ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-3145

Histological Remission in Ulcerative Colitis in Deep Remission under Treatment with Adalimumab

Antonio Tursi[1,2], Rosanna Nenna[3], Giovanni Musci[3], Walter Elisei[4], Marcello Picchio[5]

1) Territorial Gastroenterology Service, ASL BAT, Andria (BT);
2) Department of Medical and Surgical Sciences, Post-graduate School of Digestive Diseases, Catholic University, Rome;
3) Department of Pathology, Lorenzo Bonomo Hospital, Andria (BT);
4) Division of Gastroenterology, S. Camillo Hospital, Roma;
5) Division of Surgery, P. Colombo Hospital, Velletri Roma; Italy

ABSTRACT

Background & Aims: Histological remission (HR) has been recently demonstrated as the last therapeutic goal in ulcerative colitis (UC), but it is unknown whether and how it may occur. Our aim was to assess the histology during the follow-up of an UC population in deep remission under treatment with adalimumab (ADA).
Methods: We performed a retrospective study on 22 UC patients who were in deep remission and followed-up while receiving therapy with ADA. Colonoscopy in those patients was performed every year. Four-quadrant biopsies every 10 cm were obtained during each colonoscopy and assessed by hematoxylin and eosin stain. Histological activity was classified using the Geboes scale.
Results: A total of 22 patients were enrolled in the study. The mean follow-up of those patients was 28±7 months, and 2,592 biopsy specimens in total were taken during 108 colonoscopies performed during the follow-up. At the beginning of the follow-up, histological inflammation was found in 15/22 (68.2%) of patients in deep remissio while receiving maintenance ADA therapy, 8/22 (36.4%) of them with Geboes score ≥3.1. At the end of the follow-up, when patients were still in deep remission while receiving maintenance ADA therapy, only 4 patients (18.2%) had at least one biopsy specimen with evidence of any histological inflammation during the follow-up; only two patients (9.1%) had Geboes score ≥3.1.
Conclusions: Our study shows for the first time that UC patients in deep remission under ADA may reach HR, but it seems slower than other clinical or endoscopic goals.

Key words: deep remission – histological remission – adalimumab – ulcerative colitis.

Abbreviations: ADA: adalimumab; HR: histological remission; IFX: infliximab; UC: ulcerative colitis; TNF: tumor necrosing factor.

Address for correspondence:
Antonio Tursi, MD
Via Torino, 49
76123 Andria (BT), Italy
antotursi@tiscali.it
ORCID: http://orcid.org/0000-0001-5767-5541

Received: 11.11.2020
Accepted: 14.01.2021

INTRODUCTION

Histological remission (HR) has been recently pointed out as the last therapeutic goal in ulcerative colitis (UC) [1-3]. Although there is no consensus yet about the best histological index to use in real life [2, 4, 5], histological features seem to be a reliable predictor of disease outcomes after therapy, and HR seems to be the new frontier in the treatment of UC [1-3]. In fact, a recent meta-analysis. found that histologic and endoscopic remission correlated strongly, and less severe clinical disease activity, and topic 5 amino-salicylates and corticosteroid use were associated with higher HR rates [3].

Reliable literature data regarding HR under treatment with immunosuppressors or biologics are still lacking. However, HR under treatment with anti-tumor necrosing factor (TNF) α is not so promising. We previously failed to find a significant correlation between endoscopic and histological activity in UC under treatment with Infliximab (IFX) [6], and two recent studies failed to find a significant relationship between endoscopic and histologic response to adalimumab (ADA) in UC patients [7, 8]. However, we do not know whether and how the histologic inflammation in UC may change during deep remission under ADA. This considered, we assessed the histology during the follow-up of an UC population in deep remission under treatment with ADA.

METHODS

We performed a retrospective study on 22 UC patients who were in deep remission and followed-up while receiving therapy

with ADA. Deep remission in UC is defined as the reaching of clinical and endoscopic remission [9]. To be considered "in remission" for enrolment in this study, participants had to have Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo subscore for endoscopy ≤1 for at least 6 months and have had no changes in their UC medications (ADA) or any steroid use in the prior 6 months. Thus, we defined it as Mayo score ≤2 and Mayo subscore ≤1.

According to our standard procedure, colonoscopy in UC patients in deep remission under biologics was performed every year. During colonoscopy the colon was divided into 6 segments (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum). Four-quadrant biopsies every 10 cm were obtained during each colonoscopy and assessed by hematoxylin and eosin stain. Histological activity in all segments was classified using the Geboes scale [10] by two pathologists (R.N. and G.M.), blinded to the patient's disease status and endoscopic score. Histological remission was considered when Geboes score was <1.

The collection and analysis of data were performed using MedCalc® Release 7.3.0.1. Interobserver agreement was assessed by weighted kappa value and was classified as follows: poor, 0–0.20; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and excellent, 0.81–1.00. Fisher's exact test was used for categorical variables. The level of significance was p=0.05.

RESULTS

A total of 22 patients were retrospectively enrolled in the study (Table I). All patients were in deep remission at the beginning of the study; all were under treatment with ADA and took also 5 amino-salicylates orally. The mean follow-up of those patients in deep remission was 28±7 months. The mean number of biopsy specimens per colonoscopy was 24, and 2,592 biopsy specimens in total were taken during 108 colonoscopies performed during the follow-up.

All patients were under clinical and endoscopic remission during the follow-up, no change in treatment was performed during the follow-up (namely all patients continued to take ADA and 5 amino-salicylates at the same dose during the follow-up), and none of them were withdrawn during the follow-up.

The concordance between the two histopathologists in assessing inflammatory infiltrate was excellent (weighted kappa=0.89). The presence (Geboes score ≥1) and abnormality (Geboes score ≥3.1) of histological inflammation at the beginning and at the end of follow-up are reported in Fig. 1. At the beginning of the follow-up, histological features of inflammation were found in 15/22 (68.2%) of patients in deep remission while receiving maintenance ADA therapy, 8/22 (36.4%) of them with Geboes score ≥3.1. At the end of the follow-up, when patients were still in deep remission while receiving maintenance ADA therapy, only 4 patients (18.2%) had at least one biopsy specimen with evidence of any histological inflammation during the follow-up; only two patients (9.1%) had Geboes score ≥3.1, in both cases detected in the rectum (1 patient affected by pancolitis and 1 patient affected by distal colitis) (Table II).

Table I. Characteristics of the study group.

Males/Females	10/12
Indications for ADA treatment	
Steroid-dependent UC	15 (68.1)
Steroid-resistant UC	7 (31.9)
Mean (range) age (years) at the time of diagnosis	27.3 (18-49)
Mean (range) age (years) at the time of the first ADA infusion	29.20 (24-55)
Mean (range) duration (years) of the disease prior to ADA treatment	6 (1-8)
Mean (range) follow-up (months) under ADA treatment	34 (12-44)
Disease's localization	
Distal colitis	1 (4.5)
Left-sided colitis	9 (40.9)
Pancolitis	12 (54.6)
Smokers	8 (36.4)
Associated drugs	
5 Amino-salicylates	22 (100)
Mean (range) Mayo score at the beginning of the study	1 (0-1)
Mean (range) CRP at the beginning of the study (g/dl)	1.3 (0.5-4.8)
Mean (range) fecal calprotectin at the beginning of the study (mg/kg)	53.6 (21.5-101.4)

Values are expressed as number (percentage), unless otherwise specified. ADA: adalimumab; CRP: C reactive protein.

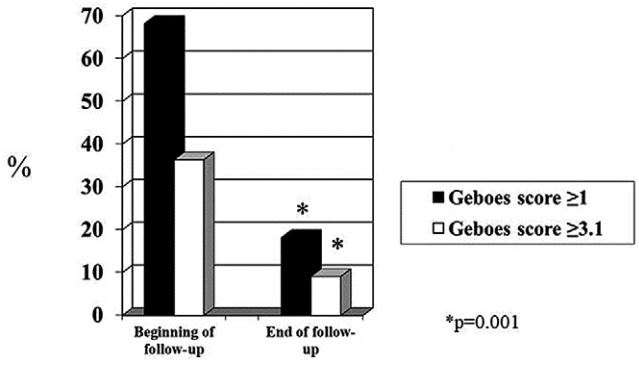

Fig. 1. Bar graphic showing the histological inflammation subdivided according to the Geboes score≥0.1 and the Geboes score ≥3.1 at the beginning and at the end of follow-up (p=0.001, Fisher's exact test).

DISCUSSION

Histological remission is becoming an important therapeutic goal because it is associated with lower disease relapse among UC patients reaching endoscopic remission [11].

Data about the HR when using IFX are not so promising. D'haens et al. [12] found that architectural alteration persisted in all adult UC patients reaching endoscopic remission under IFX, while significantly better results were obtained in pediatric UC patients [13]. Finally, we found that adult UC patients in deep remission under treatment with IFX failed to have a significant correlation with HR [6].

In this study we tried to observe what happens in UC patients in deep remission under ADA and receiving

Table II. Histological inflammation subdivided according to the extent of the disease at the beginning and at the end of follow-up

Histological inflammation	Pancolitis (12 pts)		Left-sided colitis (9 pts)		Distal colitis (1 pt)	
	Beginning of follow-up	End of follow-up	Beginning of follow-up	End of follow-up	Beginning of follow-up	End of follow-up
Geboes score ≥0.1	8 (66.6)	2 (16.6)	6 (66.6)	1 (11.1)	1 (100)	1 (100)
Right colon	8 (66.6)	-	-	-	-	-
Geboes score ≥0.1 but <3.1	6 (50)	-	-	-	-	-
Geboes score ≥3.1	-	-	-	-	-	-
Transverse	6 (60)	-	-	-	-	-
Geboes score ≥0.1 but <3.1	2 (16.6)	-	-	-	-	-
Geboes score ≥3.1	-	-	-	-	-	-
Left sided colon	4 (33.3)	1 (8.3)	6 (66.6)	-	-	-
Geboes score ≥0.1 but <3.1	3 (25)	1 (8.3)	3 (33.3)	-	-	-
Geboes score ≥3.1	1 (8.3)	-	1 (11.1)	-	-	-
Distal colon	4 (33.3)	1 (8.3)	4 (44.4)	1 (11.1)	1 (100)	1 (100)
Geboes score ≥0.1 but <3.1	3 (25)	-	-	-	-	1 (100)
Geboes score ≥3.1	3 (25)	1 (8.3)	2 (22.2)	1 (11.1)	1 (100)	-

Values are expressed as number percentage of patients (pts). (P=0.001, Fisher's exact test).

maintenance treatment with ADA. We found significantly better results than that obtained when using IFX, since almost 70% of UC patients in deep remission under ADA treatment reach HR during the follow-up. This finding differs significantly from that recently reported by other recent studies regarding the efficacy of ADA in obtaining HR. Fernández-Blanco et al. [7] found that HR (indicated by a Geboes score <3.0) was obtained in 31% of patients at 52nd week of ADA treatment, with a fair relationship with mucosal healing. More recently, the VARSITY double-blind placebo-controlled trial found that HR at week 52 (indicated by a Geboes score <2.0), occurred in only 3.1% (12 of 386) of the patients treated with ADA [8]. One possible explanation is linked to the different criteria used to describe HR. Another hypothesis is that patients with deep remission under ADA may have higher chances to reach HR. In fact, Yarur et al. [14] found that higher ADA levels were best associated with mucosal healing and HR [14]. Even if we did not assess ADA levels in our population, we can speculate that patients in deep remission may have higher ADA levels and therefore higher chances to reach HR.

This study confirms that HR is generally a slow cranial-caudal process also under treatment with ADA, and that distal colon seems to be the most refractory colonic district to HR. It has been recently reported that segmental HR in a proximal-to-distal direction occurs in the large majority of UC patients reaching HR [15], and the same process seems to occur also in UC under IFX in UC. We found that TNFα levels in rectal mucosa were not reduced despite clinical and endoscopic response to IFX [16]. Why this occurs is unknown. Leal et al. [17] found that anti-TNFα therapy significantly downregulated a subset of inflammatory genes even in patients who failed to achieve endoscopic remission. This probably means that other inflammatory ways have to be considered in UC patients in deep remission but with persistence of histological inflammation.

This study has clear limitations: the absence of the standard system for grading of histological activity, the retrospective design, the small population assessed.

CONCLUSIONS

Our study shows for the first time that UC patients in deep remission under ADA may reach HR, but it seems to be slower to achieve than other clinical or endoscopic goals. Further, prospective studies have to confirm these results and to determine the impact of HR in medium- and long-term clinical outcomes.

Conflicts of interest: None to declare.

Authors' contribution: A.T. conceived and designed the study. A.T., R.N., G.M., W.E., M.P. collected and analyzed the data, drafted the manuscript and critically revised it and approved the final version.

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