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PREDICTIVE FACTORS OF RESPONSE TO ANTI-TUMOR NECROSIS FACTOR-ALPHA IN INFLAMMATORY BOWEL DISEASE: ABOUT A MOROCCAN EXPERIENCE

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ABSTRACT

The use of biological agents, particularly anti-TNFα (tumor-necrosis factor) drugs, has revolutionized the treatment of inflammatory bowel disease (IBD). However, up to 30% of patients show no clinical benefit after induction therapy (primary non-responders), and 30-40% of patients lose their response within the first year of treatment, requiring dose escalation or switching to another biological therapy. The study aims to identify factors of poor response. This is a retrospective descriptive and analytical study conducted by the Hepato-gastroenterology department of the Hassan II University Hospital of Fez, including 122 patients with IBD, of which 41 patients with UC (33.6%) and 81 patients with Crohn's disease (66. 4%), the mean age was 40.06 years, with a clear female predominance, 106 patients received initial treatment with infliximab-based biotherapy (86.88%), adalimumab in 15 of our patients (12.3%). Only one patient (0. 82%) was treated with Golimumab. A primary non-response was observed in 7.38% of the cases and a loss of secondary response in 23.77%. Sixty-one percent of the patients had clinical improvement of symptoms after the induction treatment without loss of secondary response. Seven patients presented an intolerance to anti-TNF alpha during the induction phase with switching to another biotherapy, and two patients did not have a well-conducted inducement therapy. A platelet count of more than 450,000 cells/mm3, a serum albumin level >30g/L, and good compliance with treatment were significantly associated with an excellent response to biotherapy.

KEYWORDS: IBD, CD, UC, anti-TNFα, biotherapy, predictive factors, clinical response.

INTRODUCTION

The use of biological agents, particularly anti-TNFα (tumor-necrosis factor), has changed the history of inflammatory bowel disease. For example, in Morocco, only infliximab and adalimumab are used in Crohn's disease and ulcerative colitis, and Golimumab has been used since 2014 for ulcerative colitis.

The use of biotherapy decreased the need for surgery, reduced the number of hospitalizations, allowed weaning from corticosteroids and endoscopic mucosal healing, and improved patients' quality of life. However, up to 30% of patients show no clinical benefit after induction therapy (primary non-responders), and 30-40% of patients lose their response within the first year of treatment, needing dose escalation or switching to another biologic.[1] Our goal is to predict the patients' response to biotherapy by identifying the factors of poor response.

AIM: The present study aims to evaluate the clinical, biological, endoscopic, and histological response to biological treatments and to investigate the predictive factors of response to anti-TNFα.

PATIENTS AND METHODS

This is a retrospective descriptive and analytical study conducted by the Hepato-gastroenterology department in Fez, Morocco, including 122 patients with IBD retained on clinical, biological, endoscopic, and histological criteria and treated with anti-TNF biotherapy. Our study was spread over 11 years and nine months (March 1st, 2011, to December 31st, 2022). The data was then analyzed with SPSS 20 software. We used the Student's test for quantitative variables and the "Chi-square" test for qualitative variables. The difference was considered significant when the p-value was less than or equal to 0.05.

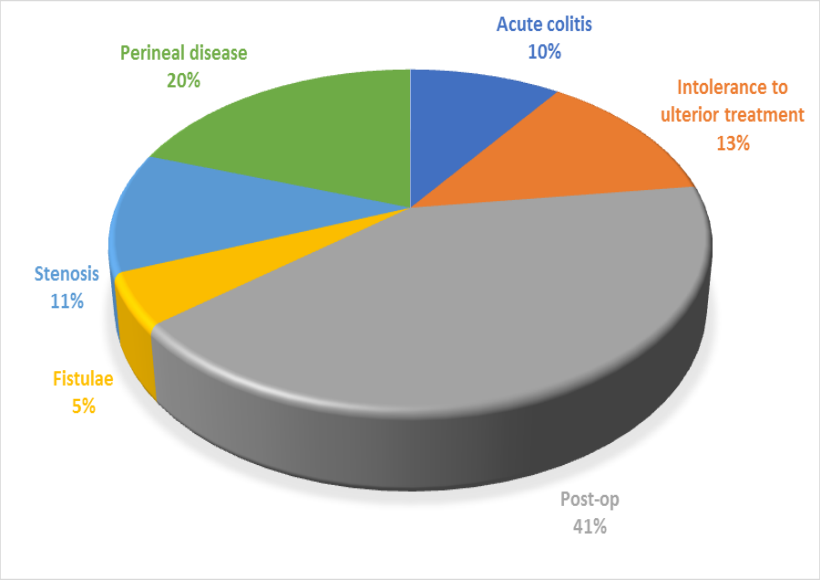
RESULTS

We included 122 patients: 41 patients with ulcerative colitis (33.6%) and 81 patients with Crohn's disease (66.4%). The mean age was 40.06 years, with extremes ranging from 18 to 73 years, with a clear female predominance (sex ratio F/H =1.34). The age of onset was 31.59 years [9y-70y]. A personal history of hypertension was found in 5 patients, diabetes in 4 patients, and 19 patients (15.57%) were smokers (9 had quit, 2 were passive smokers). Two patients had excessive alcohol consumption. Nine patients had an appendectomy at a mean age of 27.33 years. A history of veinous thrombosis was observed in 5 patients (4. 09%), and a family history of IBD in 12 patients (9.84%): 5 had UC, and 7 had Crohn's disease. Only one patient had a sister followed for colonic adenocarcinoma.

Table 1: Crohn's disease phenotype in our series.

Luminal	**22 (27.16%)**
Stenosing	18 (22.22%)
Fistulizing	6 (7.41%)
Stenosing and fistulizing	10 (12.35%)
Stenosing and fistulizing with perineal disease	6 (7.41%)
Stenosing with perineal disease	4 (4.94%)
Luminal with perineal disease	15 (18.51%)

Initial treatment with infliximab-based biotherapy was used in 106 patients (86.88%), adalimumab-based biotherapy in 15 of our patients (12.3%), and only one patient (0.82%) was treated with Golimumab. The indications for anti-TNF in UC were severe corticosteroid-resistant colitis in 24 patients (58.54%), intolerance to previous treatments in 7 patients (17.07%), and failure of the last conventional treatments in 10 patients (24.39%). The indications of anti-TNF in Crohn's disease are summarized in graph 1:



Graph 1: Indications of anti-TNF in Crohn's disease.

A primary non-response was observed in 9 patients (7.38%). Twenty-nine patients had a loss of secondary response (23.77%). Seventy-five patients (61.48%) showed clinical improvement of digestive symptoms after induction treatment without loss of secondary response. Seven patients showed intolerance to anti-TNF during the induction phase with a switch to another biotherapy.

Infliximab resulted in clinical remission without loss of secondary response in 65 of 106 patients treated (61.32%), and loss of response to infliximab was observed in 23 patients (21.69%). Primary non-response in 9 patients (8.5%) (Seven patients had an allergic reaction to infliximab during induction therapy, and two patients did not complete induction therapy). All patients had a primary response to adalimumab. It resulted in clinical remission in 9 out of 15 patients (60%) without loss of secondary response after induction therapy. Loss of response to adalimumab was observed in 6 of 15 patients (40%). In addition, clinical remission was observed in the patient who was started on golimumab with a sustained response after ten months of treatment.

Pharmacokinetic dosages were performed on 20 patients. Blind optimization was done in 9 cases because of loss of secondary response. In patients on infliximab, dosages were performed in 17 patients: they were satisfactory in

7 patients, and one patient had a high level of anti-infliximab antibodies and was switched to adalimumab. Six patients had low anti-infliximab antibodies, three were changed to adalimumab, two continued on infliximab (ustekinumab unavailability), and one had interval shortening. Low infliximab dosage was found in 10 patients with low anti-infliximab antibody levels in 5 patients who benefited from dose optimization at a dose of 10mg per 8 weeks in one patient and interval shortening in 4 patients (every six weeks). Five patients had high antibody levels, one was switched to ustekinumab, one had surgery, two had azathioprine, and one had social security problems, so he hasn't benefitted yet from an exchange.

In patients on adalimumab, the dosage was performed in 3 patients due to loss of secondary response. This revealed low adalimumab levels with low levels of anti-adalimumab antibodies in 2 patients leading to the optimization of treatment duration. However, high levels of antibodies were found in one patient, leading to a switch to ustekinumab.

Endoscopic evaluation was performed in 70 patients (57.38%) within 21 months after the start of anti-TNFα treatment. The intervals of endoscopy ranged from 5 months to 6 years. Thirty-four patients (48.58%) had completed mucosal healing, stagnation of endoscopic lesions in 18 patients (25. 71%), and worsening of lesions in 18 patients (25.71%). Among 34 patients who achieved endoscopic remission, 15 (44.12%) had histological remission. Anti-TNF α was stopped in one patient after a good response. Therapeutic de-escalation was done in 2 patients: the first remained on azathioprine alone for five months and had a severe relapse of his disease leading to the reintroduction of anti-TNF alpha. The other patient was on infliximab with interval shortening, and de-escalation was done by administering anti-TNF every eight weeks.

The different predictive factors of response to biotherapy studied were divided into patient-related, disease-related, and drug-related elements. They are summarized in the following table:

Table 2: the different predictive factors of response to biotherapy.

Predictive factors for response to biotherapy		**P value**
Age		0,826
Sex		0,18
Weight		0,25
Tobacco	In Crohn's Disease	0,9386
	In UC	0,4146
Age at diagnosis		1
Duration of the disease		0,75
Localization and extension of the disease	Isolated colonic involvement in CD	0,2718
	Isolated ileal involvement in CD	0,4628
	UC	0,6537
Behavior and phenotype of the disease	Luminal	0,9889
	Stenosis	0,6281
	Fistula	0,9889
	Perineal disease	0,3282
The severity of the disease		0,2679
Previous surgery		0,806
CRP		0,5741
Hemoglobin		0,8315
Leucocytes		0,8804
Platelets		**0,0467**
Albumin		**0,03752**
Fecal Calprotectin		0,8738
Previous treatment with anti TNF		0,2159
Mucosal healing		0,8374
The nature of biotherapy	Infliximab	0,7144
	Adalimumab	0,8745
	Golimumab	1
Compliance with treatment		**0,022**

DISCUSSION

In Crohn's disease, younger age has been associated with a better response to anti-TNF therapy in some studies, including infliximab.[1;2] However, many other studies were unable to find a relationship between age and response to infliximab[3;4], adalimumab[5;4,6], or certolizumab.[5;7;8] Similarly, in patients with ulcerative colitis, contradictory results have also been reported,

with studies showing an association between younger age[9], older age[10;11], or, most often, no impact of age[12;13] We did not find an association between the patient's age and biotherapy efficacy (p=0. 826). Several studies that evaluated the association between gender and response of Crohn's disease to anti-TNF agents did not find a relationship, either with infliximab[3;2;4;14], adalimumab[6;4], or certolizumab.[7] Similarly, in patients with ulcerative colitis, no association was reported between gender and response to infliximab[11;15], adalimumab[16], or golimumab.[13;17] In addition, we did not find an association between the patient's gender and biotherapy efficacy (p=0.18). Some studies have shown a higher response rate in lower-weight patients treated with infliximab[18;19] or adalimumab[19], while others have shown opposite results. There was no correlation between higher weight and clinical response to biotherapy in our study (p=0.25).

Smoking negatively influences disease progression in Crohn's (CD) patients.[20] Although some studies have suggested that nonsmokers with CD tend to have a better response to anti-TNF drugs with either infliximab[21] or adalimumab[22], most studies have been unable to find an association between smoking and treatment efficacy.[23] In patients with ulcerative colitis (UC), the influence of smoking on the response to anti-TNF therapy has also been controversial, as most studies report no relationship[11;9;11;16;24], but a few studies suggest a negative effect of smoking.[25] We found no effect between smoking and clinical response to biotherapy in patients who followed Crohn's disease (p=0.9386) nor those who followed UC (p=0.4146).

In a retrospective, single-centered study by Papamichael et al., out of 100 patients with CD, age at diagnosis of 25 years or older was an independent predictor of sustained clinical remission after IFX discontinuation while in clinical remission.[2] Another retrospective study of 51 IBD patients (17 CD, 30 UC, and four unclassified IBD) in deep remission at the time of anti-TNF agent discontinuation couldn't find factors that predict relapse after treatment discontinuation after a median of 36 months.[26] In our series, the age of onset of the disease didn't influence the efficacy of biotherapy (p=1).

Disease duration was assessed with the hypothesis that patients with shorter disease duration will respond better to early treatment.[27] This has been demonstrated in posthoc analyses of large clinical trials. Patients with fewer than two years of disease duration were more likely to respond to anti-TNF drugs than those with a longer disease duration.[27] Some studies have confirmed that CD patients with short disease duration tend to respond better to anti-TNF therapy, whether with infliximab[28], adalimumab[29], or certolizumab.[30] However, many other authors have been unable to confirm this association in patients treated with anti-TNF (infliximab,[31] adalimumab[5][23][6], or certolizumab.[5][32] We did not find an association between the duration of disease progression and the clinical response to biotherapy (P=0.75)

Some studies have suggested that CD patients with isolated colonic disease respond better to anti-TNF [specifically infliximab], whereas isolated ileitis has been associated with a poor response.[33] In patients with UC, the location/extension of the disease was not generally associated with response to anti-TNF agents.[34] Our series found no association between isolated colonic Crohn's disease and response to anti-TNF (P=0.2718). Isolated ileal involvement in Crohn's condition was not associated with clinical response (P=0.4628). In patients with UC, the location/extension of the disease was not associated with response to anti-TNF (P=0.6537)

The disease phenotype of patients with CD, as defined by the Montreal classification, may be associated with a response to anti-TNF therapy. Patients with simple inflammatory behavior could benefit more from anti-TNF treatment than patients with a stenotic or fistulizing phenotype.[36],[21;37] In our series, the luminal (P=0.9889), stenosing (P=0.6281), fistulizing (P=0.9889), and perineal disease (P=0.3282) were not associated with clinical response. In CD, only a few studies have evaluated the influence of disease severity on the probability of response to anti-TNF therapy, with controversial results (better response in less severe forms of CD[38], or no association.[6] Our series found no relationship between disease severity and biotherapy efficacy (p=0.2679). Some studies in patients with Crohn's disease have reported that a history of previous resection surgery is a negative predictor of response to anti-TNF therapy.[39] Nevertheless, most studies could not find an association between digestive surgery and response to anti-TNF.[40] In our series, there was no association between a history of resection surgery and clinical response to treatment (P=0.806).

Among the different biomarkers of inflammation, C-reactive protein (CRP) has been the most applied to clinical practice.[41] Many studies have confirmed an association between elevated CRP and response to anti-TNF therapy in CD, including infliximab[42], adalimumab[43], and certolizumab.[44] On the contrary, several studies have confirmed an association between low CRP levels and better response to anti-TNF therapy in UC patients, including infliximab[11;9] and adalimumab.[35] On the other hand, we did not find an association between high CRP and response to anti-TNF therapy (P=0.5741).

Some studies have reported a correlation between higher hemoglobin levels and the response of UC to anti-TNF therapy[45], whereas others could not confirm this observation in CD[18;6] Furthermore, only one study evaluated the possible association between leukocyte count and response to anti-TNF therapy (adalimumab in CD), and no correlation was found[6] Finally, only two studies evaluated the possible association between

platelet count and the probability of response to anti-TNF agents, with controversial results[6;46] In our series, we did not find an association between hemoglobin level and response to anti-TNF therapy (P=0.8315) nor leukocyte levels and response to anti-TNF treatment (P=0.8804). However, a platelet count >450,000 cells/mm3 is associated with an excellent answer to anti-TNF therapy (P=0.0467).

The association between albumin levels and response to biotherapy in patients with CD has not been adequately evaluated. This association has been assessed by several studies in patients with UC. In patients with acute severe UC, infliximab levels were significantly lower than those in moderate UC during the induction phase and were significantly correlated with albumin levels.[47] Several studies have reported higher response rates in UC patients with higher albumin levels treated with either infliximab[48], adalimumab[49], or certolizumab.[50] In our series, a serum albumin level >30g/L was consistently associated with an excellent response to biotherapy (P=0.03752)

Fecal calprotectin and lactoferrin are surrogate markers of luminal disease activity that have been suggested to predict clinical response to anti-TNF therapy[51], and this ability has been demonstrated in a few studies in both CD[52] and UC patients.[24] Our series did not find an association between calprotectin level and response to anti-TNF therapy (P=0.8738). Some studies have shown that in IBD patients, prior anti-TNF therapy is a risk factor for treatment failure with another anti-TNF agent, including infliximab[53], adalimumab[34;6] or golimumab[54;13] We found no such correlation (P=0.2159).

CONCLUSION

Anti TNFα agents have revolutionized the treatment of IBD, but the loss of primary response is a joint adverse event. Personalized medicine is emerging and will become a requirement in managing IBD patients. Identifying predictive factors of response to biotherapy in IBD patients is the first step to avoiding unnecessary treatments and reducing healthcare costs. Most studies attempting to identify poor clinical response aspects have yielded controversial results. This can be explained by the experimental settings and definitions of disease remission used. In our series, a platelet count >450,000 cells/mm3, a serum albumin level >30g/L, and good compliance with treatment were significantly associated with an excellent response to biotherapy. It is also noted that the instauration and optimization of biotherapy in our context remains a challenge due to its unavailability.

Abbreviations

Anti-TNF-alpha: Anti-Tumor Necrosis Alpha
CRP: C reactive protein
IBD: Inflammatory bowel disease
UC: Ulcerative colitis

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