The effect of gender on methotrexate prescription attitudes in Italian rheumatoid arthritis patients: the MARI study

A. Giusti[1], O.M. Epis[2], A. Migliore[3], A. Ricioppo[4], P.P. Sainaghi[5], L. Di Matteo[6], M.S. Massarotti[7], M. Govoni[8], A. Mazzone[9], G. Traballi[10], S. Ciarla[11], L. Cozzi[12], A. Roncaglione[13], M. Muratore[14], R. Laurenti[15], G. Bianchi[1]

[1]Rheumatology Unit, ASL3 - Regione Liguria, Genoa, Italy; [2]Rheumatology Unit, Grande Ospedale Metropolitano Niguarda, Milan, Italy; [3]Rheumatology, S. Pietro Fatebenefratelli Hospital, Rome, Italy; [4]Rheumatology and Infectious Diseases Unit, Department of Internal Medicine, Vimercate Hospital, Vimercate, Italy; [5]Immuno-Rheumatology Unit, AOU "Maggiore della Carità" and IRCAD (Interdisciplinary Research Center of Autoimmune Diseases), Novara, Italy; [6]Pierangeli Clinic, Pescara, Italy; [7]Department of Rheumatology, University Hospitals of Morecambe Bay NHS Foundation Trust, Lancaster, United Kingdom; [8]Rheumatology Unit, S. Anna Hospital and University of Ferrara, Italy; [9]Department of Internal Medicine, Legnano Hospital, Italy; [10]Rheumatology, Castelli Hospital, Verbania, Italy; [11]Division of Internal Medicine, Ospedale Civile di Teramo, Italy; [12]UOS Endocrinology-Rheumatology, AULSS 5 Polesana, Rovigo, Italy; [13]Rheumatology Outpatient Service, AUSL3 Serenissima, Venice, Italy; [14]Rheumatology Unit, Vito Fazzi Hospital, Lecce, Italy; [15]Rheumatology, Istituto Dermopatico dell'Immacolata IDI - IRCCS, Rome, Italy.

Abstract

Objective

The MARI study investigated the prescription patterns of methotrexate (MTX) in patients presenting with rheumatoid arthritis (RA) in Italy. The primary aims of this cross-sectional analysis from the MARI study were to investigate the effect of gender on the prescription patterns and safety of MTX therapy.

Methods

The study enrolled 1336 patients with RA. Retrospective data included patients' clinical history, previous treatment with MTX and other DMARDs, and MTX modifications in the previous 12-month period. Cross-sectional data included information about current treatment with MTX (dose and route of administration, and adverse events), concomitant medications, disease activity, and modifications of MTX treatment at study entry. The prescription patterns of MTX, rates and causes of MTX modifications were analysed according to gender.

Results

There were no significant differences related to gender in the prescription patterns of MTX, either at 6 months after starting MTX or at the time of study entry. In the 12 months prior to study entry, women (4%) were more likely to undergo MTX modifications (dose or route of administration) compared to men (2%, p=0.032), due to subjective intolerance, but this difference was no longer significant after controlling for confounders. At study entry, a higher proportion of women (27%) reported tolerability issues (nausea and weakness) related to MTX compared to men (14%, p=0.001). Although a similar percentage of males and females changed dose or route of administration of MTX at the time of study entry, the reasons for such modifications were dissimilar between genders. Particularly, a higher proportion of women underwent MTX modification due to intolerance (women 6% vs. men 1%, p=0.002).

Conclusion

In Italy, prescription patterns of MTX do not differ between genders. However, women seem to be at higher risk of adverse events leading to MTX modifications.

Key words

rheumatoid arthritis, methotrexate, gender

Andrea Giusti, MD
Oscar M. Epis, MD
Alberto Migliore, MD
Aristodemo Ricioppo, MD
Pier Paolo Sainaghi, PhD
Luigi Di Matteo, MD
Marco S. Massarotti, MD
Marcello Govoni, MD
Antonino Mazzone, MD
Gabriella Traballi, MD
Sara Ciarla, MD
Luisella Cozzi, MD
Antonella Roncaglione, MD
Maurizio Muratore, MD
Rosita Laurenti, MD
Gerolamo Bianchi, PhD

Please address correspondence and reprint requests to:
Dr Gerolamo Bianchi,
Rheumatology Unit,
ASL3 - Regione Liguria,
Via Giappone 5,
16011 Arenzano, Italy,
E-mail: gerolamo.bianchi@asl3.liguria.it

Received on November 2, 2018; accepted in revised form on February 11, 2019.

Competing interests: none declared.

Introduction

The relevance of gender medicine is increasing due to the huge amount of studies describing the significant role played by gender on the pathophysiology and response to therapy in various diseases (1-4). The concept of gender medicine, historically emphasised due to differences in the incidence/prevalence of several chronic conditions between males and females, is nowadays gaining relevance also as a determining factor in the clinical use and response to pharmacological therapies (4-6). The effect of gender on the prescription or clinical response to a pharmacological treatment may be related not only to the interaction between the therapy and sexual hormones, but even to physiological, psychological, functional, social and cultural factors that may differ between genders (4-6).

Rheumatoid arthritis (RA) is a systemic, inflammatory autoimmune disorder that primarily affects the joints, leading to cartilage destruction and bone erosions (7). The autoimmunity, which characterises RA, is not limited to the joints but represents a systemic process, producing also extra-articular manifestations. Thus, untreated RA is associated to progressive disability, increased comorbidity with systemic complications, and significant healthcare costs (7, 8).

Among therapeutic agents currently available for the treatment of RA, methotrexate (MTX) represents the first line choice, owing to its good efficacy and safety profile as well as to its low cost (9-12). In RA patients who did not respond sufficiently to the first line therapy with MTX, are usually considered and recommended other association therapies based on the combination of MTX with conventional synthetic (csDMARDs), targeted synthetic (tsDMARDs) or biologic (bDMARDs) DMARDs (11). Therefore, as also emphasised by 2016 updated EULAR Recommendations, the role of MTX in the era of bDMARDs and tsDMARDs is far from fading (11).

Although several International Recommendations/Guidelines on the use of MTX in RA foreground this csDMARD as a first line therapy, the registration studies for MTX were small and the trials' design was weak, thus generating a relevant variability in the clinical use and prescription of MTX (10-17). In this context, and to the best of our knowledge, the influence of gender on MTX prescription attitude, compliance and response patterns has never been fully investigated.

The MARI project is a "real world" observational study conceived to investigate the prescription attitudes of MTX in patients affected by RA (16, 17). The MARI project evaluated both cross-sectionally and longitudinally the prescription patterns of MTX (associated or not to other pharmacological agents) in patients presenting with RA from Italian Rheumatology Clinics.

The present analysis from the cross-sectional phase of the MARI study investigated the effect of gender on the prescription patterns and safety of MTX therapy.

Patients and methods

The MARI study was performed between December 2011 and October 2013. The study included consecutive patients fulfilling the 1987 classification criteria for RA of the American College of Rheumatology, and on treatment for at least 12 months with MTX, recruited from 60 Rheumatology Units across Italy (16, 17).

The cross-sectional phase of the MARI study gathered data, at baseline visit, regarding the patient clinical history and the previous 12 months of MTX therapy, including information about the initial MTX therapy assignment, eventual concomitant medications, occurrence of adverse events, and causes of eventual discontinuation. All data regarding past medical and pharmacological history were recorded by the physician and retrieved from medical records. At study entry, were also recorded information regarding the disease activity, the actual therapeutic status and the prescriptions/modifications of treatment at the baseline visit (16, 17). A detailed description of the methods and procedures of the MARI study have been already reported (16, 17). With respect to previous reports (16, 17), we have retrieved and inte-

grated some missing data in the MARI database, before undertaking the current analyses.

In the current study, we specifically focused on the identification of eventual gender differences in MTX prescription, response to therapy and adverse events incidence.

The following data, retrieved from the MARI database, were considered for the analyses:

- Baseline (evaluated at baseline visit) demographic, anthropometric, and clinical (related to RA) characteristics, including age, gender, weight, height, body mass index (BMI), smoke habits, menopausal status and age at menopause (where applicable), years since RA onset, duration of the symptoms before RA diagnosis, number of swollen and tender joints, patient's and physician's visual analogue scale (VAS) of the disease activity, C-reactive protein (CRP, mg/L), DAS28-CRP score, presence of erosive arthritis (overt bone erosion at the x-ray of the hand), previous history of joint replacement, presence of extra-articular involvement (skin, eyes, lung, kidney and heart), and presence of a positive test for the rheumatoid factor (RF >40 U/mL) or for the anti-citrullinated protein antibodies (ACPA >20 U/mL);
- Information regarding the management and initial therapeutic approach at the time of RA diagnosis/onset, including clinical measurements and screening before starting MTX (laboratory tests assessment, lung x-ray, and HBV/HCV serology), timing of starting MTX therapy with regard to RA onset (at disease onset, delay <6 months, between 6 and 12 months, or >12 months), initial route of administration of MTX (oral, subcutaneous, intramuscular), weekly dose of MTX at six months after starting treatment, and concurrent use of high dose of corticosteroids (>10 mg/day), non-steroidal anti-inflammatory drugs (NSAIDs), other csDMARDs (leflunomide, hydroxy-chloroquine, sulfasalazine, cyclosporine) or bDMARDs (adalimumab, etanercept, infliximab, tocilizumab, golimumab, abatacept);
- Any modification of the dose or route of administration of MTX therapy and reasons (subjective intolerance, abnormal laboratory findings, patients' preference, or physicians' preference) for modifications in the 12 months before the baseline visit;
- Actual MTX therapy (route of administration and dose), associated treatments (NSAIDs, csDMARDs, and bDMARDs), and presence of tolerability issues (signs and symptoms related to MTX therapy) at study entry baseline visit;
- Any modification of the MTX therapy at the baseline visit, including the reasons for modifications.

We first compared the baseline demographic, anthropometric and clinical characteristics between males and females. Subsequent analyses were undertaken in order to identify gender differences in the therapeutic attitudes at disease onset/diagnosis, and during the 12 months before the baseline visit, focusing primarily on modifications of the MTX route of administration or dose, and reasons for changes. Furthermore, we compared information regarding the actual therapy and the clinical decisions at baseline visit between genders. Since we found significant differences in baseline characteristics between males and females, we designed and performed multivariate analyses to control for potential confounders.

Subjects were classified into three groups according to the way of administration of MTX (oral, subcutaneous and intramuscular). The relationship between the gender and the dose of MTX was explored in two ways by considering the dose of MTX either as a continuous variable or as a dichotomic variable, distinguishing patients receiving a suboptimal dose of MTX from those receiving an appropriate dose, on the basis of current Italian Recommendation (19).

Descriptive analyses were performed with results presented as mean ± standard deviation (SD) for continuous variables, or number and percentages for categorical variables. Differences between groups of patients (males and females) were evaluated using the ANOVA or the independent *t*-test for continuous variables, or by Pearson's χ^2 test for dichotomous variables. Logistic regressions were undertaken to control for confounders. Probability (*p*) values <0.05 were considered statistically significant. Odd ratios (ORs) and 95% Confidence Intervals (95% CIs) were calculated using standard formulae. All analyses were performed using SPSS software 17.0 (Chicago, SPSS, Inc.).

Results

The MARI database comprised 1336 RA patients. The mean age ± SD was 61.4±12.7, and 265 (19.8%) subjects were men. Table I describes the baseline demographic, anthropometric and clinical characteristics of patients according to gender, recorded during the baseline visit. Men were slightly older and presented with a higher weight and height compared to women. The disease duration and the time between symptoms' onset and diagnosis were comparable between genders. Women presented with a significantly higher number of tender joints, VAS score (patient's/physician's) and DAS28-CRP score compared to men (Table I). However, when the proportion of patients with a DAS28-CRP score above 3.2 were compared, the difference between genders was no longer significant. A higher proportion of men had extra-articular involvement (women 4% *vs*. men 8%, *p*=0.019), and even after adjusting for potential confounders (multivariate model), male gender was a significant risk factor for extra-articular involvement (OR=2.2, 95% CI 1.0-4.8, *p*=0.049)

The therapeutic approach/management of the patients at the time of RA onset/diagnosis was comparable between males and females (Table II). Particularly, there were not statistically significant differences in the mean ± SD weekly dose of MTX at six months after the start of treatment (women 11.5±3.4 mg *vs*. men 11.4±3.3 mg, *p*=0.525) and in the initial route of MTX administration between genders. In addition, the proportion of patients receiving high dose corticosteroids, NSAIDs, csDMARDs or bDMARDs at the time of diagnosis was comparable in men and women.

As previously described, we first analysed the modifications (route of administration and/or dose) of the MTX ther-

Table I. Baseline (evaluated at the baseline visit) demographic, anthropometric, and clinical characteristics related to rheumatoid arthritis of the patients according to gender.

Variable	Female	Male	*p*-value
Number of patients	1071	265	-
Age (mean years ± SD)	61 ± 13	64 ± 12	0.001
Weight (mean kg ± SD)	66 ± 13	77 ± 12	<0.001
Height (mean cm ± SD)	161 ± 7	172 ± 7	<0.001
BMI (mean kg/m^2 ± SD)	26 ± 5	26 ± 3	0.131
N° Current smokers (%)	221 (21%)	44 (17%)	0.341
N° Women in menopause (%)	821 (77%)	-	-
Mean age at menopause (years ± SD)	49 ± 5	-	-
Years (± SD) since disease onset	9 ± 8	9 ± 7	0.387
Duration symptoms before diagnosis (months ± SD)	12 ± 15	13 ± 17	0.246
C-reactive protein (mean mg/L ± SD)	3.3 ± 5.7	3.9 ± 6.5	0.132
Number swollen joints (mean ± SD)	2.2 ± 4.4	2.0 ± 4.2	0.519
Number tender joints (mean ± SD)	4.0 ± 5.4	2.9 ± 4.9	0.003
Patient's VAS (mean ± SD)	5.8 ± 9.6	4.4 ± 8.5	0.024
Physician's VAS (mean ± SD)	4.6 ± 8.1	3.2 ± 4.2	0.011
DAS28-CRP (mean ± SD)	1.7 ± 1.2	1.4 ± 0.9	0.019
N° Poliarticular disease (%)	689 (64%)	164 (62%)	0.458
N° Erosive arthritis (%)	612 (57%)	153 (58%)	0.861
N° Joint replacement (%)	72 (7%)	15 (6%)	0.530
N° Extra-articular involvement (%)	47 (4%)	21 (8%)	0.019
N° Positivity rheumatoid factor (%)	675 (63%)	177 (67%)	0.253
N° Positivity ACPA antibodies (%)	593 (55%)	147 (55%)	0.976
N° DAS28-CRP > 3.2 (%)	197 (18%)	40 (19%)	0.212

Table II. Therapeutic approach/management of the patients at the time of rheumatoid arthritis diagnosis/onset (as reported by the physician or by the patient at the baseline visit) according to gender.

Variable	Female	Male	*p*-value
Number of patients	1071	265	-
Clinical screening/evaluations/measurements prior to starting MTX			
N° Laboratory tests assessment (%)	1005 (94%)	247 (93%)	0.705
N° Lung x-ray (%)	611 (57%)	156 (59%)	0.592
N° HBV/HCV sierology (%)	693 (65%)	168 (63%)	0.690
Therapeutic approach at the time of rheumatoid arthritis diagnosis/onset			
Start of MTX therapy with respect to disease onset (8 patients had missing data)	-	-	-
Number of patients with available data	1065	263	-
N° Started at disease onset (%)	186 (18%)	49 (19%)	0.667
N° Delay <6 months (%)	196 (18%)	49 (19%)	0.943
N° Delay 6-12 months (%)	169 (16%)	40 (15%)	0.783
N° Delay >12 months (%)	514 (48%)	125 (47%)	0.810
Initial route of MTX administration (20 patients had missing data)	-	-	0.920
Number of patients with available data	1055	261	-
N° Oral (%)	260 (25%)	62 (24%)	-
N° Subcutaneous (%)	175 (16%)	42 (16%)	-
N° Intramuscular (%)	620 (59%)	157 (60%)	-
Mean (mg ± SD) weekly dose of MTX at 6 months from starting MTX	11.4 ± 3.3	11.5 ± 3.4	0.525
Concomitant use of other pharmacological agents at disease onset/diagnosis	-	-	-
N° High dose (> 10 mg/day) corticosteroids (%)	125 (12%)	27 (10%)	0.496
N° NSAIDs (%)	504 (47%)	135 (51%)	0.257
N° Hydroxy-chloroquine (%)	308 (29%)	71 (27%)	0.525
N° Sulfasalazine (%)	44 (4%)	10 (4%)	0.804
N° Cyclosporine (%)	31 (3%)	7 (3%)	0.824
N° Leflunomide (%)	36 (3%)	11 (4%)	0.532
N° Biologic (%)	191 (18%)	40 (15%)	0.291

apy in the 12 months before study entry (baseline visit), including the reasons for modification. The proportion of patients undergoing a modification of the dose or route of administration was respectively 26% (n=283) in females and 29% (n=76) in males (p=0.338). There was a significantly higher proportion of women undergoing a modification due to subjective intolerance (4% in women *vs*. 2% in men, p=0.032), and a significantly greater percentage of men undergoing a change due to physicians' decision (17% in women *vs*. 23% in men, p=0.037). Regarding the other reasons for modification, no significant difference was found between genders (abnormal laborartory findings, women 3% *vs*. men 3%, p=0.887; patients' preference, women 3% *vs*. men 1%, p=0.079). Multivariate models predicting subjective intolerance and physicians' decision according to female gender were developed in order to control for baseline differences in men and women (see Table I). Within these models female gender was no longer predictive of subjective intolerance (OR=2.4, 95% CI 0.5–11.1, p=0.278), and was no more protective against modification due to physicians' decision (OR=0.7, 95% CI 0.5–1.2, p=0.202).

The Table III depicts the current MTX therapy, associated treatments and prevalence of safety/tolerability issues at the study entry (baseline visit). There was no significant difference in the current mean ± SD MTX weekly dose (11.8±4.0 mg in women *vs*. 11.6±3.5 mg in men, p=0.569), in the proportion of patients receiving a suboptimal current dose of MTX (63% in women *vs*. 63% in men, p=0.982), and in the current route of administration, between the two genders. On the other hand, and potentially in line with the observation (Table I) that women presented with a slightly more active disease, a significantly (p=0.016) higher percentage of women (52%) were receiving a concomitant DMARD compared to men (44%), with similar but non-significant figures for patients receiving bDMARDs (34% in women *vs*. 27% in men, p=0.058).

At the time of the baseline visit (Table III), 286 women (27%) and 36 men (14%) reported signs and/or symptoms

Table III. Actual MTX therapy, associated treatments and presence of tolerability issues (signs/symptoms related to MTX therapy) at study entry (baseline visit) according to gender.

Variable	Female	Male	*p*-value
Number of patients	1071	265	-
Actual (at the baseline visit) MTX therapy			
Actual mean (mg ± SD) weekly dose of MTX (30 patients had missing data)	11.8 ± 4.0	11.6 ± 3.5	0.569
N°/N° with available data MTX suboptimal actual dose (%)	663/1046 (63%)	165/260 (63%)	0.982
Actual route of MTX administration (12 patients had missing data)	-	-	0.130
Number of patients with available data	1062	262	-
N° Oral (%)	232 (22%)	56 (21%)	-
N° Subcutaneous (%)	354 (33%)	72 (28%)	-
N° Intramuscular (%)	476 (45%)	134 (51%)	-
Actual concomitant use of other pharmacological agents			
N° DMARD (%)	561 (52%)	117 (44%)	0.016
N° NSAIDs (%)	566 (53%)	144 (54%)	0.663
N° Hydroxy-chloroquine (%)	158 (15%)	37 (14%)	0.744
N° Sulfasalazine (%)	17 (2%)	4 (6%)	0.927
N° Cyclosporine (%)	13 (1%)	1 (0.4%)	0.231
N° Leflunomide (%)	17 (2%)	3 (1%)	0.585
N° Biologic (%)	356 (34%)	72 (27%)	0.058
MTX tolerability issues (adverse drug reactions) at baseline visit (not leading to discontinuation)			
N° Any adverse drug reaction (%)	286 (27%)	36 (14%)	<0.001
N° Alopecia (%)	11 (1%)	1 (0.4%)	0.316
N° Vomit (%)	5 (0.5%)	0 (0%)	0.265
N° Central nervous system* disorders (%)	6 (1%)	2 (1%)	0.713
N° Nausea (%)	175 (16%)	24 (9%)	0.003
N° Diarrhoea (%)	4 (0.4%)	0 (0%)	0.319
N° Weakness (%)	85 (8%)	9 (3%)	0.010

*Note: central nervous system disorders included nightmares and depression.

Table IV. Modifications of the MTX therapy and reasons for modifications at the baseline visit according to gender.

Variable	Female	Male	*p*-value
Number of patients	1071	265	-
N° Modification of dose or way of administration (%)	194 (18%)	46 (17%)	0.765
N° New way administration (%)	87 (8%)	16 (6%)	0.254
N° Increase MTX dose (%)	44 (4%)	18 (7%)	0.063
N° Decreased MTX dose (%)	56 (5%)	13 (5%)	0.356
N° New way administration with DAS28-CRP > 3.2 (%)	28 (3%)	6 (2%)	0.746
N° Increase MTX dose with DAS28-CRP > 3.2 (%)	16 (2%)	9 (3%)	0.041
Reasons for modification	-	-	-
N° Low efficacy (%)	52 (5%)	20 (8%)	0.082
N° Not effective (%)	6 (1%)	0 (0%)	0.222
N° Good response (%)	47 (4%)	15 (6%)	0.378
N° Not tolerated (%)	61 (1%)	2 (1%)	0.002

*Note: for some patients the type or the reason for modification was not available/reported.

suggestive for tolerability issues or adverse drug reactions related to the MTX treatment ($p<0.001$). In a multivariate model controlling for baseline differences between genders, female gender was significantly associated with tolerability issues or adverse drug reactions (OR=2.7, 95% CI 1.6–4.6, $p<0.001$). The main symptoms described were nausea and weakness, being more prevalent in women: nausea, 175 (16%) women *vs*. 24 (9%) men (OR for being woman and presenting with nausea = 2.5, 95% CI 1.3–4.9, $p=0.007$); weakness, 85 (8%) women *vs*. 9 (3%) men (OR = 2.5, 95% CI 0.9–6.2, $p=0.053$). When the same analysis was undertaken in postmenopausal women (821 patients), the results were comparable in terms of percentage and significance.

At the time of study entry and during the baseline visit (Table IV), the treating rheumatologist modified the dose or route of administration of MTX respectively in 194 (18%) women and 46 (17%) men ($p=0.765$). As depicted in Table IV, a similar proportion of women (n=87, 8%) and men (n=16, 6%) changed the way of administration during the baseline visit, without significant differences between genders ($p=0.254$). Overall, 12 men switched from oral or intramuscular MTX to subcutaneous MTX, 3 men from intramuscular MTX to oral MTX, and 1 man from subcutaneous MTX to intramuscular MTX. The corresponding figures in women were: 67 women from oral or intramuscular MTX to subcutaneous MTX, 10 women from intramuscular or subcutaneous MTX to oral MTX, and 10 women from oral or subcutaneous MTX to intramuscular MTX.

In 44 women (4%) and 18 men (7%) the MTX dose was increased ($p=0.063$), during the baseline visit. Considering patients presenting with a DAS28-CRP score >3.2, respectively 16 women (2%) and 9 men (3%) increased the MTX dose ($p=0.041$). In a multivariate model including potential confounders, the association between male gender and an increase of MTX dose in patients presenting with a DAS28-CRP >3.2 was no longer significant ($p=0.225$). The proportion of patients who were prescribed a reduction of the MTX dose was comparable between genders (5% per group). When the same analysis was undertaken in postmenopausal women (821 patients), the results were comparable in term of percentage and significance.

In most cases, the dose/route of administration was modified due to tolerability issues (more likely in women) or inadequate response to therapy (slightly more frequent in men, although not significant). In a multivariate model, controlling for baseline differences between genders, female gender was again associated with the risk of tolerability issues (OR=9.5, 95% CI 1.2–74.0, $p=0.032$)

Discussion

Our study investigated primarily the effect of gender on prescription patterns and safety of MTX in RA patients in the 12 months before study entry and at the time of the baseline visit. Being all RA patients ongoing a stable MTX treatment, we were able to compare attitudes in MTX prescription and tolerability issues between males and females, in a "real world" sample representative of the Italian RA population. Indeed, the baseline demographic (mean age, female to male ratio) and clinical characteristics (*e.g.* proportion positive RF and ACPA, extra-articular involvement) were comparable to previous Italian studies undertaken in RA patients (8, 20, 21). Therefore, the MARI population may be considered a reliable dataset for the purpose of this analysis.

We found significant differences in the disease activity and perception measures between genders. Particularly, both the mean DAS28-CRP and the mean patient's/physician's VAS score were higher in females compared to males. Similar findings have been already described in other reports (22-24), suggesting a relationship between female gender and worse disease activity and response to treatment. However, our results should be interpreted with caution, since the proportion of men and women with a DAS28-CRP above 3.2 (at baseline visit) was absolutely comparable between genders. Interestingly, males presented with a greater prevalence of extra-articular involvement with respect to females. This was unexpected, as a previous report failed to find an association between disease characteristics (such as RA presentation and pattern) and gender (25). Gossec *et al*. (25), investigating clinical patterns of involvement in RA patients, demonstrated that sicca syndrome was more frequent in women than in men, and that women were more likely to undergo distal joint surgery compared to men. Since no other differences were observed in the clinical or radiological features of the disease, the authors concluded that gender has only little impact on disease patterns, presentation and course. Our results only partially support these conclusions.

The first objective of our analysis was to investigate gender difference in prescription patterns of MTX. Interestingly, we found no differences in the weekly dose and route of administration of MTX between genders (Tables II-III), both at six months after starting MTX and at the baseline visit (study entry). As described in Table II, also the initiation of MTX therapy with respect to the disease onset/diagnosis was comparable between genders, with similar proportions of females and males starting the MTX treatment at disease onset/diagnosis, within six months, between six and twelve months or after twelve months from RA onset/diagnosis. In addition, also the percentage of RA subjects receiving a suboptimal dose of MTX at the time of study entry, notably high as previously reported (16, 17), was comparable between men and women. Overall these findings suggest that the treating rheumatologist attitudes in MTX prescription at disease onset and once the MTX treatment is stabilised are not influenced by the patient gender. To the best of our knowledge, this is the first study reporting the lack of association between gender and dose or route of administration of MTX. There is only one report from the QUEST-RA study (22), describing a similar proportion of women and men taking MTX over the course of RA that reported no interaction between the gender and the delay in the initiation of DMARDs therapy, including MTX.

At the time of RA onset/diagnosis, similar proportions of men and women were receiving concomitant high dose corticosteroids, NSAIDs, csDMARDs or bDMARDs (Table II). Interestingly (Table III), at the time of study entry (baseline visit), a higher proportion of females were receiving concomitant DMARDs (csDMARDs or bDMARDs). These findings are in line with the data from Gossec *et al*. (25), showing that women were prescribed slightly more DMARDs compared to men, and may be explained by the greater disease activity/severity in women (Table I). On the other hand, the ORA registry and the QUEST-RA study described similar proportion of men and women receiving csDMARDs and/or bDMARDs (22, 26), contrasting our results. One explanation of such discrepancy may be related to the different criteria used to define the RA populations investigated: the MARI study considered only patients ongoing MTX treatment, while the QUEST-RA and ORA registries focused on all RA patients irrespective of the treatment.

The other primary objective of our analysis was to compare the prevalence of signs and/or symptoms suggestive for tolerability issues or adverse drug reactions related to the MTX treatment between genders. When analysing the reasons for modifications of MTX treatment in the twelve months before study entry, and after controlling for potential confounders (multivariate analysis), we did not find significant differences between genders. Interestingly, at the time of the baseline visit (study entry) a significantly higher proportion of women reported nausea or weakness compared to men, leading to an overall greater prevalence of adverse drug reactions in women (Table III). Furthermore, also the percentage of women that, at baseline visit, modified the dose or route of administration of MTX due to intolerance was significantly higher compared to men (Table IV). Previous studies investigating the effect of gender on adverse drug reaction related to MTX produced conflicting results (12, 27-30). Amital *et al*. identified female gender as a significant factor predicting the risk of hepatic damage in a retrospective cohort review of patients presenting with RA or psoriasis (27). Similarly, Hoekstra *et al*., analysing data from a randomised clinical trial, demonstrated that MTX withdrawal due to hepatotoxicity and gastro-intestinal adverse events was associated with female gender (28). In another study from the Norfolk Arthritis Register (29), Authors described a trend for female patients to be more likely to stop MTX for adverse events in the first year of treatment, although this did not reach statistical significance. On the other hand, Dalkilic and colleagues failed to find an association between female gender and gastric MTX intolerance (30). In conclusion, on the basis of available literature, gender is generally considered a poor

predictor of general and organ-specific toxicity of MTX, particularly when used at the low doses (12). In this context, our study, being the first reporting a clear association between female gender and nausea or weakness, luckily interesting small numbers, is particularly important. In fact, the definition of clinical and biological predictors of MTX toxicity would be of great value in optimising treatment, monitoring, dosing regimens and route of administration, and would improve effectiveness while reducing adverse events.

Strengths and limitations of the MARI study have been already emphasised in previous reports (16, 17). Sample size and representativeness are particularly important, being included a high number of patients from academic and non-academic institutions, tertiary care units and out-patients services from different geographical regions of the North, Center and South of Italy. Moreover, direct assessment of RA subjects by treating rheumatologist provided a better reliability of clinical data and safety reporting compared to study based on health-insurance databases.

Admittedly, the study has some limitations. These include: the cross-sectional and retrospective nature of the data that reduced the possibility to identify incident events (*e.g.* MTX modifications, subclinical symptomatic adverse drug events); the inclusion of patients ongoing MTX therapy with a treatment duration longer than 12 months that reduced the possibility of defining safety and tolerability in the early phase of the disease; and the absence of data about discontinuation due to the trial's design that included only patients currently on MTX at study entry.

Conclusions

To the best of our knowledge, this is the first report describing MTX prescription attitudes in a "real world" sample of RA patients. Overall the data indicate that gender does not influence MTX therapy assigned by treating rheumatologist. On the other hand, women were more likely to report subjective intolerance leading to a modification of the dose or route of administration.

In conclusion, female gender may potentially represent a predictor of MTX toxicity. If confirmed in other studies, these findings would be of great value in optimising treatment, monitoring, dosing regimens and route of administration of MTX in real clinical practice.

References

1. LEITNER MK, KAUTZKY-WILLER A: Gender-specific differences in age associated endocrinology. *Z Gerontol Geriatr* 2013; 46: 505-10.
2. HOCHLEITNER M: Gender aspects in cardiovascular diseases. *Z Gerontol Geriatr* 2013; 46: 517-19.
3. BAGGIO G, CORSINI A, FLOREANI A *et al*.: Gender medicine: a task for the third millennium. *Clin Chem Lab Med* 2013; 51: 713-27.
4. CASSESE M, ZUBER V: Clinical trials and gender medicine. *Ann Ist Super Sanita* 2011; 47:100-3.
5. FRANCONI F, CAMPESI I: Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women. *Br J Pharmacol* 2014; 171: 580-94.
6. BIGOS KL, POLLOCK BG, STANKEVICH BA *et al*.: Sex differences in the pharmacokinetics and pharmacodynamics of antidepressants: an updated review. *Gend Med* 2009; 6: 522-43.
7. KLARESKOG L, CATRINA AI, PAGET S: Rheumatoid arthritis. *Lancet* 2009; 373: 659-72.
8. FAKHOURI W, LOPEZ-ROMERO P, ANTONELLI 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 Rheumatology: Research and Reviews* 2018; 10: 103-11.
9. KUMAR P, BANIK S: Pharmacotherapy options in rheumatoid arthritis. *Clin Med Insights Arthritis Musculoskelet Disord* 2013; 6: 35-43.
10. BIANCHI G, CAPORALI R, TODOERTI M *et al*.: Methotrexate and Rheumatoid Arthritis: Current Evidence Regarding Subcutaneous Versus Oral Routes of Administration. *Adv Ther* 2016; 33: 369-78.
11. SMOLEN JS, LANDEWÉ R, BIJLSMA J *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017; 76: 960-77.
12. ROMÃO VC, LIMA A, BERNARDES M *et al*.: Three decades of low-dose methotrexate in rheumatoid arthritis: can we predict toxicity? *Immunol Res* 2014; 60: 289-310.
13. GOODMAN SM, CRONSTEIN BN, BYKERK VP: Outcomes related to methotrexate dose and route of administration in patients with rheumatoid arthritis: a systematic literature review. *Clin Exp Rheumatol* 2015; 33: 272-78.
14. SHINDE CG, VENKATESH MP, KUMAR TM *et al*.: Methotrexate: a gold standard for treatment of rheumatoid arthritis. *J Pain Palliat Care Pharmacother* 2014; 28: 351-58.
15. FAVALLI EG, BIGGIOGGERO M, MERONI PL: Methotrexate for the treatment of rheumatoid arthritis in the biologic era: still an "anchor" drug? *Autoimmun Rev* 2014; 13: 1102-08.
16. MANARA M, BIANCHI G, BRUSCHI E *et al*.: Adherence to current recommendations on the use of methotrexate in rheumatoid arthritis in Italy: results from the MARI study. *Clin Exp Rheumatol* 2016; 34: 473-79.
17. IDOLAZZI L, ADAMI S, CAPOZZA R *et al*.: Suboptimal methotrexate use in rheumatoid arthritis patients in Italy: the MARI study. *Clin Exp Rheumatol* 2015; 33: 895-99.
18. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
19. TODOERTI M, MAGLIONE W, BERNERO E *et al*.: Systematic review of 2008-2012 literature and update of recommendations for the use of methotrexate in rheumatic diseases, with a focus on rheumatoid arthritis. *Reumatismo* 2013; 65: 207-18.
20. ROSSINI M, ROSSI E, BERNARDI D *et al*.: Prevalence and incidence of rheumatoid arthritis in Italy. *Rheumatol Int* 2014; 34: 659-64.
21. RUSCITTI P, MARGIOTTA DPE, MACALUSO F *et al*.: Subclinical atherosclerosis and history of cardiovascular events in Italian patients with rheumatoid arthritis: Results from a cross-sectional, multicenter GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) study. *Medicine* (Baltimore) 2017; 96: e8180.
22. SOKKA T, TOLOZA S, CUTOLO M *et al*.: Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther* 2009; 11: R7.
23. JAWAHEER D, OLSEN J, LAHIFF M *et al*.: Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA Study. *Clin Exp Rheumatol* 2010; 28: 454-61.
24. JAWAHEER D, MARANIAN P, PARK G *et al*.: Disease progression and treatment responses in a prospective DMARD-naive seropositive early rheumatoid arthritis cohort: does gender matter? *J Rheumatol* 2010; 37: 2475-85.
25. GOSSEC L, BARO-RIBA J, BOZONNAT MC *et al*.: Influence of sex on disease severity in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 1448-51.
26. NOURISSON C, SOUBRIER M, MULLIEZ A *et al*.: Impact of gender on the response and tolerance to abatacept in patients with rheumatoid arthritis: results from the 'ORA' registry. *RMD Open* 2017; 3: e000515.
27. AMITAL H, ARNSON Y, CHODICK G *et al*.: Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. *Rheumatology* (Oxford) 2009; 48: 1107-10.
28. HOEKSTRA M, VAN EDE AE, HAAGSMA CJ *et al*.: Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 423-26.
29. HIDER SL, SILMAN AJ, THOMSON W *et al*.: Can clinical factors at presentation be used to predict outcome of treatment with methotrexate in patients with early inflammatory polyarthritis? *Ann Rheum Dis* 2009; 68: 57-62.
30. DALKILIC E, SAHBAZLAR M, GULLULU M *et al*.: The time course of gastric methotrexate intolerance in patients with rheumatoid arthritis and psoriatic arthritis. *Mod Rheumatol* 2013; 23: 525-8.