TRABAJO ORIGINAL

Ultrasound transmural healing correlates with higher adalimumab drug concentration in Crohn's disease only in the short-term

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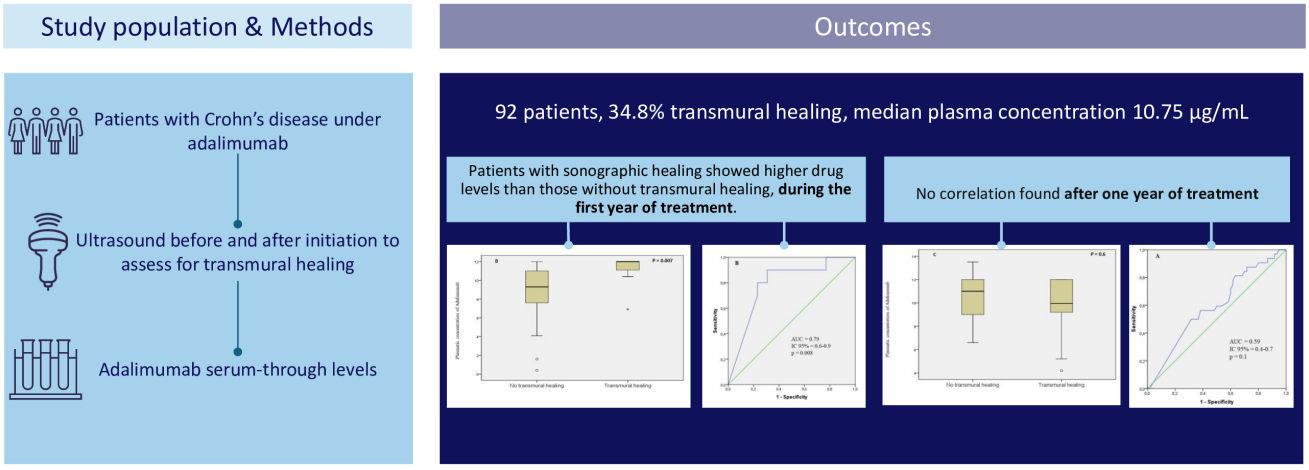

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Lay summary

During the follow-up of patients who suffer from Crohn's disease we perform ultrasound to measure the presence of intestinal healing. In patients who are under biological treatment with anti-TNF drugs, we also measure serum drug levels. This study compared both serum drug levels and ultrasound exams before and after starting therapy with adalimumab, an anti-TNF drug. We included 92 patients, from which a third showed healing in ultrasound after starting treatment. We found out that within patients that had been under therapy for less than a year, there was a correlation between higher serum drug levels and ultrasonographic healing. This relationship was not found when comparing patients that had been under treatment for more than a year. Therefore, the relationship between these two factors can be dynamic through time. This can be used in a treat-to-target strategy to optimize treatment for these patients.

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ABSTRACT

Background: anti-TNF drugs have revolutionized the treatment of Crohn's disease (CD) and have set new therapeutic targets. A direct correlation between anti-TNF trough levels and endoscopic healing in inflammatory bowel disease (IBD) patients has been established, but the association between drug levels and transmural healing assessed by ultrasound is not yet clearly defined.

Aims: to evaluate the correlation between the serum concentration of adalimumab (ADA) and sonographic transmural healing in CD patients at different times during follow-up.

Methods: in this retrospective, cross-sectional study, all patients with CD who were undergoing treatment with ADA in our center were included. Intestinal ultrasound (IUS) was performed before the initiation of the drug and for response monitoring. ADA serum-trough levels were compared between patients with and without transmural healing at different periods of time.

Results: ninety-two patients were included, and all patients showed signs of inflammatory activity in the baseline IUS. During IUS monitoring of the response to ADA, 34 (34.8 %) patients presented transmural healing. Among patients in the first year of treatment, those with sonographic healing showed higher median levels than patients without transmural healing (12.0 µg/ml *vs* 9.3 µg/ml, respectively; $p = 0.007$). There was no correlation between ADA levels and sonographic healing in patients undergoing treatment for over a year.

Conclusions: higher ADA trough levels correlated with transmural healing with ultrasound during the first year of treatment. This correlation was not found after one year of treatment.

Keywords: Crohn's disease. Intestinal ultrasound. Adalimumab. Therapeutic drug monitoring.

INTRODUCTION

Anti-tumor necrosis factor (anti-TNF) drugs are the first-line biologic treatment for Crohn's disease (CD). Given the common occurrence of non-response, close monitoring of inflammatory activity is necessary. When an inappropriate response becomes evident, determination of the serum drug concentration can be beneficial (1).

Assessment of transmural healing (TH) has been associated with better clinical outcome (3). A relationship between clinical outcome and plasma anti-TNF drug concentration has also been shown; and higher levels are associated with better outcomes (4). Several studies have shown a relationship between the highest concentration of anti-TNF drug and TH (5-9). However, studies carried out with intestinal ultrasonography (IUS) fundamentally assess the post-induction period, have limited sample sizes and their conclusions show that patients with lower serum drug concentrations do not achieve TH. For this reason, the objective of this study was to evaluate the relationship between the serum concentration of adalimumab (ADA) drug and sonographic TH at different times during the follow-up of patients with CD.

METHODS

Patient selection criteria

This was a retrospective observational, cross-sectional clinical practice study. Between January 2021 and December 2022, all patients with a diagnosis of CD (10) who were undergoing treatment in our center, for at least three months, with ADA were consecutively included. All patients had a baseline IUS performed prior to the start of treatment and at least one additional IUS for monitoring the response to treatment. In addition, all patients underwent our center's standard follow-up protocol, with visits every three to six months or every 12 months depending on clinical situation. Each visit included clinical assessment with the Harvey-Bradshaw index (inactive ≤ 4 points) (11), analytical results: fecal calprotectin (FC) and serum C reactive protein (CRP), and IUS examination, performed at the start of treatment and every three to six months if the inflammatory activity persisted or every 12 months in patients with deep remission. The determination of the serum concentration of ADA was performed after induction, in the event of loss of clinical response, in the presence of objective data of inflammatory activity (FC > 250 µg/g; CRP > 5 mg/l or pathologic IUS) (12) or routinely once a year for patients in deep remission.

The exclusion criteria were patients under 18 years of age, pregnancy, changes in the therapeutic regimen during the time between the IUS and the determination of the serum concentration of ADA and refusal of the patient to participate in the study.

Intestinal ultrasound

IUS was performed by an expert radiologist (RT) blinded to the analytical results, using an ultrasound unit (Aplio 80; Toshiba Medical Systems Corp., Tokyo, Japan). Patients had fasted overnight, and bowel preparation was not used. The following parameters were assessed: wall thickness of

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Artificial intelligence: the authors declare that they did not use artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

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the affected segment (a wall thickness > 3 mm was considered as abnormal); vascularization of the wall using color Doppler, with classification into the following grades: grade 0 (absent vascularization), grade 1 (barely visible vascularization), grade 2 (moderately visible vascularization), and grade 3 (markedly visible vascularization) (13); and presence of complications (stenosis or fistulas). TH was defined as wall thickness ≤ 3 mm, color Doppler grade 0 and the absence of complications (14).

Determination of the laboratory tests

Blood extraction and the collection of the fecal samples were usually carried out by the nurse (AC) of the Inflammatory Bowel Disease Unit. Blood extraction was performed on the day of drug administration just before administration.

The determination of the trough serum concentrations of ADA drug was carried out in a steady state situation. The analytical technique used was the enzyme immunoassay (capture ELISA, immunotolerant assay) (Promonitor®, Grifols). Samples were diluted 1:200. For ADA concentrations, the upper limit of quantification of the assay was 12.0 µg/ml, while the lower limit of detection was < 0.25 µg/ml. The range considered as therapeutic was 6-8 µg/ml for ADA (15).

For the correct collection of the FC sample, all patients were given the following instructions: collect the first stool sample of the day, avoid highly liquid or excessively solid stools, and the samples can be kept frozen after collecting (16). FC was determined by an immunoassay technique that is time-resolved fluorimetry using a lanthanide chelate (europium). The autoanalyzer used was the AQT90 (Radiometer, Copenhagen, Denmark), and the result is expressed in micrograms per gram of stool.

CPR was quantitatively determined by an immunoturbidimetric method of CRP in serum and plasma (Multigen CRP Vario®; Abbott, Wiesbaden, Germany). The result is expressed in milligrams per deciliter.

Statistical analysis

Basic descriptive statistics were used, including median and interquartile range (IQR) for continuous variables, and absolute frequency and percentages for categorical variables. Differences between FC, CRP and bowel wall thickness before and after treatment were analyzed using the Wilcoxon test. The McNemar test was used to assess the color Doppler grade and the presence of complications. For time independent evaluation of categorical variables, the Chi-squared test was used. Mann-Whitney U test was used to compare the medians between groups. Using the receiver operating characteristic (ROC) curve, the serum concentrations of ADA drug values that had the best accuracy to reflect TH were determined. The IBM Statistical Package for the Social Sciences version 22.0.0 2013 (IBM Corp., Armonk, NY, USA) was used, considering *p*-values < 0.05 as significant.

Ethical considerations

The approval of the Hospital Universitario Doctor Peset Ethics Committee was obtained to conduct the study (approval no. MONITORNOINVASIVO2020). The study protocol conforms to the Declaration of Helsinki. Patients were informed of its nature and gave their written consent.

RESULTS

Patients included and their characteristics

The main characteristics of the 92 included patients are shown in table 1. Treatment was administered with an intensified scheme in 27 (29.3 %) patients (12 patients 80 mg every two weeks and 15 patients 40 mg every week). At the time of monitoring, 36 (39,1 %) patients had less than one year of treatment. Regarding the monitoring of the inflammatory response at the time of the study, ten (10.9 %) patients presented clinical activity, ten (10.9 %) patients persisted with a CRP greater than 5 mg/l, and FC was greater than 250 µg/g in 25 (27.2 %) patients.

Plasma anti-TNF drug concentration

At the time of evaluation, six (6.5 %) patients had a subtherapeutic drug plasma concentration, 20 (21.7 %) fell within the therapeutic range, and 66 (71.7 %) patients

Table 1. *Demographic and clinical characteristics*

Variable	*n* (%)
Gender distribution (M/F)	48/44 (52.2/47.8)
Median age (IQR), years	40.5 (30.0-51.0)
Median disease duration (IQR), years	9 (4.0-16.0)
Age at diagnosis, n (%)	
< 16 years	9 (9.8)
17-40 years	70 (76.1)
> 40 years	14 (14.1)
Behavior at diagnosis, n (%)	
Inflammatory	40 (43.5)
Stenosis	17 (18.5)
Fistulizing	35 (38.0)
Location, n (%)	
Ileum	55 (59.8)
Colon	17 (14.5)
Ileum and colon	20 (21.7)
Perianal involvement, *n* (%)	14 (15.2)
Previous surgery, *n* (%)	29 (31.5)
Treatment duration, n (%)	
≤ 1 year	36 (39.1)
> 1 year	56 (60.9)

M: male; F: female; IQR: interquartile range.

exceeded this range. The median plasma concentration was 10.75 µg/ml (IQR 8.5-12.0). There were no significant differences between the plasma concentration of patients with standard regimen (median 11.1 µg/ml [IQR 8.3-12.0]) and patients with intensified doses (median 10.6 µg/ml [IQR 8.75-12.0]) (p = 0.9). Among the six patients with low plasma concentrations, antibodies to the drug were detected in only two patients.

Intestinal ultrasonography results

All patients showed signs of inflammatory activity in the baseline IUS. In this baseline exploration, some type of transmural complication was detected in 30 (32.6 %) patients: seven (7.6 %) patients showed fistulas, six (6.5 %) presented inflammatory masses smaller than 2 cm, and 17 (18.5 %) patients had inflammatory strictures. In the IUS monitoring of the response to anti-TNF treatment, 32 (34.8 %) patients presented TH. Table 2 shows the changes between the baseline IUS and the response to treatment.

Correlation between plasma concentration of adalimumab and transmural healing and other biomarkers

The median interval between the IUS and the plasmatic concentration of anti-TNF drug measurement was 5.0 days (IQR 3.1-7.0). When analyzing the overall number of patients included, no difference was found between the plasmatic concentration of ADA drug of the patients who presented TH *versus* those who did not; median 11.5 µg/ml (IQR 9.4-12.0) *vs* 10.25 µg/ml (IQR 8.1-12.0) (p = 0.1), respectively (Fig. 1).

Regarding the results based on treatment time (Fig. 1), among patients who had been on treatment for less than one year (median treatment time six months, IQR 5.0-12.0), there were significant differences in plasma drug concentration between those who had achieved TH and those who had not; median 12.0 µg/ml (IQR 8.7-12.0) *vs* 9.3 µg/ml (IQR 5.5-10.7) (p = 0.007), respectively. In this group, the assessment by quartiles showed a higher percentage

Table 2. *Findings of the baseline intestinal ultrasound and in the monitoring of adalimumab treatment*

Variables	Baseline	Monitoring	*p* (test)
Median wall thickness (IQR) (mm)	6.0 (5.0-7.0)	4.8 (2.0-6.0)	< 0.001 (Wilcoxon)
Doppler 1-3; *n* (%)	89 (96.7)	52 (56.5)	< 0.001 (McNemar)
Complications; *n* (%)	30 (32.6)	7 (7.6)	< 0.001 (McNemar)

IQR: interquartile range.

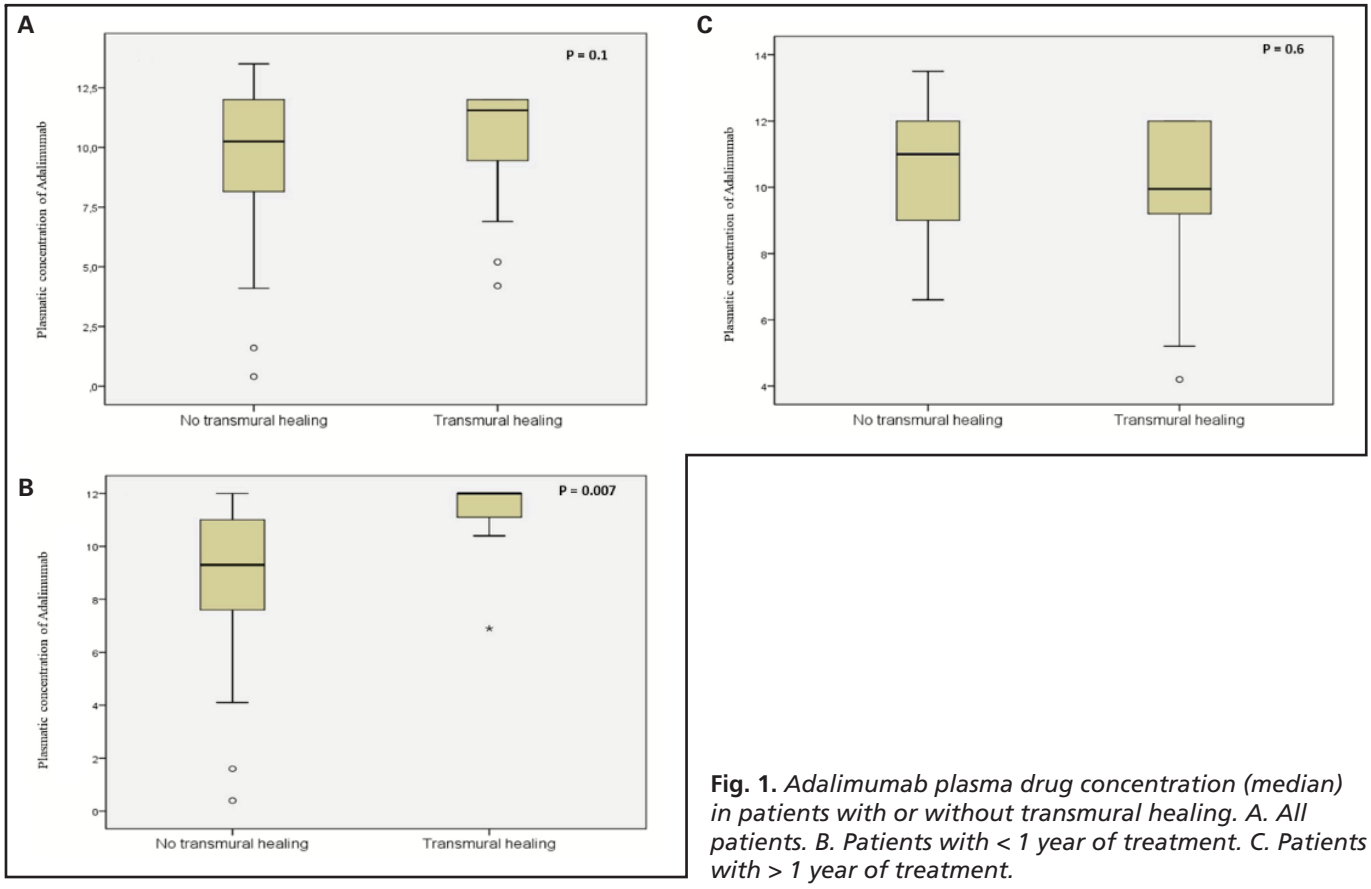

Fig. 1. *Adalimumab plasma drug concentration (median) in patients with or without transmural healing. A. All patients. B. Patients with < 1 year of treatment. C. Patients with > 1 year of treatment.*

of TH among the patients with the highest plasmatic concentration of ADA (Fig. 2). However, among patients with more than one year of treatment (median treatment time 57.0 months [IQR 28.0-85.0]), there were no differences in median plasma concentration of the drug between those with TH and those without: 9.9 µg/ml (IQR 7.7-12.0) *vs* 11.0 µg/ml (IQR 9.0-12.0) ($p = 0.6$), respectively.

Table 3 shows plasmatic concentration of ADA according to different monitoring parameters used. Among patients with an intensified treatment scheme, there was no evidence of a higher percentage of TH than among those patients with usual doses; 22.2 % *vs* 40 % patients ($p = 0.1$), respectively. Within the group of intensified patients, there were no significant differences between the plasmatic concentration of anti-TNF drug between those with TH (12.0 µg/ml [IQR 9.4-12.0]) and those without TH (10.0 µg/ml [IQR 8.2-12.0]) ($p = 0.2$).

Figure 3 shows the ROC curves of the plasmatic concentration of ADA to determine TH. The drug serum level yielding the highest accuracy to determine TH was 9.45 µg/ml (sensitivity 75 %; specificity 39 %). For the first year of treatment, the best cut-off level was 10.25 µg/ml (sensitivity 90 %; specificity 70 %).

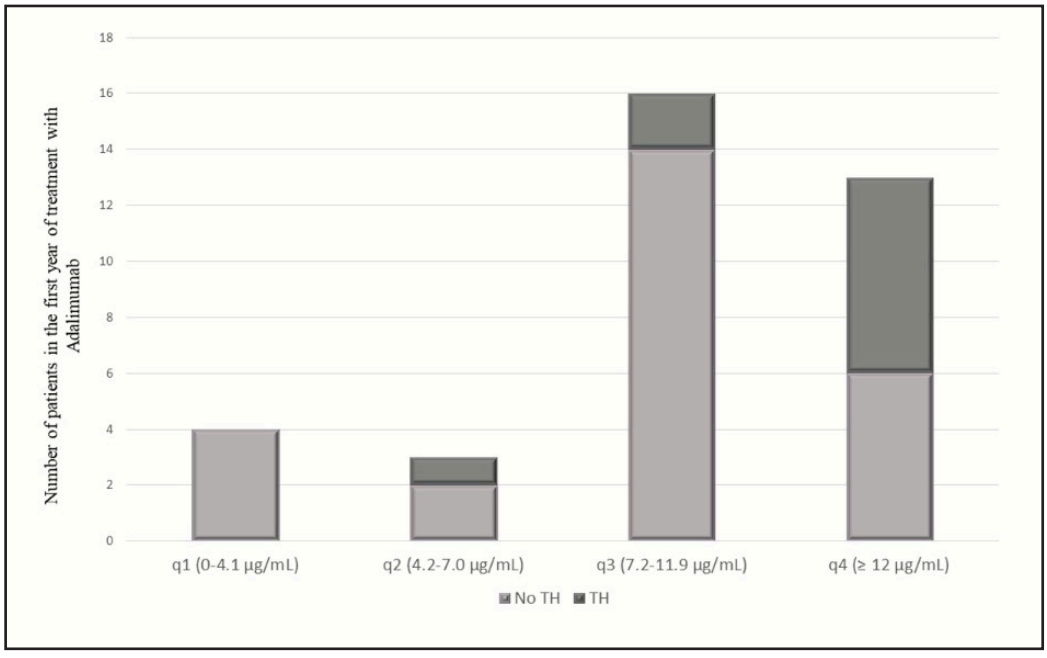

Fig. 2. *Number of patients with and without transmural healing by quartiles of adalimumab plasma concentration among patients with* **< 1 year of treatment.**

Table 3. *Plasmatic concentrations (µg/ml) of adalimumab according to different monitoring parameters*

Treatment duration (*n*)	Transmural healing			Harvey-Bradshaw < 4			C-reactive protein < 5 mg/l			Fecal calprotectin < 250 µg/g		
	Yes	No	*p**	Yes	No	*p**	Yes	No	*p**	Yes	No	*p**
Throughout (92)	11.5 (9.4-12.0)	10.2 (8.1-12.0)	0.1	10.9 (8.5-12.0)	10.4 (11.9-9.8)	0.6	10.9 (8.6-12.0)	9.4 (7.6-10.9)	0.06	10.0 (8.5-12.0)	11.9 (8.0-12.0)	0.3
< 1 year (36)	12.0 (8.7-12.0)	9.3 (5.5-10.7)	*0.007*	10.0 (7.7-12.0)	10.4 (11.2-6.0)	0.8	10.4 (8.0-12.0)	7.6 (6.8-8.6)	0.1	10.1 (8.0-12.0)	10.0 (7.7-12.0)	0.8
> 1 year (56)	9.9 (7.7-12.0)	11.0 (9.0-12.0)	0.6	11.1 (9.5-12.9)	10.4 (9.8-11.4)	0.6	11.1 (9.2-12.0)	9.9 (8.5-11.0)	0.2	10.0 (8.6-12.0)	12.0 (9.8-12.0)	0.1

All results expressed as median (interquartile range). ADA: adalimumab. *Mann-Whitney U test.

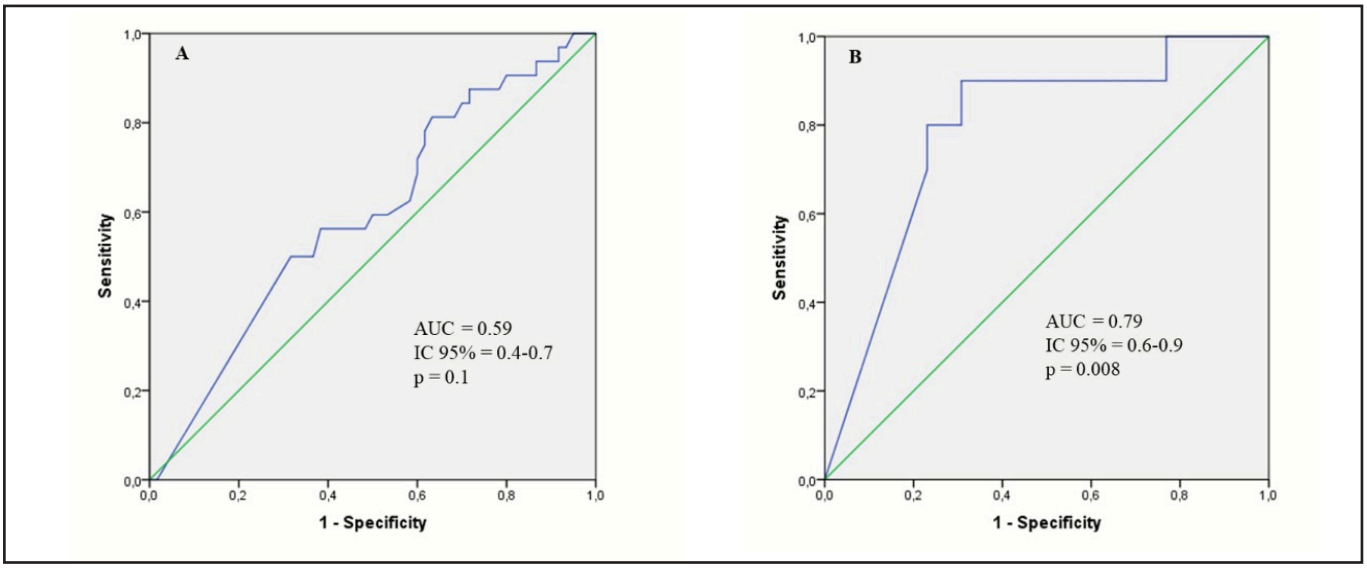

Fig. 3. *Receiver operating characteristic curve to determine the serum concentrations of adalimumab that had the best precision to reflect transmural healing (TH). A. All patients. B. Patients receiving treatment with adalimumab for < 1 year. AUC: area under the curve; 95 % IC = 95 % confidence interval.*

DISCUSSION

Our results show a significant correlation between a higher plasmatic concentration of ADA and TH, but only in those patients within the first year of treatment. The correlation between a higher plasma concentration of ADA and TH was not evident when we assessed patients with more than one year of treatment.

Other studies using IUS have shown a correlation between TH and a higher plasmatic concentration of anti-TNF drug (5-7). However, the timing of monitoring in these studies was within the first year of treatment; 14 weeks in the study by Han et al. (6) and a median of eleven months in the study by Ungar et al (5). In a sub-study of the TAILORIX trial (9), a significant difference was demonstrated between the plasma concentration of infliximab determined at week 14 and the TH determined by magnetic resonance at week 54. However, this relationship was not significant when the determination of the plasma concentration of infliximab was performed at week 54. Recently, a study has shown a lack of a relationship between TH and plasmatic concentration of anti-TNF drug (17).

The lack of a relationship between the plasma concentration of anti-TNF and TH is an issue of great importance. The intensification of treatment with the aim of achieving TH, if not guided by monitoring the plasma drug concentration, may be ineffective. In this sense, Vaughan et al. (7) showed a lower thickness of the intestinal wall among patients with standard doses compared with those patients with an intensified therapeutic scheme, without significant differences in the plasmatic concentration of anti-TNF drug in both groups. In line with these findings, our results showed that a higher percentage of TH was not found among the intensified patients, and the drug concentration among patients who achieved TH was not different from those who did not.

Both the absence of better results among intensified patients and the fact that the relationship between drug plasma concentration and TH is only evident among patients with less than one year of treatment can be explained by the pharmacological mechanisms associated with loss response to anti-TNF drugs. The lack of initial response to anti-TNF drugs may be related to a pharmacokinetic problem, where a lower drug concentration is associated with immunogenicity, which may appear at the start of treatment; or drug clearance among those with a high load initial inflammation (18). However, during maintenance, the most frequent mechanism for loss of response is pharmacodynamic (levels within the therapeutic range), as shown in two studies (19,20), although this has not been confirmed in a more recent cohort (21). In our study, the percentage of patients without TH with a low plasma drug concentration was higher (16.1 %) in patients who were in the first year of treatment than in those who had been on treatment for more than one year (6.6 %). As some authors propose (7,9), we think that when using the treat-to-target strategy, drug monitoring is necessary to correctly optimize the treatment, fundamentally when aiming for TH, which has been described as the most ambitious objective (9). Our work further supports this observation, given that only 34.8 % of patients showed TH. Prospective and longitudinal studies are needed to show the changes that have occurred in the relationship between the plasmatic concentration of drugs and the therapeutic objectives of CD.

The main limitations of this study were its retrospective and cross-sectional nature, which does not allow for the assessment of the evolution of patients in the different stages of treatment, and the low number of patients recruited.

In conclusion, the relationship between ADA concentration and TH may be dynamic throughout treatment. Plasmatic levels monitoring can optimize treatment in the treat-to-target strategy. Longitudinal studies on this topic are needed.

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