Reumatismo, 2016; 68 (4): 188-194

The impact on disability of initial treatment with methotrexate in patients with rheumatoid arthritis: results from the MARI study

M. Manara[1], L. Arcarese[2], G. Bianchi[3], V. Corbelli[4], O. Epis[5], R. Laurenti[6], A. Migliore[7], M. Muratore[8], A. Roncaglione[9], M. Rossini[10], M. Savo[11], L. Sinigaglia[1]

[1]Department of Rheumatology, Istituto Ortopedico Gaetano Pini, Milano; [2]Unit of Immunology and Rheumatology, Policlinico Universitario-Università Campus Bio-Medico, Roma; [3]Department of Rheumatology, ASL3 - Azienda Sanitaria Genovese, Genova; [4]Unit of Rheumatology, Azienda Ospedaliera S. Anna, San Fermo della Battaglia (CO); [5]Unit of Rheumatology, Ospedale Niguarda Ca' Granda, Milano; [6]Centro IDI IRCCS, Roma; [7]Unit of Rheumatology, Ospedale San Pietro FBF, Roma; [8]Unit of Rheumatology, Ospedale Galateo ASL Lecce, San Cesario (LE); [9]Rheumatology Service, Distretto 1 ULSS 12 Veneziana, Venezia; [10]Unit of Rheumatology, Department of Internal Medicine, Azienda Ospedaliera Universitaria Integrata, Verona; [11]Ospedale Spaziani, Frosinone, Italy

SUMMARY

The study aimed to assess in a population of subjects with rheumatoid arthritis (RA) treated with methotrexate (MTX) how the initial approach to the treatment influenced subsequent disability.

We performed a cross-sectional analysis of data collected during the baseline visit of the MARI study, a multicenter observational study on patients with RA on treatment with MTX for at least 12 months. Subjects who fulfilled the Health Assessment Questionnaire (HAQ) were included in the evaluation. For every patient we retrospectively evaluated the disease duration, the duration of symptoms before the diagnosis, the time elapsed before first MTX treatment, the initial MTX dose, and the concomitant medications in the first six months of therapy. Disability was defined as a DI-HAQ score ≥1.

The study population included 1015 subjects. Patients with a DI-HAQ score ≥1 had a longer duration of symptoms before diagnosis, a higher delay in treatment initiation, a lower initial dose of MTX and a more frequent co-treatment with symptomatic drugs. Disability was found less frequently in subjects treated with other concomitant disease modifying anti-rheumatic drugs (DMARDs) but not with biological agents. Logistic regression analysis identified as significant predictors of disability: older age, female sex, a longer time to complete diagnosis, a delay in starting MTX treatment higher than 6 months, and a concomitant treatment with symptomatic drugs, while a combination therapy with other DMARDs was associated with a lower risk of disability. A late diagnosis and a delay in starting a treatment with MTX are associated with poorer functional outcomes in patients with RA.

Key words: *Methotrexate; rheumatoid arthritis; disability; HAQ.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic disease characterized by an inflammatory arthritis, which can lead to permanent damage and long-term disability. Its treatment has evolved over the years with the aim not only of controlling disease activity, but also of preventing long-term damage and the related disability and mortality (1). To date, many drugs are available which have been demonstrated to be effective in controlling disease activity and reducing radiographic progression and joint damage, so that prevention of disability is considered an achievable goal.

Among the high number of available treatments, methotrexate (MTX) is considered the *anchor* drug in the treatment of RA due to its high efficacy and safety profile associated with relatively low costs, so that international guidelines recommend that it

Corresponding author
Maria Manara
Istituto Ortopedico Gaetano Pini
Via Pini, 9
20122 Milano, Italy
E-mail: maria.manara@gmail.com

should be prescribed as first line therapy in patients with RA (2).

Many studies showed that the earlier the treatment, the better the long-term outcome of the disease, and international guidelines recommend that treatment with MTX should be started as soon as the diagnosis is made (2). Moreover, recent recommendations suggest that treatment with MTX should be started at appropriate dosages to achieve the best control of disease activity (3). Nevertheless, a recent survey on Italian patients with RA followed in rheumatology settings - the *Methotrexate in the therapy of Rheumatoid Arthritis in Italy* (MARI) study - showed that the approach to treatment with MTX in these subjects is still suboptimal, with a large proportion of patients starting the treatment with a long delay from the time of diagnosis and with initial dosages below those recommended (4, 5).

On this basis, the aim of our study was to assess in a large population of subjects with RA on MTX treatment how the initial approach to the treatment with MTX could have influenced subsequent disability.

MATERIALS AND METHODS

The study was performed on data collected during the MARI study, a large multicenter observational study involving 60 rheumatology units across Italy (both hospital-based and outpatient clinics), as described elsewhere (4, 5). Patients were consecutively enrolled between December 2011 and October 2013, if they fulfilled the criteria for RA, as established in the 1987 classification of the American College of Rheumatology (6), and if they had been on treatment with MTX for at least 12 months prior to the study.

The analyses for the present study were performed on data collected during the baseline visit, which included the cross-sectional assessment of disability through the Disability Index of the Italian version of the Health Assessment Questionnaire (DI-HAQ) (7). Only patients who completed the questionnaire were included in the evaluation.

Among variables collected at baseline, we retrospectively evaluated for every patient the date of diagnosis, the duration of symptoms before the diagnosis, the time elapsed before first MTX treatment, and the initial MTX dose (*i.e.*, the dose taken in the first six months) and route of administration. We also assessed concomitant medications in the first six months of therapy, such as: symptomatic drugs [non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, analgesic drugs], other disease modifying anti-rheumatic drugs (DMARDs) (leflunomide, hydroxy-chloroquine, sulphasalazine, and cyclosporine A), and biological therapies. The presence of a positive test for either the IgM rheumatoid factor (RF >40 U/mL) or for the anti-citrullinated protein antibodies (ACPA >20 U/mL) was also recorded.

The objective of our study was to assess which patients and disease characteristics and which variables related to initial MTX treatment were associated with disability in our sample of subjects with RA on MTX treatment.

The study was approved by the local Medical Ethics Committees of the participating centers and all patients gave their signed informed consent.

Statistical analysis

According to previous studies on patients with RA (8, 9), disability was defined as a DI-HAQ score ≥1. Descriptive data of the study population are presented as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables according to normality of the distribution, and number (percentages) for categorical variables. Characteristics of patients with and without disability were compared using Student's t-test or Mann-Whitney test for continuous variables, and Pearson's χ^2-test for dichotomous variables; probability (p) values <0.05 were considered statistically significant. Predictors of disability were assessed through a logistic regression analysis. All analyses were performed using a SPSS software version 17.0 (Chicago, SPSS, Inc.).

RESULTS

Among the 1336 RA patients under treatment with MTX enrolled in the MARI study, 1015 subjects completed the HAQ at the baseline visit and therefore were included in the analysis for the present study. Characteristics of the study population are given in Table I. The mean age of the patients was 60.6 (SD: 12.7) and 820 (80.8%) were women, with a median disease duration of 6 (IQR: 3; 13) years. The median duration of symptoms before diagnosis was 6 (IQR: 4; 12) months and treatment with MTX had started at the time of the diagnosis in 185 (18.2%) patients, within 3-6 months from the diagnosis in 185 (18.2%) subjects, within 7-12 months in 167 (16.5%) patients, while 478 (47.1%) patients started MTX over 12 months after the diagnosis. The mean starting dose of MTX was 11.4 (SD: 3.3) mg/week and 248 (29.2%) of the patients were prescribed with an initial dose between 12.5 and 15 mg/week, as recommended in the last Italian guidelines (3). Only a minority of patients were initially treated with MTX alone, while 92% of the included subjects received a concomitant treatment with symptomatic drugs (corticosteroids and/or NSAIDs and/or analgesic drugs), almost 35% of patients were treated from the beginning with a concomitant DMARD, and 19% with a biological agent. About half of the study population showed a DI-HAQ score ≥1.

The comparison between patients with and without disability according to the HAQ score is reported in Table II. By comparing patients with a DI-HAQ score ≥1 to those with a DI-HAQ score <1, we observed a higher proportion of female patients among those with disability. The duration of symptoms before diagnosis was significantly higher in patients with disability as well as the proportion of subjects who started the treatment with MTX more than 6 and 12 months after the diagnosis (Figure 1). The initial dose of MTX was lower in patients with a DI-HAQ score ≥1 and they were more frequently treated with symptomatic drugs in the first 6 months, especially with corticosteroids at dosages higher than 10 mg/die (15.1% *versus* 7%, p=0.000). A DI-HAQ score ≥1 was found less frequently in subjects treated with other concomitant DMARDs in the first 6 months, while no difference was found between patients who received a concomitant biological agent at the beginning of the treatment and subjects who did not. Patients treated with biologics in the first 6 months had a higher duration of symptoms before diagnosis [median (IQR) time to diagnosis: 9 (4; 18) *versus* 6 (4; 12) months; p=0.035] and a higher frequency than subjects who started MTX treatment more than a year after the diagnosis (53.6% *versus* 45.6%; p=0.043).

Logistic regression analysis (Table III) identified as significant predictors of disability female sex, an older age, a longer time to reach diagnosis (OR: 1.017; 95% CI: 1.005-1.028) and a delay in starting MTX treatment higher than 6 months (OR: 1.485; 95% CI: 1.069-2.063). Patients initially treated with symptomatic drugs were more likely to develop disability, while a concomitant treatment with other DMARDs at the beginning was associated

Table I - Characteristics of the study population (1015 patients with Rheumatoid Arthritis on Methotrexate treatment). Values are given as mean (Standard Deviation, SD), median (interquartile range, IQR), or number (percentages).

Age (years); [mean (SD)]	6.6 (12.7)
Sex (female); [n (%)]	820 (80.8%)
Disease duration (years); [median (IQR)]	6 (3; 13)
MTX treatment duration (months); [median (IQR)]	55 (27; 103)
Time to reach diagnosis (months); [median (IQR)]	6 (4; 12)
Time of starting MTX after diagnosis; [n (%)]: - at the time of diagnosis - 3- 6 months after diagnosis - 7-12 months after the diagnosis - >12 months after diagnosis	 185 (18.2%) 185 (18.2%) 167 (16.5%) 478 (47.1%)
Starting dose of MTX (mg/week); [mean (SD)]	11.4 (3.3)
ACPA positivity; [n (%)]	569 (56.1%)
Rheumatoid Factor positivity; [n (%)]	656 (64.6%)
Concomitant medications in the first 6 months; [n (%)]: - Symptomatic drugs (NSAIDs, CS, analgesic) - Other DMARDs - Biologics	 932 (91.8%) 354 (34.9%) 194 (19.1%)

MTX: methotrexate; ACPA: anti-citrullinated peptides antibodies; NSAID: non-steroidal anti-inflammatory drugs; CS: corticosteroids; DMARDs: disease-modifying anti-rheumatic drugs.

Table II - Comparison between subjects without disability (DI-HAQ score <1) and with disability (DI-HAQ score ≥1) among 1015 patients with Rheumatoid Arthritis on Methotrexate treatment. Values are given as mean (Standard Deviation, SD), median (interquartile range, IQR) or number (percentages).

	DI-HAQ score <1 (n=511)	DI-HAQ score ≥1 (n=504)	p
Age (years); [mean (SD)]	60.1 (13)	61.2 (12.5)	0.178
Sex (female); [n (%)]	390 (76.3%)	430 (85.3%)	0.000
Disease duration (years); [median (IQR)]	6 (3; 12)	6.5 (3; 13)	0.432
MTX treatment duration (months); [median (IQR)]	57 (30; 100)	52 (25; 110)	0.356
Time to diagnosis (months); [median (IQR)]	6 (3; 12)	8 (5; 12)	0.002
Time to treatment >6 months; [n (%)]	302 (59.3%)	344 (68.5%)	0.002
Time to treatment >12 months; [n (%)]	222 (43.4%)	256 (50.8%)	0.019
Starting dose of MTX (mg/week); [mean (SD)]	11.7 (3.5)	11.2 (3.0)	0.030
ACPA positivity; [n (%)]	289 (56.6%)	280 (55.6%)	0.748
Rheumatoid Factor positivity; [n (%)]	329 (64.4%)	327 (64.9%)	0.868
Concomitant medications in the first 6 months; [n (%)]:			
- Symptomatic drugs (NSAIDS, CS, analgesic)	459 (89.8%)	473 (93.8%)	0.019
- DMARDs	198 (38.7%)	156 (31%)	0.009
- Biologics	104 (20.4%)	90 (17.9%)	0.312

MTX: methotrexate; ACPA: anti-citrullinated peptides antibodies; NSAID: non-steroidal anti-inflammatory drugs; CS: corticosteroids; DMARDs: disease-modifying anti-rheumatic drugs.

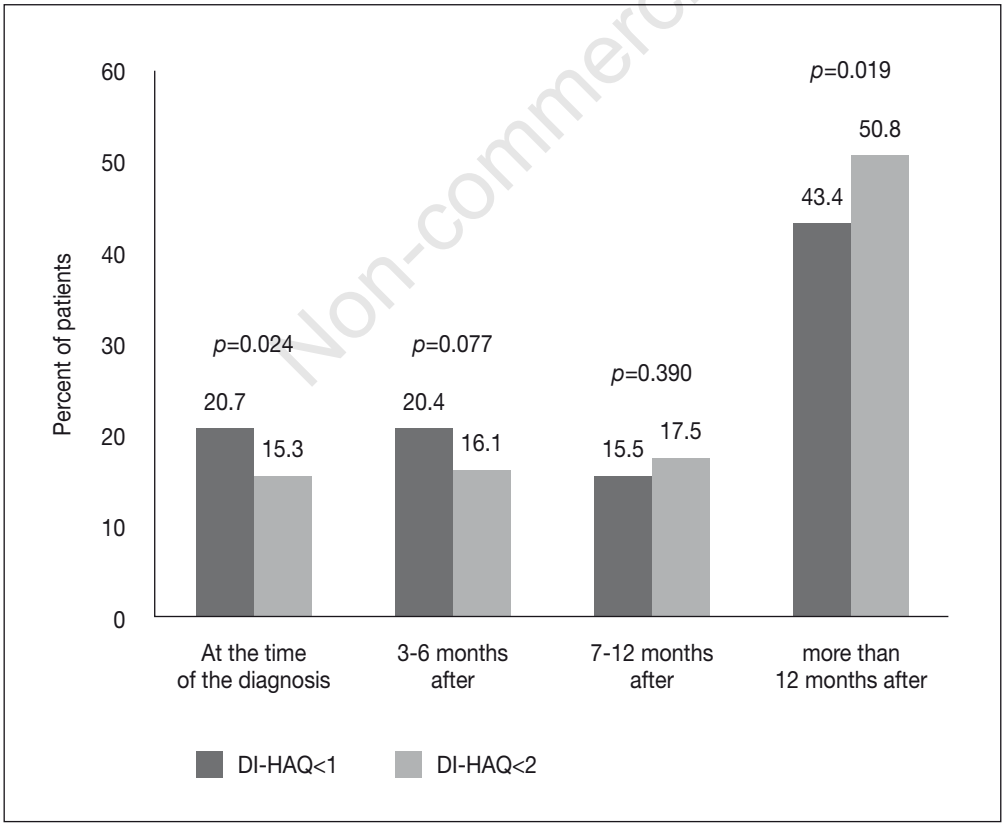

Figure 1 - Proportion of patients with and without disability according to the time of starting MTX after the diagnosis.

Table III - Logistic regression analysis for predictors of disability (DI-HAQ score ≥1) among 1015 patients with Rheumatoid Arthritis on Methotrexate treatment.

	Odds ratio	95% Confidence Interval	p
Sex (female)	1.774	1.220 - 2.578	0.003
Age (years)	1.012	1.000 - 1.024	0.043
Disease duration (years)	0.998	0.978 - 1.018	0.813
Time to diagnosis (months)	1.017	1.005 - 1.028	0.004
Time to treatment >6 months	1.485	1.069 - 2.063	0.018
Starting dose of MTX (mg/week)	0.969	0.927 - 1.013	0.162
Concomitant symptomatic drugs	1.843	1.081 - 3.144	0.025
Concomitant DMARDs	0.635	0.498 - 0.861	0.003
Concomitant biologics	0.947	0.661 - 1.356	0.765

MTX: methotrexate; DMARDs: disease-modifying anti-rheumatic drugs.

with a lower risk of disability (OR: 0.635; 95% CI: 0.469-0.861).

DISCUSSION

The results of our survey on a wide sample of subjects with RA on treatment with MTX showed that the approach to MTX therapy in the early phases of the disease could have influenced subsequent disability in these patients; an early diagnosis and treatment represent the main determinants of a good prognosis in patients with RA, together with an aggressive approach, as suggested by the preventive effect of a concomitant administration of other DMARDs in the first 6 months of therapy. The main strength of our study is the wide representativeness of our sample, which included a high number of patients treated with MTX from tertiary care units as well as outpatient services from different geographical regions of Italy, with a wide spectrum of disease durations. Moreover, direct assessment of patients by rheumatologists may provide good reliability of clinical data. However, the cross-sectional assessment of HAQ score does not provide a longitudinal evaluation of disability progression; additionally, the retrospective collection of data regarding initial phases of the disease did not allow us to obtain HAQ scores at the beginning of treatment, which have been demonstrated to be associated with subsequent disability (10, 11).

The high proportion of patients with disability in our study population (about half of the patients showed a DI-HAQ score ≥1) suggests a suboptimal control of disease activity that could be related to the not sufficiently aggressive treatment among Italian rheumatologists involved in this survey. Together with some traditional risk factors for disability such as female sex and older age (8, 11), the results of our study confirmed an association between the delay in diagnosis and in starting treatment with MTX and higher HAQ scores. These findings are in line with current EULAR recommendations on the treatment of patients with RA, which suggest that *therapy with DMARDs should be started as soon as the diagnosis is made* (2). Evidence on this topic is wide, as many studies showed that the earlier the treatment, the better the outcome for patients with RA: early diagnosis and initiation of treatment are associated with decreased disease activity, less joint damage progression, and increased functional ability assessed by HAQ (12-14). Nevertheless, our survey on a high number of Italian patients with RA on MTX treatment showed that only a minority of them started MTX within 6 months from the diagnosis (less than 40% of subjects), suggesting that many Italian rheumatologists do not follow the indication of starting MTX as soon as possible (5).

In the present analysis the starting dose of MTX, even if slightly lower in patients

with higher DI-HAQ scores, was not significantly associated with disability. However it should be highlighted that the majority of subjects were initially treated with a dose of MTX between 7.5 and 10 mg/week, while less than 30% of the patients received a starting dose of MTX between 12.5 and 15 mg, as indicated in the latest 2013 version of the Italian recommendations (3). Unfortunately, the data collected in the present survey did not allow us to establish whether an up-titration was done in these patients in the early phases of the disease.

Another finding emerging from our survey is the association between the concomitant administration of symptomatic drugs (NSAIDs, corticosteroids and/or analgesic drugs) and DI-HAQ scores ≥1. Even if patients' disease activity scores at the beginning of the treatment were not available for this survey, the use of symptomatic drugs could be considered as an indirect sign of a more aggressive disease, thus suggesting a higher frequency of disability among patients with a more active arthritis when starting MTX. This hypothesis could be further supported by the finding of a significant association between the concomitant treatment with high dosages of corticosteroids in the early phases of the disease and the subsequent disability.

RF and ACPA positivity were not significantly associated with DI-HAQ scores in our sample. The result concerning RF is in line with recent studies, which failed to find an association between RF positivity and disability progression (9, 15), while ACPA positivity significantly influenced the probability of developing erosions and subsequent disability in most studies. In our analysis, however, we considered only initial treatment, and we cannot exclude that patients with ACPA positivity may have received a more aggressive treatment in the following phases of the disease, which could have influenced their functional status at the moment of our evaluation.

Another interesting observation is that concomitant treatment with DMARDs other than MTX in the first 6 months of therapy was associated with a better prognosis of patients in terms of disability. This finding suggests that a more aggressive approach in the early phases of the disease could obtain better long-term results, even if previous studies on this topic lead to conflicting results (2). In a Cochrane meta-analysis, which compared MTX monotherapy versus MTX combination therapy with non-biologic DMARDs for RA, a significant improvement in physical function measured by HAQ was found in the MTX combination group, but only in MTX-inadequate responders (16). Conversely, more recent data from the CareRA trial did not show a different effect of MTX in combination with other DMARDs compared to MTX alone on HAQ scores in patients with early RA (17).

This observation was not replicated, however, for patients treated with biological agents in the first 6 months, who were not more likely to have higher HAQ scores. Unfortunately, we lack data on DI-HAQ and disease activity scores at the beginning of treatment, so that we could not assess whether patients treated with biologics from the beginning had a higher disease burden. However, we found that these subjects had a higher delay in diagnosis and treatment than those who did not receive a biologic agent: this delay could somehow have counterbalanced the positive effect of a more aggressive treatment. It may be highlighted, in any case, that less than 20% of the study population received a combination treatment with biologics in the first six months of treatment and less than 35% of patients were on therapy with a biological agent at the time of our evaluation, despite a median disease duration of 6 years: this finding further strengthens the hypothesis of an insufficiently aggressive treatment among Italian rheumatologists involved in this survey.

In conclusion, the results of our study showed that late diagnosis and delay in starting a treatment with MTX are associated with poorer functional outcomes in patients with RA. A more aggressive strategy of treatment in the early phases of the disease could ensure better control of subsequent disability in these subjects.

Conference presentation: paper presented at SIR Congress, 2015.

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