rates at 6 and 54 weeks when compared to placebo[3, 31, 32]. These results have been confirmed by several observational studies. The first prospective real-world study evaluating the efficacy of VDZ for CD and UC (Baumgart et al.) found that low Harvey–Bradshaw index and no recent hospitalisations in CD can be classified as independent predictors of clinical remission in week 14[9]. A French cohort (Amiot et al. - GETAID) which included 294 patients (173 CD and 121 UC), found that patients with a Harvey-Bradshaw index (HBI) score > 10 or a Mayo score > 9 at baseline were less likely to achieve steroid-free clinical remission at weeks 14 and 54[3,8]. The US VICTORY consortium cohort was a retrospective trial aiming to identify baseline clinical factors predictive of achieving clinical remission or mucosal healing[7]; it included 212 patients with moderately to severely active CD treated with VDZ. Disease severity at time of initiation and active perianal disease were the disease related factors that were found to be associated with a reduction in treatment effectiveness, (baseline severe disease activity vs. moderate disease activity: HR 0.54; 95% CI: 0.31– 0.95), baseline active perianal disease vs. no baseline peri- anal disease: HR 0.49; 95% CI: 0.27–0.88) Individuals with active perianal disease at baseline had lower rates of clinical response (*P*=0.011), steroid-free response (*P*=0.009), and steroid-free remission (*P*=0.034), but rates of mucosal healing (*P*=0.246) and progression to surgery (*P*=0.815) were similar. Disease phenotype (structuring or penetrating) was not associated with a better or worse response[7].

For **ustekinumab** the disease-related predictors identified in most trials are the **disease severity** at baseline and the disease **localization**. Disease duration, phenotype or behaviour/activity seem to have no impact on the therapeutic response. The largest observational study included 167 patients and retrospectively assessed clinical factors associated with response at 6 months. In multivariate analysis, patients with a Harvey Bradshaw Index (HBI) >7 at induction were less likely to achieve clinical response [OR: 0.26 (95% CI: 0.11–0.61)], as were patients with stricturing disease [OR: 0.29 (95% CI: 0.12–0.72)]. Patients with colonic [OR: 2.27 (95% CI: 0.76–6.75)] or ileocolonic disease [OR: 2.41 (95% CI: 1.01–5.79)] were more likely to have a clinical response[33]. The same team conducted another study (104 CD patients) which evaluated the long-term maintenance of response and one of the secondary objectives was to identify clinical factors associated with loss of response. Colonic disease (aHR 0.33 (0.11–0.98)), and ileocolonic disease (aHR 0.26 (0.10–0.68))

were associated with lower risk for loss of response during maintenance therapy. In contrast, highly active disease as defined by an HBI above 7 at induction (a HR 4.63 (1.64–13.11)) and stricturing disease phenotype (aHR 2.77 (1.10–7.01)) were associated with response attenuation [34]. In a retrospective open-label study across 42 Spanish tertiary IBD centres analysing 116 CD patients, no disease-related factors were identified for predicting the early or the long-term clinical benefit with ustekinumab[13]; same results were obtained in the study of Wils et al. from the GETAID group [11].

Previous surgery

Many studies have described previous surgery in CD patients as a negative factor for primary therapeutic response to anti-TNF [1, 4, 35, 36].

For **VDZ** most trials could not find an association between previous CD surgery and VDZ response [9, 37].

So far, **ustekinumab** has been used in patients with complex, refractory IBD, usually with prior exposure to at least one biological agent, multiple immunomodulators and with previous surgeries. Spanish trial of Khorrami *et al.* found that history of previous intestinal resection was associated with long-term failure to ustekinumab. Operated patients might suffer from a more aggressive disease with an increased risk of being refractory to medical treatment [13].

***(3)*Inflammatory biomarkers**

It has been suggested that the presence of inflammatory burden in IBD, characterized by elevated levels of different biomarkers such as the C reactive protein (CRP), fecal calprotectin, albumin, neutrophil-to-lymphocyte ratio or hemoglobin level may have an influence on the response to available biologic therapies. The most widely evaluated inflammatory markers are CRP and fecal calprotectin.

Although multiple studies have confirmed an association between baseline levels of **CRP** and response to **anti-TNF** (IFX, ADA), it is unclear if the elevated level of CRP *per se* has a predictive value or it is only a proof of inflammatory disease activity and treatment response is a consequence of the anti-inflammatory effect of the drug. Post-hoc analyses of the SONIC trial found that patients with objective evidences of inflammation (i.e., a high CRP level or visible mucosal lesions) had higher rates of corticosteroid-free clinical remission at week 26, in both the combination therapy group (63.5% vs. 27.6% patients, p<0.001) and the IFX group(47.5% vs. 27.6% patients, p=0.004) [38]. On the other hand, CHARM trial showed that ADA treated patients had better long-term response (weeks 26 and 56), irrespective of baseline CRP concentrations when compared to placebo group [21]. Moreover, in the study of Magro *et al.*, baseline CRP levels were higher in CD patients with primary nonresponse, and baseline levels greater than 15 mg/l predicted primary nonresponse with 67% sensitivity and 65% specificity. At week 14, CRP levels greater than 4.6 mg/l predicted nonresponse with similar accuracy[22,39]. Nevertheless, because the sensitivity of CRP is limited in CD as almost 30% of patients will have a normal level despite clinically active disease [22] the use of anti-TNFs should not be restricted to patients with an elevated CRP.

In UC patients, higher baseline CRP levels were associated with a higher likelihood of drug failure and need for colectomy [22, 40] and higher anti-TNF induction and maintenance efficacy could be found in patients with low CRP concentrations[40,41]. The CRP levels after initiation of anti-TNF are also predictive of response. In a recent study (Iwasa et al. 2015), the CRP level in a group of UC patients at week 2 after initial dose of anti-TNF was significantly lower in responders *versus* partial responders (p = 0.0135) or non-responders (p=0.0084), in spite of similar trough IFX levels[42]. Also, post-hoc analyses of TAILORIX trial showed that at baseline, CRP was the only biomarker correlating with endoscopic remission at week 12 (median CRP =17 mg/L in responders vs. 26 mg/L in non-responders, p= 0.025)[43]. During the maintenance period variations of CRP levels in responders vs. non-responders were not significant so, no correlation could be established.

Similar to the results reported for anti-TNFs, available studies for **VDZ** suggest that higher levels of systemic and bowel inflammation are predictive of worse outcomes. A prospective German cohort including 127 patients (Stallmach et al.) found that having lower CRP at week 14 as compared to baseline was predictive of achieving clinical remission at week 54 in both CD and UC. In UC patients, a lower CRP concentration at week 14 as compared to baseline was associated with subsequent clinical remission at week 54 in 46% as compared to 5% in patients without a decline (P = 0.003). Among the CD patients, a reduction in CRP concentration at week 14 was associated with clinical remission at week 54 in 47% of cases as compared to 9% in patients without a decline (P = 0.01) [44]. Amiot *et al.* separately analyzed CD and UC cohorts and obtained different results: they reported that a high

CRP level (>20 mg/L (p = 0.10)) was predictive of steroid-free remission at week 14 in the CD cohort, while in UC patients a CRP >20mg/L and a Mayo score >9 were accurately associated with non-response at week 14[8]. Finally, some other studies could not find any correlation between CRP and response to VDZ. The study of Baumgart *et al.* found that even though the CRP values successively decreased from week 0 to week 6 and 14 in both CD 0.98 vs. 0.898 vs. 0.72 mg/dL and UC 0.63 vs. 0.52 vs. 0.43 mg/dL, this could not reach statistical significance and so, no clinical impact could be established [9].

Trials evaluating the efficacy of **ustekinumab** have not been able to find a clear-cut relationship between the CRP levels and rates of clinical response/remission. Majority of these studies described significant decrease in CRP levels in primary responders (i.e, Ma *et al.* 2017 – 71.4% of the clinical responders at the end of follow-up had a decrease in CRP compared to CRP at induction; mean decline – 16.3mg/L, Wils *et al.GETAID* – 95% of patients with clinical benefit from ustekinumab at 3-months follow-up had a CRP decline; median decrease of CRP = 18mg/L); further on, primary response was an independent predictor of long-term response, but the predictive value of CRP was not evaluated and so, we can only speculate that there might be some correlation. Future clinical trials evaluating the role of CRP in predicting clinical response to ustekinumab are needed.

Another biomarker that is widely used in clinical practice to evaluate the luminal inflammatory activity is the **fecal calprotectin (FC)**; it-s level has been shown to accurately correlate with active colonic disease rather than ileal disease in CD and with active UC, but it-s role in predicting response to therapy is not quite well established.

Different clinical trials including patients treated with **anti-TNFs** have followed the link between calprotectin and response rates. A recent Spanish prospective cohort including 35 CD patients (Beltran *et al.* 2018) found that a higher median FC level at week 0 was independently associated with primary nonresponse (week 0: median FC level, nonresponders vs. responders 1.830 and 410 μg/g, respectively; p = 0.0025), with a sensitivity of 80% and specificity of 83% for primary nonresponse[45]. Also a significant inverse correlation was determined between FC level at week 0 and IFX level at week 14, suggesting that baseline FC levels prior to anti-TNF drugs therapy can predict the IFX levels achieved at week 14 and thus predict the clinical response[45]. Variations of FC levels after initiating the treatment have been shown to be predictive of endoscopic remission and mucosal healing in short and long-term response[43].

In **VDZ** treated patients the available data suggest that higher baseline values of FC are negative predictors of response to therapy on one hand, and on the other hand, a rapid decrease in FC levels is associated with better long-term response. Stallmach *et al.* showed in a retrospective trial that patients with UC who were in clinical remission at week 54 had a rapid decrease of FC (median FC=354mg/kg at week 14 vs. 3000mg/kg at baseline; p=0.002) followed by a steady decline of FC during the treatment[44]. These results were confirmed by another study which found that FC levels in CD and UC decreased successively from week 0, to week 6 and 14 (975 vs. 860 vs. 370 mg/dL; 1740 vs. 825 vs. 273 mg/dL, respectively)[9].

Results from RCTs evaluating **ustekinumab** (UNITI, UNIFI) for both the treatment of CD and UC reported a reduction of FC levels during the induction and maintenance period in responders compared to placebo, suggesting that monitoring FC levels during treatment may be a useful tool for predicting response[46,47,48]. Still, this role is to be determined and demonstrated in future studies.

(4)Exposure to prior therapies

Prior anti-TNF therapy is a risk factor for treatment failure with another biologic agent. Multiple **anti-TNF** agents have been available for IBD treatment for some time now, therefore it is not unusual for one patient to be exposed to more than one anti-TNF; this could have an impact on the efficacy of new therapeutic options. Most studies (clinical trials, meta-analyses or reviews) underline the importance of identifying the reason/mechanism that caused the loss of response to first anti-TNF and also the type of non-response (primary or secondary). A systematic review and meta-analysis found that the remission rate in CD patients treated with a second anti-TNF was higher when the reason to withdraw the first anti-TNF was intolerance (61%), compared with secondary (45%) or primary failure (30%)[2,49]. A review of 15 studies (including only two randomized-controlled trials), which identified patients who had discontinued infliximab (most of them because of loss of response or intolerance to infliximab) and switched to adalimumab reported highly variable

remission rates across the different studies, with short-term rates between 41% and 83%[2,50]. Regarding immunomodulators use, there are well-known SONIC and SUCCESS trials that have shown a clear benefit of combination therapy (immunomodulator and IFX)[38,51]. A recent UK prospective study (PANTS) aiming to identify predictive factors of anti-TNF failure in CD patients, found that, on univariate analyses non-use of an immunomodulator at baseline was one of the associations with primary nonresponse at week 14 for both, IFX and ADA and at week 54, for IFX[5].

VDZ effectiveness also depends on previous biologic use. Both, RCTs and observational clinical trials have identified that prior exposure to anti-TNFs is a risk factor for lower VDZ response rates. Post-hoc analyses of GEMINI trials reported higher rates of response and remission in CD patients naïve to anti-TNF compared to experienced ones (48.4% and 26.6% vs.39.7% and 21.8% at week 10); same results were also obtained for UC[3, 31, 32]. Baumgart *et al.* found that for CD no ADA use and for UC no IFX use and no anti-TNF use at all, were significantly associated with clinical remission at week 14[9]. In the US VICTORY cohort previous anti-TNF use was correlated with lower chances of achieving clinical remission and mucosal healing and with lower rates of clinical response (P=0.011), steroid-free response (P=0.020), and steroid- free remission (P=0.050), and they had higher rates of progression to surgery (P=0.051). This was incremental according to the number of TNF-antagonists they had been exposed to, but it was similar when stratified by the reason for failure of the TNF-antagonist used and whether an individual ever had a primary non-response to a TNF-antagonist[7].

Considering that most patients included in trials evaluating the efficacy of **ustekinumab** had been exposed to at least one anti-TNF, comparative analyses between naïve and experienced patients are missing. We identified one Canadian study (retrospective, including 79 patients) that found the type of preceding nonresponse to anti-TNF agent (primary vs. secondary; primary vs. intolerance) as a predictor of short-term symptomatic response with corresponding p values of 0.061 and 0.006, respectively on univariate analyses[14]. Primary non-response remained statistically significant as a predictor on multivariate analyses. This correlation may suggest that the inflammatory burden is not being driven by TNF. Therefore, switching to a biologic with a different mechanism of action is more likely to be successful than using another anti-TNF agent. Conversely, those who have a secondary loss of response to their biologic due to both enhanced antibody mediated and non-antibody mediated clearance would likely face similar challenges with ustekinumab[14]. Other observational studies could not find any association between clinical benefit and prior anti-TNF use, irrespective of anti-TNF agent or type of loss of response, but rather impact had the use of two or more immunosuppressive agents[11, 13, 33-34].

CONCLUSIONS

The recent arrival of new effective biologic therapies (VDZ and ustekinumab) for IBD besides anti-TNF has underlined even more the importance of personalization of therapy. The currently applied clinical practice of randomly commencing a biological treatment and assessing response to therapy several weeks after initiation is coupled with progression of tissue damage in non-responders, risk of systemic side- effects, and substantial health-care costs of an inefficient therapy. Prediction of therapeutic response would allow optimization of the risk/benefit ratio of biological agents used in IBD[1].

In this paper we tried to present and summarize the available data regarding potential clinical predictors of response to biological therapies. For anti-TNF agents most of the evaluated factors have not proved to be accurate enough as to enter daily clinical practice as a decisive tool to enable an individualized therapeutic approach. Factors identified as potential predictors include disease behavior/ phenotype, disease severity, CRP, prior anti-TNF exposure, but the results were variable and sometimes conflicting. For VDZ, even more discouraging results were obtained, with only few factors (disease severity and prior anti-TNF exposure) showing limited value. Regarding ustekinumab, no predicting factor has been reported yet to be helpful in clinical practice[2]. This may be due to the limited clinical experience and trials focused on this topic.

Moreover, we observed that for the same factor evaluated, different results were described for CD in comparison to UC (disease duration and severity, localization of lesions). This suggests that further attempts to establish reliable predictors should specifically address to one disease or another.

To conclude, current scientific results cannot establish a single biomarker that fulfills all criteria for

being an appropriate prognostic indicator for response to any biological treatment in IBD. Further research is needed to identify new and more reliable predictors or to better evaluate the existing ones. Potential biomarkers need prospective validation in multi-center studies with large cohorts of patients and should incorporate short-term and long-term observations[1].

Also, the optimal approach to integrating these factors into routine clinical practice should be established[52]. There is a need for well-validated, drug-specific, easy-to-use prediction models that allow clinicians to open new avenues for personalized medicine in IBD.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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