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The Adherence to the Therapy in Inflammatory Bowel Disease: Beyond the Number of the Tablets

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ABSTRACT

Objectives: The therapy of the inflammatory bowel diseases is quite complex. A partial compliance increases the relapse probability and the health expenditure. The aim of the study is to correctly study the adherence to the therapy in a single centre eliminating the bias of a different relationship of trust with different doctors.

Materials and methods: We conducted a blind prospective study on the adherence evaluated for mesalazine.

Results: 376 patients were included in the final analysis. 57.4% of the patients never missed a single dose of mesalazine, 29.3% missed 1 or 2 doses, 7.4% missed 3 to 4 doses, 5.9% missed more than 5 doses. A greater adherence among males (P = 0.015) and, in ulcerative colitis, among the group with a disease duration of less than 2 years compared to the one with a disease duration between 2 and 5 years (P = 0.04) were found. In Crohn's diseases, among the patients who had never undergone to surgical interventions, the adherence was 49.6%, compared to 51.9% among patients who underwent to one surgical resection and 78.6% among patients underwent to multiple surgical resections (P = 0.001).

Conclusions: The factors influencing the adherence to the therapy are only partly related to the prescribed therapy, but also to factors affecting the patient life: to increase the adherence rate it would be necessary not only interventions on the posology but also the psychological support to the patient at the time of the visit.

Introduction

Inflammatory bowel diseases (IBD) are a group of diseases of disimmune origin; the principal IBD are Crohns' disease (CD) and ulcerative colitis (UC) [1].

The therapy of the IBD is quite complex and depend from the disease' behaviour and disease activity in the single patient: when the disease is active, the physician has to choose a therapy to induce disease remission and then establish a therapy to maintain the remission to reduce the number of the recurrences and so the progression of the disease [2]. When medical therapy is not sufficient, the patient will undergo to surgical resection, different depending on whether is affected by UC or CD [2]. Medical therapy of the IBD includes different drug category: aminosalicylates, corticosteroids, immunosuppressants, biologics. The efficacy of the aminosalicylates in the CD is controversial [3,4]. All the authors of the reviews and of the meta-analysis agree in the efficacy of the aminosalicylates in the treatment of the UC [5,6]. In any case, the mesalazine has been shown to be a very safe drug in all meta-analysis, with a very low rate of side effects [7]. Renal involvement is very rare and includes interstitial nephritis and nephrotic syndrome; patients with a pre-existing renal dysfunction are to be monitored in this regard [2]. The patients should take the therapy for all life, at least for the UC, in order to reduce the risk of disease relapse and, especially for patients with a colic localization, to reduce the risk of developing of colorectal cancer [2].

The importance of taking the drugs at a minimum effective dose and for long periods raises questions about the patient's actual compliance with the prescription: failure to evaluate the compliance with the prescribed therapy can induce the clinician to raise the therapeutic level by considering the therapy prescribed falsely

ineffective. A partial compliance and even more the arbitrary suspension of the drug increase the relapse probability, the self-medication and so the health expenditure.

Quantification of the compliance ranges from less than 40% [8] to about 93% [9] and correlations have been found with factors such as age, concomitant therapies for the same or other pathologies, level of education [9].

However, to date there are few studies done in a single centre, with a large number of patients and with indication of therapy given by a single physician: this latter point is important because the study of the correct adherence to the therapy in a single centre dedicated to IBD would allow the patient's behaviour to be evaluated by eliminating the bias of a different relationship of trust with different doctors.

Material and methods

We conducted a blind (the questionnaire was anonymous) prospective study. Patients in therapy for IBD were randomly recruited at the outpatient clinic of the "San Giovanni Antica Sede hospital", "AOU Città della Salute e della Scienza di Torino", between June 1, 2016 and January 20, 2017.

Inclusion criteria:

- age higher than 15 years old

- CD or UC diagnosed according to ECCO criteria [10,11]

- in continuous therapy with oral mesalazine

Exclusion criteria were:

- previous surgeries for UC

- lack of informed consent.

The patients underwent to an anonymous questionnaire (see Supplementary data) to be completed alone at the time of the visit, with questions regarding the patient (sex, age, education level, comorbidity, drugs taken for other pathologies), the disease (type of IBD, years after the diagnosis, the time elapsed from the onset of the symptoms to the definitive diagnosis) and the therapy (type of therapy taken, the number of missed doses in the last two weeks, the concern for side effects, the decision to skip doses when they feel better, alternative therapies). The disease activity was evaluated by the physician. To complete the clinical characteristics of the included patients the data about, e.g., the specific biologic drug used were extracted in the aftermath by their medical records (a code has been assigned to every questionnaire).

Adherence to the therapy was evaluated for mesalazine in the two weeks prior to the visit [12]. It was decided to consider the patients adherent to the therapy if they reported to have never missed a single dose of mesalazine in the last two weeks and not-adherent to the therapy if they reported to have missed at least one dose of the mesalazine in the last two weeks.

The outcome was the discovery of factors correlated with the tendency of the patient to have a reduced compliance: sex, age, type of IBD, disease duration, the time between the onset of the symptoms and the diagnosis, the disease activity, the type of therapy, the number of drugs taken for IBD, the number of drugs taken for comorbidities, the concern about possible side effects of the therapy, the taking of alternative therapies, the education level, previous surgery for CD.

For the CD the disease activity was calculated with the Harvey-Bradshaw index [13], for the UC with the partial MAYO score [14].

Statistical considerations

Regarding the univariate analysis, to analyse the categorical variables the Fisher's exact test was used. For non-parametric variables, their normal distribution was tested with the D'Agostino-Pearson test. To compare the average of two independent samples the t-test for independent samples, if the data were normally distributed, were used, the non-parametric Mann-Whitney test, if the data were not normally distributed not even after a logarithmic transformation, were used. To test whether two variables were associated, in case the distribution of the two variables was normal, the correlation test was used, in case the distribution of the two variables was not normal, the Rank correlation test was used. Regarding the multivariate analysis the Cox proportional-hazards regression has been used.

The statistical significance level was set to 95%.

The statistical analysis was performed by using MedCalc software (version 14.8.1).

Ethical statement

The work has been approved by the ethical committees of our institution and the subjects gave informed consent to the work.

Results

The questionnaire was administered at our tertiary centre to 523 patients: 147 patients were excluded because they were not in continuous therapy with oral mesalazine (98) or because they did not complete part of the questionnaire (49). The clinical characteristics of the included patients are reported in Table 1.

Table 1

216 patients (57.4%) had never missed a single dose of mesalazine, 110 (29.3%) subjects had missed 1 or 2 doses of the therapy over the past two weeks, 28 patients (7.4%) had missed 3 to 4 doses and 22 (5.9%) had missed 5 or more doses (Figure 1).

Figure 1

Univariate analysis

The major adherence data for the whole IBD group and for CD and UC are presented in Table 2.

Table 2.

Since the subgroup of patients with IBDU was numerically weak (8 patients), it was decided to not compare this group with patients with CD or UC, but to consider these patients only in the analyzes of the whole population of 376 patients.

Type of IBD

Among UC patients, the adherence was 60.6% (89 adherents versus 58 not-adherent patients), while the adherence was 55.6% (123 adherents versus 98 not-adherent patients) in the CD group (P = 0.35).

Sex, age, education level

The adherence to the therapy among all female patients in the study lower than among the male was 50.3% (P = 0.015) (Figure 2).

Figure 2.

Even in the group of CD patients the males were statistically significant more adherent (63.4%) than females (45%) (P = 0.006). Instead, in the group of UC patients the difference was not statistically significant (P = 0.6).

In the whole population (all the P were > 0.06), among CD patients (all the P were > 0.5), as well as among UC patients (all the P were > 0.2) the adherence' rates were not affected by the age.

The school diploma did not influence the adherence to the therapy (t-test for trend P > 0.38).

Disease duration, diagnostic delay

Among the whole population, the adherence difference between the group with a disease duration between 6 and 10 years and the group with a disease duration between 11 and 15 years resulted statistically significant (P = 0.01) (Figure 3).

Figure 3

In the group of patients with CD the difference between the adherence of the patients with disease duration between > 6 and 10 years and of the patients with disease duration between > 10 and 15 years was the closer to the statistical significance (P = 0.06).

In the group of patients with UC, the adherence difference between the group with a disease duration of less than 2 years and the one with a disease duration between 2 and 5 years resulted statistically significant (P = 0.04).

In the whole population the diagnostic delay did not influence the adherence (all the P were > 0.1), as well as in CD patients (all the P were > 0.07), and even less in UC (all the P were > 0.7).

Among the whole population (P = 0.82), CD patients (P = 0.88), as well as among UC (P = 0.9) the disease activity did not influence the adherence to the therapy.

Number of medications and fear of side-effects

Among patients with CD, 17.6% (39) reported that they used to miss some dose of the therapy if they felt better, while 82.4% (182) reported that they did not miss doses even during periods of subjective well-being. Among patients with UC, 17% (25) reported that they used to miss some dose of the therapy if they felt better, while 83% (122) reported that they did not miss doses even during periods of subjective well-being.

The number of drugs for IBD did not influence the adherence to the therapy (in both tests the P was at least 0.1).

The number of other medications for other pathologies did not influence the adherence to the therapy (in each comparison the P was at least 0.47).

The fear of side effects did not influence the adherence to the therapy (the adherence difference between the 3 groups was not statistically significant, t-test for trend P > 0.45).

The taking of not-prescribed did not influence the adherence to the therapy (P = 0.44).

Number of surgical resections in CD

In CD patients, the adherence was statistically significant higher (P = 0.001) in the group in which patients underwent to multiple surgical resections compared to the other two groups.

Multivariate analysis

At multivariate analysis the data which have been confirmed to be statistically significantly related to the increase in the adherence were:

- the males were more adherent to therapy than females in the whole population (P = 0.03) and in the subpopulation of patients with CD (P = 0.01)

- the higher adherence in the group with a disease duration between 6 and 10 years compared to the group with a disease duration between 11 and 15 years in the whole population (P = 0.03)

 - in CD patients, the higher adherence (P = 0.003) in the group in which patients underwent to multiple surgical resections compared to the other two groups.

Discussion

In our population the overall adherence resulted 57.4%: although it falls within the range of those published in the literature (11% - 86%) [12,16,17], the reason why it is much lower than that was found in some studies may result from the fact that our adherence definition is narrower (it was decided to consider the patients adherent to the therapy if they reported to have never missed a single dose of mesalazine in the last two weeks, while in other studies the patients are considered adherent even if they miss 1 or two doses [12,15,16]).

The first data reported to be statistically significantly related to the increase in the adherence was the male sex: in the general population, the males were more adherent to therapy than females (P = 0.015). This data was confirmed in the subpopulation of patients with CD (P = 0.006), while it was not true for subpopulation of UC patients (P = 0.6).

Regarding the disease' duration, in patients with UC the adherence difference occurred between the group diagnosed from less than 2 years and the group diagnosed between 2 to 5 years (statistically significant, P = 0.04), with an increase in the adherence between the first and the second group of the patients. In the patients with CD there seems to be a trend, not statistically significant (P = 0.06), in the reduction of the compliance among the group of patients with a disease that lasts from 5 to 10 years and the group of patients with disease that lasts from 11 to 16 years. This observation is probably due to the fact that, in the patients with UC, the start of the therapy at the time of the diagnosis induces a rapid reduction of the symptoms (especially of the ematochezia, a symptom that greatly worries the patient), inducing in the patient the wrong thought to be "cured" and therefore causing less attention to the therapeutic regimen. Subsequently, due to the likely recurrence of the symptomatology with poor adherence to the therapy and the

consequent delivery of the patient to a third level centre, the patient compliance increases again and will not to decrease significantly anymore.

The data about the disease' activity show that the compliance is not influenced by the phase of activity of the disease, as well as the number of the drugs taken for the IBD or other pathologies.

Some characteristics of the patient independent from the disease such as their age, the education level seem to not affect the adherence to the therapy.

For the first time in the literature, we found a statistically significant difference (P = 0.001), in the patients with CD, in the compliance between the patients who underwent to surgical resection. The turning point in the adherence to the therapy seems to be between the group in which the patients underwent to one surgical resection and the group in which the patients underwent to multiple surgical resections. These data suggest that the likely patient's concern for further surgery may induce him to increase his adherence to the therapy.

In chronic diseases, especially if they have a chronic-relapsing course, as in IBD, the patient' adherence to the therapy is far from optimal [17].

This problem has been addressed by a few number of studies in the literature, through various means of evaluation of varying complexity and reliability. In one of the published studies [12], the objective was to compare three methods of evaluation of the adherence to the therapy in order to find the most representative but, at the same time, easy to perform. Unlike in our study, only barriers related to the drugs (the patient' belief in the importance of maintenance therapy when asymptomatic, and their concerns about side effects) have been found.

In the study of Delven et al. [15], the authors have identified, in a small sample (27 patients, 78% with UC and 6 22% with CD), as possible obstacles to the adherence

to the treatment, factors such as: the concomitance of other priorities to be followed (many patients have reported as the workload or the breakage of the routine on vacation or on weekends may lead to forget to take the drugs), the fear for the social stigma resulting from the pathology, the need to go often to the pharmacy, the cost of the therapies, the concern for the side effects, the size and frequency with which the tablets should be taken and, finally, the belief that the therapy is not giving any benefit. Coenen et al. [16], instead, had identified, in 471 patients with IBD, as factors that decrease the adherence to the therapy: to be single, to be less than 40 years old, a high instruction level and the therapy based on mesalazine; while, to be a self-owner worker seems to better the adherence. In no study has been analyzed a factor like the number of surgical resections in CD, and our is the first study that highlight the attention on female CD patients and on UC patients after the first 2 years of diagnosis (the last two predictors of a weak adherence).

Strengths and limitations

A potential limitation of our study is that the overall adherence to therapy has been evaluated based on that of the adherence to mesalazine (but we did not inquire the dose, number of mesalamine tablets, that the patients were supposed to take). This choice was made because the mesalazine was considered the drug most easily "forgettable" by the patients and we considered significant even a single dose lost in a short period of two weeks.

Another potential limitation of our study is that it was decided to consider the patients adherent to the therapy if they reported to have never missed a single dose of mesalazine in the last two weeks and non-adherent to the therapy if they reported having missed at least one dose of mesalazine in the last two weeks: this definition

of adherence to the therapy could seem to be strict, but the mesalazine is a drug that is usually taken throughout life, so to miss one dose in the last two weeks may be reasonably associated to miss more doses throughout life. Therefore, an adherence of 57% is probably even overestimated.

Similar studies were present in the literature, but there are no studies with a so large number of patients included in a single centre and cared by a single physician (M. A.): this allowed us, for the first time in literature, to evaluate the patient' behaviour by eliminating the confounding factor that a different relationship of trust with different doctors could have on patient' compliance.

In conclusion, the study shows that the factors influencing the adherence to the therapy are only partly related to the pathology itself (incidence of surgical intervention and duration of illness) or to the prescribed therapy, but also to factors affecting the patient itself (sex, tendency to skip therapy if he feels better). For all these reasons, to increase the adherence rate to the therapy in patients with IBD, which is still too low, it would be necessary not only interventions on the drug' posology but also the psychological support to the patient at the time of the gastroenterological visit.

In our view, in order to improve patient compliance, the doctor should tailor the therapy for each patient, reducing the number of tablets at the lowest effective dose and emphasizing to the patient the importance of following his therapeutic regimen. The optimization of the doctor-patient relationship in this context would have the role of improving the adherence to the therapy and, in turn, of reducing the risk of complications related to the disease and the health care costs.

Further studies of the adherence performed together with general practitioners would be useful to assess the actual patient' adherence (through measurement of actual boxes of medication prescribed to the patient by his family doctor).

Conflicts of Interest Statement

None to declare.

References

[1] Longo D, Fauci AS, Kasper DL, et al.. Harrison's principles of internal medicine. New York (NY): The McGraw-Hill Companies; 2012.

[2] Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis. 2017;11:769-784.

[3] Singleton JW, Hanauer SB, Gitnick GL, et at. Mesalamine capsules for the treatment of active Crohn's disease: results oa 16-week trial. Gastroenterology. 1993;104:1293–1301.

[4] Feagan BG. Editorial: 5-ASA therapy for active Crohn's disease: old friends, old data and a new conclusion. Clin Gastroenterol Hepatol. 2004;2:376–378.

[5] Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006:CD000543.

[6] Sutherland LR, Martin F, Bailey RJ, et al. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. Gastroenterology. 1997;112:1069–1077.

[7] Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious

adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut. 2002;51:536–539.

[8] Selinger CP, Eaden J, Jones DB, et al. Modifiable factors associated with nonadherence to maintenance medication for inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:2199-2206.

[9] Trindade AJ, Tinsley A, Kornbluth A, Ullman TA. The MMAS-8, a screening tool for determining nonadherent behavior, should not be dismissed in IBD. Am J Gastroenterol. 2012;107:951-952; author reply 952.

[10] Magro F, Gionchetti P, Eliakim R, et al. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. J Crohns Colitis. 2017;11: 649-670.

[11] Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. J Crohns Colitis. 2017;11:3-25.

[12] Moss AC, Lillis Y, Edwards George JB, et al. Attitudes to mesalamine questionnaire: a novel tool to predict mesalamine nonadherence in patients with IBD. Am J Gastroenterol. 2014;109:1850-1855.

[13] Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980;1:514.

[14] Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008;14:1660-1666.

[15] Devlen J, Beusterien K, Yen L, Ahmed A, Cheifetz AS, Moss AC. Barriers to

mesalamine adherence in patients with inflammatory bowel disease: a

qualitative analysis. J Manag Care Spec Pharm. 2014; 20: 309-314.

[16] Coenen S, Weyts E, Ballet V, et al. Identifying predictors of low adherence in

patients with inflammatory bowel disease. Eur J Hepatol. 2016;28:503-507.

[17] Bucci C, Zingone F, Tammaro S, Iovino P, Santonicola A, Ciacci C. Factors

Predicting the Adherence to the Therapy of Italian IBD Patients. Gastroenterol

Res Pract. 2017;2017:6719345. doi: 10.1155/2017/6719345. Epub 2017 Aug

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Table 1. The clinical characteristics of the included patients (n = 376)

Disease, n (%)	
CD	221 (58.8)
UC	147 (39.1)
IBD-U	8 (2.1)
Sex, n (%)	
Males	214 (57)
Females	162 (43)
Age (years old), n (%)	
< 20	4 (1.2)
20 - 30	47 (12.1)
31 - 50	152 (40.5)
51 – 70	145 (38.7)
> 70	28 (7.5)
Disease duration (years), n (%)	
< 2	27 (7.2)
2 - 5	55 (14.5)
6 - 10	87 (23.3)
11 – 15	61 (16.2)
➢ 15	146 (38.8)
Disease activity	
remission	252 (67.1)
mild to moderate	71 (18.8)
severe	53 (14.1)

Drugs in addition to the mesalazine	
azathioprine	70 (18.6)
adalimumab	43 (11.4)
prednisone	93 (24.7)

Table 2. Adherence for the whole inflammatory bowel disease group, Crohn's disease and ulcerative colitis

	IBD (Adherent/ not-adherent)	CD (Adherent/ not-adherent)	UC (Adherent/ not-adherent)
Sex			
• F	81/80	43/52	36/26
• M	135/80	80/46	53/32
Age			
• <=30	30/20	18/12	11/7
• 31-50	77/75	47/47	29/27
• 51-70	89/55	53/34	35/20
• >70	20/10	5/5	14/4
Disease duration (years)			
• <2	14/13	8/6	4/6
• 2-5	35/20	16/13	19/6
• 6-10	58/29	31/18	25/11
• 11-15	28/33	16/21	12/11
• >15	81/65	52/40	29/24
Diagnostic Delay			

• <1	144/119	72/67	71/50
• 1-5	53/26	39/18	13/6
• >5	19/15	12/13	5/2
Disease activity			
• severe	29/23	14/13	14/9
• mild/ moderate	43/29	29/21	13/7
• remission	144/108	80/64	62/42
Number of drugs for IBD			
• 1	77/73		
• 2	69/39		
• 3	69/49		
Number of drugs for other diseases			
• 0	95/74		
• 1	47/41		
• 2	34/21		
• 3	12/8		
• 4	8/9		
• >=5	20/7		

Fear of side
effects

- very
worried
102/84

- quite
worried
88/55

- slightly
worried
26/21

Not-
prescribed
therapies

- 0
177/126

- >=1
39/34

School
diplomas

- element.
school
21/15

- second.
school
62/35

- high
school
105/82

- degree
28/28

Surgical
resection

- 0   62/63

- 1   28/26

- >=2   33/9

IBD = inflammatory bowel disease; CD = Crohn's disease; UC = ulcerative colitis; F = female; M = male; element. = elementary; second. = secondary

Figure 1. Adherence to mesalazine therapy in the two weeks prior to the visit in patients affected by inflammatory bowel disease

Figure 2. Sex and adherence to the therapy in the two weeks prior to the visit in patients affected by inflammatory bowel disease

Figure 3. Influence of the disease duration on the therapy adherence in the two weeks prior to the visit in patients affected by inflammatory bowel disease