Original Research Article

Predictive factors of endoscopic mucosal healing in patients with chronic inflammatory bowel diseaseson biotherapy

Abstract:

Achieving mucosal healing is the main goal in the treatment of patients with chronic inflammatory bowel diseases (Crohn's disease and Ulcerative Colitis). Nevertheless, mucosal healing predictors after medical treatment remain unknown. The purpose of this study was to determine the rates of mucosal healing and to characterize its predictive factors in patients with IBD treated with Anti-TNF alpha. We conducted a retrospective descriptive and analytical study between January 2019 and March 2022 in the hepato-gastroenterology I department, within the Mohamed V Military Instruction Hospital in Rabat.We collected demographic, clinical, and biological data of patients being treated for IBD with anti TNF alpha therapy, and who have undergone a colonoscopy before initiating treatment and after 1-year of treatment. In this study, mucosal healing was defined as the absence of ulcerated lesions during the 1-year follow-up colonoscopy. Among 60 patients on anti TNF-alfa therapy for IBD; 43 were included in our study with 10 patients having Ulcerative Colitis and 33 having Crohn's Disease. Overall, 22 patients had mucosal healing (approximatively 51%): 60% in the UC group and 48,50% in the CD group. Regarding associated factors, in all patients, fecal calprotectin was retained as the only significant predictive factor of mucosal healing. The overall rate of endoscopic mucosal healing in our study was of 51,20% with faecalcalprotectin being identified at follow-up coloscopy as a predictive factor. Nevertheless, none of the studied factors were retained when the two groups were analyzed separately.

Keywords: Chronic inflammatory bowel diseases; Mucosal healing; anti-TNF alpha.

1.Introduction:

Chronic inflammatory bowel diseases (IBD), include several entities such as Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis, that can be serious and particularly debilitating. Several studies have agreed on a multifactorial origin incriminating a dysfunction of the intestinal flora, environmental factors and genetic factors[1]. Its treatment is first and foremost medical; however, surgery is reserved exclusively for patients presenting with complications or for those not responding to medical treatment.

The advent of biotherapies has considerably reduced the need for surgery, allowing clinical, biological and endoscopic improvement[2]. Consequently, endoscopy, which remains the cornerstone of the initial diagnosis, is also crucial during follow-up.

Achieving mucosal healing isthe main goal in the management of IBD, because it is associated with reducing the risk of dysplasia and colon cancer and therefore a better evolution in both short and long terms. It could also make it possible to select the patients in whom a therapeutic de-escalation would be possible.

Nowadays, new diagnostic approaches to mucosal healing (such as biological markers and imaging) should reduce the need for endoscopy[3].
The aim of our study is to specify the rate and predictive factors of endoscopic mucosal healing in patients with chronic inflammatory bowel diseaseson biotherapy.

2.Materials and Methods:

2.1 Study Design and Patients:

This is a descriptive and analytical retrospective study conducted in the hepato-gastroenterology department 1 of the Mohamed V Military Instruction Hospital in Rabat between January 2019 and March 2022, including 43 cases of IBD (Crohn's disease and ulcerative colitis) who were on Anti TNF alpha (Infliximab/Adalimumab) as monotherapy or in combination therapy, and who underwent pre-treatment and 1 year follow-up colonoscopies.
Assessing mucosal healing for Crohn's disease was based on the Simplified Endoscopic Score for Crohn's Disease (SESCD), as for ulcerative colitis, it was based on the Mayo Endoscopic Subscore. In both groups, endoscopic mucosal healing was defined as the absence of ulcerated lesions on the follow-up colonoscopy.

2.2 Predictor Variables and Data Source:

- Our demographic and clinical data were collected from the patients' medical records: Age, sex, type of IBD, age of onset, history of intravenous corticosteroid therapy, as well as severity of the flare-up in admission. The latter was assessed based on: Crohn's Disease Activity Index (CDAI) or Best score for Crohn's disease and Modified Oxford criteria for UC.
- Biological data were also collected before initiating the treatment and on the 1-year follow up colonoscopy, namely: CRP level, hemoglobin, White blood cell (WBC) count, albumin level and fecal calprotectin.
- Data regarding medical therapies administered before and during the study period, as well as any treatment adjustments, were also collected:

➔ Infliximab infusions were administered using a 5 mg/kg body weight dose intravenously over 2 hours at weeks: 0, 2 and 6 for the induction phase and then every 8 weeks for maintenance phase.

➔ Adalimumab was injected at a loading dose of 160 mg, then 80 mg and then 40 mg subcutaneously every two weeks.

➔ For patients receiving combination therapy, thiopurines were administered at the full dose (Azathioprine 2.0–2.5 mg/kg, Mercaptopurine 1.0–1.5 mg/kg) since the start of treatment.

2.3 Statistical Analysis:

Statistical analysis was performed using SPSS20 software taking into account the different variables: age, sex, type of IBD, age of onset, history of corticosteroid therapy, use of combo

therapy, severity of the flare-up, biological data on admission and on the one year follow up, and whether or not mucosal healing has been achieved.
➔Continuous (or quantitative) variables with normal distribution are presented as mean (standard deviation [SD]); non-normal variables are reported as median (interquartile range [IQR]). Qualitative (or categorical) variables are expressed as numbers and percentages.
➔When comparing biological parameters between baseline and endoscopic follow-up, the non-parametric Wilcoxon test was used, since the sample sizes were less than 30.
➔The assessment of the factors associated with mucosal healing used the binary logistic regression test in univariate and multivariate analysis.

3. Results:

3.1 Descriptive statistics:

A total of 43 patients with IBD were included, the overall mean age being of 40 years with a sex ratio of 1.15 (20 women for 23 men) and an overall age of onset of 33 years. As for corticosteroid therapy, all patients with UC had received intravenous corticosteroid therapy before starting anti-TNF alpha therapy. On the other hand, only 42% of CD patients had received corticosteroid therapy. The flare of the disease was judged severe on admission in 60% of patients with UC and in 57% of patients with CD.

Regarding the treatment:

- 80% of patients with UC were put on anti-TNF alpha and azathioprine (AZA) versus only 20% of patients on infliximab (IFX) alone
- 87% of patients with Crohn's disease were put on combo therapy.

For the initial biological assessment: CRP levels were higher in patients with UC than in patients with CD (with the average rate being of 84.8 versus 46.5), just likeWBC count (which were higher in UC patients). The mean hemoglobin level was the same for both UC and CD and the albumin level was somewhat lower in patients with UC than those with CD.

On the follow-up, there was a decrease in CRP and WBC levels both in the UC group and in CD as well as an increase in Hb and albumin levels for the 2 groups of diseases. Concerning fecal calprotectin, the overall mucosal healing rate was of 51% i.e22 out of 43 patients: 6 patients out of 10 (i.e. 60%) for UC and 16 patients out of 33 (i.e. 48.5%) for the CD group.

Table 1 reflects the descriptive statistics of the main demographic, clinical and biological data as well as the rate of mucosal healing in all of our patients.

Features	All patients	UC group	Chron'sdisease

	N= 43	N= 10	group N=33
Age (years)[1]	**40,12 +/- 13,59**	**40,3 +/- 14,36**	**40,06 +/- 13,57**
Sex[2]			
Man	23 (53,50%)	6 (60%)	17 (51,50%)
Woman	**20 (46,50%)**	4 (40%)	16 (48,50%)
Age of onset of disease[1]	33,81 +/-13,20	35,60 +/- 14,14	33,27 +/- 13,08
Corticosteroidtherapy			
No			
Yes	19 (44,19%) 43 (55,81%)	0 (0%) 10 (100%)	19 (57,60%) 14 (42,40%)
Combotherapy			
No	6 (13,95%)	2 (20%)	4 (12,10%)
Yes	37 (86,05%)	8 (80%)	29 (87,90%)
Severity			
No	18 (41,86 %)	4 (40%)	14 (42,4%)
Yes	25 (58,14 %)	6 (60%)	19 (57,60%)
Initial assessment			
CRP level	55,28±57,30	84,82+/- 90,07	46,51+/- 41,06
Hb	11,1+/- 2,4	11,4 +/- 2,59	11,17 +/- 2,47
WBC count	8483 +/- 3875	10030,30 +/- 6368,15	8000,62+/- 2661,33
Albumin	29,7+/-6,5	26,5 +/- 5,93	31,00 +/- 6,42
Follow up			
CRP level	16,8+/-24,2	17,42+/- 37,29	16,68 +/- 19,47
Hb	12,1 +/-2,0	12,5 +/- 1,15	11,99 +/- 2,24
WBC count	6067+/-2564	7490,00+/-3752,16	5636,83 +/- 1962,40
Albumin	34,8 +/-3,8	35,6 +/- 4,45	34,53+/-3,67
Faecalcalprotectin	389,7 +/- 380,3	421,33 +/- 389,83	381,15 +/- 383,42
Mucosal healing			
No	21 (48,80%)	4 (40%)	17 (51,50%)
Yes	22 (51,20%)	6 (60%)	16 (48,50%)

[1]: expressed as means and standard deviations; [2]: expressed in numbers and percentages
UC: Hemorrhagic rectocolitis. CRP: C-reactive protein. Hb: Hemoglobin. WBC: White blood cells. Alb: Albuminemia.

Table 1: **Descriptive statistics of the main demographic, clinical and biological data as well as the rate of mucosal healing in all of our patients**

3.2 Analytical statistics:

The univariate analysis of all the patients included in the study (both CD and UC) highlights the severity of the initial disease (OR= 0.13 / CI: [0.033; 0.542] / p=0.005), the CRP level (OR=0.81 / CI: [0.711; 0.940] / p=0.005), hemoglobin level (OR=1.99 / CI: [1.176; 3.396] / p=0.011) and faecal calprotectin (OR=0.97 / IC: [0.956; 0.994] / p=0.012) at follow-up as

statistically associated with endoscopic mucosal healing. However, the multivariate analysis by adjusting other parameters retains only the increase in faecal calprotectin level (OR= 0.98/ CI: [0.957; 0.999]; p= 0.045) as statistically associated with a lower chance of mucosal healing.

Table 2a**nalyses statistically factors associated to mucosal healing in all patients included in the study.**

Associated factors	**Univariate analysis**			**Multivariate analysis**		
	Brut OR	IC 95%	p-value	Adjusted OR	IC 95%	p-value
Age (years)						
< 40 y.o	1					
> 40 y.o	0,909	[0,275 ;3,008]	0,876			
Sex						
Man	1					
Woman	1,33	[0,401 ;4,437]	0,639			
Age of onset of disease						
< 30 y.o	1					
> 30 y.o	1,100	[0,332 ;3,640]	0,876			
Corticosteroidtherapy						
No	1					
Yes	0,615	[0,183 ;2,072]	0,433			
Disease						
UC	1					
Crohn'sdisease	0,627	[0,149 ;2,642]	0,627			
Combotherapy						
No	1					
Yes	6,562	[0,696 ;61,853]	0,100			
Severity						
No	1			1		
Yes	0,134	[0,033 ;0,542]	0,005	0,451	[0,021 ; 9,516]	0,609
Initial assessment	1,002	[0,991 ; 1,013]	0,727			
CRP level	1,182	[0,912 ; 1,531]	0,206			
Hb	1,000	[1,000 ; 1,000]	0,352			
WBC count	0,988	[0,893 ; 1,092]	0,811			
Albumin						
Follow up						
CRP level	0,814	[0,711 ; 0,940]	0,005	0,970	[0,815 ; 1,154]	0,731
Hb	1,998	[1,176 ; 3,396]	0,011	1,342	[0,481 ; 3,746]	0,574
WBC count	1,000	[1,000 ; 1,000]	0,467			
Albumin	1,254	[0,989 ; 1,591]	0,062			
Faecalcalprotectin	0,975	[0,956 ; 0,994]	0,012	0,978	[0,957 ; 0,999]	0,045

UC: Hemorrhagic rectocolitis. CRP: C-reactive protein. Hb: Hemoglobin. WBC : White blood cells.

Table 2: **Analytical statistics of factors associated to mucosal healing (in all patients included in the study)**

4. Discussion:

Mucosal healing in patients with IBD has become the primary goal of treatment. It leads to better long-term remission rates, better quality of life, less need for hospitalization and surgery, as well as lower neoplastic risk[4]. Immunosuppressive therapies such as methotrexate, thiopurines and anti-TNF-alpha have helped achieve this healing [5][6].

Emerging data indicate that early initiation of anti-TNF-alpha prevents mucosal damage in patients with IBD and thus leads to better long-term outcome[7].

Mucosal healing informs of treatment efficacy making it an important prognostic marker for long-term evolution[8].

The main aim of our study was to determine the predictive factors of this mucosal healing. Several studies have been carried out focusing on obtaining mucosal healing and the factors associated with this healing which includes[9]:

- A prospective study by Sipponem et al [10] showed that faecal calprotectin and lactoferrin were closely correlated with the endoscopic activity of Chron's disease under anti-TNF-α therapy. This study involved 15 patients with severely active CD and endoscopy was performed at weeks 0 and 12. In patients with mucosal healing (CDEIS (Crohn's Disease Endoscopic Index of Severity)< 3), the concentration of faecal calprotectin and lactoferrin fell significantly ($p < 0.001$).

- A randomized controlled double-blind SONIC trial [11]whose main objective was to assess the tolerance of Infliximab (IFX) in monotherapy and of the combination IFX plus Azathioprine (AZA) in moderate to severe CD patients having never received immunomodulatory treatment. The IFX+AZA combination was more effective than IFX monotherapy ($p=0.02$) for achieving remission without corticosteroids.

- Kiss et al[12]analyzed 210 Hungarian patients with CD and showedthatnormalization of CRP levels at week 12 is one of the strongestpredictors of clinicalefficacy and mucosalhealingduring the first year of treatmentwithAdalimumab (ADA) . In this study, it was revealed that normalization of CRP levels (defined as CRP < 10 mg/L) at week 12 after initiation of ADAtherapy was predictive of mucosal healing ($p= 0.001$). Clinical remission after 2 years of therapy and a strictly luminal disease also predicted mucosal healing.

In our study, we obtained a mucosal healing rate of 51.20% finding out that fecal calprotectin level ($p= 0.045$) on the 1-year follow-up colonoscopy is the only factor (among all demographic, clinical, and endoscopic data) which can be considered statistically associated with mucosal healing in IBD. However, when separately analyzing patient subgroups, no factor was statistically significant.

5. Conclusion:

In conclusion, endoscopy is the cornerstone of diagnosis and follow-up for IBD patients. However, due to the invasive and costly nature of endoscopic examinations, it was deemed necessary to develop non-endoscopic means of evaluation such as biological and radiological ones. Our study has retained fecal calprotectin as a predictor of endoscopic mucosal healing. Unfortunately, the main limitations of our study remain the relatively small number of patients compared to Western series and the failure to take into account certain factors such as the body mass index on admission as well as the notion of smoking.

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