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Adherence to biological therapies in patients with chronic inflammatory arthropathies

Adherencia a las terapias biológicas en pacientes con artropatías inflamatorias crónicas

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Abstract

Introduction: The aims of the study were to quantify adherence, determine the factors that can predict adherence and identify the consequences of poorer adherence in patients with chronic inflammatory arthropathies treated with biological therapies in daily clinical practice.

Method: A descriptive, observational and retrospective study was carried out. Patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis who started a biologic therapy between 1 January 2009 and 31 December 2016 were included. Variables related to socioeconomic status, the disease, the biological therapy and hospital resources were included. Adherence was calculated by using the medication possession ratio.

Results: Three hundred and sixty-two patients and 423 lines of biological therapy were included. Mean age ± standard deviation was 50.3 ± 13.9 years, and 228 (53.9%) were women. The percentage of adherent patients was 187 out of 216 (87%) in rheumatoid arthritis, 91 out of 107 (85%) in ankylosing spondylitis and 84 out of 100 (84%) in psoriatic arthritis. Greater adherence was associated with more frequent visits to the pharmacy service (*odds ratio* 1.2, 95% confidence interval: 1.1-1.3 [$p<0.001$]) and poorer adherence with a failure to attend scheduled appointments at the rheumatology clinic (*odds ratio* 0.2, 95% confidence interval: 0.1-0.9 [$p=0.030$]). There were no differences between

KEYWORDS
Rheumatoid arthritis; Psoriatic arthritis; Ankylosing spondylitis; Biological therapies; Adherence to medication; Risk factors.

Resumen

Objetivo: Los objetivos del estudio fueron cuantificar la adherencia, determinar los factores predictivos y conocer las consecuencias de una menor adherencia, en la práctica clínica diaria, en pacientes con artropatías inflamatorias crónicas tratados con terapias biológicas.

Método: Estudio descriptivo, observacional y retrospectivo. Se incluyeron pacientes con artritis reumatoide, espondilitis anquilosante y artritis psoriásica que iniciaron una terapia biológica entre el 1 de enero de 2009 y el 31 de diciembre de 2016. Se recogieron variables sociodemográficas, relacionadas con la enfermedad, sobre las terapias biológicas y los recursos hospitalarios. La adherencia se calculó mediante la ratio media de posesión.

Resultados: Se incluyeron 362 pacientes y 423 líneas de terapia biológica. La media de edad ± desviación estándar fue de 50,3 ± 13,9 años; 228 (53,9%) fueron mujeres. El porcentaje de adherentes fue de 187 de 216 (87%) en artritis reumatoide, 91 de 107 (85%) en espondilitis anquilosante y 84 de 100 (84%) en artritis psoriásica. La adherencia se relacionó con acudir con más frecuencia a la consulta del servicio de farmacia (*odds ratio* de 1,2; intervalo de confianza 95%: 1,1-1,3 [$p<0,001$]) e inversamente con no acudir a las consultas de reumatología en la fecha prevista (*odds ratio* de 0,2; intervalo de confianza 95%: 0,1-0,9 [$p=0,030$]).

PALABRAS CLAVE
Artritis reumatoide; Artritis psoriásica; Espondilitis anquilosante; Terapias biológicas; Adherencia a la medicación; Factores de riesgo.

adherent and non-adherent patients in terms of the number of hospital resources used.
Conclusions: There are no differences in adherence to biological therapies among patients with chronic inflammatory arthropathies. Adherence correlates with attendance at outpatient appointments, but this does not imply an increase in the use of hospital resources.

No hubo diferencias en el número de recursos hospitalarios utilizados por pacientes adherentes y no adherentes.
Conclusiones: La adherencia a las terapias biológicas entre las artropatías inflamatorias crónicas es similar. Dicha adherencia se correlaciona con la frecuentación a consultas externas, pero no implica un aumento del consumo de recursos.

Introduction

The introduction of biological therapies (BT) in the treatment of chronic inflammatory arthropathies (CIA) such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) has led to a pharmacotherapeutic revolution that has brought about considerable improvements in the prognosis of CIA and in patients' quality of life[1]. However, the healthcare system bears a high economic burden because CIA are chronic diseases and the cost of BT is very high[2-5]. The lack of adherence in chronic treatments is a genuine universal problem that compromises their effectiveness and can result in the worsening of the disease, death and rising healthcare costs[6,7].

There are publications on adherence in CIA[7-10], although most address patients with RA. Few data are available on the factors that predict adherence to BT in patients with CIA[11] and the consequences for the healthcare system[11,12].

The objectives of this study were:

1. To quantify adherence to BT in a cohort of patients diagnosed with CIA in daily clinical practice.
2. To determine the factors that can predict adherence to BT.
3. To identify the consequences, in terms of hospital resources, of poor adherence to BT.

Methods

A retrospective, descriptive and observational study was carried out. The study was conducted at a third-level hospital that provides healthcare to 564,452 citizens. The Pharmacy Service (PS) has a specialized clinic for patients with BT and CIA, with a workload of 3,000 consultations per year (7.5% of the total outpatient activity of the PS). All patients who attend this clinic are looked after by a pharmacist specializing in hospital pharmacy. Intravenous BT are administered at the Day Hospital (DH), part of the same hospital.

The study included adult patients diagnosed with RA, AS or PsA who were being treated by the Rheumatology Clinic, who fulfilled the 1987 American College of Rheumatology classification criteria for RA[13], the modified New York criteria for classification of AS[14,15] or the CASPAR classification criteria for PsA[16], and who had started a BT with abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, tocilizumab or ustekinumab between 1 January 2009 and six months before the study end date (31 December 2016), with a minimum BT duration of 180 days.

In order to obtain clinical information, each patient's electronic medical records were consulted. The data collected on the diseases and the use of drugs were consistent with the pattern of routine clinical practice. At the beginning of the BT, demographic variables (age, sex), sociocultural variables (employment status, educational level, smoking habits, size of home town, distance between home and hospital), clinical variables (years since diagnosis, comorbidities according to the Charlson Index[17]), and analytical parameters, such as C-reactive protein, erythrocyte sedimentation rate and haemoglobin levels at the start of the BT, were collected.

For the purposes of assessing the potential consequences of non-adherence, the health resources used by patients in Specialized Care during the adherence-measurement period were taken into account: number of hospital admissions, visits to the hospital's emergency department, visits to the Rheumatology Clinic, visits to other clinics, visits to the PS outpatient clinic and the Day Hospital, and imaging tests (X-rays, nuclear magnetic resonance and nuclear medicine). In order to make proper comparisons, the average consumption per patient and year of BT was calculated.

In relation to BT, concomitant treatments at the start of the BT (methotrexate, leflunomide and glucocorticoids), dose regimen, route of administration and the therapy line number were recorded. Any patients concomitantly using any psychotropic drugs of the groups N05B, N05C, N06A, N06B, N06C and N06D, according to the Anatomical Therapeutic Chemical (ATC) Classification System[18], were recorded due to the possible relationship between lack of adherence and psychoactive treatment[19].

Adherence was calculated by using the medication possession ratio (MPR), which is defined as the number of dispensed medication doses divided by the total number of days in the period analysed. Data on the number of BT dispensations given to the patient were obtained from electronic records in the Silicon® program. In the case of treatments administered in the DH, the days on which the patient attended the unit, which were recorded in the Oncofarm® program, were taken into account. Interruptions due to hospital admissions or pregnancy were deducted.

To calculate the number of days in the period analysed, the dose prescribed by the rheumatologist, rather than the dose indicated in the data sheet, was taken into account. Dose optimization and intensification were therefore taken into consideration.

To assess possible factors that could predict better adherence to BT and the consequences of poor adherence, the sample was divided into two groups: lines of BT in which patients were adherent (MPR ≥ 0.8) and lines of BT in which patients were non-adherent (MPR < 0.8).

The statistical analysis was carried out by means of the SPSS program. A descriptive analysis of the study sample was performed. Quantitative variables were expressed as mean ± standard deviation (SD) if they had a normal distribution and as the median and interquartile range (IQR) if they did not have a normal distribution. Categorical variables were expressed as absolute values and percentages. To establish differences between quantitative variables, the Student's *t*-test (for two variables) or Mann-Whitney U test was used. In the case of qualitative variables, the chi-square test was performed. Values were considered statistically significant when $p < 0.05$.

To assess possible factors that could affect adherence, a multivariate logistic regression analysis was performed with variables that were significant in the univariate study.

The study complied with Law 15/1999 of 13 December on the Protection of Personal Data. The data were used exclusively for the research conducted as part of this study, and were kept anonymous and confidential. The study was approved by the Healthcare Research Ethics Committee, under code 2014/187.

Results

The sample consisted of 362 patients, who accounted for 423 lines of BT. The median duration of BT was 823 days (IQR 419-1,459) in the adherent group (MPR ≥ 0.8) and 891 days (IQR 608-1,443) in the non-adherent group (MPR < 0.8), with no differences between the two groups.

The clinical, sociodemographic and pharmacological characteristics of the initial patient sample are shown in table 1.

The mean adherence ± SD measured according to the MPR was 0.89 ± 0.16. There were no differences between the pathologies: the mean ± SD was 0.90 ± 0.17 in RA, 0.89 ± 0.16 in AS and 0.89 ± 0.15 in PsA. The percentage of patients with an MPR ≥ 0.8 was similar across all three diseases: 187 in RA (87%), 91 in AS (85%) and 84 in PsA (84%).

Table 2 shows the MPR data separately for each BT. Given the difference in the number of lines between the different BT, it was not possible to perform a statistical analysis that showed statistically significant differences between them.

The sample was divided into two groups: adherent patients (MPR ≥ 0.8; $n = 362$) and non-adherent patients (MPR < 0.8; $n = 61$). Table 3 shows the factors analysed in the univariate study.

The logistic regression analysis showed that better adherence to BT correlated with more frequent visits to the PS (*odds ratio* [OR] 1.2; 95% confidence interval [CI]: 1.1-1.3; $p < 0.001$) and inversely correlated with a failure to attend scheduled Rheumatology Clinic appointments (OR 0.2; 95% CI: 0.1-0.9; $p < 0.001$).

Table 1. General characteristics of patients

Age in years	***n*=423**
Mean ± SD	50.3 ± 13.9
Sex, *n* (%)	***n*=423**
Females	228 (53.9)
Males	195 (46.1)
Education level, *n* (%)	***n*=229**
University	35 (15.3)
Upper secondary/Vocational education	65 (28.4)
Basic	124 (54.1)
No schooling	5 (2.2)
Employment status, *n* (%)	***n*=349**
Homemaker/employed	169 (48.4)
Unemployed/on sick leave/studying	79 (22.6)
Retired	101 (28.9)
Smoker[1]	***n*=283**
	86 (30.4)
Comorbidities (Charlson index)[2]	***n*=422**
0-3	154 (36.5)
4-9	201 (47.6)
> 10	67 (15.9)
Undergoing treatment with a psychoactive drug[3]**, *n* (%)**	***n*=420**
	141 (33.6)
Size of the patient's home town, *n* (%)	***n*=423**
< 5,000 residents	24 (5.7)
5,000-20,000 residents	127 (30.0)
> 20,000 residents	272 (64.3)
Distance between home and hospital, *n* (%)	***n*=423**
< 10 km	238 (56.3)
≥ 10 km	185 (43.7)
Disease	***n*=423**
Rheumatoid arthritis	216 (51.1)
Ankylosing spondylitis	107 (25.3)
Psoriatic arthritis	100 (23.6)
Years since diagnosis, mean ± SD	***n*=423**
	8.3 ± 8.1
Erythrocyte sedimentation rate (mm/h), median (IQR)	***n*=396**
	23.0 (1-140)
C-reactive protein (mg/L), median (IQR)	***n*=391**
	9.0 (0-120)
Haemoglobin (mg/dL), mean ± SD	***n*=406**
	13.4 ± 1.6
Concomitant methotrexate, *n* (%)	***n*=423**
	166 (39.2)
Concomitant leflunomide, *n* (%)	***n*=423**
	29 (6.9)
Concomitant glucocorticoids, *n* (%)	***n*=411**
	247 (60.1)
Daily glucocorticoids dose (mg), mean ± SD	***n*=411**
	4.9 ± 5.3
Biological therapy, *n* (%)	***n*=423**
Adalimumab	180 (42.5)
Etanercept	121 (28.6)
Golimumab	35 (8.3)
Abatacept	25 (5.9)
Tocilizumab	29 (6.8)
Certolizumab	20 (4.7)
Infliximab	11 (2.6)
Ustekinumab	2 (0.5)

BT: biological therapy; IQR: interquartile range; *n*: number of lines of biological therapy; SD: standard deviation.

The total number of lines of BT analysed was 423. The values presented in this table refer to the number of lines for which data were available on the variables analysed.

[1]Active smoker at the start of the BT. [2]Validated index to measure prognostic comorbidity in clinical studies. A value of 1 point was assigned to patients with a score of 0-3, a value of 2 points to those with a score of 4-9, and a value of 3 points to those with a score of ≥ 10. [3]Patients undergoing treatment with a psychoactive drug.

Table 2. Adherence measured in accordance with the medication possession ratio of the lines of biological therapy

Biological therapy, *n*=423	Medication possession ratio: mean ± SD
Abatacept[1]**, *n*=25**	0.86 ± 0.19
Adalimumab, *n*=180	0.88 ± 0.17
Certolizumab, *n*=20	0.92 ± 0.15
Etanercept, *n*=121	0.88 ± 0.17
Golimumab, *n*=35	0.94 ± 0.11
Infliximab, *n*=11	0.91 ± 0.15
Tocilizumab[1]**, *n*=29**	0.93 ± 0.11
Ustekinumab, *n*=2	0.89 ± 0.16

SD: standard deviation.

[1]Joint results of biological therapy with intravenous and subcutaneous administration.

With respect to the consequences of poor adherence to BT, no statistically significant differences were detected between the adherent and non-adherent groups. The results are outlined in table 4.

Discussion

The data obtained on the percentage of adherent patients were similar to those published in studies on patients with RA, and ranged from 85.7% to 88.8%[8,9]. The percentage of adherent patients with PsA and AS (89% for both diseases) was similar to the percentage of adherent patients with RA. Arturi P *et al.*[10] reported similar findings in their publication, which found that patients with AS presented a similar degree of adherence to patients with RA.

The factor that correlated most with adherence to BT was frequent attendance at PS appointments. Furthermore, a failure to attend rheumatology appointments on the scheduled date was found to be a predictor of non-adherence. We were not able to find any studies on patients with CIA and BT that reported a correlation between these aspects, although the relationship has been contemplated in other conditions such as HIV[20]. Therefore, the fact that patients with more involvement in the healthcare system and greater trust in healthcare professionals have a higher likelihood of adhering to biological therapies represents a novel finding.

In line with our results, studies published on the Spanish population have reported no differences with respect to age, sex or biological therapy line number and adherence to BT[8,9]. However, Calip *et al.*[11] conducted a study in 2018 that related increased age, female gender and presence of comorbidities with poorer adherence, although the adherence data in that study, which was conducted in the United States, differed greatly from ours; just 37% of the patients were considered adherent.

With respect to BT-related aspects, the use of subcutaneously administered BT could be a predictor of non-adherence[9] with respect to intravenously administered BT. However, our study found no differences in terms of whether the BT was administered at the DH or during a home visit (subcutaneous). This difference between our study and the published data may be due to the low number of BT that were administered intravenously in our study. Moreover, we found no differences with respect to the different dosing intervals, unlike other studies on RA, which reported that weekly administration as opposed to monthly administration was a predictor of poor adherence to BT[8]. This inconsistency with the results of our study could be attributed to the fact that we performed a joint analysis of patients with RA, PsA and AS. No differences were found in adherence between patients with optimized and non-optimized dosage regimens, which could explain the lack of influence of the dosing interval type on adherence.

Our work presented significant differences between the number of patients with adalimumab or etanercept with respect to other BT, a factor that ruled out a comparative analysis between the different BT. When BT were grouped according to their mechanism of action (those with an anti-tumour necrosis factor alpha mechanism of action versus those

Table 3. Factors that may influence non-adherence to biological therapy. Univariate study

	Lines of BT with MPR≥0.8, *n*=362	Lines of BT with MPR<0.8, *n*=61	*p*-value[1]
Age in years			
Mean ± SD	49.7 ± 13.8	49.8 ± 14.3	0.968
Sex, *n* (%)			
Females	201 (55.5)	27 (44.3)	0.068
Males	161 (44.5)	34 (55.7)	
Years since diagnosis			
Mean ± SD	8.2 ± 8.0	8.5 ± 9.4	0.938
Education level, *n* (%)			
University	35 (16.9)	0 (0.0)	0.172
Upper secondary/Vocational education	57 (27.5)	8 (36.4)	
Basic	111 (53.6)	13 (59.1)	
No schooling	4 (1.9)	1 (4.5)	
Employment status, *n* (%)			
Unemployed/on sick leave/studying	64 (21.2)	15 (31.3)	0.192
Retired	86 (28.6)	15 (31.3)	
Employed/homemaker	151 (50.2)	18 (37.5)	
Size of the patient's home town, *n* (%)			
< 5,000 residents	24 (6.6)	0 (0.0)	0.107
5,000-20,000 residents	109 (30.1)	18 (29.5)	
> 20,000 residents	229 (63.3)	43 (70.5)	
Distance between home and hospital, *n* (%)			
< 10 km	207 (57.2)	31 (50.8)	0.215
≥ 10 km	155 (42.8)	30 (49.2)	
Comorbidities (Charlson index), *n* (%)[2]			
0-3	135 (37.4)	19 (31.1)	0.126
4-9	174 (48.2)	27 (44.3)	
≥ 10	52 (14.4)	15 (24.6)	
Smoker[3], *n* (%)			
Yes	67 (27.6)	19 (47.5)	0.011
No	176 (72.4)	21 (52.5)	
Undergoing treatment with a psychoactive drug[4], *n* (%)			
Yes	120 (33.4)	21 (34.4)	0.493
No	239 (66.6)	40 (65.6)	
Disease			
Rheumatoid arthritis	187 (51.7)	29 (47.5)	0.819
Ankylosing spondylitis	91 (25.1)	16 (26.2)	
Psoriatic arthritis	84 (23.2)	16 (26.2)	
Haemoglobin (mg/dL), mean ± SD	13.3 ± 1.6	13.3 ± 1.6	0.758
C-reactive protein (mg/L), median (IQR)	8 (0-120)	8 (0-105)	0.293
Erythrocyte sedimentation rate (mm/h), median (IQR)	21 (1-140)	31 (5-96)	0.060
Therapy line number, *n* (%)			
1st line	217 (59.9)	34 (55.7)	0.315
Subsequent lines	145 (40.1)	27 (44.3)	
Type of BT, *n* (%)			
Anti-TNF-α	315 (87.0)	52 (85.2)	0.418
Non-anti-TNF-α	47 (13.0)	9 (14.8)	
Concomitant methotrexate at the start, *n* (%)			
Yes	148 (45.0)	18 (35.3)	0.125
No	181 (55.0)	33 (64.7)	
Concomitant glucocorticoids at the start, *n* (%)			
Yes	214 (60.6)	33 (56.9)	0.345
No	139 (39.4)	25 (43.1)	
Glucocorticoids dose, mg, mean ± SD	5.2 ± 5.5	5.2 ± 6.2	0.567
Concomitant leflunomide, *n* (%)			
Yes	27 (8.3)	2 (3.9)	0.216
No	298 (91.7)	49 (96.1)	
BT dose regimen at the start, *n* (%)			
Every 7 days	120 (33.1)	23 (37.7)	0.615
Every 14 days	171 (47.2)	29 (47.5)	
Every 28 days or more	71 (19.6)	9 (14.8)	
Optimization of the BT dose regimen, *n* (%)			
Yes	108 (29.8)	14 (23.0)	0.173
No	254 (70.2)	47 (77.0)	
Place where the BT was administered, *n* (%)			
Away from the hospital	324 (89.5)	55 (90.2)	0.545
In the Day Hospital	38 (10.5)	6 (9.8)	
No. visits to the RC per patient/year of BT, mean ± SD	2.50 ± 1.40	2.40 ± 1.90	0.168
No. no-shows to RC appointments, per patient/year of BT mean ± SD	0.05 ± 0.15	0.17 ± 0.38	0.004
No. visits to PS, per patient/year of BT, mean ± SD	7.97 ± 3.19	5.5 ± 3.02	<0.001

To calculate the percentages, the number of events was divided by the number of adherent or non-adherent patients.
Anti-TNF-α: anti-tumour necrosis factor alpha; BT: biological therapy; IQR: interquartile range; MPR: medication possession ratio; *n*: number of patients; RC: Rheumatology Clinic; PS: Pharmacy Service; SD: standard deviation.
[1]Values were considered statistically significant when $p<0.05$. [2]Validated index to measure prognostic comorbidity in clinical studies. [3]Active smoker at the start of the biological therapy. [4]Patients undergoing treatment with a psychoactive drug.

Table 4. Consequences of non-adherence to biological therapy

	Adherent patients (MPR≥0.8), *n*=362	Non-adherent patients (MPR<0.8), *n*=61	*p*-value[1]
No. admissions/year of BT, mean ± SD	0.13±0.34	0.24±0.56	0.054
No. visits to emergency dept/year of BT, mean ± SD	0.31±0.56	0.56±1.07	0.069
No. MRIs/year of BT, mean ± SD	0.15±0.33	0.15±0.37	0.707
No. nuclear medicine tests/year of BT, mean ± SD	0.06±0.42	0.05±0.29	0.535
No. X-rays/year of BT, mean ± SD	1.50±1.93	2.10±3.19	0.110
No. visits to Specialized Care/year of BT, mean ± SD	3.50±4.63	4.80±6.22	0.153

To calculate the percentages, the number of events was divided by the number of adherent or non-adherent patients.
BT: biological therapy; MPR: medication possession ratio; MRI: magnetic resonance imaging; SD: standard deviation.
[1]Values were considered statistically significant when $p<0.05$.

with another mechanism of action), no differences were found between the two groups, although in a publication by Smolen *et al.* (2019)[7], the use of anti-tumour necrosis factor alpha was a predictor of adherence, not compared to other BT but compared to synthetic disease-modifying drugs.

According to our results, poorer adherence to BT does not translate into a higher number of emergency department visits, hospital appointments or hospital admissions. However, these data are not consistent with other studies on patients with CIA, in which non-adherent patients made significantly greater use of resources compared to adherent patients[11,12]. One possible explanation for this finding is that non-adherent patients reduce their dosage independently when they feel well, much like when healthcare professionals optimize BT in a more regulated way when a patient is stable[21].

One of the limitations of our study was its retrospective nature; however, the ability to conduct an eight-year follow-up study represented an advantage. Another potential limitation was the single method used to assess adherence. However, the application of a method such as the Morisky-Green test in such patients does not seem to be as useful as in other pathologies[8]. Moreover, given the retrospective nature of the study, the use of a questionnaire would not be valid for prior therapies.

Conclusions

According to the data obtained, patients with RA, AS and PsA present no differences in terms of their adherence to BT. It would seem that adherence to BT is not influenced by sociodemographic or pharmacological factors. However, a correlation was detected between a patient's level of cooperation with the pharmacist or doctor and his or her adherence. The use of BT at lower doses due to a lack of adherence does not translate into a reduction in the survival of the BT or a rise in the use of healthcare resources.

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Conflict of interests

No conflict of interest.

Presentation in Congresses

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Contribution to the scientific literature

In the case of patients undergoing treatment with biological therapies, there are no differences in the adherence of patients diagnosed with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis.

Sociodemographic and medication-related factors were not found to influence adherence. However, patients with greater involvement in the healthcare system have a higher probability of adhering to biological therapies.

Our study found that poor adherence to biological therapies by patients with chronic inflammatory arthropathies does not imply a greater use of hospital resources by these patients, in contrast to patients with other diseases.

Appendix

Authors/members of the Working Group IRIDIS (Rheumatology, Immunology and Immune-Mediated Diseases):
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