Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

ORIGINALS
Bilingual edition English/Spanish

Adherence to treatment with adalimumab, golimumab and ustekinumab in patients with inflammatory bowel disease

Adherencia al tratamiento con adalimumab, golimumab y ustekinumab en pacientes con enfermedad inflamatoria intestinal

María Calvo-Arbeloa[1], Ana María Insausti-Serrano[2], Amaya Arrondo-Velasco[1], María Teresa Sarobe-Carricas[1]

[1]Pharmacy Department, Complejo Hospitalario de Navarra, Pamplona. Spain. [2]School of Health Sciences, Universidad Pública de Navarra, Tudela. Spain.

Author of correspondence
María Calvo Arbeloa
Servicio de Farmacia
Complejo Hospitalario de Navarra
Calle Irunlarrea, 3,
31008 Pamplona (Navarra), Spain.
Email:
mariacl1640@gmail.com

Received 13 September 2019;
Accepted 16 December 2019.
DOI: 10.7399/fh.11325

How to cite this paper
Calvo-Arbeloa M, Insausti-Serrano AM, Arrondo-Velasco A, Sarobe-Carricas MT. Adherence to treatment with adalimumab, golimumab and ustekinumab in patients with inflammatory bowel disease. Farm Hosp. 2020;44(2):62-7.

Abstract

Objective: Inflammatory bowel disease comprises a group of chronic relapsing inflammatory disorders affecting the bowel. In the last decade, the advent of biological drugs brought about a drastic change in the treatment of the disease. Adalimumab, golimumab and ustekinumab are three biologic agents that patients can self-administer subcutaneously after collecting them from the pharmacy department. However, for the treatment to be effective, adherence is paramount. The purpose of the present study is to evaluate adherence in patients who collected all three drugs from the dispensary of a tertiary care hospital.

Method: A cross-sectional observational analysis was carried out of patients who had been receiving treatment with adalimumab, golimumab and ustekinumab for at least four months. The medication possession ratio was calculated based on information extracted from the pharmacy dispensing records. Patients with a ratio ≤ 85% were enrolled in the study and asked to respond to Morisky-Green Medication Adherence Questionnaire.

Results: One-hundred and seventy-eight patients were included, of whom 60.1% (107) were male and 30.9% (55) had been treated previously with other biologics. According to the pharmacy dispensing records, mean adherence was 91.79%, with 45 patients (25.28%) classified as scarcely compliant (≤ 85%). The Morisky-Green Medication Adherence Questionnaire revealed that carelessness about administering the drug

KEYWORDS
Therapeutic adherence; Biological therapy; Adalimumab; Golimumab; Ustekinumab; Inflammatory bowel disease.

Resumen

Objetivo: La enfermedad inflamatoria intestinal es un grupo de trastornos crónicos, inflamatorios y recidivantes que afectan al intestino. En la última década, los fármacos biológicos han supuesto un gran cambio en la terapia de esta enfermedad. Adalimumab, golimumab y ustekinumab son tres de ellos que se administran por vía subcutánea tras su dispensación en los servicios de farmacia de los hospitales. Para que se alcance la efectividad del tratamiento es necesaria una adecuada adherencia al mismo. El objetivo del presente trabajo fue evaluar la adherencia en pacientes que recogían los tres fármacos en el servicio de farmacia de un hospital de tercer nivel.

Método: Se realizó un estudio analítico observacional de corte transversal en el que se incluyó a pacientes que recibían tratamiento con los anteriores fármacos durante al menos cuatro meses. Se recogió la tasa de posesión de la medicación proporcionada por el registro de dispensaciones y se seleccionó a los pacientes que presentaron un valor inferior o igual al 85%. A estos pacientes se les aplicó el cuestionario de medida del cumplimiento terapéutico de Morisky-Green.

Resultados: Se incluyeron 178 pacientes, de los cuales el 60,1% (107) fueron hombres y el 30,9% (55) habían sido tratados con otros fármacos biológicos previamente. La adherencia media, según el registro de dispensaciones, fue del 91,79% y se clasificó a 45 pacientes (25,28%) como mal adherentes (≤ 85%). La no administración en la fecha indica-

PALABRAS CLAVE
Adherencia terapéutica; Terapia biológica; Adalimumab; Golimumab; Ustekinumab; Enfermedad inflamatoria intestinal.

at the right time and forgetfulness were the main reasons for therapeutic non-adherence. Female sex (*odds ratio* 0.42; $p = 0.013$) and lengthy treatments ($p = 0.002$) were associated to lower adherence rates.
Conclusions: Although most patients in the studied population were seen to be compliant, low levels of adherence were observed in a number of patients who would benefit from interventions aimed at boosting their adherence. It must be said, however, that the statistical power of this study should be enhanced in order to increase the significance of the results obtained.

da y el olvido se identificaron como principales razones de la falta de cumplimiento terapéutico según el resultado del test de Morisky-Green. El sexo femenino (*odds ratio* 0,42; $p = 0,013$) y la duración del tratamiento ($p = 0,002$) se asociaron a una peor adherencia a la medicación.
Conclusiones: El porcentaje de adherencia obtenido resultó elevado en la población de estudio, pero se identificaron pacientes mal cumplidores susceptibles de recibir intervenciones para mejorar su adherencia. No obstante, se debería aumentar la potencia estadística para mejorar la validez de los resultados obtenidos.

Introduction

Inflammatory bowel disease (IBD) comprises a group of chronic relapsing inflammatory conditions mainly affecting the bowel. Such conditions are Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC)[1]. Although these conditions have of late shown an increasing incidence, efforts to determine their etiology have so far been fruitless[2,3].

As regards clinical management, fecal calprotectin (FC) is a biomarker that makes it possible to accurately identify the presence of mucosal lesions and correlate the extent of mucosal damage to the response to the treatment applied[4].

The goals of treatment in patients with IBD include inflammation suppression, mucosal healing and symptom remission. To achieve them, clinicians can avail themselves of two classes of drugs: biologics and non-biologics (aminosalicylates, corticosteroids, antibiotics, immunomodulators, prebiotics and probiotics)[5].

The former class of drugs heralded an about-face in the therapeutic approach to IBD. Currently approved drugs in this category include infliximab, vedolizumab, adalimumab, golimumab (only for UC) and ustekinumab (only for CD). These agents modulate inflammation, inducing and maintaining the clinical response[6]. According to GETECU (Spanish Working Group on CD and UC), first-line treatment in patients with these conditions should be based on conventional (non-biologic) drugs, with biologics to be reserved for patients who fail conventional agents. The exception to this rule would be patients with an aggressive onset, where biologics could be used as first-line treatment[7,8].

For a drug to be optimally effective, good therapeutic adherence is of the essence. The World Health Organization (WHO), defines adherence as the extent to which a person's behavior (taking medication, following a diet and/or executing lifestyle changes) corresponds with agreed recommendations from a healthcare provider.

A concept that is akin yet different from adherence is persistence, which is defined as the length of time over which treatment is maintained[9].

According to a systematic review carried out in 2013 by López *et al.*, adherence to adalimumab and infliximab is highly variable, ranging from 36.8 to 96%[10].

Poor therapeutic adherence could result in the loss of clinical response and a higher risk of developing adverse reactions, which tend to impair the patients' quality of life and increase the healthcare bill[11].

An understanding of the factors that may potentially influence treatment adherence could help identify patients likely to be poor adherents so that more attention can be focused on them. These factors can be classified into 4 categories: demographic (sex, age…); clinical (IBD type, age at diagnosis…); treatment-related (type of drug, administration route...); and psychosocial (quality of life, perception of the disease…)[12].

Several methods have been developed to measure adherence in patients with chronic conditions. The most common ones are those based on questionnaires and those based on pharmacy dispensing records.

As regards questionnaires, the most commonly used validated questionnaires to determine adherence in patients with IBP are the following: the Morisky-Green Medication Adherence Questionnaire (MAQ)[13]; the Visual Analog Scale (VAS); the Forget Medicine Scale[14]; and the 5-Medication Adherence Report Scale (MARS-5)[15], commonly used to determine adherence in patients with chronic conditions. The 8-item Morisky Medication Adherence Scale, an IBD-specific scale developed based on the MAQ questionnaire, was also used[16].

The medication possession ratio (MPR) is an easy-to-calculate low-cost tool to determine adherence to a given medication. In the case of anti-TNF agents, it has been shown that an MPR < 80% is associated with a loss of response, which results in a poorer prognosis[17].

According to the literature, the most accurate estimation of treatment adherence is usually obtained by combining two methods such as MPR and self-administered questionnaires[18].

The overarching goal of the present study was to use the MPR score to determine adherence to treatment with adalimumab, golimumab and ustekinumab in patients afflicted with IBD who obtained such agents from the pharmacy dispensary of a tertiary care hospital.

Secondary endpoints included a comparison of the adherence rates obtained using the MAQ questionnaire and the MPR scale (in the subgroup of patients where adherence was ≤ 85%); an identification of factors responsible for non-adherence; an analysis of the relationship between adherence and effectiveness of treatment (according to the FC levels present) in patients with adherence ≤ 85%; and, lastly, an evaluation of persistence and the reasons why previous treatments with biologic agents were discontinued.

Methods

Between January and June 2019. a cross-sectional observational analysis was carried out to determine adherence to treatment drawing upon data obtained from the dispensation records of the pharmacy department of a tertiary care hospital. Potential causes of non-adherence were analyzed based on the answers to the MAQ questionnaire given by the subgroup of patients exhibiting adherence 85% according to the pharmacy dispensing records.

Inclusion criteria were as follows: patients had to be older than 18 years; they were required to have been diagnosed with either CD or UC; and they had to have been on adalimumab, golimumab or ustekinumab for four months or longer. They were also required to have a MPR ≤ 85%. Indeed, although most studies use an 80% threshold[10], a decision was made to establish an 85% cutoff in order to enhance the statistical power of the results. Patients with disabling mental illness were excluded.

The variables recorded for the whole patient population were sociodemographic (age, sex) and clinical (type of treatment, length of treatment, previous use of other biologics and use of concomitant drugs). In the poor adherence group the variables analyzed fell into two groups: sociodemographic variables (weight, height, smoking status, educational status and occupational status) and clinical variables (diagnosis, age at diagnosis, duration of the disease [in months], reason for discontinuation of other biologics, MAQ questionnaire results, discontinuation of treatment, hospital admissions, infections requiring deferral of treatment; and FC levels).

The MPR rate was calculated using data from the pharmacy dispensing records corresponding to the previous 4 months. The formula is as follows:

$$TPM = [(\text{nr of units dispensed} - \text{nr of units returned}) / (\text{nr. of units prescribed})] \times 100$$

MAQ is a standardized self-administered questionnaire designed to measure therapeutic adherence on the basis of four yes/no questions that the patient must answer[13].

The analysis also investigated whether patients had received any previous biological treatment, the reasons for discontinuing it and their persistence, which was calculated as the length of treatment from the initial to the last prescription issued.

The SSPS 25.0 software package was used for the statistical analysis. An initial analysis was made of the whole patient population, which was followed by a second analysis that only included the low-adherence subgroup. First of all, an univariate analysis was performed. Differences between continuous variables were calculated using either Student's t-test or its nonparametric equivalent to identify differences between continuous variables (depending on normality). The chi-squared test was used for categorical variables. Significant variables ($p \leq 0.05$) were included in a logistic regression model.

Prior to filling in the questionnaire, the low adherence patients included in the study ($n = 32$) were required to sign an informed consent form granting the research team access to their clinical records. The study was authorized by the relevant Ethical Committee.

Results

Figure 1 provides details on patient adherence to the different types of treatment. Firstly, the pharmacy dispensation records for the 178 patients who met the inclusion criteria were used to determine their adherence to treatment over the previous four months. The records revealed that 45 of those patients exhibited an adherence rate ≤ 85%. Of those 45 patients, only 32 were eventually included in the study.

Of the 13 patients who were not included, 6 had discontinued their treatment, 1 had to be admitted for acute leukemia, 4 did not show up to collect their medication, and another 2 patients refused to participate.

Of the total sample, 107 (60.10%) subjects were male, with a mean age of 46.08 (14.86) years. Of them 136 (76.40%) were treated with adalimumab, 15 (8.42%) with golimumab and 27 (15.16%) with ustekinumab. Mean duration of treatment was 135.18 (93.33) weeks. Forty-six patients (25.80%) received concomitant treatment with mesalamine and 55 (30.90%) had received previous treatment with other biologics, particularly infliximab (22.50%). The demographics of the poor adherence group are shown in table 1.

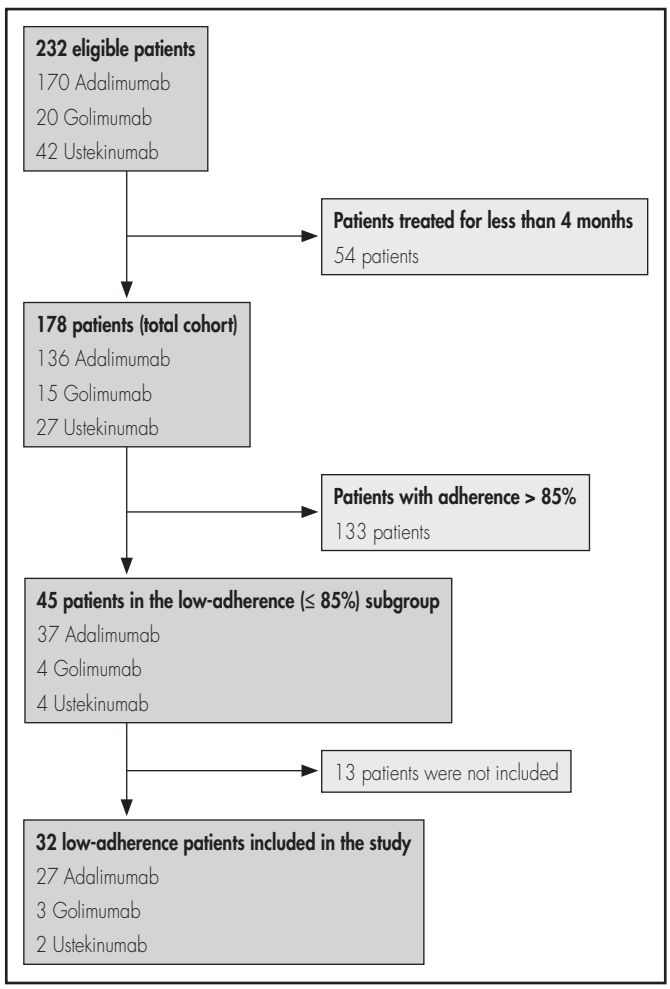

Figure 1. *Overview of the study cohort.*

A mean adherence rate of 91.79% (± 11.62) was obtained for the 178 patients included in the study. Mean adherence was 91.15% for adalimumab, 91.74% for golimumab and 95.05% for ustekinumab ($p = 0.045$). The pharmacy dispensing records revealed that 45 patients (25.28%) exhibited low levels of adherence (≤ 85%).

Within the subgroup of low adherence patients ($n = 32$), mean adherence was 75.6% (± 12.95), with no statistically significant differences between the drugs. After administering the MAQ questionnaire to this group of patients, 15 were classified as noncompliant (46.9%) and 17 (53.1%) as compliant. The first question about forgetting to take their medication was answered in the affirmative by 9 patients (28.10%) while the second question on taking the medication at the right time was answered negatively by 20 patients (62.50%). The third and fourth questions were answered in the affirmative by 1 patient (3.10%).

The results of the MPR and the MAQ questionnaire were compared for this subgroup de patients. Mean adherence among patients classified as compliant was 79.33 % (± 10.51); among non-compliant patients it was 71.38% (± 14.46) ($p = 0.064$).

Lastly, an analysis was made of the relationship between adherence and the demographic and/or clinical factors of both the whole patient population and the low-adherence subgroup. Firstly, an univariate analysis was carried out of the variables studied in both patient groups. Given the high number of variables, concomitant treatments and the type of biologic drug used previously were excluded from the analysis. The results are shown in tables 2 and 3.

On the multivariate analysis, only female sex and the length of treatment were associated to lower adherence levels (table 3).

Discussion

The results of the present study show high levels of adherence (91.79%) for the overall patient sample, with 45 patients (25.28%) identified as scarcely compliant.

No reports exist in the literature that compare the adherence to the three subcutaneously administered agents used to treat IBD. The first systematic review on the adherence to anti-TNF drugs was published in 2013 and includes 13 studies on 93,998 patients. Four of the studies reviewed determined the patients' adherence to infliximab and adalimumab using the MPR. Mean adherence to adalimumab was shown to be 83.1% (36.8-96%), which is lower than the 91.15% adherence rate found in the present study[10]. Other, more recent, studies obtained even lower adherence rates for adalimumab (57%) also using the MPR. These differences between earlier studies and the present one could be due to the fact that, in the former, adherence was evaluated over a longer period of time (24 months)[19].

A retrospective cohort study from the United States used the MPR rate to study adherence to golimumab and adalimumab in 27 and 226 patients respectively. It obtained an adherence rate of 95% for golimumab (similar to our 91.74%) and 77% for adalimumab[20]. As regards ustekinumab, no study was found that looked into adherence in an IBP population. Nonetheless, a Canadian study on psoriasis obtained a mean adherence of 93.5%, similar to the 95.05% found in the present study[21]. However, it must be taken into account that the clinical situations evaluated are different.

In this study, female sex was found to be associated to poorer therapeutic adherence, which is in line with earlier findings. In a systematic review, López *et al.* identified four studies where female sex is associated to poorer adherence[10]. In the same vein, a Swedish study on golimumab identified women as less compliant (hazard ratio [HR] 6.59; confidence interval [CI]: 95%: 1.04-41.62)[22]. A study on ustekinumab showed higher adherence levels in men (OR =1.28 (1.08-1.51) p= 0.004)[23].

In this study it was also found that the longer the treatment, the poorer the adherence. A Spanish study on patients treated with aminosalicylates revealed a statistically significant association ($p = 0.05$) between increased duration of treatment and poorer adherence[24].

Table 1. Sociodemographic profile of patients in the low-adherence subgroup

Variable	Category	Poor adherents (%) (*n* = 32)	Adalimumab (%) (*n* = 27)	Golimumab (%) (*n* = 3)	Ustekinumab (%) (*n* = 2)
Sex	Male	14 (43.80)	12 (44.40)	1 (33.30)	1 (50.00)
	Female	18 (55.20)	15 (55.60)	2 (65.67)	1 (50.00)
Age	Mean SD	45.28 (12.18)	45.22 (12.04)	48 (15.77)	58 (2.82)
Occupational status	Employed	24 (75.00)	22 (81,50)	2 (65.67)	0 (0.00)
	Unemployed	8 (25.00)	5 (18.50)	1 (33.30)	2 (100.00)
Smoking status	Smoker	11 (34.40)	10 (37.00)	0 (0.00)	1 (50.00)
	Non-smoker	21 (65.60)	17 (63.00)	3 (100.00)	1 (50.00)
Educational status	No education	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Primary	5 (15.60)	3 (11,10)	1 (33.30)	1 (50.00)
	Secondary	14 (43.80)	13 (48.10)	0 (0.00)	1 (50.00)
	University	13 (40.60)	11 (40.70)	2 (65.67)	0 (0.00)
Weight	Mean SD	68.63 (14.17)	70.56 (14.33)	58 (10.39)	58.5 (4.95)
Height	Mean SD	167.75 (9.89)	168.56 (10.20)	166 (5.91)	159.5 (10.60)
BMI	Mean SD	24.47 (4.08)	24.93 (4.06)	21.13 (3.19)	23.3 (4.98)
Diagnosis	CD	24 (75.00)	22 (81,50)	0 (0.00)	2 (100.00)
	UC	8 (25.00)	5 (18.50)	3 (100.00)	0 (0.00)
Age at diagnosis	Mean SD	32.88 (11,59)	33.78 (11,10)	28.67 (17.15)	27 (15.97)
Duration of disease (months)	Mean SD	160.06 (115.13)	135.37 (95.18)	232 (114.05)	372 (169.70)
Concomitant treatments	Corticosteroids	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Mesalamine	3 (9.40)	2 (7.40)	1 (33.30)	0 (0.00)
	Azathioprine	8 (25.00)	5 (18.50)	2 (65.67)	1 (50.00)
	Methotrexate	1 (3.10)	1 (3.10)	0 (0.00)	1 (50.00)
	Tacrolimus	1 (3.10)	1 (3.40)	0 (0.00)	0 (0.00)
Length of treatment (weeks)	Mean SD	190.69 (125.73)	191.33 (119.04)	216 (248.29)	144 (0.00)
Previous use of biologics	Yes	11 (34.40)	8 (29.60)	1 (33.30)	2 (100.00)
	No	21 (65.60)	19 (70.40)	2 (65.67)	0 (0.00)
Biologic type	Infliximab	11 (34.40)	8 (29.60)	1 (33.30)	2 (100.00)
	Golimumab	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Certolizumab	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Adalimumab	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Others	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Reason for discontinuation	Primary failure	8 (25.00)	6 (22.20)	0 (0.00)	2 (100.00)
	Secondary failure	3 (9.40)	2 (7.40)	1 (33.33)	0 (0.00)

BMI: body mass index; CD: Crohn's disease; SD: standard deviation; UC: ulcerative colitis.

Table 2. Results of the uni- and multivariate analyses of the total patient sample

Variable	Univariate analysis				Multivariate analysis[3]		
	Chi squared	OR	CI 95%	*p* value	OR	CI 95%	*p* value
Sex[1]	6.16	0.42	(0.21-0.84)	0.013*	0.438	(0.216-0.888)	0.022*
Age[2]			(–3.65-6.48)	0.583			
Length of treatment (weeks)[2]			(18.64-80.62)	0.002*	0.995	(0.991-0.998)	0.006*
Previous use of biologics[1]	0.17	0.86	(0.42-1.77)	0.683			

[1]Chi-squared test or Fisher Exact Test ($n < 5$). [2]Student's t-test for independent samples. [3]Multivariate logistic regression. CI: confidence interval; OR: odds ratio.
*$p \leq 0.05$.

Table 3. Results of the univariate analysis in the low-adherence subgroup

Variable	Chi squared	OR	CI 95%	*p* value
Sex[1]	0.16	0.75	(0.18-3.06)	0.688
Age[2]			(–11.44-6.36)	0.565
Occupational status[1]	0.38	0.60	(0.12-3.09)	0.691
Smoking status[1]	2.58	3.55	(0.73-13.32)	0.108
Educational status[1*]	0.01	1.05	(0.26-4.32)	0.946
BMI[2]			(–2.02-3.94)	0.514
Diagnosis[1]	0.38	1.67	(0.32-8.59)	0.691
Age at diagnosis[2]			(–11.41-5.11)	0.441
Duration of disease (months)[2]			(–78.87-90.42)	0.890
Concomitant use of aminosalicylates[1]	0.24	1.87	(0.15-22.93)	0.621
Concomitant use of immunosuppressors[1]	0.276	1.50	(0.33-6.83)	0.712
Previous use of biologics[1]	0.744	1.92	(0.43-8.61)	0.388
Length of treatment (weeks)[2]			(–140.07-38.60)	0.255
Discontinuation of treatment[1]		1.45	0.25	(0.02-2.71)
Hospital admissions[1]		0.11	1.39	(0.20-9.71)
Infections in the last 4 months[1]		1.88	0.50	(0.35-0.72)
Treatment intensification[1]		0.376	1.66	(0.32-0.59)
FC levels (µg/g)[3]				0.105

[1]Chi-squared test or Exact Fisher Test ($n < 5$). [2]Student's t-test for independent samples. [3]Mann-Whitney Nonparametric U Test for independent samples. *Subjects with primary and secondary education are grouped separately from those with a university education. BMI: body mass index; CI: confidence interval; FC: fecal calprotectin; OR: odds ratio.

Of the total 178 patients, 55 (30.9%) had received some form of previous treatment. The most commonly used drug was infliximab (22.5%). In the low adherence subgroup, patients who had received previous treatment had only taken infliximab, which had been discontinued in 72% of them as a result of primary failure in the course of the first few infusions. In line with the findings in this study, an analysis of the persistence to biologic agents in IBD by Chen *et al.* showed that the majority of patients begin their biologics-based therapy with either adalimumab, which is maintained for a mean of 1.04 years, or infliximab, which is maintained for 0.88 years[25]. In our study, the 136 patients on adalimumab exhibited a higher persistence rate, with a mean of 2.9 years.

The MAQ questionnaire was administered in our study in order to obtain a more accurate determination of adherence and to understand who some patients show poor levels of adherence. MAQ was also applied un one of the first studies on patients on mesalamine, but the results obtained were not comparable to those of the present study[24]. Using a simple set of questions, Billioud *et al.* concluded that forgetfulness in taking the medication was the chief culprit for non-adherence in 24.6% de los patients[26].

FC levels were analyzed in order to determine whether lack of adherence played a role in the effectiveness of treatment, but the two parameters did not appear to be related in a statistically significant manner. Sipponen *et al.* found that a 12-week-long treatment with anti-TNF agents resulted in a significant decrease of FC levels ($p = 0.001$)[27].

The present study is subject to several limitations. The main one is related to the fact that adherence was monitored over a period of only four months. It has been found that, in the setting of chronic diseases, adherence should be measured over at least six months[28]. In addition, the percentages presented herein may be slightly distorted as they were calculated on the basis of the date on which the drugs were dispensed, which could have been entered incorrectly. Another shortcoming about this method is that the fact that a drug was dispensed does not necessarily imply that the patient actually administered it[29].

Another limitation of this study has to do with its statistical power. The number of patients classified as scarcely compliant was too low for any associations observed in that subgroup of patients to be considered statistically significant. It would be useful to include patients on infliximab or vedolizumab in the analysis as this would provide a broader overview of adherence to all biologic agents in the setting of IBD.

Lastly the MAQ questionnaire was selected because it is an easy-to-respond to, general-purpose questionnaire used to measure adherence in patients with chronic conditions. As regards the MMAS-8. although it is a questionnaire specifically validated for IBP, De Castro *et al.* pointed out that its accuracy in detecting noncompliant patients is questionable[30].

On the other hand, one of the strengths of this study lies in the fact that it is the first study to compare the adherence to the three drugs analyzed. It therefore affords a valuable insight into the adherence to the subcutaneous biologic agents used to treat IBD. Moreover, as recommended by other authors, adherence was measured using two indirect methods, namely the MPR rate and the MAQ questionnaire[17].

As all the patients included in this study came from one single hospital, the results cannot be extended to the whole European, or even Spanish, population as there may well be demographic, clinical and treatment protocol-related differences between different sites.

To conclude, the adherence rate obtained in the present study is high for the general population and 75% lower for patients classified as scarcely compliant. Female sex and length of treatment were associated to poorer therapeutic adherence.

Funding

No funding.

Conflict of interests

No conflict of interest.

Contribution to the scientific literature

Low adherence to treatment reduces therapeutic effectiveness and negatively impacts patients' quality of life, resulting in increased hospital admissions and higher healthcare costs. Several studies have been published on adherence in the setting of immunological disorders, but most of them focus on one or more of the first monoclonal antibodies that reached the market, such as infliximab o adalimumab. As far as inflammatory bowel disease is concerned, no original study has yet been published that looks into the adherence to the three subcutaneously administered monoclonal antibodies approved for this indication, i.e. adalimumab, golimumab and ustekinumab.

An understanding of adherence to medication in the inflammatory bowel disease population is crucial to detect patients with poor therapeutic adherence. Once these patients have been identified, healthcare providers can develop interventions geared toward boosting adherence and achieving therapeutic success.

Bibliography

1. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl. 1989;170:2-6. DOI: 10.3109/00365528909091339
2. Fernández A, Hernández V, Martínez-Ares D, Sanromán L, Luisa de Castro M, Ramón Pineda J, *et al.* Incidence and phenotype at diagnosis of inflammatory bowel disease. Results in Spain of the EpiCom study. Gastroenterol Hepatol. 2015;38(9):534-40. DOI: 10.1016/j.gastrohep.2015.03.001
3. Dutta AK, Chacko A. Influence of environmental factors on the onset and course of inflammatory bowel disease. World J Gastroenterol. 2016;22(3):1088-100. DOI: 10.3748/wjg.v22.i3.1088
4. Guardiola J, Lobatón T, Cerrillo E, Ferreiro-Iglesias R, Gisbert JP, Domenech E, *et al.* Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU) on the utility of the determination of faecal calprotectin in inflammatory bowel disease. Gastroenterol Hepatol. 2018;41(8):514-29. DOI: 10.1016/j.gastrohep.2018.05.029
5. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, *et al.* Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011;60(5):571-607. DOI: 10.1136/gut.2010.224154
6. Cabriada JL, Vera I, Domenech E, Barreiro-de Acosta M, Esteve M, Gisbert JP, *et al.* Recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis on the use of anti-tumor necrosis factor drugs in inflammatory bowel disease. Gastroenterol Hepatol. 2013;36(3):127-46. DOI: 10.1016/j.gastrohep.2013.01.002
7. Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. Early Crohn disease: a proposed definition for use in disease-modification trials. Gut. 2010;59(2):141-7. DOI: 10.1136/gut.2009.187120
8. Dignass A, Lindsay JO, Sturm A, Windsor A, Colombel JF, Allez M, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis Part 2: Current management. J Crohns Colitis. 2012;6(10):991-1030. DOI: 10.1016/j.crohns.2012.09.002
9. Burkhart PV, Sabate E. Adherence to long-term therapies: Evidence for action. J Nurs Scholarsh. 2003;35(3):207. DOI: 10.1016/S1474-5151(03)00091-4
10. López A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L. Adherence to Anti-TNF Therapy in Inflammatory Bowel Diseases: A Systematic Review. Inflamm Bowel Dis. 2013;19(7):1528-33. DOI: 10.1097/MIB.0b013e31828132cb
11. Carter CT, Waters HC, Smith DB. Effect of a continuous measure of adherence with infliximab maintenance treatment on inpatient outcomes in Crohn's disease. Patient Prefer Adherence. 2012;6:417-26. DOI: 10.2147/PPA.S31115
12. Vangeli E, Bakhshi S, Baker A, Fisher A, Bucknor D, Mrowietz U, *et al.* A Systematic Review of Factors Associated with Non-Adherence to Treatment for Immune-Mediated Inflammatory Diseases. Adv Ther. 2015;32(11):983-1028. DOI: 10.1007/s12325-015-0256-7
13. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67-74. DOI: 10.1097/00005650-198601000-00007
14. Severs M, Zuithoff PN, Mangen MJ, van der Valk ME, Siersema PD, Fidder HH, *et al.* Assessing Self-reported Medication Adherence in Inflammatory Bowel Disease: A Comparison of Tools. Inflamm Bowel Dis. 2016;22:2158-64. DOI: 10.1097/MIB.0000000000000853
15. Selinger CP, Eaden J, Jones DB, Katelaris P, Chapman G, McDonald C, *et al.* Modifiable factors associated with nonadherence to maintenance medication for inflammatory bowel disease. Inflamm Bowel Dis. 2013;19:2199-206. DOI: 10.1097/MIB.0b013e31829ed8a6
16. Trindade AJ, Ehrlich A, Kornbluth A, Ullman TA. Are your patients taking their medicine? Validation of a new adherence scale in patients with inflammatory bowel disease and comparison with physician perception of adherence. Inflamm Bowel Dis. 2011;17:599-604. DOI: 10.1002/ibd.21310
17. Van der Have M, Oldenburg B, Kaptein AA, Jansen JM, Scheffer RCH, van Tuyl BA, *et al.* Non-adherence to Anti-TNF Therapy is Associated with Illness Perceptions and Clinical Outcomes in Outpatients with Inflammatory Bowel Disease: Results from a Prospective Multicentre Study. J Crohns Colitis. 2016;10(5):549-55. DOI: 10.1093/ecco-jcc/jjw002
18. Ibarra Barrueta O, Morillo Verdugo R. Lo que debes saber sobre la adherencia al tratamiento. Barcelona: Euromedice; 2017.
19. Wentworth BJ, Buerlein RCD, Tuskey AG, Overby MA, Smolkin ME, Behm BW. Nonadherence to Biologic Therapies in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018;24(9):2053-61. DOI: 10.1093/ibd/izy102
20. Khilfeh I, Guyette E, Watkins J, Danielson D, Gross D, Yeung K. Adherence, Persistence, and Expenditures for High-Cost Anti-Inflammatory Drugs in Rheumatoid Arthritis: An Exploratory Study. J Manag Care Spec Pharm. 2019;25(4):461-7. DOI: 10.18553/jmcp.2019.25.4.461
21. Hsu DY, Gniadecki R. Patient Adherence to Biologic Agents in Psoriasis. Dermatology. 2016;232(3):326-33. DOI: 10.1159/000444581
22. Rundquist S, Eriksson C, Nilsson L, Angelison L, Jaghult S, Bjork J, *et al.* Clinical effectiveness of golimumab in Crohn's disease: an observational study based on the Swedish National Quality Registry for Inflammatory Bowel Disease (SWIBREG). Scand J Gastroenterol. 2018;53(10-11):1257-63. DOI: 10.1080/00365521.2018.1519597
23. Doshi JA, Takeshita J, Pinto L, Li P, Yu X, Rao P, *et al.* Biologic therapy adherence, discontinuation, switching, and restarting among patients with psoriasis in the US Medicare population. J Am Acad Dermatol. 2016;74(6):1057-65. DOI: 10.1016/j.jaad.2016.01.048
24. Lopez A, Billioud V, Peyrin-Biroulet C, Peyrin-Biroulet L. Adherence to Anti-TNF Therapy in Inflammatory Bowel Diseases: A Systematic Review. Inflamm Bowel Dis. 2013;19(7):1528-33. DOI: 10.1097/MIB.0b013e31828132cb
25. Chen C, Hartzema AG, Xiao H, Wei YJ, Chaudhry N, Ewelukwa O, *et al.* Real-world Pattern of Biologic Use in Patients With Inflammatory Bowel Disease: Treatment Persistence, Switching, and Importance of Concurrent Immunosuppressive Therapy. Inflamm Bowel Dis. 2019;25(8):1417-27. DOI: 10.1093/ibd/izz001
26. Billioud V, Laharie D, Filippi J, Roblin X, Oussalah A, Chevaux JB, *et al.* Adherence to Adalimumab Therapy in Crohn's Disease: A French Multicenter Experience. Inflamm Bowel Dis. 2011;17(1):152-9. DOI: 10.1002/ibd.21491
27. Sipponen T, Savilahti E, Karkkainen P, Kolho KL, Nuutinen H, Turunen U, *et al.* Fecal Calprotectin, Lactoferrin, and Endoscopic Disease Activity in Monitoring Anti-TNF-alpha Therapy for Crohn's Disease. Inflamm Bowel Dis. 2008;14(10):1392-8. DOI: 10.1002/ibd.20490
28. McMahon J, Jordon M, Kelley K, Bertagnolio S, Hong S, Wanke C, *et al.* Pharmacy adherence measures to assess adherence to antiretroviral therapy: Review of the literature and implications for treatment monitoring. Clin Infect Dis. 2011;52(4):493-506. DOI: 10.1093/cid/ciq167
29. Pages-Puigdemont N, Isabel Valverde-Merino M. Methods to assess medication adherence. Ars Pharm. 2018;59(3):163-72. DOI: 10.30827/ars.v59i3.7387
30. De Castro ML, Sanromán L, Martín A, Figueira M, Martínez N, Hernández V, *et al.* Valoración de la adhesión terapéutica en la enfermedad inflamatoria intestinal. Comparación entre una escala de autoevaluación y un índice farmacéutico de dispensación de medicamentos. Rev Esp Enferm Dig. 2017;109(8):542-51. DOI: 10.17235/reed.2017.5137/2017