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Progress in the Study of Inflammatory Bowel Disease Patients with Primary Non-Responsiveness

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Abstract

Inflammatory bowel disease (IBD) is a group of chronic, nonspecific intestinal inflammatory disorders characterized by localized and systemic inflammation. The use of biologic agents in the treatment of IBD patients is widespread, and the occurrence of primary non-responsiveness during treatment is also significant. This review briefly summarizes the possible reasons for primary non-responsiveness in IBD patients, as well as predictive markers and current strategies to address it, providing a theoretical reference for early identification and management of IBD patients who do not respond to treatment.

Keywords

Inflammatory Bowel Disease, Primary Non-Responsiveness , Anti-Tumor Necrosis Factor

1. Introduction

Inflammatory bowel disease (IBD) is a group of chronic inflammatory diseases of the intestines, including Crohn's disease (CD) and ulcerative colitis (UC). It is a chronic relapsing condition characterized by localized and systemic inflammation that can affect the entire gastrointestinal tract and the mucosa of the colon [1], as well as multiple organs and systems [2]. In the past 50 years, the incidence of inflammatory bowel disease has been on the rise globally [3]. The incidence in the Asian region has also been increasing year by year [4]. Although the etiology

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and pathogenesis of inflammatory bowel disease are not yet clear, most studies believe that immune factors are the main cause and are closely related to a variety of factors such as genetics, living environment, and gut microbiota [5] [6], uncontrolled aberrant intestinal immune responses play a significant role in the development of inflammatory bowel disease [7].Currently, the associations between proinflammatory and anti-inflammatory immune cells and molecules, as well as various genetic predispositions, gut microbiota, and environmental factors (such as diet, smoking, and physiological stress, among others), are continuously being evaluated to obtain a comprehensive understanding of the pathogenesis of inflammatory bowel disease [8]. For the treatment of inflammatory bowel disease, a wide range of therapies including 5-aminosalicylic acid, corticosteroids, immunomodulators, and biological agents targeting tumor necrosis factor (TNF)-α, $\alpha 4\beta 7$ integrin, and interleukin (IL)-12/23 are extensively used. Particularly, anti-tumor necrosis factor-α antibodies represent the most advanced first-line biological agents currently available [9]. Many of these have demonstrated good efficacy and safety [10], significantly reducing the risk of surgery, hospitalization, and associated complications in patients with severe IBD [11]. Moreover, it is gratifying to note that nearly two-thirds of IBD patients maintain deep remission over a long period of time with biologics maintenance therapy [12]. Despite the widespread use of anti-TNF drugs significantly improving the quality of life for patients, reducing the need for steroid treatment, promoting mucosal healing, and decreasing the rates of surgery and complications [11], however, there are still 30% - 40% of patients who do not respond to the initial induction dose of anti-TNF-α medication [13]. Therefore, early identification or prediction of non-responsiveness to anti-TNF medication is crucial for clinical practice. Currently applied to clinical biomarkers, including CRP, ESR, p-ANCA, ASCA and fecal calcium protein [14], predicting treatment response, especially before administrating biologics [15]. Primary non-response (PNR) primarily refers to the lack of response or remission in IBD patients to monoclonal antibody treatment, including a complete lack of response as well as partial response without full remission. PNR to anti-TNF medication can be described as insufficient improvement in clinical signs or symptoms after the induction phase, leading to the discontinuation of the medication [16]. At present, there is no uniform definition, but a commonly used definition is that there is no significant improvement in the clinical symptoms and signs of patients after 8 - 12 weeks of induction treatment with anti-TNF-α monoclonal antibodies [13]. This article reviews the potential causes of PNR, predictive biomarkers, and related response measures that are currently known.

2. Potential Causes of Primary Non-Response

Although some risk factors associated with primary non-response (PNR) have been identified, its mechanisms are not yet clearly defined [17]. It is currently believed that inflammation not mediated by tumor necrosis factor-α (TNF-α)

may lead to the transformation from primary non-response to response, and certain pro-inflammatory pathways can even be regulated through the inhibition of TNF-α [18]. Multiple factors may be associated with the occurrence of PNR, including factors that affect drug clearance and drug concentration in patients with inflammatory bowel disease, as well as inflammation processes not driven by TNF [19] [20] [21]. In patients with inflammatory bowel disease, drug clearance and metabolism may be affected by a variety of factors, such as an individual's ability to metabolize drugs, liver function, changes in intestinal permeability, and alterations in the gut microbiome. These factors could lead to insufficient drug concentrations in the body, thus affecting the efficacy of treatment. Furthermore, inflammation processes not driven by TNF may also play a crucial role in the occurrence of PNR. The progression of inflammatory bowel disease involves abnormal production and regulation of various inflammatory mediators and cytokines, and these factors may interact with the action of TNF-α. Therefore, non-TNF-driven inflammation processes might result in non-responsiveness to TNF-α treatment.

2.1. Factors Affecting Drug Concentration

Trough concentration refers to the lowest point of drug concentration before the next dose is administered, which is also known as the minimum effective drug concentration clinical response has been shown to positively correlate with the trough concentrations of anti-tumor necrosis factor-α (TNF-α) drugs [22]. A study found that at week 6 of treatment, the trough concentration of vedolizumab in primary non-responders (20.3 μg/mL) tended to be lower compared to secondary non-responders (30.7 μg/mL), indicating that low antibody concentrations might be a reason for primary non-response [23]. During the induction process, subtherapeutic concentrations of anti-TNF drugs appear to be one of the greatest risk factors for primary non-response, as non-immunogenic clearance results in lower drug levels [16]. Studies have shown [24], Higher concentrations of anti-TNF drugs are associated with better treatment outcomes, while lower drug concentrations and the presence of anti-drug antibodies are associated with primary non-response and secondary non-response. The average expected increase in serum dose escalation of adalimumab (ADA) concentration is 5.5 μg/mL. Initial dose escalation of adalimumab (ADA) concentration, age, and body mass index may affect the ability to achieve target dose escalation of adalimumab (ADA) concentrations after dose escalation. A prospective study that included 1610 patients with Crohn's disease found [25], The only factor independently associated with primary non-response was a lower drug concentration at week 14. Infliximab (IFX) concentrations of at least 7 mg/L and adalimumab concentrations of at least 12 mg/L were associated with clinical remission at 14 weeks. As for the impact of body mass index (BMI) on drug clearance, further in-depth research is needed to draw definitive conclusions. A study found that trough concentrations of infliximab (IFX) were inversely correlated

with visceral fat area and the ratio of visceral fat to skeletal muscle area, but not related to body mass index [26]. Another study found that patients with a baseline BMI below 18.5 kg/m^2 had a 3.42 times higher risk of primary non-response compared to patients with a BMI above 18.5 kg/m^2 [27]. Although the impact of body mass index on drug clearance is not clear, evidence from several other studies suggests that there is a close relationship between drug concentrations and clinical response.

2.2. Losses through the Gastrointestinal Tract

Studies have found that compared to responders, the characteristic of fecal microbiota in primary non-responders is an increased relative abundance of Proteobacteria and Actinobacteria [28]. For infliximab, the greatest drug loss seems to occur during phases when serum drug concentrations are highest and mucosal inflammation is most severe [29]. In ulcerative colitis patients, infliximab is lost in the stool. High concentrations of infliximab in the stool on the first day after the start of treatment are associated with primary non-response [29]. These findings suggest that alterations in the gut microbiome and losses of drug concentrations may be related to primary non-response. The increased relative abundance of Proteobacteria and Actinobacteria could be linked to treatment failure. Additionally, the loss of the drug in stool may impact the drug's action within the intestines, leading to the occurrence of primary non-response.

2.3. Patient Factors

In patients receiving infliximab treatment for the first time, a younger age is significantly correlated with a good clinical response, indicating that early responders tend to be younger than non-responders [30]. Another study focusing on Indian non-responders found that in ulcerative colitis patients, the average age of onset for primary non-responders was lower, although the difference was not statistically significant [31]. Marin *et al.* first evaluated the relationship between comorbidities in patients with inflammatory bowel disease and primary non-response to anti-tumor necrosis factor-α (TNF-α) drugs. The study [32] results indicated that chronic obstructive pulmonary disease (COPD) and solid tumors were identified as potential factors associated with primary non-response. In addition, the use of corticosteroids and the type of IBD (ulcerative colitis vs Crohn's disease) were also significantly associated with primary non-response to anti-TNF-α medication. It is noteworthy that the only extraintestinal disease significantly associated with primary non-response was hepatobiliary pancreatic disease. Therefore, the presence of comorbidities should be taken into consideration when selecting a treatment plan. A younger age, the presence of comorbidities, the type of IBD, and other extraintestinal diseases may be related to the occurrence of primary non-response. Taking these factors into account collectively can help in formulating personalized treatment plans, improving treatment efficacy, and predicting patient responses to therapy.

3. Predictive Biomarkers for Primary Non-Response

3.1. Serological Markers

3.1.1. Anti-Neutrophil Cytoplasmic Antibodies (ANCAs)

Anti-neutrophil cytoplasmic antibodies (ANCAs) are autoantibodies targeted against antigens within the cytoplasm of neutrophils [13]. ANCAs are considered to be diagnostic markers for ANCA-associated vasculitis (AAV). In patients with ulcerative colitis (UC), about 10% - 80% of patients are positive for p-ANCA, but do not present AAV; therefore, p-ANCA can serve as a diagnostic marker for UC [33] [34] [35] [36]. A single-center study [13] included 50 patients with ulcerative colitis (UC) who were receiving induction therapy with anti-tumor necrosis factor-α (TNF-α) drugs for the first time, and tested for PR3-ANCA. In this study, a positive PR3-ANCA was defined as greater than or equal to 3.5 U/mL. The study found that a positive PR3-ANCA can predict primary non-response to anti-TNF-α drugs in UC patients. Furthermore, in a study by Ferrante *et al.* (2007) on the prediction of early response to infliximab in patients with ulcerative colitis, it was found that patients with the serotype p-ANCA+/ASCA− had a significantly reduced early clinical response [30]. Interestingly, similar findings have been observed in Crohn's disease (CD), where CD patients with refractory intestinal disease carrying the p-ANCA/ASCA serotype had lower response rates. However, the significance of this association may be related to the small sample size of patients carrying this serotype, and further research is needed to confirm these results.

3.1.2. Hemoglobin

Oussalah *et al.* (2010) conducted a retrospective multicenter study that included 191 patients with ulcerative colitis (UC) treated with infliximab over a period of 9 years. They defined primary non-response to infliximab as the lack of clinical response between the fourth and twelfth weeks after the first infusion, resulting in treatment discontinuation. The univariate analysis found that an initial hemoglobin level ≤ 9.4 g/dL and having more than 8 bowel movements per day at the start were positive predictors of primary non-response. In the multivariate logistic regression analysis, an independent positive predictor was determined, namely "initial hemoglobin ≤ 9.4 g/dL" [37]. Additionally, in a retrospective analysis of patients with Crohn's disease (CD), the study found that the incidence of primary non-response was 3.26 times higher when baseline hemoglobin was below 10 g/dL compared to patients with hemoglobin levels above 10 g/dL [27]. A domestic study also found that low hemoglobin is an independent risk factor for primary non-response to infliximab [38]. Therefore, objective assessment of the patient's condition and correction of anemia are beneficial for inducing and maintaining remission in inflammatory bowel disease.

3.1.3. Serum Albumin

Serum albumin is a common clinical serum test indicator. Recent studies have found that changes in serum albumin within the first two weeks of anti-TNF

therapy can predict primary non-response (PNR), endoscopic outcomes, timing of colectomy, and failure of anti-TNF treatment in patients with ulcerative colitis (UC). The study observed that a decrease in albumin levels at week two compared to baseline was associated with a 4.26-fold increased risk of anti-TNF treatment failure [39]. However, one study measured albumin levels in patients receiving infliximab at an interval of 10 months and found no significant difference (4.3 mg/dl vs. 4.4 mg/dl) [40]. Another study conducted by Kumar *et al.* (2023) found that in UC patients, higher baseline levels of C-reactive protein (CRP) and lower albumin levels were significantly associated with PNR. In the prediction of PNR after 14 weeks of anti-TNF treatment, an albumin threshold of ≤3.6 g/dL had a sensitivity of 82.0% and specificity of 77.7%. For Crohn's disease (CD) patients, lower baseline albumin levels and postoperative recurrence were significantly associated with PNR, and there was also a higher risk of tuberculosis reactivation. In predicting PNR at 14 weeks, an albumin threshold of ≤3.3 g/dL had a sensitivity of 70.1% and a specificity of 75% [31].

3.1.4. C-Reactive Protein (CRP)

C-reactive protein (CRP) is a clinical marker reflecting disease activity. An increased inflammatory burden associated with elevated baseline CRP levels may result in insufficient reduction of the inflammatory burden during the induction or remission phase of anti-TNF drug treatment [27]. Patients with higher baseline serum CRP levels tend to have lower serum concentrations of infliximab [41]. A retrospective study by Song *et al.* (2019), which included 283 patients with Crohn's disease (CD), found that a baseline CRP > 1 mg/dL might be a clinical factor for the occurrence of PNR, with an increased incidence rate of PNR by 3.58 times compared to patients with CRP ≤ 1 mg/dL. Moreover, the combination of baseline CRP level and the rate of CRP decline may have significant correlations with both short-term and long-term responses during the entire treatment period [27]. Recent research has found that matrix metalloproteinase 3 (MMP3), chemokine CCL2, and CRP can independently predict primary non-response to infliximab in patients. The study also discovered that in the second week after infliximab treatment, serum CCL2 concentrations in CD patients with PNR were lower than those in responders [18].

3.2. Immunological Markers

3.2.1. Oncostatin M (OSM)

Oncostatin M (OSM) is part of the IL-6 cytokine family and signals through receptor complexes composed of the gp130 co-receptor (similar to all members of the IL-6 family) and OSMR or leukemia inhibitory factor receptor-β [42]. OSM plays a role in hematopoiesis, bone remodeling, liver regeneration, and various chronic inflammatory diseases, including rheumatoid arthritis [43]. In their 2017 study, West *et al.* (2017) found that high levels of OSM and its receptor OSMR are expressed in the intestinal tissue of patients with inflammatory bowel disease, promoting an inflammatory response in intestinal stromal cells [44].

Additionally, the expression of OSM and OSMR is positively correlated with the severity of mucosal inflammation, suggesting that OSM is a potential biomarker and therapeutic target for IBD. Recent studies have further confirmed the expression of OSM and its associated receptors in the mucosa and serum of IBD patients. A study investigating five clinical scenarios found that higher levels of OSM in the colon are associated with poor prognosis and primary non-response to biologic therapy. The study also discovered that OSM may serve as a tissue and serum marker for newly diagnosed IBD patients and Crohn's disease patients who relapse after surgery [42]. Furthermore, an international study indicated that in patients with ulcerative colitis, higher baseline levels of OSM and interstitial expression of OSM-R (OSM receptor) could predict primary non-response at 14 weeks, but no significant difference was observed in CD patients [31]. Consequently, OSM holds promise as a good biological marker for failure of anti-tumor necrosis factor-α monoclonal antibody treatment in IBD patients [45].

3.2.2. Interleukin-7 (IL-7)

Interleukin-7 (IL-7) is a cytokine that regulates cellular lymphoid homeostasis and is primarily produced by epithelial cells and stromal cells. The IL-7 receptor (IL-7R) regulates the expression of pro-apoptotic and anti-apoptotic BCL-2 family members and activates PI3K and JAK/STAT pathways, providing signals for cell proliferation and anti-apoptosis [46]. In patients with Crohn's disease, high baseline expression of IL-7R on stromal cells can predict primary non-response at 14 weeks [31]. However, in patients with ulcerative colitis (UC), although IL-7R expression levels were higher, there was no significant statistical difference. These research findings provide clues for further exploration of predictive molecules associated with primary non-response.

3.3. Genetic Markers

Currently, there is widespread interest in genetic markers for predicting the response to infliximab (IFX) treatment. A study involving whole-exome sequencing and data analysis of 139 Korean individuals treated with IFX identified five candidate genetic variants associated with primary non-response to IFX monoclonal antibody therapy (rs145751680, rs34069439, rs117642371, rs2228273, rs34099160). Among these variants, the rs2228273 in the ZNF133 gene was validated in German patients with Crohn's disease. Additionally, the study pinpointed the optimal genetic variant associated with the loss of response to IFX treatment (rs9144). Furthermore, multivariate regression analysis revealed that concomitant use of thiopurines/6-mercaptopurine and a body weight below 50 kg at the first use of IFX were related to primary non-response. This indicates that a combined genetic and clinical model is superior to models that only include genetic variables or only clinical variables [47]. Recent studies have found that the levels of TNF mRNA in primary non-responders among adults are significantly higher than in treatment responders. This finding suggests that in pa-

tients with inflammatory bowel disease who have high expression of TNF mRNA, consideration should be given to using higher doses of anti-TNF medication right from the start of treatment [20].

3.4. Genotypic Markers

There is some variability in the research findings regarding the relationship between HLA-DQ A1*05 and the response to anti-tumor necrosis factor treatment. Pascual *et al.* conducted a single-center retrospective cohort study including patients with inflammatory bowel disease who were receiving their first anti-TNF treatment and had determined HLA-DQA1*05 status. Their study results showed that among HLA-DQ carriers, there was no statistically significant difference in primary non-response to anti-TNF treatment, nor was there any difference in secondary loss of treatment response. Therefore, they concluded that HLA-DQ A1*05 cannot be used as a predictor of primary non-response to anti-TNF treatment [48]. However, a retrospective study by María and colleagues suggests that HLA-DQ A1*05 is associated with the secondary loss of response rate (SLR) in IBD patients who received adalimumab treatment but were not under immunosuppression [49]. Furthermore, in terms of the immunogenicity of TNF antagonists, HLA-DQA1*05:01/HLA-DQA1*05:05/HLA-DRB1*03 alleles may help predict responses or adverse reactions to therapy [50]. The discrepancies in these research findings may be related to factors such as sample size, disease characteristics of the included patients, and other variables.

4. Measures to Address Primary Non-Response

4.1. Granulocyte and Monocyte Apheresis (GMA)

Granulocyte and monocyte apheresis (GMA) combined with anti-tumor necrosis factor (TNF) medication is considered a treatment option for ulcerative colitis patients who have an insufficient response to biologics. A small-sample case study found that in cases of UC with insufficient response to biologics, combining GMA with vedolizumab (VDZ) may be a therapeutic option [51]. Moreover, a study that included 47 UC patients suggested that GMA combined with anti-TNF therapy is a safe and effective treatment method after loss of response to biologics, significantly reducing the levels of clinical disease activity and biomarkers. This combination therapy is suitable for populations with limited treatment options [52].

4.2. Combination Therapy

A study suggests that the concurrent use of thiopurine drugs may be beneficial in patients with ulcerative colitis undergoing biologic therapy, but this effect was not observed in Crohn's disease patients. Additionally, no clear benefit was observed for UC patients who started using thiopurine drugs only after six months from the initiation of therapy [53]. However, another study indicates that patients using immunomodulatory drugs concurrently are more likely to expe-

rience primary non-response (PNR) [47].

4.3. Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring (TDM) can be used to identify patients with primary non-response (PNR) to anti-TNF-α drugs who have therapeutic drug concentrations and no anti-drug antibodies (ADAs). It is recommended to switch these patients to alternative biologics rather than second-line anti-TNF-α drugs [22]. In both first-line and second-line anti-TNF-α therapy, therapeutic drug monitoring is associated with higher drug survival rates [54], Increasing drug concentrations is associated with better clinical response and remission rates [55]. Higher concentrations of anti-TNF drugs have been demonstrated to lead to higher rates of treatment success [16], Monitoring anti-TNF drug levels can help improve treatment outcomes, especially in cases of primary non-response [56]. Reactive TDM should be conducted for all biologics in the treatment of primary non-response and secondary non-response. It is recommended that discontinuation of infliximab or adalimumab treatment should not be considered before reaching drug concentrations of at least 10 - 15 μg/mL [57]. There is a positive correlation between drug concentrations and good clinical efficacy in IBD. Reactive TDM allows for a more rational management of primary non-response and secondary non-response to anti-TNF therapy, and it is more cost-effective compared to empirical dose optimization. Proactive TDM aimed at target drug concentrations shows better therapeutic outcomes compared to empirical dose escalation and/or reactive TDM. Active TDM can also effectively guide the de-escalation or discontinuation of infliximab in IBD patients in remission [58].

4.4. Other Biologics

Combining personalized monitoring of anti-drug antibodies with therapeutic drug monitoring can predict drug failure before clinical symptoms appear and facilitate timely transition to alternative medications, providing better treatment outcomes for patients with inflammatory bowel disease [59]. A real-world retrospective study by Sablich *et al.* (2023) included 100 patients with ulcerative colitis who received biologic immunotherapy, dividing them into an infliximab (IFX) group and a vedolizumab (VDZ) group, and assessed the efficacy and safety of both drugs while analyzing the reasons for primary non-response and secondary loss of response. The study found that the proportion of primary non-response was higher in the IFX group (30%) compared to the VDZ group (9%), and that VDZ was superior to IFX in terms of clinical efficacy, drug persistence, and steroid-free remission [60]. These research results are expected to guide the choice of biologics for patients with inflammatory bowel disease in clinical practice.

5. Summary

Inflammatory bowel disease, being a chronic nonspecific intestinal disorder, still

requires further research to clarify its mechanisms of occurrence. However, the introduction of biologics has brought about clinical benefits for patients with inflammatory bowel disease, but the occurrence of PNR not only hinders the induction of remission in patients but also increases their economic burden. Therefore, studying and monitoring biomarkers and genetic markers can help predict patient responses to biologic therapy and identify PNR early on, which is very important for improving patient quality of life, reducing adverse reactions, and decreasing the rate of surgeries.

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Conflicts of Interest

There are no interests and disputes in this article.

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