ORIGINAL ARTICLES

Rheumatoid arthritis monotherapy in the Jak inhibitors Era. Current prevalence and associated factors in a multicenter study

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ABSTRACT

Background: Combined therapy constitutes the standard of care in RA. Jak inhibitors (Jaki) have shown efficacy in monotherapy, a modality used in cases where it is not possible to use Disease-Modifying Anti Rheumatic Drugs (csDMARDs).

Objectives: To estimate the prevalence (total and by drug), reason for using and the increase over the time of bDMARDs or tsDMARDs as monotherapy after the availability of the Jaki. To analyze the differential characteristics between patients with monotherapy vs combined therapy.

Methods: Cross-sectional multicenter study. Consecutive patients with a diagnosis of RA (ACR/EULAR 2010) under treatment with bDMARDs or tsDMARDs started from 2013 were included. Socio-demographic, clinic, and therapeutic data were collected.

Results: A total of 505 RA patients were included. Since 2013, the prevalence of monotherapy usage was (any) 49%. The drugs used as monotherapy were Jaki in 41% and TNF-blockers in 30%. The leading causes of monotherapy use were intolerance/adverse events (62%), medical decision or lack of adherence (37.7%). The highest socioeconomic level and a better functional status at diagnosis were predictors of monotherapy use. The use of the second line of treatments and less polypharmacy were independent factors associated with this therapeutic modality.

Conclusions: The current prevalence of monotherapy in RA was 49%, the Jaki were the most used drug in this modality. Monotherapy increases from year to year. There are differential characteristics in patients using monotherapy.

Keywords: Rheumatoid arthritis; Biological therapies; DMARDs; Attitude of health professionals.

INTRODUCTION

Biological (bDMARDs) and targeted synthetic disease--modifying antirheumatic drugs (jak inhibitors) (tsDMARDs) for the treatment of rheumatoid arthritis (RA) are commonly used in patients with active disease who have not responded to treatment with conventional disease-modifying antirheumatic drugs (csDMARDs) or presented intolerance to them[1,2].

The EULAR recommendations suggest that bDMARDs and tsDMARDs should be combined with csDMARDs, because is the most effective treatment regimen currently available for RA patients. These guidelines also state that in patients who cannot use csDMARDs as co-medication, interleukin-6 (IL-6) pathway inhibitors and tsDMARDs (jaki) may have some advantages when used as monotherapy, compared to other DMARDs. However, biologic monotherapy is more frequently used in clinical practice than would be reported[1,3].

According to different international registries, the frequency of use of bDMARDs agents as monotherapy ranges from 12 to 39%[2]. In 2013, an Argentinean multicenter study showed 21.4 % of monotherapy3, which precedes the introduction of tsDMARDs in our country. The increased use of bDMARDs as monotherapy includes methotrexate adverse events, efficacy (good response to biologicals) or simply lack of patient adherence[2].

Due to the lack of updated local data and the changing reality of treatment patterns, we believe that it is essential to carry out this study, additionally, we believe that the study is relevant due to its impact on the efficacy of combined therapy and adherence to treatment.

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Our objective was to evaluate the proportion of RA patients treated with bDMARDs or tsDMARDs in monotherapy in our setting. To evaluate the participation of the Jaki in this therapeutic modality, we took as a starting point the year of the introduction of this mechanism of action in Argentina (2013). As a secondary objective, we evaluated the reasons for discontinuing csDMARDs. In addition, we describe the frequency of monotherapy use for each individual drug, and the year-to-year prevalence of monotherapy. Finally, we analyzed disease-related factors that were associated with monotherapy.

METHODS

Observational, cross-sectional and retrospective study, (based on the clinical records). Ten rheumatology centers distributed across Argentina with proven experience in research and real life studies were invited to participate. Each center evaluated the 50 consecutive patients who attended their regular consultation during the study period, July to December 2021, with the following inclusion criteria: RA diagnosis (ACR/EULAR 2010 criteria), 18 years old or older, patients had to be treated with b/tsDMARDs[4], and treatment initiation should have been in 2013 or after. Demographic data, disease duration, presence of rheumatoid factor (RF) and anti-Cyclic Citrullinated Peptide antibody (ACPA), previous and current treatment with csDMARDs, bDMARDs and tsDMARDs and reasons for discontinuing csDMARDs were collected from medical records. All Data regarding on current or previous use as monotherapy were collected at the last visit.

An electronic Case Report Form (eCRF) was developed, and data were entered in each center according to the protocol. The data collected retrospectively at the time of diagnosis was: Medical history including time of symptoms onset (years), Date of diagnosis, RF and ACPA, disease activity at diagnosis (DAS 28), a presence of bone erosion in hands radiographs, Smoker (current-past) and comorbidities (arterial hypertension, MACE, etc.). Data collected at the moment of presential visit were: Date, TJC and SJC (28), VASph, VASp, HAQ-DI, ESR, CRP, presence of bone erosion in radiographs, and extra-articular manifestations. Treatment data: Current use of: csDMARDs, bDMARDs and tsDMARDs, treatment duration (months), treatment line (second, third), use as monotherapy actually or in any moment, Reasons for monotherapy (patient decision, an adverse event to csDMARDs, etc.), monotherpy duration.

Statistical Analysis

STATA 12 statistical package was used. Continuous variables were informed as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution and categorical variables as frequency and distribution. T-test or Mann-Whitney test were used for the bivariate analysis of continuous variables and Chi-squared test for categorical variables. Prevalence of monotherapy use was established. Logistic regression analysis was performed to assess the factors associated with monotherapy, with the current use of biologic or tsDMARDs monotherapy as a dependent variable and patient demographics and baseline characteristics as independent variables. Odds Ratio (OR) and 95% confidence intervals (95%CI) were calculated, and a p-value less than 0.05 was considered statistically significant.

Ethical considerations

The study was reviewed and approved by the Ethics Committee of the Hospital Italiano de La Plata (5/19/2021) according to requirements of Law 11.044 and regulatory decree 3385/08, as well as national and international ethical guidelines. In the retrospective observational design of the study, in which subjects data were coded and anonymized according to Law 25326, informed consent was not obtained.

RESULTS

A total of 505 patients were included, 88% women, with a mean age (m) of 58 years (SD ± 13.5) and disease duration of 13 years (SD ± 7.8). Patient's characteristics and treatment data are shown in Table I and II. Since 2013, the frequency of monotherapy use (ever) was 49% (95% CI: 45-53); at the last visit, the prevalence of monotherapy use was 41% (95% CI 37-45). The leading causes of monotherapy use were csDMARD intolerance 39.9%, an adverse event to MTX 22% (Hepatic 38%, Gastrointestinal 24%, Hematological 11%, Alopecia 11%), physician"s decision 20.2% and lack of patient´s adherence to csDMARDs 17.7%.

Regarding patients in monotherapy the treatment pattern was: Jaki: 41% (IC 95%: 35-48), TNF-blockers: 30% (IC 95%: 24-37) and IL6-blockers: 16% (IC 95%: 12-22). Figure 1 shows the frequency of monotherapy for each type of treatment, it is observed that the Jaki is used in a more significant proportion in monotherapy (56.6% vs 43.4%). The prevalence of monotherapy increased year after year since 2013 with a peak in 2019, this can be seen in Figure 2.

Among patients currently on monotherapy (n=207), 59% started a bDMARDs or tsDAMRDS in this modality; in those starting as combined therapy, the median time to monotherapy was 12 months (IQR: 7-25). 67%

Table I. Characteristics of the RA patients

Features (at diagnosis)	n 505
Residents in Ciudad Autonoma de Buenos Aires	28%
Residents in Provinces	72%
Age at diagnosis (years), M (SD)	45 (13)
Female Gender	88%
Health insurance (yes).	86%
Employment status (active).	59%
Disability certificate.	52%
Socioeconomic level (medium-high stratum)	23%
Time of onset of symptoms at diagnosis (years) Med (IQR)	6 (3-11)
RF positive	88%
ACPA positive	73%
Disease activity at diagnosis (DAS 28), Med (IQR)	5.4 (4.6-6.1)
HAQ at diagnosis, M (SD)	1.2 (0.7)
Erosion (X-ray)	44%
Smoker (current-past)	33%
Comorbidities (any-yes)	45%
Extra-articular manifestations (any)	19%
Features (last visit)	
Current Age, M (SD)	58 (13)
Over 65 years (yes)	36%
Time from diagnosis to last visit (follow-up/ disease duration, years) M (SD)	13 (7.8)
Disease activity (DAS 28), Med (IQR)	3.1 (2.3-4.2)
HAQ, M (SD)	0.8 (0.6)
Erosion (X-ray)	65%
Comorbidities (any-yes)	59%

M: Mean, SD: standard deviation, IQR: interquartile range, RF: rheumatoid factor, ACPA: Anti citrulline peptide antibody, HAQ: health assessment questionnaire.

Table II. Current Treatment features

	n 505
Methotrexate	48%
Leflunomide	6%
Other DMARDs	5%
TNF-blockers	42%
IL6-blockers	11%
JAK-Inhibitors	30%
Others bDMARDs	17%
First Line of biological treatment or Jaki %	44%
bDMARDs or tsDMARDs exposure time (months) Med (IQR)	34 (21-64)
Polypharmacy (>4 drugs)	54%
Polypharmacy (>5 drugs)	37%

M: Mean, SD: standard deviation, IQR: interquartile range, RF: rheumatoid factor, ACPA: Anti citrulline peptide antibody, HAQ: health assessment questionnaire.

of patients were in their second line of advanced treatment. The total time in monotherapy was 2.1 (IQR: 1.1-3.8) years; there were 13% of patients returned to combined therapy.

In the univariate analysis, work-active patients (64% vs 55%, p <0.05), a higher socioeconomic status (31.4% vs 17.2% p <0.01), lower mean HAQ at diagnosis (1.1 vs 1.3, p <0.05), 2nd or further line of advanced therapy vs 1st line (53% vs 33%, p <0.01), lower frequency of polypharmacy (45.6% vs 60%, p <0.02) and longer mean time of biological treatment (47 months vs 39 months, p <0.01) showed association with the use of monotherapy. These variables were entered in a logistic regression model where socioeconomic level (medium--high stratum), HAQ at diagnosis, Line of advanced treatment and Polypharmacy (>4 drugs) were associated independently with monotherapy (Table III).

DISCUSSION

The synergy of methotrexate and TNF-blockers has been widely demonstrated[5]. Evidence from the immunopathology supports that this additive action, is related with the main effect of TNF-blockers on innate immunity (macrophages and neutrophils) and MTX on B and T cells. In addition this theory supports MTX use would also inhibit the formation of anti-drug an-

Table III. Logistic Regression (dependent variable: current monotherapy)

Variable	OR	CI 95%		p
Employment status (active).	1.32	0.86	2.02	0.19
Socioeconomic level (medium-high stratum)	2.15	1.32	3.49	0.00
HAQ at diagnosis, M (SD)	0.70	0.52	0.94	0.01
First Line of biological treatment or JAKi (yes)	0.45	0.3	0.7	0.00
Polypharmacy (>4 drugs) (yes)	0.60	0.39	0.91	0.01
bDMARDs or tsDMARDs exposure time (months)	0.99	0.98	1	0.05

TNF: Tumor necrosis factor; IL: Interlekin; JAKi: Janus kinase inhibitor.

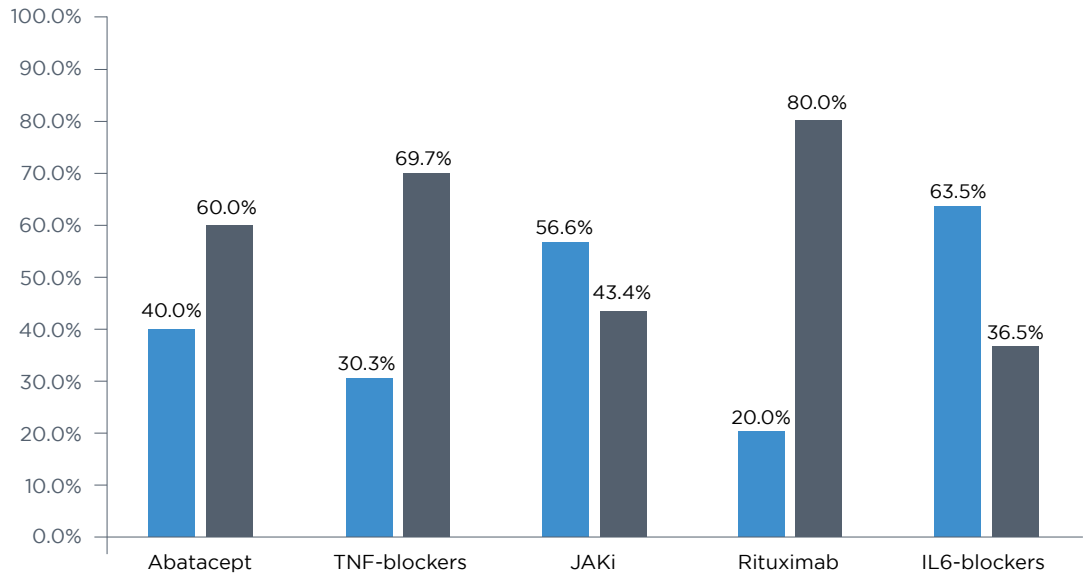

Figure 1. Frequency of monotherapy by drug.
TNF: Tumor necrosis factor; JAKi: Janus kinase inhibitor; IL6: Interlekin 6.

tibodies[6].

The arrival of other mechanisms of action, such as IL6-blockers, with a broader effect on the immune system, changed the paradigm of combined therapy since clinical trials such as AMBITION and ADACTA demonstrated that monotherapy treatment with IL-6-blockers it was as effective as the combined therapy with MTX and superior to TNF-blockers in monotherapy[7,8]. Subsequent pivotal trials of Jaki, such as ORAL solo (Tofacitinib), RA-BEGIN (Baricitinib), and SELECT MONOTHERAPY (Upadacitinib), have demonstrated the efficacy of these molecules in monotherapy. This evidence led to the incorporation of the recommendation for using these drugs as monotherapy in the EULAR guidelines[1].

Before the introduction of Jaki, real-life registry studies showed that the prevalence of monotherapy use in Europe and the United States ranged between 30% and 38%[9]. In Argentina, Sommerfleck et al, in a multicenter study including over 1000 patients, established a prevalence of monotherapy of 21%, the leading cause for csDMARDs discontinuation being intolerance and adverse events to MTX[3]. Later, in 2016, two monocentric studies, one conducted in La Plata and the other in Buenos Aires, showed a prevalence of monotherapy of 32 and 35%, respectively. This last study, carried out in a population belonging to the same health insurance, showed that 40% of the csDMARDs discontinuations were because of patient preference[10,11].

The adherence to csDMARDs is a central issue for

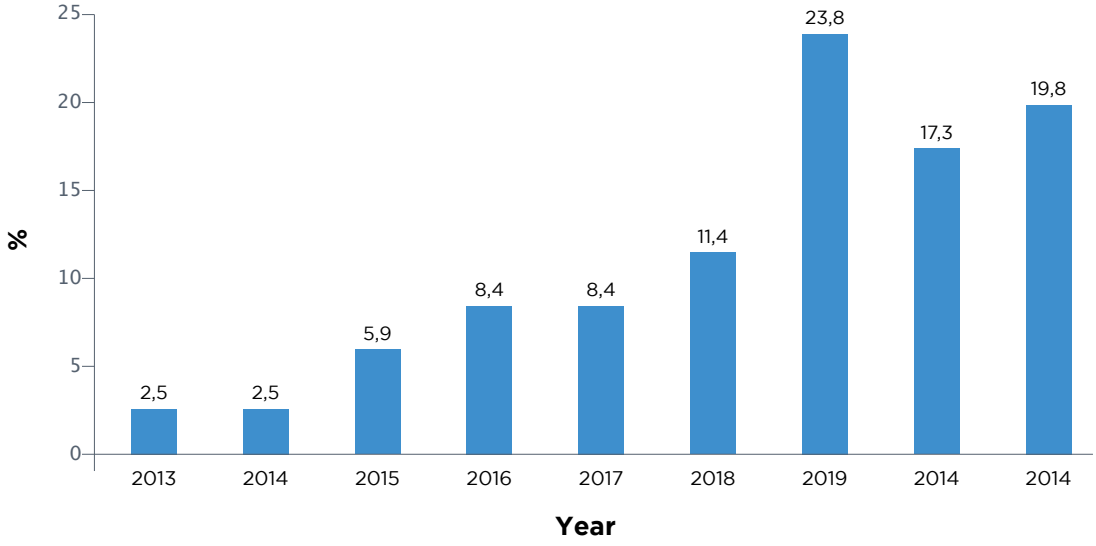

Figure 2. Frequency of monotherapy by year.

therapeutic success. In Argentina, the CQR (Compliance Questionnaire on Rheumatology) and the SMAQ (Simplified Medication Adherence Questionnaire) showed that adherence to csDMARDs was only 50%, with patient decisions as the primary cause of discontinuation. There are studies in closed populations in centers in Canada which shown that, despite the medical prescription, 58% of the patients did not pick up the medication (csDMARs) from the pharmacy[12].

Our study was based on the premise that the use of monotherapy would have increased in recent times due to two fundamental reasons: the appearance of Jaki (with proven efficacy in this modality) and a change in therapeutic behaviour based on more patient participation. Therefore, initiation of biological or jaki treatment after 2013, the year the first Jaki was approved in Argentina, was mandatory at inclusion, in order to capture the impact of these in monotherapy.

We found a greater use of monotherapy compared to previous publications. Since 2013, at least 49% of patients had experienced this therapeutic modality at some time, and at the last visit the current prevalence was 41%. The reasons for the use of monotherapy are still led by intolerance and adverse events to MTX; almost 40% were due to the decision of the patient or the doctor, without questions of efficacy or safety. It is also important to note that about 60% of patients started treatment as monotherapy[13].

In the distribution of monotherapy use by drug, the Jaki were, in proportion, those that contributed the most to the use of monotherapy with 41%, followed by TNF-blockers (30%) and IL-6 inhibitors (16%), leaving in evidence that since its appearance, the jaki were the ones that contributed the most to this therapeutic modality. Analyzing each group of drugs individually, IL-6 had the highest percentage of use as monotherapy (63%), followed by JAKi (57%). Finally, we could also show that the proportion of patients on monotherapy increased year after year.

Regarding the features related to monotherapy, a higher socioeconomic level and a lower functional disable according to HAQ (basal) were positively associated; this could represent a patient profile that chooses monotherapy. Socioeconomic status may reflect insured patients and active workers, factors that also impact adherence to methotrexate. Additionally, the baseline HAQ could also be a strong predictor of therapeutic efficacy in general, therefore these patients have a baseline status that allows the use of monotherapy with better results than patients with a greater functional impact at the time of diagnosis. On the other hand, could also reflect a physician's preference.

Likewise, polypharmacy was negatively associated with monotherapy, meaning that monotherapy reduces the chance of polypharmacy, although not taking methotrexate results in not using folic acid, which significantly reduces the amount of drugs. Monotherapy was observed also mostly in second or further lines of advanced treatments, this can be attributed to the fact that advanced first-line treatments are generally TNF--blockers, mostly combined with csDMARDs.

It is essential to highlight the weaknesses of the study, these having to do with its retrospective nature and the review of medical records, increasing the chance of information bias. As strengths, we can consider that it is a representative number of patients from multiple

centers across Argentina. Including patients initiating treatment since 2013 allows us to see a population with characteristics representing current treatment trends.

In conclusion, we can confirm that in our setting the prevalence of monotherapy is higher than in previous reports, this increase was observed year after year and we can confirm that Jaki fulfilled a fundamental role in behavior change since they are the most used drug in this modality. We can also conclude that there is a patient profile for the use of monotherapy.

These results are important in justifying a therapeutic approach to a payer in light of data on adherence to methotrexate and the use of Jaki or IL6 blockers as monotherapy.

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