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Predictive Factors of Biologic Therapy Failure in Crohn's Disease

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Abstract **Original Research Article**

Anti–tumor necrosis factor (anti-TNF) agents have markedly improved the management of Crohn's disease (CD); however, a substantial proportion of patients experience primary non-response (PNR) or secondary loss of response (SLR), limiting long-term treatment efficacy. This retrospective descriptive and analytical study included 71 patients with CD treated with anti-TNF therapy to determine the rate of therapeutic failure and identify predictive factors. Treatment failure was defined as absence of clinical improvement at week 14 for infliximab and week 8 for adalimumab (primary non-response), or secondary loss of response during follow-up confirmed by clinical, biological, endoscopic, or radiological assessment. Primary non-response occurred in 16.9% of patients, while 52.1% developed secondary loss of response, leaving only 31% with sustained response to the initial biologic therapy. Multivariate logistic regression analysis identified low body mass index (OR = 0.045, p = 0.003) and elevated platelet count (OR = 1.0000, p = 0.004) as independent predictors of anti-TNF failure. These findings highlight the high frequency of therapeutic failure in CD and underscore the importance of early identification of predictive factors to optimize personalized and pharmacokinetically guided treatment strategies.

Keywords: Crohn's Disease, Biologic Therapy, Anti-TNF.

INTRODUCTION

Crohn's disease (CD) is one of the two main entities within inflammatory bowel disease, alongside ulcerative colitis [1]. First described in 1932 by Burrill Bernard Crohn and colleagues as "regional ileitis" [2], CD is a chronic, idiopathic, immune-mediated disorder characterized by transmural and segmental inflammation that may involve any part of the gastrointestinal tract, particularly the terminal ileum and colon [3][4]. Its pathogenesis remains incompletely understood and is thought to result from a complex interaction between immune dysregulation, genetic susceptibility, environmental factors, and alterations in the gut microbiota [3][5].

The incidence and prevalence of CD are increasing worldwide, and the disease typically follows a relapsing–remitting course that may lead to complications such as strictures and fistulas [3]. Diagnosis is based on a combination of clinical, endoscopic, histological, and radiological findings, with nonspecific symptoms such as abdominal pain and diarrhea often predominating [6][7]. Although there is no curative treatment , therapeutic advances—including corticosteroids, immunosuppressants, and more recently biologic therapies—have significantly improved outcomes [8][9]. However, a substantial proportion of patients exhibit primary non-response or secondary loss of response to anti-TNF agents [10]. Therefore, the aim of this study is to determine the rate of biologic therapy failure in Crohn's disease and to identify predictive factors associated with this failure.

2. MATERIALS AND METHODS

2.1 Study Design and Patients

This is a retrospective descriptive and analytical study conducted in the hepato-gastroenterology department 1 of the Mohamed V Military Instruction Hospital in Rabat between January 2024 and December 2025.

We included all patients with a confirmed diagnosis of Crohn's disease who were treated with anti-TNF–based biologic therapy, either as monotherapy or in combination with an immunosuppressant, and who experienced therapeutic failure. Patients with incomplete or non-exploitable medical records, or those not meeting the inclusion criteria, were excluded from the analysis.

The primary objective was to determine the rate of therapeutic failure to anti–tumor necrosis factor (anti-TNF) agents defined as primary non-response or

secondary loss of response in patients followed for Crohn's disease, and to identify factors associated with such failure.

2.2 Predictor Variables and Data Source

All patients with Crohn's disease treated with anti–tumor necrosis factor (anti-TNF) therapy who experienced therapeutic failure were identified and included in the analysis. Treatment failure was defined as primary non-response at week 14 for infliximab and at week 8 for adalimumab, or as secondary loss of response occurring beyond these time points, confirmed by clinical assessment and supported by biological, radiological, or endoscopic findings.

Data were collected from medical records using a standardized data extraction form and analyzed with Jamovi statistical software. The variables assessed included epidemiological data (age, sex, smoking history, prior surgery, and body mass index); clinical characteristics (age at diagnosis, disease duration, and disease activity); biological parameters (hemoglobin, white blood cell count, platelet count, albumin, C-reactive protein, and fecal calprotectin); endoscopic findings (disease location, disease phenotype, and presence of ano-perineal involvement); therapeutic data (type of anti-TNF agent, combination therapy with immunosuppressants, and use of intravenous corticosteroids); and disease outcomes, including the occurrence of primary non-response or secondary loss of response.

2.3 Statistical Analysis

The statistical analysis was conducted in two stages. First, a descriptive analysis was performed to summarize the baseline characteristics of the study population. The overall rate of therapeutic failure was calculated, as well as the respective rates of primary non-response (PNR) and secondary loss of response (SLR). Failure rates were also analyzed according to the specific anti-TNF agent used.

Second, an analytical study was carried out using binary logistic regression to identify predictive factors associated with anti-TNF failure in Crohn's disease. Quantitative variables were expressed as mean ± standard deviation, while qualitative variables were presented as numbers and percentages. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1 Descriptive Statistics

A total of 71 patients were included in the study. The mean age was 44.9 ± 14.6 years (range: 19–76), with a male predominance (62% men, 38% women; sex ratio 1.6). Eight patients (11.3%) had a history of smoking, all of whom were male, and 32 patients (45.1%) had a prior history of surgery. Regarding nutritional status, 52.1% were underweight, 42.3% had a normal body mass index, and 5.6% were overweight.

The mean age at diagnosis was 33 ± 13.4 years (range: 11–66), and the mean disease duration was 11.8 ± 6.65 years (range: 1–31). Disease activity, assessed using the Harvey–Bradshaw Index (HBI), showed that no patients were in remission; 11.3% had mild activity, 83.1% had moderate activity, and 5.6% had severe disease.

Biologically, the mean hemoglobin level was 10 ± 1.77 g/dL (range: 6.1–15), mean white blood cell count was 8,500 ± 3,738/mm³ (range: 2,900–17,700), and mean platelet count was 406,673 ± 152,326/mm³ (range: 29,900–821,000). The mean albumin level was 31 ± 6.49 g/L (range: 15–42), mean C-reactive protein was 98.3 ± 67.5 mg/L (range: 19–360), and mean fecal calprotectin was 1,371 ± 795 µg/g (range: 110–3,203).

According to the Montreal classification, ileal involvement was observed in 8.5% of patients, colonic involvement in 22.5%, and ileocolonic disease in 69%. An inflammatory phenotype was present in 22.5%, a stricturing phenotype in 15.5%, and a fistulizing phenotype in 62%. Perianal disease was identified in 50.7% of cases.

Regarding therapy, infliximab was prescribed in 62% of patients and adalimumab in 38%. Combination therapy was administered in 95.8% of cases, all with azathioprine, and 40.8% received intravenous corticosteroids.

In terms of outcomes, 12 patients (16.9%) experienced primary non-response (defined as lack of clinical improvement at week 14 for infliximab and week 8 for adalimumab). Among the remaining 59 patients, 37 (52.1%) developed secondary loss of response during follow-up, confirmed clinically and supported by biological, endoscopic, or radiological findings. Overall, only 22 patients (31%) maintained a sustained response to the initially prescribed anti-TNF agent.

Table 1 presents the descriptive statistics of the main demographic, clinical, and biological characteristics of the study population.

3.2 Analytical Statistics

Predictors of biologic therapy failure were first assessed using univariate analysis, which identified low body mass index (underweight) (OR = 0.162; 95% CI: 0.047–0.558; p = 0.004) and longer disease duration (OR = 0.904; 95% CI: 0.821–0.995; p = 0.040) as factors significantly associated with anti-TNF therapeutic failure.

Subsequently, multivariate logistic regression analysis was performed to determine independent predictors of treatment failure. In this model, low body

mass index remained independently associated with anti-TNF failure (OR = 0.045; 95% CI: 0.0059–0.339; p = 0.003). Elevated platelet count was also identified as an independent predictor (OR = 1.0000; 95% CI: 0.999–1.000; p = 0.004).

Table 2 summarizes predictive factors of failure related to biologic therapy in univariate and multivariate analysis

Table 1: Baseline Characteristics of the Study Population (n = 71)

Variable	Value
Demographics	
Age (years)	44.9 ± 14.6
Sex (M/F)	44/27 (62% / 38%)
Disease History	
Disease duration (years)	11.8 ± 6.65
Age at diagnosis (years)	33 ± 13.4
Smoking history	Yes 8 (11.3%), No 63 (88.7%)
Prior surgery	Yes 32 (45.1%), No 39 (54.9%)
Anthropometrics	
BMI	Underweight 37 (52.1%), Normal 30 (42.3%), Overweight 4 (5.6%)
Disease Activity	
HBI score	9.85 ± 1.92
Montreal Classification	
Location	L1 (Ileal) 6 (8.5%), L2 (Colonic) 16 (22.5%), L3 (Ileocolonic) 49 (69%)
Phenotype	B1 (Inflammatory) 16 (22.5%), B2 (Stricturing) 11 (15.5%), B3 (Fistulizing) 44 (62%)
Perianal involvement	Yes 36 (50.7%), No 35 (49.3%)
Laboratory Parameters	
Hemoglobin (g/L)	10 ± 1.77
WBC (/mm³)	8,500 ± 3,738
Platelets (/mm³)	406,673 ± 152,326
Albumin (g/L)	31 ± 6.49
CRP (mg/L)	98.3 ± 67.5
Fecal calprotectin (µg/g)	1,371 ± 795
Therapy	
IV corticosteroids	Yes 29 (40.8%), No 42 (59.2%)
Combination therapy	Yes 68 (95.8%), No 3 (4.2%)
Anti-TNF agent	ADA 27 (38%), INF 44 (62%)

Table 2: Predictive factors of failure related to biologic therapy in univariate and multivariate analysis

Associated Factors	Univariate Analysis			Multivariate Analysis		
	OR	CI	p-Value	OR	CI	p-Value
BMI:						
Normal			NS			
Overweight						
Underweight	0,162	(0,047–0,558)	0,004	0,045	(0,0059–0,339)	0,003
Location:						
Ileal						
Colonic			NS			
Ileocolonic						
Phenotype:						
Stricturing						
Inflammatory			NS			
Fistulizing						
Platelets:	1,000	(1,000–1,00)	0,187	1,0000	(0,999–1,000)	0,004
Disease duration:	0,904	(0,821–0,995)	0,040	NS		

4. DISCUSSION

Anti–tumor necrosis factor alpha (anti-TNFα) agents have substantially improved the management of Crohn's disease by reducing inflammation, hospitalization rates, and the need for surgery, while enhancing patients' quality of life. Nevertheless, a significant proportion of patients either fail to respond initially (primary non-response, PNR) or lose response over time (secondary loss of response, SLR), thereby limiting the long-term efficacy of these therapies. Primary non-response is often related to disease severity and extent, the presence of complications, genetic background, inadequate drug exposure, or poor adherence. Secondary loss of response, occurring after an initial clinical benefit, is commonly associated with immunogenicity, subtherapeutic drug levels, disease complications, comorbidities, or genetic factors [11].

In our cohort of 71 patients treated with anti-TNFα, 16.9% experienced primary non-response, while 52.1% of initial responders developed secondary loss of response during follow-up, leaving only 31% with sustained therapeutic benefit. Multivariate analysis identified low body mass index (BMI) and elevated platelet count as independent predictors of treatment failure (OR = 0.045, p = 0.003; OR = 1.0000, p = 0.004, respectively). These findings are consistent with previous reports. Roda *et al.,*(2016) described PNR rates ranging from 10–30% and SLR rates between 23–46%, influenced by disease severity, complications, immunogenicity, and drug levels [11]. Similarly, Kennedy *et al.,*(2019) and Chanchlani *et al.,*(2024) identified low anti-TNF serum concentrations, anti-drug antibodies, and complicated phenotypes (stricturing or fistulizing disease) as predictors of therapeutic failure [12][13]. More recently, Hu *et al.,*(2024) reported that low BMI and elevated inflammatory markers such as CRP were associated with an increased risk of non-response[14] , while Wang *et al.,*(2023) and Kumar *et al.,*(2024) highlighted the potential role of genetic factors, prior surgery, and specific biomarkers in influencing treatment outcomes [15][16]. Collectively, these data underscore the heterogeneity of response to anti-TNF therapy and the importance of identifying predictive factors to optimize personalized management strategies.

In clinical practice, however, therapeutic failure encompasses heterogeneous situations and requires a rigorous diagnostic approach before confirmation. The initial step is to reassess the diagnosis, as conditions such as intestinal tuberculosis, lymphoma, or other colitides may mimic Crohn's disease. Disease-related complications—including abscesses, fibrotic strictures, or gastrointestinal malignancy—must also be excluded, as they necessitate specific management strategies. Furthermore, persistent symptoms may be related to alternative causes such as bile acid diarrhea, superimposed infections (e.g., *Clostridioides difficile*, CMV), irritable bowel syndrome, or other chronic gastrointestinal disorders. True therapeutic failure should only be retained when active inflammatory lesions are objectively confirmed by endoscopy or cross-sectional imaging, after exclusion of infection and malignancy.

With regard to infliximab, primary failure is defined as the absence of clinical response by week 14, with reported rates of approximately 30% in pivotal trials and 11–24% in real-world studies. Combination therapy with immunomodulators during induction may reduce primary failure by limiting immunogenicity. Secondary loss of response, estimated at approximately 13% per year, requires confirmation of active inflammation before therapeutic adjustment. Optimization strategies include shortening infusion intervals, increasing the dose (up to 10 mg/kg), or adding an immunosuppressant. Therapeutic drug monitoring may assist in guiding these decisions, particularly in patients with low trough levels without detectable anti-drug antibodies. However, despite early improvement following optimization, only 30–40% of patients maintain a sustained long-term response.

Overall, the management of anti-TNF failure remains complex and highlights the necessity of individualized, evidence-based, and pharmacokinetically guided therapeutic strategies in Crohn's disease.

5. CONCLUSION

In this retrospective study of 71 patients with Crohn's disease treated with anti-TNF agents, therapeutic failure was common, with 16.9% primary non-response and 52.1% secondary loss of response, leaving only 31% with sustained benefit.

Low body mass index and elevated platelet count were identified as independent predictors of treatment failure, supporting the role of nutritional status and systemic inflammation in therapeutic outcomes. These findings are consistent with previous reports highlighting the multifactorial nature of anti-TNF failure [16].

Early identification of predictive factors and careful confirmation of true therapeutic failure are essential to optimize management. Personalized, pharmacokinetically guided strategies may help improve long-term outcomes in patients with Crohn's disease.

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