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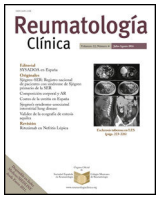

Original Article

Not the same, but is it the same? Cycling of biologic agents in rheumatoid arthritis. Experience in the Instituto Mexicano del Seguro Social☆

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ABSTRACT

Introduction: Available data for biocomparable drugs are not enough to make clear decisions with respect to the potential consequences of a change for non-medical reasons in efficacy, security and inmunogenicity in patients. In the near future, options on biological treatments, biocomparable drugs, non biocomparable drugs and new chemical synthesis options will grow. Therefore, it is important to know how patients behave in persistence of treatment after a change for non- medical reasons, which already happens on a regular basis in social security institutions in Mexico. This information will help us to better understand the standard of treatment for patients with chronic immunomediated conditions.
Objective: The primary objective was to measure the impact of change for non-medical reasons in patients with rheumatoid arthritis (RA) treated with an innovative biological on persistence of treatment after changing to a biocomparable drug or a non-biocomparable drug, compared with those patients staying with the innovative biological.
Study design: This is an observational study (non-interventionist) of paired cohorts, where an historic cohort obtained by review of clinical records of stable patients in which no modifications to treatment were made for at least six months is compared with two cohorts of patients whose treatments were switched to another treatment with the same therapeutic mechanism for-non-medical reasons (cycling).
Results: We included 264 RA patients (ACR/EULAR, 2010); 132 were switched for non-medical reasons, and 132 were not switched. Two-hundred and thirty (87.1%) were female. Average age was 53.9 years, ranging from 16 to 84 years. Two-hundred and sixty-three patients were Latino (99.6%); one was Caucasian. Persistence of treatment 12 months after the change was 84.8% (85.8% in Enbrel/Infinitam, 78.9%

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for Remicade/Remsima). No statistical difference was found with respect to RA clinical activity measured by DAS28 12 months after the switch ($P > .05$). In the 134 switched patients, 20 discontinued the new treatment due to lack of efficacy of the new drug and were changed to a different drug with a different biologic target. Although no differences were found in the cohorts of switched patients with respect to DAS 28 after 12 months of use, we did find differences in the frequency of adverse events. Forty-two patients had an adverse event in the drug switch cohorts: 33 in the Enbrel-Infinitam group and 9 in the Remicade-Remsima group.

Conclusions: The persistence of treatment after switching from an innovative drug to a biocomparable or a non- biocomparable in RA patients did not show statistically significative differences in our cohorts, but we did find a higher number of adverse events when comparing those who were changed with those who continued on an innovative drug. Twenty patients in the switch groups had to receive a new drug with a different biological target due to lack of efficacy of the switched drug.

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Palabras clave:
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No es el mismo pero ¿es igual? *Cycling* de agentes biológicos en artritis reumatoide. Experiencia en el Instituto Mexicano del Seguro Social

R E S U M E N

Introducción: Los datos disponibles para los biocomparables comercializados actualmente no son concluyentes con respecto al potencial impacto del cambio por razones no médicas sobre la eficacia, la seguridad y la inmunogenicidad en los pacientes. En el futuro se expandirán las opciones de tratamiento biológico, biocomparable, no bio-comparables y otros de síntesis química, por lo que es importante conocer cómo se comporta la persistencia al tratamiento tras un cambio por razón no médica, que ya ocurre como un hecho habitual en los servicios médicos de seguridad social en México, ya que esto nos ayudará a entender los mejores estándares de tratamiento para pacientes con enfermedades inmunomediadas crónicas.

Objetivos: El objetivo primario fue evaluar el impacto del cambio por razón no médica en pacientes con Artritis Reumatoide (AR) estables tratados con biológico innovador sobre la persistencia en el tratamiento, después de cambiar a un biocomparable o a un no biocomparable, en relación con los pacientes que continúan con el biológico innovador.

Diseño del estudio: Estudio observacional (no intervencionista) de cohortes emparejado, donde se comparó una cohorte histórica obtenida por la revisión de historias médicas de pacientes estables que no fueron cambiados de tratamiento por al menos seis meses, con dos cohortes de pacientes que fueron cambiados de tratamiento por razones no médicas a otro fármaco con la misma diana terapéutica (cycling).

Resultados: Se incluyeron 264 pacientes con diagnóstico de AR (ACR/EULAR, 2010); 132 pacientes que fueron cambiados de tratamiento por razones no médicas por un fármaco de mecanismo similar de acción y 132 pacientes que no fueron cambiados de tratamiento. De los 264 pacientes participantes en el estudio, 230 pacientes (87.1%) corresponden al sexo femenino. El promedio de edad fue 53.9 años, la edad mínima 16 años y máxima 84 años. 263 pacientes corresponden a raza latina (99.6%), y uno de raza blanca. La persistencia en 12 meses posterior al cambio fue del 84.8% (85.8% para el grupo Enbrel-Infinitam y 78.9% para el grupo Remicade-Remsima). No encontramos evidencia estadística de diferencias respecto a la actividad de la AR medida por DAS28 ($p > 0.05$). Veinte pacientes suspendieron el tratamiento tras el cambio, todos ellos debido a falta de eficacia, necesitando un segundo cambio de tratamiento. Al comparar pacientes de cambio vs pacientes que no cambiaron, se observaron 42 pacientes con registro de evento adverso, estos corresponden al grupo de cambio de Enbrel-Infinitam 33 pacientes; y al grupo de cambio de Remicade-Remsima 9 pacientes. No se observó una diferencia estadísticamente significativa al comparar las proporciones de pacientes que presentaron eventos adversos ($p > 0.05$).

Conclusiones: La persistencia al tratamiento, posterior al cambio de un medicamento innovador a un medicamento biocomparable o a un no biocomparable en pacientes con AR no demostró diferencias estadísticamente significativas entre ambos grupos de tratamientos, describiéndose un mayor número de eventos adversos al comparar los que sufrieron cambio en relación con los continuadores. Es importante señalar que en 20 pacientes del grupo de cambio hubo de iniciarse un nuevo agente biológico por falta de eficacia, a diferencia del grupo que no tuvo cambio.

Rheumatoid arthritis (RA) is a complex, autoimmune, systemic, chronic connective tissue disease that primarily affects the peripheral joints. Extra-articular manifestations are common. It has a major impact on the patient's quality of life and entails very significant economic and social costs. Without adequate treatment, the course of the disease is progressive and leads to irreversible structural joint damage, functional impairment, decreased quality of life and shortened life expectancy. Early diagnosis and treatment are very important to reduce structural damage.[1]

The biological drugs have revolutionised the treatment of many acute and chronic diseases, including immune-mediated inflammatory diseases such as RA and spondyloarthropathies, among others, and have enabled more effective symptom control, improved quality of life measures, improvements in work productivity, and other important clinical and social outcomes.

The expiry of the patents of several widely used biological drugs opens the door to marketing biocomparables (biosimilars), and this

should provide additional treatment options for patients in multiple therapeutic areas.[2]

The health authorities have established specific guidelines over the last decade to demonstrate pre-clinical and clinical comparability between biosimilars or biocomparables and innovative biologicals. In the case of monoclonal antibodies or fusion proteins, their intrinsic complexity in terms of structure, and the heterogeneity introduced by subtle changes in product manufacturing, should be at the forefront of critical discussion. Several biocomparable products having been approved and marketed, the consequences of switching patients from an innovative to a biocomparable or non-biocomparable drug are not yet fully understood. Although there are now many publications on the subject, the results are highly heterogeneous in terms of patient outcomes and study design; the NOR-SWITCH[3] study, for example, which grouped six indications and 394 patients, found that 30% of patients who were switched to the infliximab biosimilar showed worsening of their disease. This was not significant compared to those who remained on the innovative drug, where 26% deteriorated. However, the study has several limitations, for example it grouped together diseases of varying behaviour and aetiology for analysis. Similarly, in the DANBIO registry study,[4] where the behaviour of three diseases (including RA) was studied before and after the non-medical switch in 802 patients treated with infliximab, it can be observed that 16% of patients who were switched to the biosimilar abandoned treatment due to lack of efficacy or adverse events, and although there were no differences in disease activity 3 months before and after the switch, it was concluded that the patients' annualised retention rate was lower for the biosimilar, as after retention rates were adjusted they were 86.8% (95% CI: 84.8–88.8) for the innovative drug infliximab versus 83.4% (95% CI: 80.8–86.2) for the biosimilar, with a *P*-value of .03 which was clinically significant, corresponding to an absolute difference of 3.4%.

In the BIOSWITCH[5] cohort of patients with RA, ankylosing spondylitis and psoriatic arthritis, 24% of patients who were switched to the infliximab biosimilar abandoned treatment within 6 months. Eighty percent had to receive the innovative drug again, and although disease worsening was attributed to a subjective rather than objective increase in painful joint count and the patients' general condition, these findings merit further investigation.

The Mexican procurement system for reimbursement of drugs relies on bids based on the International Non-proprietary Name (INN). The bid that offers the lowest cost per unit always wins; thus, automatic substitution may occur in many patients, making it difficult to trace the drugs that patients are receiving and to correctly determine any potential drug-related adverse events.[6,7]

The above offers us an opportunity to assess the potential impact of non-medical switching (NMS) on patients' treatment persistence and to describe the rates and reasons for discontinuation after NMS. Furthermore, and given the abovementioned potential traceability issues, we would like to establish the prescribing physician's level of knowledge about switching to a compound with the same therapeutic target but made by another manufacturer (cycling) at the pharmacy level (automatic substitution).

Given that treatment persistence can have a major impact on the risk-benefit profile of the drug and progression of the disease, as well as the fact that there will be more biological, biocomparable, non-biocomparable and other chemically synthesised treatment options in the future, we believe it is important to study treatment persistence after cycling, as this will help us understand the best standards of treatment for patients with chronic immune-mediated inflammatory diseases. Precisely due to the necessary increase in therapeutic tools, it is very important that treating physicians are aware of their patients' treatments, so that they can comply adequately with pharmacovigilance and the traceability of adverse events in their patients.[8–10]

Material and methods

This study was conducted in the rheumatology outpatient clinics of seven hospitals of the Mexican Social Security Institute, two in Mexico City and one in each of the following cities: Guadalajara, Torreón, Monterrey, Chihuahua and Querétaro. The information was collected by the rheumatologists who directly manage the patients included in the study.

An observational cohort study of paired cohorts, both historical, was conducted of stable RA patients (2010),[11] who were not switched from treatment for at least 6 months, versus a cohort of patients who were switched to a drug with a similar mechanism of action (cycling). Data collection from clinical records began in August 2018 and ended in the last week of January 2019, when the projected sample was met. The clinical records of RA patients who received Enbrel or Remicade from January 2014 onwards was reviewed. All the patients who received Enbrel or Remicade had failed with methotrexate and at least two other disease-modifying drugs before they were eligible to receive a biological agent at the institution where we conducted the study. The patients were allocated to each cohort according to the first biological agent they received.

The date of the non-medical switch was the index date of the cycling group, after they had been stable on the innovative drug for at least 6 months. A study period of 12 months was recorded, and a retrospective review was carried out after the index date. Treatment stability was defined as no significant change in the patient's clinical status, no change in concomitant/adjuvant treatment based on an increase in dosage or frequency, and no increase in the dosage or frequency of the biological drug.

We determined whether there was an impact on treatment persistence after cycling in RA patients treated with innovative infliximab (Remicade) or innovative etanercept (Enbrel) whose treatment had been stable for at least 6 months before switching to a biocomparable (Remsima) or a non-biocomparable (Infinitam), respectively.

The control patients were those who were not switched between treatments. They were selected retrospectively so that they could be paired with those who had been switched in terms of key clinical factors (Table 1). The index date of the patients who were not switched was defined as the date when there was treatment stability according to standard clinical criteria for 6 months after starting the innovative biological. The same study period duration of 12 months was applied in this group to determine the primary endpoint. This endpoint was the assessment of treatment persistence after switching to a biocomparable or a non-biocomparable.

We also describe the reasons for discontinuation after switching, including medical reasons such as safety, i.e., an adverse event or loss of efficacy, and non-medical reasons. And we recorded how treating physicians were informed about cycling at the pharmacy level (automatic substitution), and the methods for reporting the decision.

Two comparisons of interest were suggested from the current context, namely cycling from innovative drug to biocomparable and cycling from innovator to non-biocomparable. Similar persistence rates are assumed for innovative, biocomparable and non-biocomparable products to estimate sample size. The calculation also assumes a significance level of 5%. A 50:50 division is also assumed for patients switched to the biocomparable and non-biocomparable group. With a persistence rate with the original drug of 75% and a persistence rate with the switch drug of 50% and

Table 1
Demographic characteristics of the participants.

	Enbrel-Enbrel group (n = 94)	Enbrel-Infinitam group (n = 113)	Remicade-Remicade group (n = 38)	Remicade-Remsima group (n = 19)	*P*
Male	10	12	8	4	n.s.
Female	84	101	30	15	n.s.
Latino	94	112	38	19	–
Caucasian	–	1	–	–	–
Age in years, mean (SD)	54.8 (13,2)	52.4 (13.2)	55.1 (14.1)	55.6 (15.8)	n.s.
Treatment time of the disease, years	8.7	8.6	8.7	8.9	n.s

expecting to detect a 25% difference in persistence rates, a total sample of 264 patients is needed, with 80% power.

The calculation assumed a significance level of 5%. The primary outcome was assessed as treatment persistence related to discontinuation for any reason during the 12-month study period. The Kaplan-Meier method was used to estimate treatment persistence (with 95% confidence intervals). We estimated the hazard ratio (HR) of discontinuation by fitting the Cox proportional hazard model for factors collected in the reference period for patients switched to a biosimilar versus those switched to a non-comparable biological drug, and for those who were switched in general versus those who were not (those kept on innovative therapy).

For the proportion of patients with treatment persistence we performed logistic regression analysis and estimated the odds ratio (OR) after adjusting the effects of the reference factor to assess the factors associated with persistence. We used descriptive statistics to summarise the demographic and disease characteristics. Univariate and multivariate analyses were used for the primary and secondary endpoints. We performed a separate analysis for the patients who switched from biological to biocomparable treatments, and the patients who switched from biological to non-biocomparable treatments.

We applied a two-sided nominal significance level of .05. In the multivariate analysis phase, we used the stepwise method for selecting the model.

We summarised the reasons for discontinuation and the adverse events, including lack of efficacy. All adverse events were recorded and used clinical judgement in attributing adverse events to treatment, and it was recorded if this attribution was not evident in the record or if the reason was not shown. Categorical data analysis tools such as the $\chi 2$ test were used. The physicians' level of knowledge about cycling was qualitatively assessed by a locally developed questionnaire and percentages were calculated. Specific communication channels were described using the same questionnaire. We collected this information retrospectively for the cohort of patients whose treatment was switched.

Results

Two hundred and sixty-four consecutively selected patients with a diagnosis of RA participated in the present study: 132 patients who were switched and 132 patients who were not switched and remained on their allocated treatment. Patients were also divided into two groups according to the molecule they were receiving (and this in turn determined the biocomparable or non-biocomparable molecule they were switched to in the case of cycling), resulting in 207 patients in the Enbrel group and 57 in the Remicade group. These groups were further divided according to whether they were switched for non-medical reasons or not. Of the 264 patients participating in the study, 230 (87.1%) were female and 34 (12.9%) were male. The average age was 53.9 years, with a minimum age of 16 years and a maximum age of 84 years. Two hundred and sixty-three patients were Latino (99.6%); only one patient was white. When testing homogeneous groups, no statistically significant differences were detected in the demographic variables gender, age, and race ($P > .05$).

Table 2
Summary of study results.

The management of 132 patients did not change during the study
Patients with Enbrel at the start: 207
Continuers: 94
Switchers: 113
Patients with Remicade at the start: 57
Continuers: 38
Switchers: 19

Of the 207 patients in the Enbrel group, 94 (45.4%) were continuers and 113 (54.6%) were switched to a non-biocomparable treatment (Infinitam). Of the 57 Remicade patients, 38 (66.7%) were continuers and 19 (33.3%) were switched to a biocomparable drug (Remsima) (Table 2).

Twenty patients (15.2%) from the arm of 132 patients in the cycling group were identified as discontinuing and needing another treatment before the year, while 84% (112 patients) of the same group continued on the same treatment for the entire follow-up. The 20 patients who discontinued post-cycling required another biological treatment. The most common drugs in the Enbrel-Infinitam group were abatacept and tocilizumab (7 patients, respectively) and the most common drug in the Remicade-Remsima group was certolizumab (3 patients, 15.0%).

There were 116 women (87.9%) and 16 men (12.1%) in this group of 132 patients who were switched to a non-biocomparable or a biocomparable. In terms of race, 131 were Latino (99.2%) and only one was white (.80%). In the Enbrel-Infinitam group there were 101 women (89.4%) and 12 men (10.6%), with an average age of 52.4 years and a treatment time of 8.6 years. In the Remicade-Remsima group there were 15 females (78.9%) and 4 males (21.0%), all of Latino race and with average of 8.9 years on treatment. The average age observed was 55.6 years.

No statistically significant differences were observed in the demographic variables, gender, race, age, or time on treatment.

An overall persistence of 84.8% was observed in the analysis of persistence in the 12-month period after switching the 132 patients. By patient group, depending on whether they switched to a non-biocomparable or a comparable biological drug, there was an annual persistence rate of 85.8% in the Enbrel switch group and an annual persistence rate of 78.9% in the Remicade switch group. No statistically significant difference was observed ($P = .67$) on evaluating these percentages (Table 2).

In an analysis of the persistence time calculated from the time of cycling to the time of discontinuing treatment in the Enbrel-Infinitam versus Remicade-Remsima switch groups, a statistically significant difference in persistence time was observed between the groups of patients, persistence being shorter in the Remicade-Remsima group (16, 4.0 ± .82 for Enbrel-Infinitam vs. 4, 4.0 ± .82 for Remicade-Remsima) ($P < .05$) (Table 3).

For the next sections, we should highlight that in some cases complete patient data could not be collected and analyses were

Table 3
Persistence of the patients after drug switch.

Cycling	Total	Discontinued	Continued
Enbrel-Infinitam	113	16 (14.2%)	97 (85.8%)
Remicade-Remsima	19	4 (21.1%)	15 (78.9%)
Total	132	20 (15.2%)	112 (84.8%)

based on observed data (p̈er protocol)̈ without imputing values for missing data.

In the cycling group of 132 patients, mean disease activity scores measured by DAS28 (Disease Activity Score 28-joints) per visit were observed. In both the Enbrel-Infinitam and Remicade-Remsima switch groups, the significance of the mean difference between the baseline visit and visit 4 (final 12 months) was assessed; a statistically significant change was not observed in either case ($P > .05$). The mean DAS28 score was also compared between the two groups at both baseline visit and visit 4, and a statistically significant difference was not detected in any case ($P > .05$).

No significant differences were found ($P > .05$) on analysing the mean change in DAS28 between the baseline visit and visit 4 (12 months) by each group independently.

On assessing the mean baseline-visit 4 switch (month 12), no statistically significant difference ($P > .05$) was observed in the groups of switched patients, in either the Enbrel-Infinitam or the Remicade-Remsima group.

As part of the information available in the study documents, of the 132 patients whose initially prescribed drug was switched, it was observed that in the Enbrel group the physician was informed 72.6% of the time by the patient and 14.2% of the time by the head of the institution. In the Remicade group, the doctor was informed of this switch by the patient 42.1% of the time, and 5.3% of the time by the head of the institution. As additional information, in most cases the physician was informed after the new drug had been applied and dispensed. It was not reported in all cases when the physician was informed of the switch.

Of the entire study population (n = 264), a total of 68 adverse events were recorded in 59 patients, with a higher number in the cycled patients, regardless of the biological agent used (48 adverse events or 70.5% of the 68 adverse events). A statistically significant difference was observed when comparing the proportions of patients with an adverse event ($P < .05$) between groups (Table 4).

Regarding the most frequent adverse events in the total number of patients (264), lack of efficacy was recorded in 20 (7.6%), all in the cycling group. Respiratory tract infection was observed in 9 patients (3.4%): in 3 patients (2.3%) in the cycling group and in 6 patients (4.5%) in the group that did not switch treatment. Again, of the total number of patients, RA reactivation was reported in 6 patients (2.3%), where 5 patients (3.8%) were in the cycling group and one patient (.8%) in the group that did not switch treatment.

The Kaplan Meier technique was used for the statistical analysis in the cycled patient population where the event of interest was discontinuation of treatment (post-cycling) and the time it took for this to occur. One hundred and thirty-two patients were analysed in whom a switch of treatment for non-medical reasons was observed, of these 19 were in the Remicade-Remsima group, and 113 in the Enbrel-Infinitam group. Thus, it was observed that the primary event of interest, i.e., discontinuation of treatment after cycling, occurred in 4 patients (21.1%) in the Remicade-Remsima group, and in 16 (14.2%) patients in the Enbrel-Infinitam group.

Statistical comparison of the means of estimated time to treatment discontinuation between the two study groups using the Log Rank test, which is a test of equality of time distributions, results in a P-value of .002. Therefore, we can conclude that the null hypothesis of equality is rejected, i.e., statistically significant differences are declared between both groups of patients under study with respect to the average time taken to discontinue treatment. There is a tendency towards earlier discontinuation in the Remicade-Remsima vs. the Enbrel-Infinitam cycling group. However, it is important to mention that there is a significant disproportion in the total number of patients for each group and the number of times the discontinuation event occurs in each group, which is a limitation of this study.

In the logistic regression analysis, the variable of interest is discontinuation (1 = yes, 0 = no) of post-cycling treatment. Different logistic regression model options with different combinations of independent variables were adjusted. The variables that entered the analysis were initial biological treatment (Remicade or Enbrel), the non-biocomparable or biocomparable biological treatment that was switched to post-cycling, categories of age, gender, BMI, time of disease diagnosis, presence of adverse events, baseline DAS28, DAS28-V4 (12 months), final ESR, final CRP.

After adjustment of different models, only one variable was found to have significantly contributed to whether or not there was a biological treatment discontinuation event, this was the biological treatment that was switched to (Infinitam or Remsima).

For the biological treatment variable non-biocomparable vs. biocomparable (Infinitam vs. Remsima) a positive beta value (1.501) was observed, which was significant ($P = .007$). Therefore, setting Infinitam as the reference treatment, starting with Remsima results in a risk (OR) of more than 4 times (4.5) that the post-cycling treatment discontinuation event will occur compared to those who switched to Infinitam. However, it is important to mention that there is a significant disproportion in the total number of patients for each group and the number of times the event of interest (post-cycling treatment discontinuation) occurred, which was only 20 cases out of 132. This is a limitation for drawing a conclusion and this data should be viewed with caution.

Discussion

The results obtained in a real-life setting to assess treatment persistence in patients switched to treatment with a biocomparable or to a non-biocomparable for non-medical reasons showed an overall persistence of 84.8% in our study. The differences in persistence when assessing groups according to their grouping by previously used and switch drug (Enbrel-Infinitam or Remicade-Remsima) were not statistically significant. Although not related to NMS, but to treatment persistence, a similar result was obtained in a retrospective study assessing persistence with biologicals in RA patients that used the database of the South Korean National Health System, comparing the persistence at 12 months of adalimumab, etanercept, infliximab and abatacept as first- and second-line treatment, where adalimumab, etanercept and infliximab had similar levels of persistence during the year after treatment initiation when used as first-line treatment. However, when used as second-line therapy, etanercept and abatacept had higher persistence rates than infliximab or adalimumab.[12] These results may be largely due to similarities in efficacy demonstrated by previous comparisons with these treatments.[13–15]

Analysis of persistence in the 12-month period after cycling in the 132 patients showed statistically non-significant differences, with 85.8% persistence for those treated with Infinitam (n = 113, 6 patients discontinued) and 78.9% for the group treated with Remsima (n = 19, 4 patients discontinued) ($P = .67$); when analysing this persistence in patients who discontinued treatment by assessing

Table 4
Comparison of adverse events between groups.

Adverse events	Total population: 264	Cycling group: 132	Continuer group: 132	*P*
Total	68	48 (70.5%)	20 (29.4%)	<.05
Any adverse event	59 (22.3%)	42 (31.8%)	17 (12.9%)	.0002
Lack of efficacy of switch	20 (7.6%)	20 (15.2%)	–	–

the mean time to treatment discontinuation (16 for the Infinitam-treated group and 4 in the Remsima group), the difference was statistically significant ($P = .0076$). These differences, although statistically significant when analysing persistence time in months calculated from the time of cycling until discontinuation of treatment in favour of the Infinitam group, may be related to the significant disproportion in the total number of patients for each group and the number of times the discontinuation event occurred in each group, which is a limitation of the result to be considered, not finding a statistically significant risk ratio for treatment discontinuation, according to the proportional hazard statistical results (Cox proportional hazard model).

The reason for discontinuation of treatment post-cycling was lack of efficacy in 20 patients, representing 100% of the patients who discontinued.

Overall analysis of the adverse events showed statistically significant differences when analysing the groups of continuers and switchers, and adverse events were more frequent in the latter (31.8% vs. 12.9%; $P = .0002$). This result is mainly due to lack of efficacy being identified as a post-switch adverse event. In a study published in 2018 evaluating 6 months of real-life follow-up of patients switching from Remicade to its biosimilar Remsima, in patients with RA, psoriatic arthritis and ankylosing spondylitis, discontinuation was mainly due to an increase in subjective characteristics of tender joint count and the patients' overall assessment of disease activity and/or subjective adverse events, possibly explained by nocebo effects and/or incorrect causal attribution effects. No similar results are found in the literature that specifically evaluate a comparison between the two treatments used in our study after NMS.

Analysis of the clinical variables – assessed as a whole with the DAS28 – indicative of disease activity showed no statistically significant differences during follow-up according to the treatment used post-cycling (Infinitam or Remsima).

An interesting finding of our research is that in the institution where the study was conducted the treating physician is usually not informed of the decision for a non-medical change of treatment – in this study, a switch to a drug of a similar mechanism of action from a different manufacturer – that will affect their patient, as 82%–90% of the changes were reported to the physician after the new drug was dispensed and by the patient him or herself. Only in a very few cases was the physician informed through the regular administrative channels where the non-medical change of treatment was made. The implications of this may impact the traceability of adverse events to the correct drug, specifically with respect to the difficulty in attributing an adverse event in a patient who has received an innovative drug and a biocomparable or non-biocomparable indistinctly over time, and which has not been promptly and regularly reported to the treating physician through the regular channels.

Treatment persistence of biological medicines in the real world has been suggested as a proxy for the effectiveness of the treatment, being a composite measure for efficacy and adverse drug events.[14] Therefore, the fact that 20 patients in the cycling group had to be switched to a second biological highlights the need for close follow-up of any patient who is switched to a different treatment for non-medical reasons.

Our study has the limitations of a retrospective study based on information from the medical records of patients in a public institution, and its limited number of patients, especially in the Infinitam group, which prevents drawing definitive conclusions. It should also be borne in mind that this was a real-life, non-randomised study (selection bias), which may limit the interpretation of the results. We also believe that longer-term follow-up data are needed, as in our case the patients were seen retrospectively.

There were no statistically significant differences between the two treatment groups in treatment persistence after a non-medical switch from an innovative drug to a biocomparable drug or to a non-biocomparable drug in RA patients.

Conflict of interests

The authors have no conflict of interests to declare.

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