Adalimumab versus Azathioprine to Halt the Progression of Bowel Damage in Crohn's Disease: Application of Lémann Index

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Abstract

Background: The Lémann Index was recently developed to evaluate the cumulative bowel damage in patients with Crohn's disease.

Aims: To search for a difference between adalimumab and azathioprine to halt the progression of bowel damage in active Crohn's disease, using the Lémann Index.

Methods: A single-centre, retrospective study was conducted. Patients with Crohn's disease were included if they had colonoscopy and magnetic resonance enterography performed within 4 months from the start of adalimumab or azathioprine, and repeated after 12 months of therapy. Primary outcome was reached if the increase of Lémann Index after 12 months of treatment was < 0.3, the drug was not stopped, and the use of systemic steroids was continued for no more than 3 months.

Results: Ninety-one patients were enrolled, 31 (34.1%) of them treated with adalimumab and 60 (65.9%) with azathioprine. Sixty-seven percent of patients treated with adalimumab reached the primary outcome compared to 28.3% of patients treated with azathioprine (p = 0.0006). The Lémann Index in the group on adalimumab therapy decreased after 12 months (from 9.9 to 8.8), while in the group on azathioprine therapy it increased (from 7.7 to 8.8).

Conclusion: Treatment with adalimumab halts the progression of bowel damage in Crohn's disease while that with azathioprine does not.

Key Words: Anti-TNF; Colonoscopy; Magnetic resonance enterography; Small intestine; Thiopurine

1 Introduction:

Crohn's disease (CD) is a chronic disease characterized by different patterns including chronically active disease, intermittent disease and disease with remission periods over years. Considering the behaviour, CD at the onset is generally inflammatory, but later it turns into a fibrostenotic and fistulising pattern [1].

The Lémann Index (LI) is a recently developed score, aiming to stage CD by calculating the cumulative bowel damage (CBD), even in absence of clinical and biochemical activity [2]. In fact, the LI incorporates clinical, surgical, endoscopic and radiological findings of all segments of the gastrointestinal tract into a single score. The progression of bowel damage is defined as LI increase > 0.3 points during a period of 12 months [3].

There are still few studies in literature focusing on the course of LI following a therapy with biological or immunosuppressive agents. Two recent clinical trials have demonstrated the significant halt of CBD progression in a subgroup of CD patients after 12 months of treatment with an anti-tumor necrosis factor (TNF) drug ($p = 0.007$ and $p = 0.043$, respectively) [4,5].

The aim of our study was to evaluate, using the LI, for the first time in literature, the difference of efficacy between adalimumab and azathioprine therapies, in halting CBD progression among patients with active CD.

2 Material and methods:

In this single-centre, retrospective study, consecutive medical records of patients with CD diagnosis, selected from the database of the inflammatory

bowel disease (IBD) Unit of San Giovanni Antica Sede-Molinette Hospital, Turin, Italy, were analysed.

The inclusion criteria were:

- CD diagnosis confirmed according to ECCO guidelines [6];
- At least one year of follow-up available;
- Start of azathioprine or adalimumab therapy because of active CD;
- Colonoscopy and magnetic resonance enterography (MR-E) performed at T0 (within 4 months before starting the drug, according to the routine protocol of our centre). In addition, esophagogastroduodenoscopy (EGD) and/or pelvic MR performed if clinically necessary;
- Repetition at T1 (12 months +/- 2 months after the start of the treatment) of the instrumental examinations carried out at T0.

The exclusion criterion was:

- To be treated with combination therapy with azathioprine and adalimumab.

The choice between azathioprine and adalimumab was made, case by case, through clinical judgment of the 30-years IBD expert physician of the team (M.A.), mainly according to ECCO guidelines [6]. In practice, steroids-dependent patients were treated with azathioprine while steroid-refractory or -intolerant or azathioprine-failure patients were treated with adalimumab; patients with perianal disease were treated with adalimumab.

A numerical identification code was associated to each patient and a database was compiled with the collected information of each subject, reporting the following data:

- Personal data: age, gender, year of birth, smoking status;

- Clinical history: age at diagnosis, age at the start of drug treatment, years of disease, disease location;

- Inflammatory indexes and clinical activity: C-reactive protein (CRP), Harvey-Bradshaw index (HBI);

- LI (calculated by us, how reported in all studies focusing on this index);

- Presence of perianal disease;

- Instrumental examinations: colonoscopy, MR-E, EGD, pelvic MR;

- Therapy (duration and dosage): adalimumab, azathioprine, previous therapy with biological drug, dose-escalation of the biological drug, use of corticosteroids;

- Surgical history.

Primary outcome:

- To compare the percentage of patients in whom the treatment with azathioprine or that with adalimumab halted the progression of CBD, defined as an increase of LI < 0.3 in 12 months, without stopping the drug and without having used systemic corticosteroids for a period > 3 months.

Secondary outcomes:

- Evaluation of the progress of LI from 0 to 12 months in patients who used one of the two drugs;
- Correlation of the primary outcome with: years of disease before the start of the drug therapy, gender, smoking habits, previous intestinal resection, previous biological therapy, presence of perianal disease.
- According to Pariente et al. [2], evaluation of the progress in the following subcategories of LI: upper tract (U), small bowel (S), colon / rectum (C) and anal region (P). Each tract was further divided into segments: 3 segments for the upper digestive tract (oesophagus, stomach, and duodenum), 6 for the colon/rectum (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum), and 1 for the anus.

Focusing on the small bowel, each lesion within 20-cm length was considered to represent one segment, and the number of segments was capped at 20. For each organ, surgical procedures were defined in the protocol by grade of severity on an ordinal scale ranging from 0 (none) to 3 (resection). Stricturing and penetrating lesions were defined and illustrated in the protocol by grade of severity on an ordinal scale, ranging from 0 (none) to 3 (maximal) for diagnostic method. The most severe surgical procedure for each segment was assessed on the basis of medical history. Stricturing and penetrating lesions of maximal severity were assessed at each segment with the appropriate imaging techniques; for example, for stomach, these lesions were determined separately at each examination, using MRI, CT scan if available, and EGD. The rounded

coefficients that were applied to the number of segments with stricturing and penetrating lesions of each severity grade, in order to calculate the predicted organ index, are reported in the original paper [2].

2.1 Statistics

Considering the continuous variables normally distributed, the arithmetic mean was calculated; for those not normally distributed, the transformation into a logarithmic scale was performed and then the geometric mean was calculated, otherwise the median was calculated. In case of continuous variables normally distributed or normally distributed after logarithmic transformation, the independent samples t-test was used to compare the means of two independent samples. As for continuous variables, not normally distributed despite the logarithmic transformation, the Mann-Whitney test was performed. The chi-square test was used to compare two groups of categorical variables. The Wilcoxon test was performed to compare the trend of paired samples for non-normal continuous variables despite logarithmic transformation. The paired t-test was used to compare the trend of paired samples for continuous variables distributed in a normal manner or if they were normally distributed after logarithmic transformation. The multivariate analysis was performed applying the logistic regression test. The results with $p < 0.05$ were considered statistically significant.

The statistical analysis was performed with MedCalc Statistical Software version 18.9.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018).

2.2 Ethical considerations

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008). The study protocol was approved by the Ethical Committee “A.O.U. Città della Salute e della Scienza di Torino - A.O. Ordine Mauriziano - A.S.L. Città di Torino” on October 4, 2018 (code: 0098528).

3 Results:

The medical records of 300 patients, visited between January and April 2019, were analysed. Two hundred and nine patients were excluded from the study because they did not meet the inclusion criteria, or they met the exclusion criteria (**Figure 1**).

Figure 1.

Thus, 91 patients were included in the study. The clinical characteristics of this cohort is shown in **Table 1**.

Table 1.

Geometric mean of CRP was 7.0 mg/L, 95% confidence interval (CI): 5 – 9,8 mg/L; median HBI was 6 (mild clinical activity), 95%CI: 5 – 8 (mild – moderate clinical activity).

Of the 91 patients included in the study, 60 (65.9%) were treated with azathioprine and 31 (34.1%) with adalimumab. The comparison between the clinical characteristics of these two groups is shown in **Table 2**.

Table 2.

Regarding LI at T0, its median in patients treated with adalimumab was 9.9 (95%CI: 3.2 - 15.8) *versus* 7.7 (95%CI: 3.7 - 11.5) in those treated with azathioprine (p = 0.734). The CBD before starting the therapy was comparable in the two groups.

During the 12 months of follow-up, two patients (6.5%) stopped adalimumab and 16 patients (26.7%) stopped azathioprine due to side effects or primary failure. Three patients in the adalimumab group (9.7%) underwent to dose escalation every week.

Twenty-one (67.8%) of the 31 patients treated with adalimumab reached the primary outcome *versus* 17 patients (28.3%) out of 60 in the azathioprine group (p = 0.0006) (**Figure 2**).

Figure 2.

LI score, in patients treated with adalimumab, did not progress in a statistically significant manner during the year of therapy (from 9.9 at T0 to 8.8 at T1, p = 0.669) (**Figure 3**).

Figure 3.

In the azathioprine-treated group the LI score progressed from 7.75 at T0 to 8.80 at T1 (p = 0.074) (**Figure 4**).

Figure 4.

Regarding the subcategories of LI, the progression during the 12 months of therapy in the two groups (S and C) is reported in **Table 3**.

Table 3.

The analysis on the S subcategory showed that the LI at T0 and at T1 remained unchanged (1.30) among patients treated with adalimumab (no progression of damage occurred). On the other hand, in the group treated with azathioprine, an increase in the LI of 0.5 points was observed after 12 months with a statistical difference (p = 0.03). Focusing on the C segment, the value of the LI among patients treated with adalimumab decreased from 5.8 (T0) to 4.4 after one year (p = 0.899) while in the group treated with azathioprine the score did not change over time (5.8 at T0, 5.8 at T1, p = 0.181)

We also investigated the effect of possible predictors of drug response. The results are reported in **Table 4**.

Table 4

In multivariate analysis, none of these predictors reached statistical significance ($p > 0.097$).

4 Discussion:

CD is characterized by a persistent transmural inflammatory with consequent CBD which progresses over time even in patients with apparent clinical remission of symptoms [7]. In the past, the main outcome of medical therapies for CD was the clinical remission, intended solely as a resolution of symptoms, while currently the objectives are much more complex, including histological remission and halting the progression of CBD [8].

Our study demonstrated that adalimumab achieved a greater success than azathioprine in halting the progression of CBD, in avoiding dropping out of therapy for side effects and in reducing the assumption of corticosteroid for more than 3 months during the study period ($p = 0.0006$). This figure is relevant considering that patients treated with adalimumab had a longer history of disease than those treated with azathioprine (13 years *versus* 5 years) ($p = 0.056$), and the percentage of patients previously treated with biological drugs,

a possible factor of non-response, was higher (16.1% *versus* 5%, respectively) (p = 0.078) [9].

Our results are in line with the data of Bodini et al. [8] however, these authors selected patients in clinical remission and did not include specifically an adalimumab-treated group.

For the first time in the literature, we compared the efficacy of adalimumab *versus* azathioprine in the ability to halt the progression of damage in the four categories into which the gastrointestinal tract has been divided (U, S, C and P). Adalimumab therapy has prevented the damage progression in the small bowel (the analysis on the S subcategory showed that the LI at T0 and at T1 remained unchanged with LI = 1.30), while azathioprine did not (an increase in the LI of 0.5 points was observed after 12 months with a statistical difference, p = 0.03). Focusing on the C segment, the value of the LI among patients treated with adalimumab did not change significantly neither for adalimumab (p = 0.899), nor for azathioprine (p = 0.181). From these results it can be hypothesized that both adalimumab and azathioprine halt the damage progression in the colon / rectum. It was not possible to carry out the comparison in the subcategories U and P due to the low sample size of patients with damage in these locations.

We subsequently investigated whether potential predictive factors were related to the achievement of the primary outcome. The years of disease at the beginning of treatment were not a predictor of response either for adalimumab (p = 0.526), or for azathioprine (p = 0.324). The difference between the years of disease before the start of azathioprine (5 years) or adalimumab (13 years) was at the limit of statistical significance (p = 0.056). This could be due to the real-

life design of our study, in which azathioprine was the first choice in steroid-dependent patients, while adalimumab was prescribed in azathioprine-failure patients, in steroid-refractory or -intolerant patients or in those affected by perianal disease. Focusing on gender, there was a general tendency to a greater response among females for both drugs: this implies that gender does not correlate with the therapeutic choice. Being an active smoker did not influence the achievement of the primary outcome in the adalimumab group while in the azathioprine group a tendency towards a favourable response was observed in not active smokers (34.4%) compared to active smokers (21.4%). Focusing on surgical history, among patients treated with adalimumab the response was higher in those never operated compared with those who had a previous history of surgery ($p = 0.059$); on the contrary, in the azathioprine group, the drug appeared to have a slight tendency to be more effective in patients with history of at least one surgical resection (30.8% *versus* 26.4%). A trend, at the limit of significance ($p = 0.056$), to reach a favourable primary outcome, among patients with history of perianal disease, was observed in the adalimumab group while in the azathioprine group a double response rate was found (34.1% *versus* 15.8%) in patients without history of perianal disease. Finally, in the group treated with adalimumab, previous therapy with biological drugs did not represent a negative prognostic factor of response ($p = 0.690$).

From the study also emerged that 25% of patients treated with azathioprine suspended the drug because of side effects or primary failure *versus* 6% of those on adalimumab therapy. Hence, adalimumab had a much better safety and handling profile than azathioprine.

Conversely, it should be noted that the evaluation of the efficacy of azathioprine in a single year can invalidate the results in absolute terms, since, from a clinical point of view, the 12-month period may not be sufficient to observe a full therapeutic response of the immunosuppressant [10], permitting only to demonstrate a lack of worsening of the CDB (which should be the minimal target to continue azathioprine); in fact, a more objective evaluation of the efficacy of azathioprine could be performed only 2-3 years after the beginning of the drug.

Furthermore, the different economic impact on the health system deserves to be discussed with respect to the two pharmacological treatments. On average, in Italy adalimumab therapy has an annual cost of about € 2500-3000 per patient compared to € 200-250 with azathioprine [11].

The retrospective design is the major limitation of our study. However, it should be considered that the clinical characteristics of the two groups (included the CBD and so the state of disease progression) are not statistically different (a propensity-score analysis would not add benefit). Furthermore, the monocentric nature of the study, in which only one clinician (M.A.) gave indications to instrumental examinations and therapy to all patients, improves the homogeneity of the study. The use of MR-E did not induce a selection bias because in our centre all patients with CD of small bowel candidate to biologic drugs undergo to MR-E before starting this therapy and one year after. Another critical aspect is that not all the instrumental examinations indicated by the LI were performed in all patients; however, in the case of EGD and of pelvic MR, both literature and clinical practice suggest that these diagnostic methods

should be performed only in symptomatic patients [6]. Finally, the sample size was not very large, but this is the first study comparing, as primary outcome, adalimumab with azathioprine in halting CBD progression in active CD and it showed to have the statistical power to reach the primary outcome ($p = 0.0006$).

5 Conclusions:

In conclusion, adalimumab appears to have better therapeutic efficacy than azathioprine in halting the progression of CBD, assessed with LI, in patients with active CD. Considering the different mechanism of action and the lower cost of azathioprine, its role can still be hypothesized in patients with colonic involvement and without perianal disease. Adalimumab, on the other hand, is absolutely preferred in patients with CD located only in the small bowel or with a history of perianal disease. The data of our study deserve to be confirmed by prospective studies with larger sample size.

Conflicts of Interest Statement

None to declare.

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Table 1. Clinical characteristics of the included patients

Parameter	Value
Age at the beginning of the drug (mean)	41.5 years (range: 15-75 years)
Years of disease before drug starts (median)	5 years, 95%CI: 4 - 9.3
Number of surgeries	**None:** 51 patients (56.0%) **1 resection**: 22 patients (24.2%) **2 resections:** 14 patients (15.4%) **3 resections:** 1 patient (1.1%) **4 resections:** 3 patients (3.3%)
Sex	**Males:** 49 patients (53.8%) **Females:** 42 patients (46.2%)
Smoking habits	**Current:** 44 patients (48.4%) **Ex:** 21 patients (23.1%) **Never:** 26 patients (28.5%)
Montreal classification (localization)	**L1 (ileal):** 32 patients (35.2%) **L2 (colonic):** 16 patients (17.6%) **L3 (ileocolonic):** 35 patients (38.4%) **L4 (upper)**: 8 patients (8.8%)

Montreal Classification (Behaviour)	**B1 (non-stenosing, non-penetrating):** 25 patients (27.5%) **B2 (stenosing):** 44 patients (48.3%) **B3 (penetrating):** 22 patients (24.2%)
Perianal disease	**P (perianal disease):** 33 patients (36.3%)

CI = confident interval

Table 2. Comparison between azathioprine and adalimumab groups at T0

Parameter		adalimumab	azathioprine	*p*
Age at the beginning of the drug (mean)		45.1 years	39.6 years	0.806
Years of disease before the start of the drug (median)		13 years	5 years	0.056
Sex	Males	17 patients (54.8%)	32 patients (53.3%)	0.892
	Females	14 patients (45.2%)	28 patients (47.6%)	
Smoking habits	Current	16 patients (51.6%)	28 patients (46.7%)	0.665
	Never or ex	15 patients (48.4%)	32 patients (53.3%)	
Surgical resections	Never	14 patients (45.2%)	26 patients (43.3%)	0.868
	Ever	17 patients (54.8%)	34 patients (56.7%)	
Biological drugs	Naïve	26 patients (83.9%)	57 patients (95%)	0.078
	Experienced	5 patients (16.1%)	3 patients (5%)	

Disease localization	Only small bowel	11 patients (35.5%)	24 patients (40%)	0.676
	Colon involved	20 patients (64.5%)	36 patients (60%)	
History of perianal disease	Yes	14 patients (45.2%)	19 patients (31.7%)	0.207
	No	17 patients (54.8%)	41 patients (68.3%)	
HBI		6 95%CI: 5 - 8.4	6.5 95%CI: 5 – 8.1	0,817

HBI = Harvey-Bradshaw index; CI = confident interval

Table 3. Progression in the specific Lémann Index subcategories

Subcategory	Azathioprine		p	Adalimumab		p
	T0 LI	T1 LI	value	T0 LI	T1 LI	value
S	1.6	2.1	0.03	1.3	1.3	0.125
C	5.8	5.8	0.181	5.3	4.4	0.899
U	N/A	N/A	N/A	N/A	N/A	N/A
P	N/A	N/A	N/A	N/A	N/A	N/A

T0 = before drug start; LI = Lémann Index; T1 = 1-year follow-up; S = small bowel; C = colon / rectum; U = upper tract; P = anal region; N/A = not applicable due to the low sample size of patients with damage in these locations.

Table 4. Predictors of response.

Subcategory	Azathioprine		p value	Adalimumab		p value
	Primary outcome reached			Primary outcome reached		
	Yes	No		Yes	No	
Disease duration (years, 95%CI)	7 (1.0-17)	4 (2.6-7.4)	0.324	13 (2-15.9)	10.5 (4-20)	0.526
Sex						
male (n, %)	6/32 (18.8)		0.220	10/17 (58.8)		0.246
female (n, %)	11/28 (39.3)			11/14 (78.6)		
Smoking habits						
active (n, %)	6/28 (21.4)		0.271	11/16 (68.7)		0.903
non-smoking (n, %)	11/32 (34.4)			10/15 (66.7)		
Previous bowel resections						
no (n, %)	9/34 (26.5)		0.716	14/17 (82.3)		0.059
yes (n, %)	8/26 (30.8)			7/14 (50)		
Biologic-naïve						
yes (n, %)	N/A		N/A	18/26 (69.2)		0.690
no (n, %)	N/A			3/5 (60%)		
Perianal disease						

no (n, %)	14/41 (34.1)	0.145	9/17 (52.9)	0.056
yes (n, %)	3/19 (15.8)		12/14 (85.7)	

CI = confidence interval; N/A = not applicable

Figure 1. Flow chart of the inclusion process of patients

Figure 2. Comparison between adalimumab and azathioprine in reaching primary outcome (increase of Lémann Index after 12 months < 0.3 and drug not stopped and use of systemic corticosteroids for no more than 3 months)

Figure 3. Progression of Lémann Index in the adalimumab group

Figure 4. Progression of Lémann Index in the azathioprine group