EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2020.19053

Original Article

Disease-modifying antirheumatic drug prescription patterns in adult rheumatoid arthritis patients in routine clinical practice in Spain

Blanca Hernández Cruz[1], Inmaculada Ureña Garnica[2], Ricardo Sánchez Parera[3], Esteban Rubio Romero[4], Jerusalén Calvo Gutiérrez[5], Antonio García Sánchez[6], Carlos Rodríguez Escalera[7], Federico Navarro Sarabia[1]

Abstract

Objective: To describe disease-modifying antirheumatic drug (DMARD) patterns in routine clinical practice in adult rheumatoid arthritis (RA) patients and to ascertain the reasons for methotrexate (MTX) discontinuation.

Methods: A cross-sectional observational study was conducted from March to October 2014 at the Rheumatology Units of seven hospitals in Spain. In a single visit, the treating rheumatologist completed an online case report form. This report contained sociodemographic and RA variables. This study was conducted in accordance with Good Clinical Practice and local and national research legislations.

Results: A total of 301 patients (71% women) with a mean age of 56.7±14.0 years and disease duration of 3.6±1.5 years were examined. The patients had RA with moderate disease activity, at least one poor prognostic factor, and comorbidities. The mean time between RA diagnosis and prescription of the first conventional synthetic DMARD (csDMARD) was 2.4±6.0 months. A total of 295 patients (98%) started the first csDMARD on monotherapy. MTX was the most-prescribed first-line drug (n=233, 79%). The mean treatment time of the first-line csDMARD was 27.0±19.4 months. Of these patients, 98% progressed to a second-line csDMARD; 118 patients were changed to another DMARD, mainly due to inefficacy (51, 37%), adverse events (AEs, 37, 27%), or intolerance (18, 13%). The use of MTX as second-line therapy reduced from 79% to 51%. At the time of the study, 200 patients (66%) received a csDMARD as monotherapy and 45 (15%) a combination of ≥2 csDMARDs. Fifty-five (18%) patients were being treated with a biological drug in monotherapy (16, 29%) or in a combination with a csDMARD (39, 71%), mainly MTX, 147 patients (57%) received steroids. Biological DMARD were prescribed as the second line for 42% of patients and 51% of patients received the third-line therapy or beyond. The rate of AEs that motivated a change in the csDMARD was 34%.

Conclusion: MTX was the most-used csDMARD as first and second-line therapy together with corticosteroids. The combination of two or more csDMARDs as first-line treatment was very infrequent. MTX toxicity and intolerance were higher and more significant than inefficacy but progressively decreased with use.

Keywords: Antirheumatic agents, disease modifying antirheumatic drugs, conventional syntetic antirheumatic drugs, biologic disease modifying antirheumatic drugs, rheumatoid arthritis, prescription drugs

ORCID iDs of the authors:
B.H.C. 0000-0001-6423-3610;
I.U.G. 0000-0003-4428-7376;
R.S.P. 0000-0001-6543-3948;
E.R.R. 0000-0001-7402-8880;
J.C.G. 0000-0001-6822-5589;
A.G.S. 0000-0001-5450-1968;
C.R.E. 0000-0003-1888-8637

Cite this article as: Cruz BH, Garnica IU, Parera RS, Romero ER, Gutiérrez JC, Sánchez AG, et al. Disease-modifying antirheumatic drug prescription patterns in adult rheumatoid arthritis patients in routine clinical practice in Spain. Eur J Rheumatol 2020; 7(4): 149-57.

[1] Department of Rheumatology, Virgen Macarena University Hospital, Seville, Spain
[2] Department of Rheumatology, Regional University Hospital of Malaga, Malaga, Spain
[3] Department of Rheumatology, San Cecilio University Hospital, Granada, Spain
[4] Department of Rheumatology, Virgen del Rocio University Hospital, Seville, Spain
[5] Department of Rheumatology, Reina Sofia University Hospital, Cordoba, Spain
[6] Department of Rheumatology, Virgen de las Nieves Hospital, Granada, Spain
[7] Department of Rheumatology, Melilla Regional Hospital, Melilla, Spain

Address for Correspondence: Blanca Hernández Cruz; Department of Rheumatology, Virgen Macarena University Hospital, Seville, Spain

E-mail: blancahcruz@gmail.com

Submitted: March 16, 2019
Accepted: April 11, 2020
Available Online Date: September 3, 2020

Introduction

Significant changes have been made to the diagnostic and therapeutic approaches to rheumatoid arthritis (RA) in recent years (1). Since 2010, the "treat to target" (T2T) strategy has been employed to diagnose and treat the disease (2). The T2T strategy is based on the implementation of certain principles: treating to target, measuring outcomes, early diagnosis, appropriate treatment and efficient use of drugs, as well as managing comorbidities rather than focusing on specific recommendations concerning which drug to prescribe (2, 3). This strategy has proven to be beneficial in various disease outcomes (4).

Nevertheless, the treatment of RA patients continues to be challenging for rheumatologists for various reasons: the changeable clinical course and chronic nature of the disease; the lack of serum, synovial, or imaging biomarkers that can predict therapeutic response (5); and the wide-ranging effica-

cy, adverse reactions, and toxicity of the various disease-modifying antirheumatic drugs (DMARDs) (1, 6). Conventional synthetic DMARDs (csDMARDs), with or without low or very low doses of corticosteroids, have been the first-line treatment for RA for many years (1, 7-9). Methotrexate (MTX) has established itself as the gold standard of treatment (7-9) with excellent cost-effectiveness. However, MTX is not suitable for all patients, either due to comorbidities that contraindicate its use (such as hepatitis B virus infection) or the onset of adverse events (AEs). The incidence of AEs associated with MTX monotherapy is estimated at 76/1,000 patient-years and 15-999/1,000 patient-years when MTX is administered in combination with csDMARDs, or with biological DMARDs (bDMARDs) (6). The inefficacy of MTX is another problem with efficacy rates of 30%-40% only (6-9). Furthermore, some patients refuse to use MTX (10). When MTX cannot be used, treatment guidelines recommend leflunomide (LEF) or sulfasalazine (SSZ) in combination or as sequential monotherapy (11-14). In Spain, the current recommendations for the treatment of RA patients state that after 3 months of treatment with MTX (20-25 mg/week orally PO or subcutaneously SC) plus steroids, if the patient has persistent activity or toxicity, a second trial with csDMARD can be done (14). A trial with a bDMARD can also be done considering the clinical characteristics and the presence of poor prognostic variables (11-14). However, in our setting, a recent study of csDMARD prescription patterns in RA found significant variability in its prescription (15). However, reliable data on the efficacy of MTX and the rate of AEs associated with its use in usual clinical practice are lacking. The objective of this study was to describe csDMARD prescription patterns in routine clinical practice in adult RA patients in Spain to analyze the response to treatment, and to ascertain the reasons for MTX discontinuation.

Main Points

- In our study, most of the patients were initially treated with MTX as single first csDMARD (79%) in combination with low doses of corticosteroids (57%). The combination of csDMARD therapy as first-line treatment was very infrequent.
- MTX had to be stopped due to AEs and inefficacy in 40% of the patients. This led to prescription of subsequent csDMARD treatment lines or monotherapy with bDMARD.
- The length and frequency of MTX use decreased progressively.
- The first bDMARDs were started after one or two failures in one-third of cases.
- According to the T2T strategy, RA treatment is dynamic, with changes after a few months depending on disease activity and toxicity of the drug.

Methods

Design of study and population

An analytical, cross-sectional observational study was conducted at the Rheumatology Departments of six tertiary-care hospitals and one second-level hospital located in the south of Spain between March and October 2014.

Inclusion criteria: Consecutive patients, 18 years and above, with adult RA in accordance with the 2010 American College of Rheumatology/European League Against Rheumatisms (ACR/EULAR) classification criteria were included (16). Patients diagnosed between 2008 and 2012 and treated with at least one csDMARD were also included.

Exclusion criteria: Patients without RA, patients diagnosed with diseases other than RA, and patients lost to follow-up were excluded.

The study was conducted in accordance with the World Medical Association's Declaration of Helsinki and with local and national research legislation. The study was approved by the Ethics Committee of Andalusia, Code SAR-FAM-2213-02-2213 (Approval Date: December 2, 2013).

Collection and assessment

Data were collected after a single visit, during which the treating rheumatologist informed the patients about the study and obtained their consent to participate. The rheumatologist filled an online case report form based on the patients´ medical history, electronic prescriptions, and information obtained directly from every patient. In addition to sociodemographic variables, information about the patients' RA was also collected. It was important to emphasize the time between diagnosis and prescription of the first DMARD and type and number of DMARDs, including reasons for switching treatment and its duration.

The disease activity was assessed using the 28-joint count disease activity score of four variables with erythrosedimentation rate (DAS28). The efficacy was assessed according to European League Against Rheumatism (EULAR) response (17). Endocrine, metabolic, cardiovascular, and musculoskeletal comorbidities were defined in accordance with ready set definitions.

Statistical analysis

Sample size: The sample size was calculated according to the number of patients who stopped MTX in the follow-up, which was estimated to be 30%-40%. The calculation was done with one-sample comparison of proportion with the hypothesized value formula. The assumptions were as follows: alpha=0.05 (two-sided); power=0.95; probability (p)=0.2. We estimated 240 patients were required. With an alternative probability of p=0.4, we estimated 290 patients were and 5% was added for loss to follow-up.

A descriptive analysis was carried out by calculating the measures of central tendency, dispersion, and frequency distributions. A new line of csDMARD therapy was defined as a dose adjustment of the existing treatment, discontinuation of the current csDMARD, or a change of csDMARD.

RA activity was analyzed for the total population. For patients whose treatment had not changed since the initial prescription, DAS28 at the onset of csDMARD treatment was compared with DAS28 at the study visit. For the patients who had numerous treatment changes, DAS28 at the onset was compared with DAS28 at the end of each line of DMARD therapy.

A multivariate logistic regression analysis was conducted by constructing various models. The dependent variable was the change of treatment. The independent variables were the patient's global assessment (PtGA), the physician's global assessment (PGA), and DAS28. The data were analyzed with IBM Statistical Package for Social Sciences program version 22.0 (IBM SPSS Corp.; Armonk, NY, USA).

Results

Of the 315 patients enrolled, 14 (4%) were excluded because of screening failures. In total, 301 patients (43 patients in each hospital) were examined. A total of 71% of patients were women with a mean age of 56.7±14.0 (standard deviation, SD) years and a disease duration of 3.6±1.5 years.

The patient characteristics are detailed in Table 1. At the time of the administration of the first csDMARD, the patients had moderate disease activity and at least one poor prognostic factor. The comorbidity rate was higher than 30%. The mean time elapsed between RA diagnosis and prescription of the first csDMARD was 2.4±6 months. There were no differences between

Table 1. Demographic and clinical data of patients included in the SARFAME study.

Characteristic	Value
N=301	Median (IQR), (Min-Max)
Age (years)	57.0 (48.2-66.0), (19.2-90.5)
Weight (kg)	70 (62-80), (41-116)
Height (m)	1.6 (1.6-1.7), (1.3-1.9)
Disease duration (years)	3.4 (2.1-5), (1.4-6.5)
Time elapsed since RA diagnosis until prescription of the first csDMARD (years)	0 (0-0.1), (0-4.4)
Swollen joints (0/28)	0 (0-2), (0-14)
Tender joints (0/28)	1 (0-3), (0-18)
RA patient global VAS cm (0-10)	3 (2-6), (0-6)
ESR (mm/h)	14 (6-22.5), (0-105)
CRP (mg/L)	3 (1-7), (0-121)
DAS28-ESR (baseline)	3.1 (2.1-4.2), (0.4-7.2)
	n (%)
Women	214 (71)
RF+	200 (66)
ACPA+	111 (37)
Erosions	122 (48)
Current smoking	54 (18)
Disease activity according to DAS28-ESR in first line sDMARD treatment (n=261)	n (%)
≤2.6	17 (6)
≤3.2	18 (7)
>3.2	226 (87)
Comorbidities	
Endocrine or metabolic system	118 (39)
Musculoskeletal system	112 (37)
Cardiovascular system	96 (32)

SD: standard deviation; ACPA: anticitrullinated protein antibodies; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drugs; csDMARD: conventional synthetic disease-modifying ant rheumatic drugs; ESR: erythrocyte sedimentation rate; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; VAS: visual analog scale; Min: minimum; Max: maximum.

the third-level of care hospitals and the second-level of care hospitals (data not shown).

Rheumatologists' prescription patterns

In total, 292 patients (97%) began csDMARD treatment with monotherapy and 5 patients (2%) with two or more csDMARDs (Figure 1 and Table 2). MTX was the most prescribed csDMARD in monotherapy, followed by leflunomide (LEF). Other treatments in 22 patients (7%) were mainly hydroxychloroquine/chloroquine and SSZ. Most of the patients (81%) treated with MTX received it orally. Only 2.8% changed to subcutaneous administration and reported improved efficacy or tolerance. Three patients (0.9%) were prescribed a first-line bDMARD as monotherapy with no further treatment changes. No patient received triple therapy. The mean maintenance time of the first-line csDMARD was 27±19.4 months.

In all, 294 patients (98%) who initially received first-line csDMARD changed to a second-line csDMARD. The main reasons why 118 patients changed to another csDMARD were: (1) inefficacy (n=51, 37%), (2) AEs (n=37, 27%), (3) intolerance (n=18, 13%), and (4) other causes (n=12, 4%; Figure 1).

The use of MTX monotherapy as second-line treatment decreased from 79% to 51%, while the use of LEF increased from 12% to 19%. The main reason for changing from second-line csDMARDs to MTX, LEF, or combination therapy, as well as from combination therapy to a csDMARD as monotherapy was a lack of response (62% and 50%, respectively). Fifty percent of patients treated with MTX and 77% of patients treated with LEF as second-line monotherapy changed treatment because of intolerance or AEs. Dual therapy increased from 2% baseline to 24%, one patient was treated with triple therapy (Table 2). bDMARDs were prescribed for 42% of patients as second-line treatment. The duration of the second-line csDMARD treatment was 18±16.6 months.

The choice of MTX as third-line csDMARD therapy decreased to 20% (n=66), while LEF and other csDMARDs increased to 16%. The use of combination therapy as third-line treatment increased to 44%. bDMARDs as third-line therapy and beyond were prescribed in 51% of cases. Of the 233 patients treated with MTX initially, 44 (19%) changed to other csDMARDs. In 58 patients (25%) other csDMARDs were added to MTX. Seven (64%) of the 11 patients changed from LEF to MTX because of a lack of efficacy. All patients who switched from LEF to combined therapy did so because inefficacy (Figure 1). Of the 124 patients who switched from one csDMARD to another, 80 patients (65%) changed just once, primarily from MTX monotherapy or combined with other csDMARDs. Of the 35 patients who changed twice due to inefficacy, 97% had been treated with MTX as monotherapy and/or combined with other first- or second-line csDMARDs. These patients were similar to the overall population in terms of age (57 years) and gender (74% women). At the time of changeover due to drug inefficacy, they presented a DAS28 of 4.7 and a visual analog scale score of 6.2 (data not shown). For the cases with associated comorbidity, csDMARDs, primarily MTX, were chosen as monotherapy for first-line treatment in 99% of cases. In these patients, csDMARDs as monotherapy continued to be the treatment of choice in subsequent treatment lines. The use of combination therapy during the study increased from 1%-2% at baseline to 23%-26% at the end of the study in this subpopulation of patients.

At the time of the study, 200 patients (66%) were receiving csDMARDs as monotherapy,

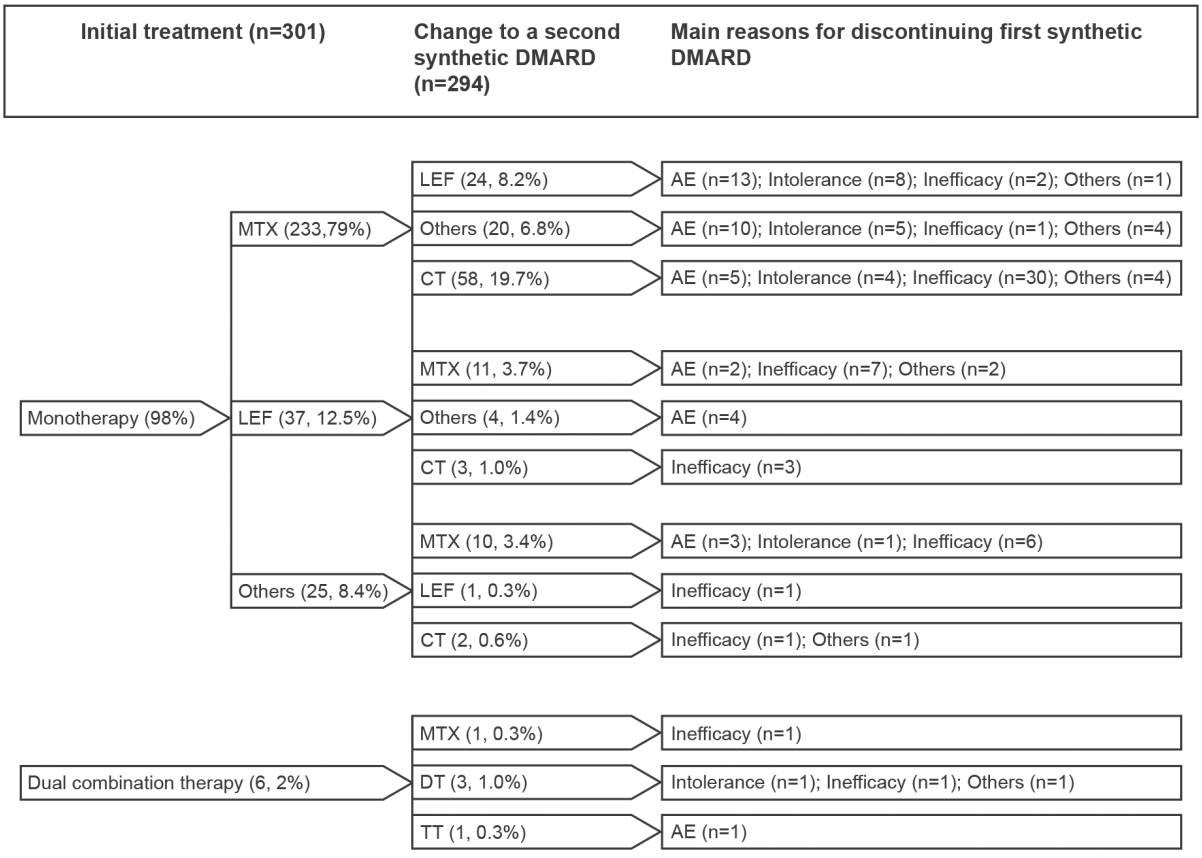


Figure 1. First line of DMARDs. DMARD prescription patterns during the first 27 months after treatment failure because of inefficacy, toxicity, or intolerance to the first DMARD. The rest are patient preferences, lack of adherence, planned pregnancy, and follow-up losses.
AE: adverse event; CT: combination therapy; DT: dual therapy; LEF: leflunomide; MTX: methotrexate; synthetic: synthetic disease; TT: triple therapy; DMARD: modifying antirheumatic drug.

and 45 (15%) received a combination therapy with csDMARDs. Of these, 150 (75%) patients were on MTX. A total of 55 patients (18%) were being treated with bDMARDs: 16 (29%) with bDMARDs as monotherapy and 39 (71%) in combination with csDMARD. Of these 35 (94%) were on MTX (Figure 2). Of 301 patients, 205 (61%) were on MTX at the study visit. Five patients received tocilizumab monotherapy and four patients received etanercept monotherapy. Regarding NSAIDs, 174 (58%) patients used it at the first evaluation, and 150 (50%) continued NSAIDs at the study visit. A total of 147 patients (57%) received corticosteroids concomitantly at the first evaluation, and 112 (37%) continued corticosteroids at the study visit.

Disease activity

The DAS28 fell significantly in most patients (4.9±1.4 vs 3.2±1.5; p<0.001). A total of 87% of patients with first-line csDMARD therapy presented moderate-to-high disease activity. Sixty-three percent (n=112) of patients who changed treatment thrice presented moderate-to-high disease activity at the third change. In the subgroup of patients who maintained their initial csDMARD treatment (152, 51%), a

Table 2. Activity and conventional synthetic disease-modifying antirheumatic drugs in each line of treatment.

		Maximum dose
Line of treatment	n (%)	Median (IQR), (Min-Max)
First, n (%)		301 (100)
Months of treatment, median (min-max)		22.7 (10.6-39.6); (0.0-77.5)
Disease activity Score, median (min-max)		5 (3.9-5.8); (0.5-8.5)
csDMARDs Monotherapy		
MTX (mg/week)	233 (77)	20 (15-20), (7.5-25)
LFN (mg/day)	37 (12)	20 (20-20), (20-20)
HCLQ (mg/day)	16 (5.3)	400 (200-400), (200-400)
SSZ (g/day)	5 (1.7)	2 (1-3), (0.5-3)
CLQ (mg/day)	1 (0.3)	250 (250-500), (250-500)
Combinations of synthetic DMARDs		
MTX+HCLQ* (mg/week+mg/day)	2 (0.6)	7.5+200
		20+200
SSZ+HCLQ (g/day + mg/day)	2 (0.6)	1,500+200
MTX+SSZ (mg/week + g/day)	1 (0.3)	15+2
Biologic DMARDs	4 (1.3)	
Second line, n (%)		294 (98)

Table 2. Activity and conventional synthetic disease-modifying antirheumatic drugs in each line of treatment (continued).

		Maximum dose
Line of treatment	n (%)	Median (IQR), (Min-Max)
Months of treatment, median (min-max)		13.0 (5.9-27.9), (0.0-61.3)
Disease Activity Score, median (min-max)		3.3 (2.2-4.8), (0.5-7.9)
csDMARDs Monotherapy		
MTX (mg/week)	151 (51)	20 (15-20), (7.5-25)
LEF (mg/day)	39 (13)	20 (20-20), (10-20)
HCLQ (mg/day)	16 (5)	200 (200-400), (200-400)
SSZ (g/day)	9 (3)	2 (1-3), (1-3)
CLQ (mg/day)	2 (0.6)	250 (250-500), (250-500)
Combinations of csDMARDs		
MTX+LEF (mg/week + mg/day)	21 (7)	12.5 (7.5-15) +10 (10-20)
MTX+SSZ (mg/week/day)	19 (6.4)	15 (10-20) + 2 (1.5-3)
MTX+ HCLQ (mg/week + mg/day)	9 (3)	17.5 + 200
HCLQ+SSZ (mg/day + g/day)	2 (0.6)	200 + 2
LEF+SSZ+HCLQ (mg/day `+ g/day + mg/day)	1 (0.3)	20 + 2 + 200
LEF+MTX+SSZ (mg/day + mg/week + g/day)	1 (0.3)	20 + 7.5 + 1.5
Biologic DMARDs	23 (7.8)	
Third line, n (%)		136 (45)
Months of treatment, median (min-max)		11.0 (4.2-28.1), (0.0-64.9)
Disease Activity Score, median (min-max)		3.9 (2.6-4.8), (0.4-7.7)
csDMARDs Monotherapy		
Methotrexate (mg/week)	26 (20)	15 (12.5-20), (10-22.5)
Leflunomide (mg/day)	20 (16)	20 (20-20), (20-20)
Sulfasalazine (g/day)	8 (5.5)	2 (1-3)
Hydroxychloroquine	7 (5.5)	200 (200-400)
Chloroquine mg/day	1 (0.7)	250 (250-500), (250-500)
Combinations of csDMARDs		
LEF+MTX (mg/day + mg/week)	18 (14)	10+15
MTX+SSZ (mg/week + g/day)	11 (8.6)	10 (15-20)+2 (2-2)
HCLQ+MTX (mg/day + mg/week)	9 (7)	200+20
MTX+HCLQ (mg/week + mg/day)	9 (7)	15 (10-20)+200 (200-400)
LEF+SSZ (mg/week+ mg//day)	1 (0.7)	20+2
HCLQ+LEF (mg/day + mg/day)	1 (0.7)	200+20
MTX+SSZ+HCLQ (mg/week + g/day + mg/day)	1 (0.7)	10+2+200
LEF+SSZ+HCLQ (mg/day + g//day + mg/day)	1 (0.7)	20+2+200
LEF+MTX+SSZ (mg/day + mg/week + g/day)	1 (0.7)	10+15+2
MTX+LEF+SSZ+HCLQ (mg/week +mg/day+ mg/day)	1 (0.7)	10+10+200
Biologic DMARDs	21 (16.5)	
Combo with MTX	39 (71)	
Monotherapy	16 (29)	

DMARDs: disease modifying antirheumatic drugs; scDMARD: synthetic conventional DMARD; IQR: interquartile range; Min: minimum value; Max: maximum value; DAS: disease activity score; MTX: methotrexate; LFN: leflunomide; HCLQ: hydroxychloroquine; SSZ: sulfasalazine; CLQ: cloroquine.

significant fall in DAS28 after a mean of 3 years versus the beginning of treatment was observed (4.7±1.5 vs 2.8±1.3; p<0.001).

The multivariate analysis did not identify predictor variables for changing the treatment (gender, age, elapsed time from diagnosis until the first treatment, PtGA, PGA, and RA activity).

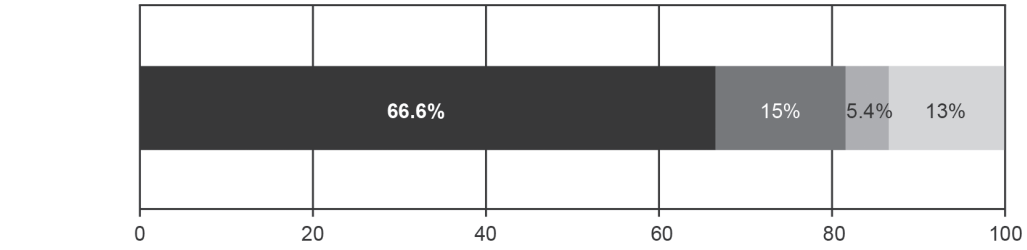
Safety

Overall, the rate of AEs identified as causing a change in the treatment with csDMARDs was 34.3% (95% CI 27.0-42.9). The most common AEs were liver abnormalities with an incidence rate of 12.4 cases (8.4-17.7) per 100 patient-years, 7.6 cases (4.5-12.2) per 100 patient-years of gastrointestinal symptoms, and 4.8 cases (2.4-8.5) per 100 patient-years of skin reactions (Table 3). These AEs were the cause of the first-line MTX discontinuation for 40% of cases.

Discussion

This observational study of routine clinical practice highlights the csDMARD prescription patterns in adult RA patients in Spain. The demographic and clinical characteristics of the sample show adult women, with 3 years of RA, with moderate activity, comorbidities, and poor prognostic variables (FR+ and/or ACPA+ and erosive disease). The first DMARD, a csDMARD as monotherapy in most of cases (98%), was prescribed shortly (2.4±6 months) after diagnostic confirmation with the addition of corticosteroids in half of the cases. Only 2% of patients were prescribed first-line csDMARD combinations, which increased to 18% by the end of the study. The first-line csDMARD therapy lasted a little more than 2 years. However, prescription of bDMARDs as the first-line treatment was extremely low (0.9%). A rapid escalation or maximum doses of MTX as the first-line treatment is recommended, with or without a low dose of corticosteroid. In case the activity persists, the treatment should be changed in 3-6 months (1, 4, 7-9, 11-14), according to the traditional formula (18). However, the "T2T" strategy had implementation problems due to health systems and economic issues such as the income level of the country and the health care expenditure per capita. Other implementation difficulties are the patient´s access to care, mainly rheumatologist access, and geographic area, with differences between rural and urban areas. Same importance can be given to the rheumatologist preferences and, of course, the patients' with their RA characteristics and comorbidities (19).

In the United States, the prescription patterns for patients with early RA are very different.



Synthetic DMARDs		Biological DMARDs	
Monotherapy (n=200)	**Combination (n=45)**	**Monotherapy (n=16)**	**Combination with synthetic DMARDs (n=39)**
MTX (75%)	MTX/ Other synthetic DMARDs (88.8%)	TCZ (31.2%)	Etanercept/sDMARDs (35.9%)
LEF (14.5%)	SFZ/ Other synthetic DMARDs (8.8%)	Etanercept (25%)	TCZ/sDMARDs (20.5%)
CQ/HCQ (6.5%)		Abatacept (12.5%)	Adalimumab/sDMARDs (20.5%)
SFZ (4%)		Adalimubab (12.5%)	Golimumab/sDMARDs (5%)
		Infliximab (12.5%)	Rituximab/sDMARDs (5%)
		Certolizumab (6.25%)	Infliximab/sDMARDs (5%)
			Abatacept/sDMARDs (5%)
			Certolizumab/sDMARDs (2.5%)

Figure 2. Current treatment at the time of the SARFAME study.
bDMARD: biological disease-modifying antirheumatic drug; CQ/HCQ: chloroquine/hydroxychloroquine; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine; csDMARD: conventional synthetic disease-modifying antirheumatic drug; TCZ: tocilizumab.

Table 3. Adverse events.

Adverse event, n (%)	First change (n=60)	Second change (n=25)	Third change (n=14)	Incidence rate × 100 patient-years (95% CI)
Abnormal liver function	23 (38)	8 (32)	2 (14)	12.4 (8.4-17.7)
Gastrointestinal symptoms	13 (22)	3 (12)	-	7.6 (4.5-12.2)
Skin reactions	6 (10)	4 (16)	3 (21)	4.8 (2.4-8.5)
Blood cell disorders	5 (8)	3 (12)	3 (21)	4.3 (2.0-7.8)
Fatigue	-	1 (4)	2 (14)	1.3 (0.3-3.8)
Respiratory symptoms	4 (7)	-	-	1.8 (0.5-4.6)
Infections	1 (1.7)	-	1 (7)	1.3 (0.3-3.8)
Alopecia	2 (3)	1 (4)	-	1.3 (0.3-3.8)
Neurological disorders	1 (2)	1 (4)	-	0.4 (0.01-2.4)

Percentage calculated from the total number of patients who switched because of an AE.
CI: confidence interval; RA: rheumatoid arthritis.

Kern et al. (20) analyzed a large sample of 63,101 RA patients, of which 52% received csDMARD, 68% as monotherapy; 20% bDMARD; <1% Janus Kinase inhibitors, 56% opioid treatment, and 45% never received a DMARD for 3.5 follow-up years. They assumed that this gap in the treatment was due to the kind of insurance coverage and health providers, as well as the access to rheumatologist (19). The data were confirmed by other studies in the United States (19-22). In Canada, MTX was used as first line of treatment in 92% of cases with early RA; of which 42% of cases received combinations of csDMARD. In 27% of Canadian patients, MTX was used as oral monotherapy, 22% received subcutaneously, and corticosteroids were added in 30%-40% of cases (23). In Europe, a great variability in prescription patterns of DMARDs, related to differences in health systems and reimbursement, was observed (24). However, ≈70% of the European RA patients from United Kingdom, Germany, and Spain were treated with csDMARD; ≈80% of them with MTX, and 15%-30% in combination with corticosteroids (24). There were differences between the type of csDMARDs and frequency of bDMARD treatment in the three countries. In Sweden, the frequency of use of any DMARD was 64%, and the use of bDMARDs was 15%, with variability be-

tween different geographic areas (25). In Italy, this figure was 80% and 3%, respectively (26). In Germany, it was recently observed that the frequency of prescription of a csDMARD during the first year of the disease was a low 41%. csDMARD plus bDMARD were prescribed in 2% of cases. bDMARD monotherapy was given in 1% of cases, and corticosteroids were prescribed in 55% of cases (27). The data from our study show results similar to those of some European countries and Canada, with high rates of MTX use in combination with corticosteroids as the most common first-line pattern (22-27).

As in these aforementioned countries, in our study the persistence of the first line of treatment was greater, while the length of the second and third lines was increasingly lower (20, 22-27). It is interesting to note that the treatment with csDMARDs as second- and third-line decreased progressively. The use of biological drugs increased in direct correlation with the number of prior treatment lines. The proportion of patients with bDMARDs as first line was low. This is explained by the fact that in the trials of early RA, the treatment with MTX and corticosteroids is as effective as with a bDMARD, but much more affordable. In Spain, the drugs are financed by the National Health System. If an RA patient needs a bDMARD, the Andalusian Hospital Pharmacy will give the authorization. However, this kind of regulation may interfere with the prescription. In our study, most monotherapy treatments were prescribed for patients with comorbidities and/or intolerance to csDMARDs. As expected, tocilizumab and etanercept were the preferred bDMARDs for monotherapy.

Rapid changes in the subsequent treatment lines were a consequence of RA activity and in a lesser degree due to toxicity. An 87% of baseline of our RA patients had moderate-to-high activity according DAS28, with a mean of 4.9±1.4. After 3-year follow-up, the DAS28 was 3.2±1.5. Our multivariate analysis could not identify predictors of response, perhaps because of the great variability in the prescription of DMARDs in Spain (17, 28), and especially in the prescription of bDMARDs (28). Variability is explained by the differences in the health system within the Spanish geographic areas and differences among the rheumatologists, instead of variables related to the RA per se (15, 19, 21, 28). The activity data were similar in the United Kingdom, Germany, Sweden, and Canada (23-26).

Combination therapy with two or more csDMARDs raises more questions than answers, particularly when they are associated with high doses of corticosteroids (1, 29, 30). According to the EULAR and ACR guidelines, combination therapy in first-line is not recommended (12, 13, 31). In addition, patients prefer a safe drug taken once a day and simple posology (10, 32). Besides, the rheumatologist prefers effective, safe, cheap, and simple treatments (33, 34). This, together with the multiple options of treatment available today, explains why combination therapy is being prescribed less frequently in clinical practice.

The toxicity of MTX is undeniable, leading to discontinuation rates of up to 20%-30% (6-9, 35-37). The toxicity of MTX is greater when used in rapid escalation, higher doses, or in combination with azathioprine or cyclophosphamide. The rates of AE related to MTX reported in the literature are about 30% (13%-47%). The frequency of severe AE was low or very low (7, 8, 35-38). The most frequent toxicity manifestations related to MTX were gastrointestinal symptoms (dyspepsia, nausea, vomiting, stomatitis, diarrhea, appetite loss) in 20%-70% cases. These are mildly severe and dose dependent. An increase in liver tests (aspartate and/or alanine aminotransferase) was observed in 69%-70% of cases (35-38). At least one episode of elevated liver enzymes was observed in 20% of cases. The elevation reached twice the upper limit in 13%, and only in 3.7% of cases MTX was stopped due to liver toxicity (7, 8, 35-38). Skin related AE were the third in frequency (alopecia, hair loss, pruritus, rash, or eczema), and were reported in 9% of cases (7, 8, 35-38). The rate of cytopenia observed in one cell line related to MTX was 5%, thrombopenia 4%, and pancytopenia 0.9-1.4%. Other AEs such as headache, depression, blurred vision, malaise, and fatigue had a rate of 5%. In our study, the type and frequency of AE were similar (Table 2). The mean dose of MTX used in our study was between 15 and 25 mg/week, orally, in most of the cases. With doses greater than 15 mg/week PO, there is no efficacy increase due to gastrointestinal transport saturation in the absorption of MTX. Nevertheless, the toxicity, mainly digestive, can increase. In Spain 25 mg of MTX as tablets costs 1.25€ and, the same dose in a prefilled syringe costs about 35€. This may influence the selected administration route, and also effectiveness and toxicity. Gastrointestinal symptoms were one the most common AEs in our study. We observed no AE of special interest or mortality attributed to MTX. Recently, Burmester et al. (38) reviewed the data of MTX toxicity of the two studies with double-blind oral MTX and adalimumab in early MTX "naïve" and in MTX failure RA. In these two different groups of patients, the rate of AE for MTX was 28% and 23%, respectively. Most of the AEs were mild and the most common were infections, nausea, and/or vomiting. A total of 14% and 4% of patients had severe AE, and this caused the suspension of the drug in less than 1% of the cases.

Only in the early RA trial the MTX toxicity was higher with higher doses (38). These data are similar to our data. The proportion of AEs also increased with each new treatment line implemented. It indicates that a subset of patients with high disease activity and toxicity to first-line csDMARDs is difficult to treat. Improved disease activity was observed, but more than half of cases with high disease activity, as assessed by the DAS28, can be attributed to those patients who took up to three treatment changes. The current T2T treatment strategy and the latest EULAR recommendations support the fast increase of subcutaneous or intravenous MTX to 25-30 mg/day plus folic acid supplementation, with a low dose of corticosteroids as the most effective first-line treatment for RA patients with high disease activity and poor prognostic factors (12). However, to follow-up with this strategy, rheumatologists must closely monitor patients to promptly identify those who, for toxicity reasons or lack of efficacy, do not respond at all to first-line therapy. In such cases, the rheumatologist should quickly adjust csDMARD therapy or introduce bDMARDs to improve patient outcomes. One work from the Ontario Best Practice Research showed, similar to our work, that after the first line with MTX, the more common option is to add new csDMARDs, the addition of bDMARD being less common. Patients with previous monotherapy most frequently changed their monotherapy (39). In clinical practice, one-third of patients cannot be treated with MTX due to mixed inefficacy and toxicity (6), and other csDMARDs such as LEF or SSZ can be used (1, 11-14). In our study monotherapy with csDMARDs different from MTX was used as first-line treatment in 27% of cases with or without corticosteroids, and MTX had to be suspended due to toxicity in 30% of the cases.

The main advantage of this study is that it assessed patient clinical practice and follow-up with rheumatologists. Although the study reviewed patient medical histories, an interview with each patient was also conducted and information was verified by consulting the electronic prescriptions. The drawbacks include the cross-sectional nature of study and a significant variability in prescribing habits among rheumatologists. Besides, a major concern is that the adherence cannot be assessed in this type of observational study. However, the consecutive enrolment of pa-

tients and the data collected, which reflect prescribing patterns in clinical practice, support the obtained results.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Andalusia (Approval Date: December 2, 2013; Approval Number: SAR-FAM-2213-02-2213).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.H.C., I.U.G., R.S.P., E.R.R., J.C.G., A.G.S., C.R.E., F.N.S.; Design - B.H.C., I.U.G., R.S.P., E.R.R., J.C.G., A.G.S., C.R.E., F.N.S.; Supervision - B.H.C., F.N.S.; Materials - B.H.C., I.U.G., R.S.P., E.R.R., J.C.G., A.G.S., C.R.E., F.N.S.; Data Collection and/ or Processing - B.H.C., I.U.G., R.S.P., E.R.R., J.C.G., A.G.S., C.R.E., F.N.S.; Analysis and/or Interpretation - B.H.C.; Literature Search - B.H.C.; Writing Manuscript - B.H.C.; Critical Review - B.H.C., I.U.G., R.S.P., E.R.R., J.C.G., A.G.S., C.R.E., F.N.S.

Acknowledgements: The authors would like to thank Mr. Luis Dochao, English Philology PhD from the Complutense University of Madrid for the revision of the text and Isabel Caballero at Dynamic Science S.L for providing editing support. The authors are fully responsible for opinions, conclusions and interpretation of data.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received a research grant from the Andalusian Foundation of Rheumatology. This funding was used for the logistics of the study: research fees, payment to Dynamic SC for all the logistic related to the study. The authors did not receive funding related to the project.

References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016; 388: 2023-38. [Crossref]
2. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, T2T Expert Committee. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010; 69: 631-7. [Crossref]
3. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016; 75: 3-15. [Crossref]
4. Vermeer M, Kuper HH, Bernelot Moens HJ, Hoekstra M, Posthumus MD, van Riel PL, et al. Adherence to a treat-to-target strategy in early rheumatoid arthritis: Results of the DREAM remission induction cohort. Arthritis Res Ther 2012; 14: R254. [Crossref]
5. Baker JF, Tan YK, Conaghan PG. Monitoring in established RA: Role of imaging and soluble biomarkers. Best Pract Res Clin Rheumatol 2015; 29: 566-79. [Crossref]
6. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe D, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying antirheumatic drugs for rheumatoid arthritis: Abridged Cochrane systematic review and network meta-analysis. BMJ 2016; 353: i1777. [Crossref]
7. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis 2009; 68: 1086-93. [Crossref]
8. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: A systematic review of the literature. Ann Rheum Dis 2009; 68: 1094-9. [Crossref]
9. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen JS. Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clin Exp Rheumatol 2003; 21: S179-85.
10. Nash P, Nicholls D. Perceptions of methotrexate use in rheumatoid arthritis by rheumatologists and their patients: An Australian survey study. Int J Rheum Dis 2013; 16: 652-61. [Crossref]
11. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014; 73: 492-509. [Crossref]
12. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. 2016 update. Ann Rheum 2017; 76: 960-77. [Crossref]
13. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken) 2016; 68: 1-25. [Crossref]
14. Sanmartí R, García Rodríguez S, Álvaro Gracia JM, Andrew JL, Balsa A, Cáliz R, et al. Actualización 2014 del Documento de Consenso de la Sociedad Española de Reumatología sobre el uso de terapias biológicas en la artritis reumatoide. Reumatol Clin 2015; 11: 279-94. [Crossref]
15. Ferraz-Amaro I, Seoane-Mato D, Sanchez-Alonso F, Martin-Martinez MA. Synthetic disease-modifying antirheumatic drug prescribing variability in rheumatoid arthritis: A multilevel analysis of a cross-sectional national study. Rheumatol Int 2015; 35: 1825-36. [Crossref]
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-81. [Crossref]
17. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am 2009; 35: 745-57. [Crossref]
18. Emery P. Early rheumatoid arthritis: Therapeutic strategies. Scand J Rheumatol Suppl 1994; 100: 3-7. [Crossref]
19. Ford JA, Solomon DH. Challenges in implementing treat-to-target strategies in rheumatology. Rheum Dis Clin North Am 2019; 45: 101-12. [Crossref]
20. Kern DM, Chang L, Sonawane K, Larmore CJ, Boytsov NN, Quimbo RA, et al. Treatment patterns of newly diagnosed rheumatoid arthritis patients from a commercially insured population. Rheumatol Ther 2018; 5: 355-69. [Crossref]
21. Jönsson B, Kobelt G, Smolen J. The burden of rheumatoid arthritis and access to treatment: Uptake of new therapies. Eur J Health Econ 2008; 8 (Suppl 2): S61-86. [Crossref]
22. Gaitonde P, Bozzi LM, Shaya FT. Factors associated with use of disease modifying agents for rheumatoid arthritis in the National Hospital and Ambulatory Medical Care Survey. Semin Arthritis Rheum 2018; 47: 649-53. [Crossref]
23. Moura CS, Schieir O, Valois MF, Thorne C, Bartlett SJ, Pope JE, et al. Treatment strategies in early rheumatoid arthritis methotrexate management: Results from a prospective cohort. Arthritis Care Res (Hoboken) 2020; 72: 1104-11. [Crossref]
24. Emery P, Solem C, Majer I, Cappelleri JC, Taralllo M. A European chart review study on early rheumatoid arthritis treatment patterns, clinical outcomes, and healthcare utilization. Rheumatol Int 2015; 35: 1837-49. [Crossref]
25. Neovius M, Simard JF, Askling J, ARTIS study group. Nationwide prevalence of rheumatoid arthritis and penetration of disease-modifying drugs in Sweden. Ann Rheum Dis 2011; 70: 624-9. [Crossref]
26. Fakhouri W, Lopez-Romero P, Antonelli S, Losi S, Rogai V, Buda S, et al. Treatment patterns, health care resource utilization and costs of rheumatoid arthritis patients in Italy: Findings from a retrospective administrative database analysis. Open Access Rheumatol 2018; 10: 103-11. [Crossref]
27. Steffen A, Holstiege J, Klimke K, Akmatov MK, Bätzing J. Patterns of the initiation of disease-modifying antirheumatic drugs in incident rheumatoid arthritis: A German perspective based on nationwide ambulatory drug prescription data. Rheumatol Int 2018; 38: 2111-20. [Crossref]
28. López-Longo FJ, Seoane-Mato D, Martín-Martínez MA, Sánchez-Alonso F, emAR II Group. Variability in the prescription of biological drugs in rheumatoid arthritis in Spain: A multilevel analysis. Rheumatol Int 2018; 38: 589-98. [Crossref]
29. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: The CareRA trial. Ann Rheum Dis 2015; 74: 27-34. [Crossref]

30. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Ann Rheum Dis 2014; 73: 1331-9. [Crossref]
31. Chatzidionysiou K, Emamikia S, Nam J, Ramiro S, Smolen J, van der Heijde D, et al. Efficacy of glucocorticoids, conventional and targeted synthetic disease-modifying antirheumatic drugs: A systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2017; 76: 1102-7. [Crossref]
32. Alten R, Krüger K, Rellecke J, Schiffner-Rohe J, Behmer O, Schiffhorst G, et al. Examining patient preferences in the treatment of rheumatoid arthritis using a discrete-choice approach. Patient Prefer Adherence 2017; 10: 2217-28. [Crossref]
33. van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Dijkmans BA, Boers M. Why are Dutch rheumatologists reluctant to use the COBRA treatment strategy in early rheumatoid arthritis? Ann Rheum Dis 2007; 66: 974-6. [Crossref]
34. Hifinger M, Hiligsmann M, Ramiro S, Severens JL, Fautrel B, Watson V, et al. Patients' preferences and economic considerations play an important role in treatment decisions: A discrete choice experiment among rheumatologists. Rheumatology (Oxford) 2017; 56: 68-76. [Crossref]
35. Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. Cochrane Database Syst Rev 2014; 2014: CD000957. [Crossref]
36. Schnabel A, Herlyn K, Burchardi C, Reinhold-Keller E, Gross WL. Long-term tolerability of methotrexate at doses exceeding 15 mg per week in rheumatoid arthritis. Rheumatol Int 1996; 15: 195-200. [Crossref]
37. Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review. Eur J Med Chem 2018; 158: 502e516. [Crossref]
38. Burmester GR, Kaeley GS, Kavanaugh AF, Gabay C, MacCarter DK, Nash P, et al. Treatment efficacy and methotrexate-related toxicity in patients with rheumatoid arthritis receiving methotrexate in combination with adalimumab. RMD Open 2017; 3: e000465. [Crossref]
39. Pope JE, Rampakakis E, Movahedi M, Cesta A, Li X, Couto S, et al. Treatment patterns in rheumatoid arthritis after discontinuation of methotrexate: Data from the Ontario Best Practices Research Initiative (OBRI). Clin Exp Rheumatol 2018; 36: 215-22.