Adherence to current recommendations on the use of methotrexate in rheumatoid arthritis in Italy: results from the MARI study

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Abstract

Objective

The aim of this study was to assess how the management of rheumatoid arthritis (RA) with methotrexate (MTX) in Italy is adherent to current national recommendations.

Methods

We performed a cross-sectional and retrospective analysis of data collected from the MARI study, a multicentre survey on Italian patients with RA on treatment with MTX for at least 12 months. Retrospective data included patient's clinical history, previous treatment with MTX, screening tests performed before MTX prescription. Cross-sectional data were collected about current treatment with MTX, concomitant medications, and disease activity. Each proposition of the 2013 Italian recommendations on the use of MTX in RA was reformulated in terms of audit criteria, and adherence to provided indications was evaluated for every patient.

Results

Among the 1336 included patients, less than 40% had started treatment with MTX within 3-6 months from the diagnosis and nearly 30% of them were prescribed with an initial dose of MTX between 12.5 and 15 mg/week. Screening for HBV and HCV infection as well as chest x-ray was performed in a proportion of patients around 60% and more than 90% of them underwent lab tests before MTX prescription and regularly throughout the treatment. Folic acid supplementation was given at recommended dosages in a high proportion of patients.

Conclusion

Our survey showed a good adherence of Italian rheumatologists to recommendations regarding safety issues with MTX in RA, but a suboptimal approach in terms of time and dosage of the treatment in the early phases of the disease.

Key words

methotrexate, rheumatoid arthritis, recommendations

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Introduction

The approach to the treatment of rheumatoid arthritis (RA) has evolved over the last decades from a conservative strategy, mainly focused on controlling disease activity, to a more aggressive strategy aimed at preventing long-term damage and related disability and mortality (1). In this context, early treatment with a disease-modifying drug has proven to be efficacious not only in reducing clinical symptoms, but also in preventing articular damage and long-term consequences of the disease. A number of clinical trials have demonstrated that methotrexate (MTX) – alone or in combination with other disease-modifying anti-rheumatic drugs (DMARDs) – is highly effective, with a good safety profile and relatively low costs; indeed it is still considered the "anchor" drug in the treatment of RA, and international guidelines recommend that it is prescribed as first line therapy in patients with RA (2). Nevertheless, despite the widespread use of MTX over the years, the use of this drug and the approach toward treatment with MTX has often been influenced by the physician's personal experience rather than by evidence derived from clinical trials. Such variability has thus led the scientific community to set out recommendations in the attempt of standardising the approach to treatment (3).

The first Italian recommendations on the use of MTX in RA were issued in 2008, and were put together based on the "3E initiative" recommendations, adapted to the needs of the Italian population and integrated with new propositions built on the experience of Italian rheumatologists (4); in 2013 these recommendations were further updated, in consideration of the new evidence from more recent studies (5).

Because adherence to treatment guidelines seems to be associated to better control of disease activity, we decided to investigate how closely such recommendations are mirrored in current management of RA with MTX in Italy (6).

Materials and methods

The present study was a cross-sectional and retrospective survey based on the data collected from the recent MARI trial, a large multicentre observational study involving 60 rheumatology units across Italy (both hospital-based and outpatient clinics). Performed between December 2011 and October 2013, the study had recruited all consecutive patients who (i) fulfilled the criteria for RA – as established in the 1987 classification of the American College of Rheumatology (7) – and (ii) who had been on treatment with MTX for at least 12 months prior to the study (8).

Retrospective data on patient clinical history was collected at baseline visit, whereas ongoing therapy, changes to therapy, and patient's clinical status were evaluated in all visits (baseline throughout follow up). In detail, among the retrospective data recorded at baseline: duration of symptoms, time elapsed since the final diagnosis, time of first MTX treatment, initial MTX dose (*i.e.* the dose taken in the first six months) and route of administration, concomitant medications, screening tests performed before MTX prescription. Concomitant medications assessed were: non-steroidal anti-inflammatory drugs, other DMARDs such as leflunomide (LFN), hydroxy-chloroquine (HCQ), sulfasalazine (SSZ), and cyclosporine (CYC), and biological therapies. As to current MTX treatment, information collected included: current dose and route of administration, changes in the MTX dose or route of administration in the previous 12 months, and planned changes in MTX treatment. Finally, the clinical assessment addressed disease activity scores, and the presence of a positive test for either the Rheumatoid Factor (RF >40 U/ml) or for the anti-citrullinated protein antibodies (ACPA >20 U/ml) was recorded. Patients were classified as having 'erosive arthritis', when an overt bone erosion was evident from the hand x-ray.

The MARI study also addressed the rheumatologists' behaviour and attitude toward patients with RA prescribed with MTX, and thus included a semi-structured self-administered questionnaire for the rheumatologist to fill out once, before starting patients assessment.

The primary objective of our study was to assess how closely disease manage-

Table I. Proportion of patients with rheumatoid arthritis on methotrexate treatment satisfying audit criteria derived from Italian recommendations. Values are given as number of subjects fulfilling the criteria / number of subjects assessed (percentages).

Theme of care	Recommendation	Criteria	Attainment
Preliminary tests	The work-up for RA patients who are MTX candidates should include the following tests: liver function tests; serum albumin; blood cell counts; serum creatinine.	Patients with lab tests performed before starting MTX	1252/1336 (93.7%)
	The work-up for RA patients who are MTX candidates should include the following tests: … hepatitis B and C serology.	Patients with hepatitis B and C serology performed before starting MTX	861/1336 (64.4%)
	The work-up for RA patients who are MTX candidates should include … chest x-ray.	Patients with x-ray performed before starting MTX	767/1336 (57.4%)
	MTX treatment should not be introduced during pregnancy	Female patients potentially pregnant with pregnancy test performed before starting MTX	42 /385 (10.9%)
MTX dosage	The therapeutic range of MTX is 7.5-25 mg/week.	Patients with current MTX dosage between 7.5-25 mg/week	1283 /1314 (97.6%)
	The optimal initial strategy is a starting dose of 12.5-15 mg/week.	Patients with starting MTX dosage between 12.5-15 mg/week	298 /1044 (28.5%)
	As MTX-related toxicity is dose-dependent, the maximum weekly dose of 25 mg should not be exceeded.	Patients with current MTX dosage under 25 mg/week	1313 /1314 (99.9%)
Folic acid supplementation	Weekly supplementation with folic acid ... should be administered to reduce the risk of adverse events/intolerance	Patients supplemented with folic / folinic acid	1282/1336 (96%)
	Weekly supplementation with folic acid (5-10 mg/week) should be administered ...	Patients supplemented with folic acid at a dosage between 5-10 mg/week	789/869 (90.8%)
Monitoring	Transaminases (AST, ALT) are the most useful laboratory parameters for monitoring liver toxicity due to MTX. CBC and renal function tests should also be performed in patients receiving MTX. These tests should be performed … every 4-12 weeks to check for hepatic, haematological or renal toxicity.	Patients with lab tests performed every 4-12 weeks	1179 /1314 (89.7%)

RA: rheumatoid arthritis; MTX: methotrexate.

ment in RA attains to the latest national recommendations. Hence we assessed each proposition of the 2013 Italian recommendations, distinguishing stringent indications from more general suggestions. We then evaluated the adherence to stringent indications included in the recommendations by establishing specific audit criteria and by checking whether the management of each patient from the MARI study meets our audit criteria (9). Observance of the generic suggestions, instead, was not evaluated and was presented as descriptive results of the study population.

Likewise, we performed a similar evaluation on data derived from questionnaires filled out by each participating rheumatologist to assess the general behavior of the rheumatologists toward patients with RA treated with MTX.

As a secondary objective of our study, for explorative purposes, we compared attainment of audit criteria for patients diagnosed with RA before and after 2008 (publication year of the "3e initiative" recommendations).

The study was approved by the local Medical Ethics Committee and all patients gave signed Informed Consent.

Statistical analysis

Descriptive analyses were performed on the whole study population and results were presented as mean (Standard Deviation, SD) or median (interquartile range, IQR) for continuous variables after checking for normal distribution, and number (percentages) for categorical variables. Attainment to audit criteria was evaluated for each definition in all subjects with available data and presented as the proportion of subjects satisfying the specific criterion among subjects assessed. Differences between groups of patients were evaluated using Pearson's χ^2 test for dichotomous variables and probability (p) values <0.05 were considered statistically significant. All analyses were performed using a SPSS software v. 17.0 (Chicago, SPSS, Inc.).

Results

The study population included 1,336 RA patients under treatment with MTX. The mean age of the patients was 60.9 (SD: 12.7) and 1071 (80.2%) were women. The median disease duration was 6 (IQR: 3,13) years and the median treatment duration was 47 (IQR: 22,88) months. Treatment with MTX had started at the time of the diagnosis in 235 (17.6%) patients, within 3-6 months from the diagnosis in 245 (18.3%)

subjects, within 7-12 months in 209 (15.6%) patients, and 639 (47.8%) patients started MTX over 12 months after the diagnosis.

The proportion of patients satisfying audit criteria derived from Italian recommendations is reported in Table I. More than 90% of patients underwent lab tests before MTX prescription, and screening for HBV and HCV infection as well as chest x-ray was performed in a proportion of patients around 60%; conversely, a pregnancy test was performed in a very low percentage of potentially childbearing female patients (11%). Throughout the treatment, lab tests were performed every 4-12 weeks in almost 90% of the patients for monitoring drug toxicity, and folic acid supplementation was given at recommended dosages in a high proportion of patients. Treatment dose of MTX was within the recommended range for most of the patients, even though less than 30% of the patients were prescribed with an initial dose between 12.5 and 15 mg/week, as recommended: the majority of them (49.5%) was treated with an initial dose of 10 mg/week, and more than 15% of patients received an initial treatment with 7.5 mg/week of MTX (Fig. 1).

Further descriptive analyses were performed according to suggestions derived from non-binding indications included in recommendations. Over 75% of the included subjects were treated with parenteral MTX from the beginning. Among patients initially treated with oral MTX, 35% of them switched to parenteral MTX, while an increase in MTX dosage was reported in 22.7% of patients. Side effects not leading to treatment discontinuation were reported in 26.6% of the included subjects. Only a minority of patients were initially treated with MTX alone (4.8%), while 52.8% of the included subjects received a concomitant treatment with symptomatic drugs (corticosteroids and/or NSAIDs). Almost 35% of patients were treated from the beginning with a concomitant DMARD, and 17.3% with a biological agent. Among patients initially treated with MTX alone or in combination only with symptomatic drugs, 5% of them subsequently

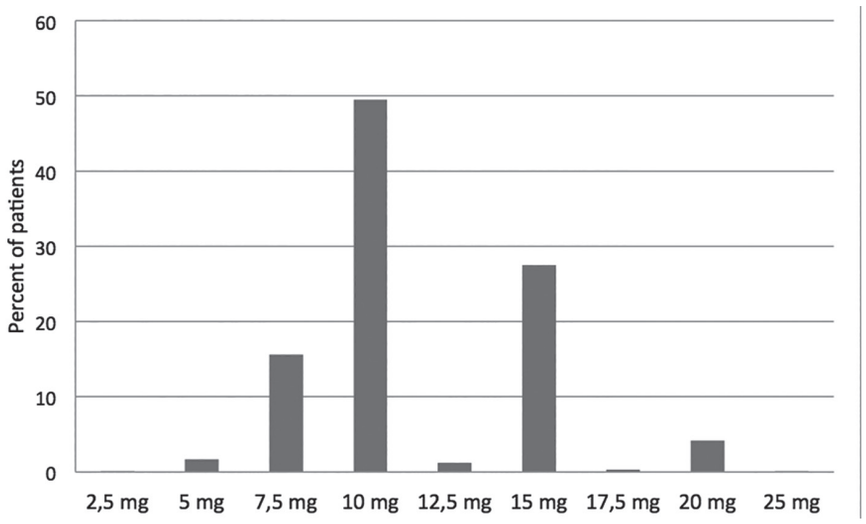

Fig. 1. Proportion of patients according to initial dose of MTX.

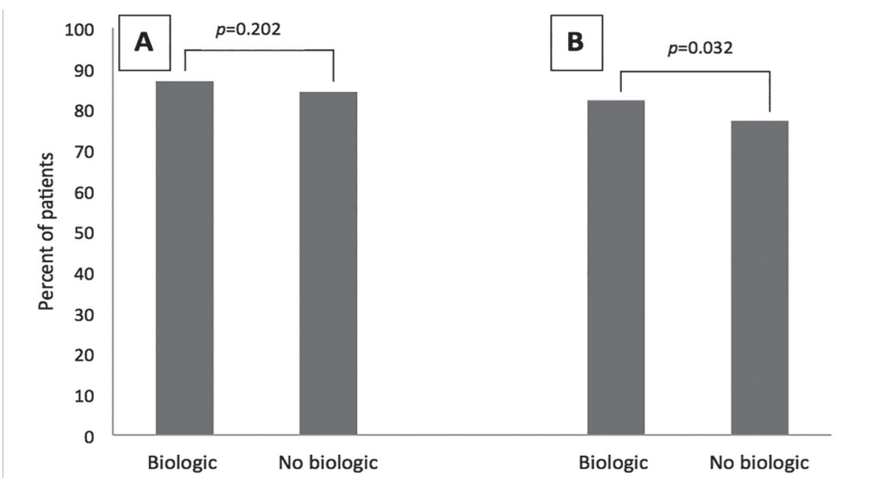

Fig. 2. Proportion of patients with poor prognostic factors among subjects treated with MTX in combination on not with a biological agent.
A. Poor prognostic factors: Rheumatoid Factor positivity and/or ACPA positivity and/or erosive disease; **B**. poor prognostic factors: ACPA positivity and/or erosive disease.

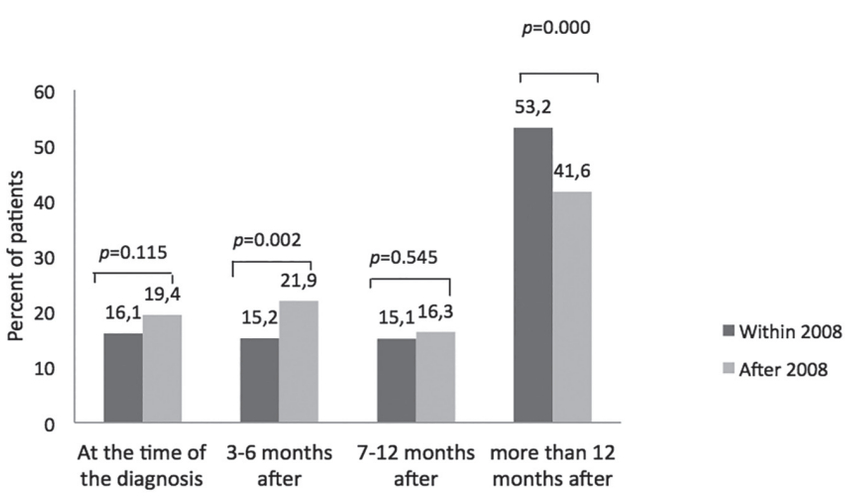

Fig. 3. Proportion of patients according to the time of starting MTX after the diagnosis.

Table II. Proportion of rheumatologists with a reported approach to methotrexate treatment in rheumatoid arthritis in line with audit criteria derived from Italian recommendations. Values are given as number of subjects fulfilling the criteria / number of subjects assessed (percentages).

Theme of care	Recommendation	Criteria	Attainment
Preliminary tests	MTX treatment should not be introduced during … alcohol abuse	Patients suggested to reduce alcohol consumption when starting treatment with MTX	58/65 (89.2%)
Folic acid supplementation	Weekly supplementation with folic acid (5-10 mg/week) should be administered to reduce the risk of adverse events/intolerance.	Patients supplemented with folic acid	64/65 (98.5%)
	In most cases, it should be taken 24 hours after MTX.	Folic acid administered 24 hours after MTX*	49/65 (75.4%)
Monitoring	Transaminases (AST, ALT) are the most useful laboratory parameters for monitoring liver toxicity due to MTX.	Transaminases tested for monitoring treatment toxicity	64/65 (98.5%)
	Blood cells count … should also be performed in patients receiving MTX.	Blood cells count tested for monitoring treatment toxicity	64/65 (98.5%)
	Renal function tests should also be performed in patients receiving MTX.	Renal function tested for monitoring treatment toxicity	54/65 (83.1%)
Surgery	The administration of MTX (at ≤10 mg/week) can be continued in RA patients who undergo orthopaedic surgery ... MTX dosage reduction or treatment discontinuation may be considered for doses ≥10 mg per week in patients undergoing major surgery	MTX not discontinued during orthopaedic surgery	6/65 (9.2%)
Pregnancy	MTX must be discontinued at least 3 months before conception (both in men and in women)	Women requested to discontinue the treatment with MTX at least 3 months before conception**	64/65 (98.5%)

RA: rheumatoid arthritis; MTX: methotrexate.
*folic acid administered concomitantly with MTX: 2; the day before MTX: 2; 24 hours after MTX: 49; 48 hours after MTX: 11; other scheme: 1.
**MTX discontinued at the time of conception: 1; 3 months before: 19; 4 months before: 6; 6 months before: 31; >6 months before: 8.

added another DMARD and 21.6% of them added a biological agent. Patients treated with a biologic had poor prognostic factors (Rheumatoid Factor positivity and/or ACPA positivity and/or erosive disease) in more than 85% of cases, but this proportion was not significantly different from the proportion of patients with poor prognostic factors among those not treated with a biological agent (Fig. 2). However, when only ACPA positivity and/or erosive disease were considered as poor prognostic factors, a significant difference was found between subjects treated and not treated with a concomitant biologic.

When prescriptive habits of rheumatologists included in the study were compared with recommendations (Table II), over 98% of the rheumatologists reported a standard approach to the patient consistent with recommendations about folic acid supplements prescription, transaminases and blood cells count monitoring, MTX discontinuation before pregnancy, and suggestion to reduce alcohol consumption. Less than 90% but more than 70% of the rheumatologists prescribed folic acid in the recommended time frame after MTX administration, and performed renal function tests to check for drug toxicity. When usual approach to MTX treatment during orthopaedic surgery was investigated, less than 10% of the rheumatologists reported to continue the treatment with MTX and none of them to reduce MTX dosage.

By comparing patients with a diagnosis formulated within 2008 to those diagnosed with RA after 2008, we observed a higher proportion of patients with an initial dosage of MTX in the recommended range (12.5–15 mg) among patients diagnosed after the publication of the 2008 recommendations (34.2% *vs*. 23.7%; p=0.000). Moreover, a treatment beginning within 6 months was more frequent in subjects with a diagnosis formulated after 2008 (21.9% *vs*. 15.2%; p=0.002), while a delayed treatment (more than 1 year after the diagnosis) was less frequent in this group (41.6% *vs*. 53.2%; p=0.000) (Fig. 3).

Discussion

The present survey aimed to compare the real-practice management of patients with RA and treated with MTX against national guidelines. Overall results from our study show a good adherence to national recommendations among Italian rheumatologist, although highlighting some potentially critical aspects such as a low initial dosage of MTX administered to patients and a delayed time to treatment.

In fact, in the early phase of the disease less than 30% of the patients received a starting dose of MTX between 12.5 and 15 mg, as recommended in the lat-

est 2013 version of Italian recommendations. On one hand this might suggest caution on behalf of rheumatologists in administering MTX early in the disease, on the other this may simply be explained by the fact that indications in the previous Italian recommendations (2008) suggested to start with lower dosages, *i.e.* 7.5 mg, and successively increase the dosage (4). This second hypothesis would seem more likely and indeed be reflected in our findings reporting a high proportion of patients with an initial dose between 7.5 and 10 mg/week. Moreover, these data are in line with those emerging from other surveys on patients with RA on MTX treatment, where a high proportion of patients with a current MTX dosage of 10 mg/week was found (10). Unfortunately, data collected in the present survey did not allow us to establish if an up-titration was done in these patients in the early phase of the disease, as recommended.

An underlying concern of behalf of rheumatologists and attention to safety issues with MTX, would however be suggested by other findings. The maximum recommended dosage was hardly ever exceeded, and concomitant supplementation with folic acid at the suggested dosages was prescribed in the great majority of cases. Lab tests were performed prior to MTX prescription for almost all patients who were also regularly checked during the treatment. On the other hand, specific screening for hepatitis B and C as well as a chest X-ray was assessed only in 60% of the patients before treatment. Despite a high attention paid to concerns related to MTX treatment and pregnancy (almost all rheumatologists declared to request patients to discontinue the treatment at least 3 months before conception), pregnancy test before MTX prescription was performed only in a minority of potentially childbearing female patients. Again, however, the requisite of pregnancy test prior to prescription has changed compared to the earlier version of the recommendations and is no longer indicated. A cautious approach was also found in relation to patients undergoing orthopedic surgery: most of the rheumatologists discontinued the treatment with MTX during surgery, even if current recommendations suggest to continue it for dosages ≤10 mg/week; however, a specific distinction between different dosages of MTX (≤ or >10 mg/week) was not formulated in the questionnaire.

Another fundamental finding emerging from our survey is the delay in time of treatment initiation (11). Even if a specific proposition was not included in the recommendation for MTX use, general recommendations for the management of RA state as a mainstay of the therapeutic approach to RA that "therapy with DMARDs should be started as soon as the diagnosis is made" (2). In our survey only 17.6% of the patients started MTX at the time of the diagnosis, while almost 50% of them initiated the treatment more than 12 months after the diagnosis.

Because patients recruited had very different disease durations, we investigated whether the rheumatologist's approach to patients had changed during years, by comparing subjects diagnosed prior to 2008 with those diagnosed after 2008 (*i.e.* the year of the "3E initiative" recommendations publication) (3). We found that in recent years a higher proportion of patients was treated at the time of the diagnosis and a treatment beginning over 1 year from the diagnosis was less frequent. Moreover, the proportion of patients with a starting dosage of MTX between 12.5 and 15 mg was significantly higher in the last years, compared to previous years of the study. These findings suggest that, despite the treatment strategy with MTX still not being satisfactorily compliant with that recommended, last years have seen a positive trend toward a more aggressive approach to the disease. Our results are quite different from those emerged from the CORRONA registry, where no significant modifications were found in the treatment of RA with MTX before and after the publication of the ACR treatment recommendations in 2008 (12). A possible explanation for this discrepancy relies on the different time frame analysed in the two studies: patients from the CORRONA study were included only until December 2009, while subjects in our study were included until October 2013; the longer time frame analysed since the publication of treatment recommendations in 2008 could have allowed us to observe also less rapid changes in treatment strategies of rheumatologists.

Even if preferences on the way of administration of MTX were not addressed by the Italian recommendations, we found a high proportion of patients being treated from the beginning with parenteral MTX and a good percentage of subjects successively switching from oral to parenteral administration, a proportion significantly higher than that reported in a similar survey on US population (10). This finding, however, is in agreement with literature which appears to indicate parenteral MTX as more efficacious than the oral formulation, at least in some studies (13-15). Likewise, Italian recommendations did not provide any specific indications as to the initial combination therapy: we found that only a half of our study population was treated in the first 6 months with MTX alone or in combination with symptomatic drugs, while a high proportion of patients received a concomitant DMARD or biological agent. Moreover, among those patients initially treated with MTX without other concomitant DMARDs, over 25% of them successively added a DMARD or a biologic. Even if the lack of retrospective data on disease activity did not allow us to evaluate how disease activity scores guided rheumatologists' choices, we found a higher proportion of patients treated with biological agents among those with markers of aggressive disease, such as ACPA positivity or erosive arthritis; this result allows us to hypothesise that a proper risk stratification could have been done when a biological agent was added, according to data from clinical studies in which a higher benefit from combination therapy in patients at risk of rapid radiographic progression was demonstrated (16).

The main strength of our study is the wide representativeness of our sample, which included a high number of patients from tertiary care units as well as outpatient services from different geographical regions of Italy. Moreover, direct assessment of patients by rheumatologists may provide a better reliabil-

ity of clinical data compared to similar studies performed on health-insurance databases or based on self-reported patients characteristics.

On the other hand, this study has some limitations. The cross-sectional and retrospective design does not allow to collect punctual data on transient events (infections, surgery, pregnancy) and consequent changes in treatment, as well as on clinical data driving the physicians' decisions; however, further data are expected from the longitudinal phase of the study. The inclusion of patients with a treatment duration longer than 12 months precludes the possibility to evaluate the treatment strategy in early phases of the disease. Finally, data on treatment discontinuation could not be obtained with a study design which includes only patients currently treated with MTX: in this light, the creation of large registries is expected to provide more reliable data on this topic.

Conclusions

This large survey on patients with RA on MTX treatment showed a good adherence of Italian rheumatologists to recommendations regarding safety issues with MTX, as well as a softer approach to the treatment, especially in the initial phases of the disease, for which recommendations indicate a more aggressive start. The stratification of the population by the time of diagnosis seems to indicate a positive modification of treatment strategies over time, toward a more aggressive approach characterised by an earlier therapy with higher dosages of MTX. Longitudinal studies are expected to provide further data on this issue.

References

1. SOKKA T, ENVALDS M, PINCUS T: Treatment of rheumatoid arthritis: a global perspective on the use of antirheumatic drugs. *Mod Rheumatol* 2008; 18: 228-39.
2. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *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.
3. VISSER K, KATCHAMART W, LOZA E *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.
4. DE LEONARDIS F, ALIVERNINI S, BONACCI E *et al*.: Italian consensus on the recommendations about the use of methotrexate for the treatment of rheumatic diseases with a focus on rheumatoid arthritis: results from the "3E initiative". *Reumatismo* 2010; 62: 34-45.
5. 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.
6. FRANSEN J, LAAN RF, VAN DER LAAR MA, HUIZINGA TW, VAN RIEL PL: Influence of guideline adherence on outcome in a randomised controlled trial on the efficacy of methotrexate with folate supplementation in rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 1222-6.
7. 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.
8. IDOLAZZI L, ADAMI S, ALTOMONTE L *et al*.: Suboptimal Methotrexate Use in Rheumatoid Arthritis Patients in Italy: The MARI study. *Clin Exp Rheumatol* 2015; 33: 895-9.
9. COTTRELL E, CRABTREE V, EDWARDS JJ, RODDY E: Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. *BMC Fam Pract* 2013; 14: 170.
10. CURTIS JR, ZHANG J, XIE F *et al*.: Use of oral and subcutaneous methotrexate in rheumatoid arthritis patients in the United States. *Arthritis Car Res* 2014; 66: 1604-11.
11. EMERY P, SALMON M: Early rheumatoid arthritis: time to aim for remission? *Ann Rheum Dis* 1995; 54: 944-7.
12. HARROLD LR, HARRINGTON JT, CURTIS JR *et al*.: Prescribing practices in a US cohort of rheumatoid arthritis patients before and after publication of the American College of Rheumatology treatment recommendations. *Arthritis Rheum* 2012; 64: 630-8.
13. 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.
14. BRAUN J, KASTNER P, FLAXENBERG P *et al*.: Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008; 58: 73-81.
15. BINGHAM SJ, BUCH MH, LINDSAY S, POL. LARD A, WHITE J, EMERY P: Parenteral methotrexate should be given before biological therapy. *Rheumatology* 2003; 42: 1009-10.
16. VISSER K, GOEKOOP-RUITERMAN YP, DE VRIES-BOUWSTRA JK *et al*.: A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. *Ann Rheum Dis* 2010; 69: 1333-7.