Methotrexate in Italian patients wiTh Rheumatoid Arthritis (MITRA study): an observational study about the use of methotrexate in early RA patients and the adherence to the EULAR 2013 recommendations. A project of the Italian Society for Rheumatology

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Abstract

Objective

To assess the delay between the disease onset and the beginning of methotrexate (MTX) treatment in RA patients and to evaluate the Italian rheumatologists' adherence to the EULAR 2013 recommendations.

Methods

MITRA is an Italian multicentre observational study carried out on DMARD-naïve RA patients recruited in an 18-month period starting from 2015. The data related to the patients' characteristics at baseline will be presented.

Results

332 patients from 13 Italian centres were recruited: the median delay between the onset of symptoms and the beginning of MTX was 197 days (102–431); in 20% of patients a treatment with DMARDs was started within the first 90 days from the onset of symptoms. The clinical target selected was DAS28 remission in 64.2% of cases and low disease activity in 35.8%. Among patients in DAS28 high disease activity, 92.6% received a control visit which was rescheduled within the first 3 months, similarly to those in DAS28 moderate disease activity (91.6%). A DMARD monotherapy was prescribed in 319 patients, while a combined therapy of DMARDs was preferred in 13 cases; 282 patients were treated with MTX. Glucocorticoids were prescribed in 229 patients: the median dosage was of 5 mg (IQR 5–7.5) of prednisone equivalent/day.

Conclusion

Diagnostic delay in RA patients continues to be longer than expected. The choice of low disease activity as a target is still very frequent and tight control does not seem to be based on disease activity. This paper offers a realistic and detailed picture of the clinical practice among Italian rheumatologists.

Key words

rheumatoid arthritis, delay, adherence, EULAR recommendations, treat to target

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that can become highly disabling if not adequately treated, with a significant impact for both patients and the society (1-3). Currently it is well known that early treatment initiation allows to reach better outcomes in the short and long term, and international recommendations encourage to pursue the treat to target and tight control strategies in order to quickly control the disease (4-8). Methotrexate (MTX) is still the "anchor" drug for the treatment of RA based on its good profile in terms of efficacy, safety and costs, and based on the possibility to tailor its dosage and route of administration (9-11).

However, international recommendations also allow a combination of conventional disease-modifying antirheumatic drugs (DMARDs), suggesting that MTX should be considered as a part of the first treatment strategy. Therapy must be arranged by an experienced rheumatologist who can optimise the pharmacological dosage based on the patient's needs, choose the most appropriate route of administration and evaluate the need for a combined therapy. The treat to target strategy recommends an optimisation of the pharmacological dosage using a step-up therapy in case the selected target is not reached, and suggests the introduction of a second-line therapy with biotechnological drugs when conventional DMARDs treatment is not adequate (12-14). To date, not much is known in daily clinical practice about the adherence to the principles suggested by the international recommendations (15).

The primary aims of the study were to assess the delay between the onset of the disease and the beginning of MTX treatment and to evaluate the Italian rheumatologists' adherence to the EULAR recommendations, 2013 update (12). The secondary aims were to evaluate the delay between the diagnosis and the beginning of a treatment with DMARDs, the time between the onset of symptoms and the first rheumatologic evaluation, the initial dosage of MTX and its route of administration, the rate of combined DMARDs therapy at the beginning and the concurrent use of glucocorticoids (GCs).

Materials and methods

Study design

This is an Italian multicentre observational study carried out on DMARD-naïve RA patients. Data were collected following good clinical practice, without modifying the clinical decision of the rheumatologists involved. Patients were recruited in an 18-month period from 2015 with a minimum follow up of 12 months. Patients who started a biologic treatment were no longer observed. The study was approved by the local ethics committees and carried out in accordance with the Declaration of Helsinki and according to the EU directives concerning Good Clinical Practice.

Recruitment criteria

Patients aged ≥18 years diagnosed with RA, based on the opinion of a rheumatologist, who started the first treatment with conventional DMARDs were recruited; all patients signed an informed consent.

Characteristics of the participating centres

A total of 13 centres from different areas of the Country, including large University departments and small rheumatologic hospital centres, were involved: an early arthritis clinic (EAC) was active in 61.5% of centres, while 38.5% presented a fast track for a first visit, in accordance with the regional plan. In 76.9% of cases, a territorial training event for general practitioners has been organised over the last 3 years.

Clinical assessment

Patients' characteristics collected at baseline were sex, age, ethnicity, comorbidities, time elapsed between the onset of symptoms (the first appearance of a sign or symptom attributable to the disease by the physician) and the first rheumatologic evaluation, time elapsed between the first rheumatologic evaluation and RA diagnosis, time elapsed between the RA diagnosis and the beginning of DMARD; fulfilment of ACR/EULAR 2010 classification criteria for RA (16). Clinical data related to

the number of tender and swollen joints on 28 joint count, functional disability using the health assessment questionnaire disability index (HAQ-DI) and the presence of x-ray erosions were also collected. Pain, patient global assessment of disease activity (PGA), Global Health (GH), patient acceptable symptom state (PASS) and physician global assessment of disease activity (PhGA) were measured on a 0 to 100 mm Visual Analogue Scale (VAS). Laboratory measures included rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA), erythrocyte sedimentation rate (ESR) and C-reactive protein serum levels (CRP). Pharmacological data regarding treatment, dosage and route of administration, concurrent GCs treatment and the potential previous therapies (non-steroidal anti-inflammatory drugs - NSAIDs and/or GCs) were recorded. Disease activity was measured by DAS28 and data relating to the target selected were collected. At baseline, the timing for follow-up visits was also recorded.

Statistical methods

Continuous data are presented as mean and standard deviation (SD) or median and interquartile range (IQR) when appropriate. For categorical variables, absolute and relative frequencies are reported. To test the hypothesis whether the timing of rescheduled first follow up visit is independent of DAS28 disease activity, a Fisher's exact test is performed. Data were collected and managed using Research Electronic Data Capture (REDCap). Analyses were performed using R statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' demographic and clinical characteristics at baseline

Three hundred and thirty-two patients from 13 Italian centres were included. Their main characteristics are presented in Table I. The enrolled patients were predominantly women (75.6%), with an average age of 57 years; in almost all cases they were Caucasian (95.8%). Based on the BMI, 51% of patients were normal weight, 30.3% overweight

Table I. Demographic and clinical characteristics of patients at baseline.

Number of patients	number	332
Age	mean (SD), years	57.03 (13.9)
Female	number (%)	251 (75.6)
Caucasian ethnicity	number (%)	316 (95.8)
BMI	number (%), underweight	6 (2)
	number (%), normal weight	153 (51)
	number (%), overweight	91 (30.3)
	number (%), moderately obese	37 (12.3)
	number (%), severely obese	8 (2.7)
	number (%), very severely obese	5 (1.7)
Smoker	number (%)	68 (20.9)
ACR/EULAR score	mean (±SD)	7 (1.6)
Erosion (patient with at least one erosion)	number (%)	108 (34.5)
Erosions typical of RA	number (%)	56 (18)
IgM RF	number (%), negative	142 (43)
	number (%), previous positivity	3 (0.9)
	number (%), positive	185 (56.1)
IgG ACPA	number (%), negative	147 (45.1)
	number (%), previous positivity	1 (0.3)
	number (%), positive	178 (54.6)
Glucocorticoids	number (%), previous treatment	78 (23.7)
	number (%), concurrent treatment	108 (32.8)
NSAIDs	number (%), concurrent on demand	95 (28.6)
	number (%), concurrent treatment	42 (12.7)
VAS Pain	mean (SD)	59 (27.5)
	median (IQR)	65 (40-80)
VAS PtGA	mean (SD)	59.5 (26.2)
	median (IQR)	60 (50-80)
VAS GH	mean (SD)	49.5 (27.4)
	median (IQR)	50 (25-70)
PASS	mean (SD)	36.4 (27.5)
	median (IQR)	34.5 (12.5-50)
VAS PhGA	mean (SD)	50.5 (22.7)
	median (IQR)	50 (30-70)
Morning stiffness	mean (SD), minutes	72.2 (129.3)
	median (IQR), minutes	30 (10-120)
TJC28	mean (SD)	7 (5.9)
	median (IQR)	6 (3-10)
SJC28	mean (SD)	4.7 (4.6)
	median (IQR)	3 (1-7)
DAS28	mean (SD)	4.8 (1.4)
HAQ-DI	mean (SD)	1 (0.7)
ESR	median (IQR), mm/h	25 (12-46)
CRP	median (IQR), mg/dl	1.97 (0.3-7.4)

Percentages are calculated based on available data.
SD: standard deviation; IQR: interquartile range; BMI: body mass index; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; NSAID: non-steroidal anti-inflammatory drug; VAS Pain: pain assessment by a visual analogue scale; VAS PtGA: patient's global assessment of disease activity by a visual analogue scale; VAS GH: patient's assessment of global health by a visual analogue scale; PASS: patient acceptable symptom state; VAS PhGA: physician's global assessment of disease activity by a visual analogue scale; TJC28: tender joint count (28 joints); SJC28: swollen joint count (28 joints); DAS28: disease activity score (on 28 joints evaluated); HAQ-DI: health assessment questionnaire disability index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

and 16.7% suffered from moderate or severe obesity. At baseline, patients presented with a DAS28 reflecting moderate disease activity (mean±SD 4.8±1.4), with a median of 6/28 tender joints (IQR 3–10) and 3/28 swollen joints (IQR 1-7) and an average functional disability of 1 (SD ± 0.7) evaluated with the HAQ-DI questionnaire, and a 30-minute-long morning stiffness (IQR 10-120). At the time of enrolment, the median ESR was 25 mm/h (IQR 12–46) and CRP was 1.97 mg/dl (IQR 0.3–7.4). The average score of the ACR/EULAR 2010 classification criteria was 7 (SD ± 1.6): 5.8 (±1.3) in seronegative patients, 6.6 (±1.1) in patients with low positive RF or ACPA, 7.9 (±1.3) in patients with high positive RF or ACPA; 97% of patients experienced arthritis for over 6 weeks before diagnosis, 34.5% of patients had at least one erosion and 18% of the whole population presented RA typical erosions (17, 18). Patients with a positive RF were 56.1%, and ACPA positivity was present in 54.6% of patients. At baseline, 32.8% of the patients were taking GCs orally, 28.6% were taking NSAIDs when needed, while 12.7% were taking NSAIDs at full-dose.

Table II. Timing of rescheduled first follow up visit based on the disease activity at baseline.

DAS28 Disease activity at baseline	Rescheduled first follow up visit number of patients (%)			
	After 1 month	After 2 months	After 3 months	After >3 months
DAS28≤3.2	1 (2.6)	15 (39.5)	18 (47.4)	4 (10.5)
DAS28 >3.2 and ≤ 5.1	6 (3.9)	63 (40.6)	73 (47.1)	13 (8.4)
DAS28>5.1	15 (11.1)	44 (32.6)	66 (48.9)	10 (7.4)

Data were available for 328/332 patients.

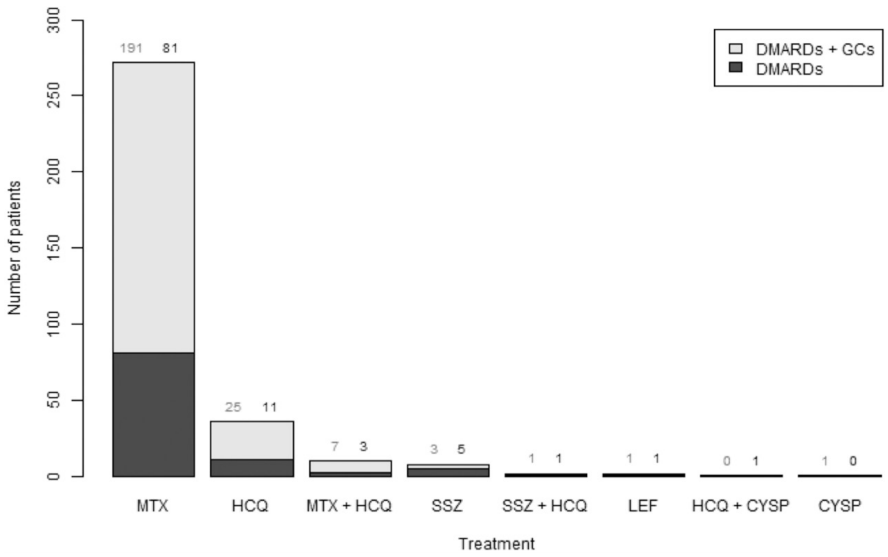

Fig. 1. First therapeutic prescription made by Italian rheumatologists.
A concurrent prescription of NSAID was allowed and not taken into account for this evaluation.

Time to referral, diagnosis and treatment

In our population, the median timespan between the onset of symptoms and the first rheumatologic examination was 133 days (IQR 61–317), while the time elapsed between the first rheumatologic visit and RA diagnosis was 27 days (IQR 0–52). Once the diagnosis was confirmed, DMARD therapy was immediately started in 74.1% of the cases (median [IQR] delay of DMARD prescription from diagnosis 0 days ([0–2]), so that the time elapsed between the first rheumatologic visit and the beginning of DMARD therapy was collectively of 35 days (IQR 10-79). Therefore, the median delay between the onset of the disease and the beginning of any DMARDs therapy was 205 days (IQR 105–528); 19.9% of patients started a DMARD treatment within the first 90 days from the onset of symptoms.

In a sub-analysis of patients prescribed with MTX (alone or in combination therapy), the time-interval between the onset of symptoms and the first rheumatologic examination was 127 days (IQR 61–335), while the time elapsed between the first rheumatologic visit and RA diagnosis was 27 days (IQR 0–52). The timespan between the first rheumatologic visit and the beginning of MTX was 35 days (IQR 11–72). As a result, the median delay between the onset of the disease and the beginning of MTX was 197 days (IQR 102–431). In the group of patients treated with DMARDs other than MTX, the lag between the onset of symptoms and the first rheumatologic examination was 142 days (IQR 63–197), while RA diagnosis followed first rheumatologic visit of 30 days (IQR 0-52). The time interval between the first rheumatologic visit and the beginning of DMARDs different from MTX was 42 days (IQR 6–160). Median delay between the onset of the disease and the beginning of a DMARD different from MTX was 239 days (IQR 118–386).

Therapeutic target selected

The clinical target selected by the rheumatologists was DAS28 remission in 64.2% of the cases, and DAS28 low disease activity in 35.8% of patients; clinicians declared the therapeutic target was shared with the patient in 98.2% of cases.

Tight control

At baseline, 135 patients were in DAS28 high disease activity, 155 were in moderate disease activity and 38 in low disease activity. At baseline, follow-up visits were rescheduled. Among patients in high disease activity, 92.6% of the patients received the control visit within the first 3 months, while 7.4% had a control visit after over 3 months. Among patients in moderate disease activity, 91.6% received a follow-up visit

within the first 3 months, while 8.4% of patients had a control visit which was rescheduled more than 3 months apart. For those in low disease activity, a follow up visit was rescheduled within the first 3 months for 89.5% of patients, while 10.5% had a control visit rescheduled after over 3 months; no correlation was found between the timing with which the follow-up visit was rescheduled and the DAS28 disease activity (p=0.081). Complete data concerning the timing of rescheduled first follow up visit is presented in Table II: data were available for 328 patients.

Treatment with DMARDs at baseline

In our population, DMARD monotherapy was prescribed in 319 patients: 272 patients were treated with MTX, 36 patients with hydroxychloroquine (HCQ), 8 patients with sulfasalazine (SSZ), 2 patients with leflunomide (LEF) and 1 patient with cyclosporine (CYA).

A combined DMARDs therapy was prescribed at baseline in 13 patients: the combination selected was MTX + HCQ in 10 cases, HCQ + SSZ for 2 patients while 1 patient was treated with HCQ + CYA. No one was treated with a combination of more than 2 DMARDs. Among the 282 patients treated with MTX (272 patients treated with MTX monotherapy and 10 patients treated with MTX in combined therapy), the subcutaneous route of administration was selected in 94.3% of cases, intramuscular MTX was preferred in 2.85% of patients and the oral formulation was chosen in 2.85% of the cases. For 200 patients the initial dosage of MTX was 15 mg/week, for 3 patients the dosage was 12.5 mg/week, for 65 patients the dosage was 10 mg/week, for 13 patients a 7.5 mg/week dosage was chosen while only 1 patient started taking over 15 mg/week. The first therapeutic choice made by rheumatologists is shown in Figure 1.

Contraindication to MTX

In 22/50 patients not treated with MTX, clinicians reported the presence of a contraindication to the treatment. Out of those, 13 patients started HCQ, 5 cases were treated with SSZ, 2 cases with LEF, 2 patients with CYA (1 treated with a monotherapy, 1 treated with a combined therapy of CYA + HCQ). No clarification about the type of contraindication was available.

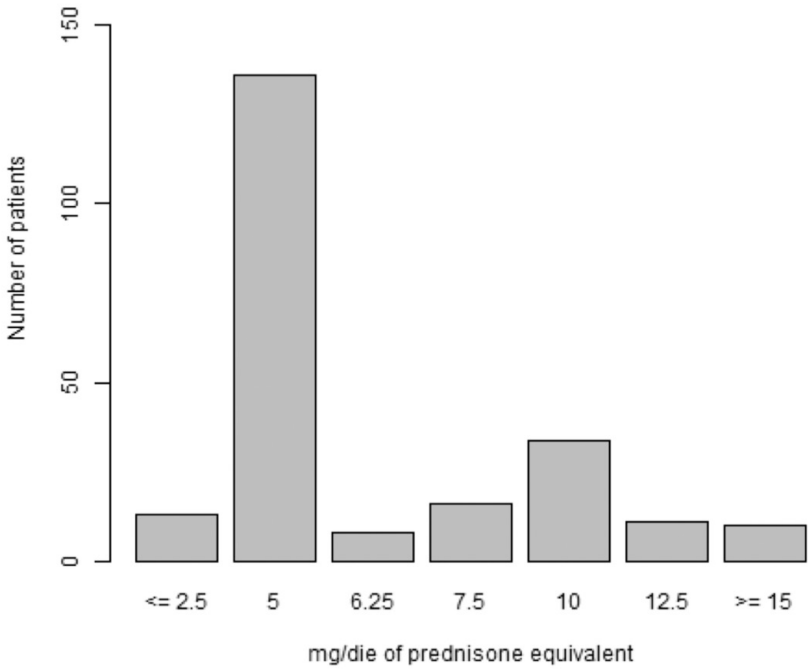

Fig. 2. Prescription of glucocorticoids at diagnosis.

Treatment with GCs

GCs were prescribed at the beginning of the treatment in 229 patients. The median initial dosage was of 5 mg (IQR 5–7.5) of prednisone equivalent/day: 65.4% of patients started with a dosage up to 5 mg/day, 10.5% took a dosage >5 mg/day but ≤7.5 mg/day, 24.1% took more than 7.5 mg/day. Further details about the prescription of GCs are shown in Figure 2. Among patients treated with MTX (both monotherapy and combined therapy), GCs were prescribed in 70.2% of cases while 62% of patients treated with DMARDs different from MTX received a concurrent treatment with GCs.

Discussion

The abatement of the diagnostic delay is still one of the most challenging issues in the management of early RA. In the last 20 years, the availability of EACs (19) has certainly allowed to significantly reduce the diagnostic delay, nevertheless a late search for medical care tends to increase this delay (20). At baseline, our population showed clinical characteristics in line with similar European cohorts (21, 22). The median delay before starting a treatment with a DMARD in general was of 205 days, while the time between the onset of symptoms and the beginning of MTX was of 197 days. In a recent work based on the US military's TRICARE program, the time elapsed between the onset of symptoms and the first prescription of a DMARD was of 125 days (±175.4) with evidence of a progressive reduction over time (23). Similarly, a study assessing the delay based on the autoantibody status of RA showed a therapeutic delay of 17 weeks (24). In other groups, the average time before starting a suitable treatment appeared to be much longer (25, 26). In general, for the European population, the median delay in the assessment of RA patients has been reported to be of 24 weeks, while the rate of patients seen during the so-called "window of opportunity" was extremely variable (8–42% of patients) (27). In our population, only 20% started a treatment with DMARD within the first 90 days from the onset of symptoms, consistently with a recent large work about delay in the UK (28). Despite being in line with data concerning the delay in Europe, the diagnostic delay in our population continues to be

far longer than expected in light of the importance of an early diagnosis in patients with RA (6, 29).

One of the main aims of this work was to assess the adherence of Italian rheumatologists to the 2013 EULAR recommendations (12): this first work allowed us to evaluate the adherence to the first 7 recommendations. The first recommendation suggests starting treatment with DMARDs as soon as the diagnosis is made. In our population, the time elapsed between diagnosis and DMARD prescription had a median of 0 (IQR 0-2) days and, once the diagnosis was confirmed, a therapy was immediately started in 74.1% of the cases.

The second recommendation suggests that therapeutic decisions should be directed in order to achieve a pre-determined target of disease activity (12). A target of DAS28 remission was chosen for about 64% of patients, in the remaining cases a target of low disease activity was preferred. This recommendation would also suggest aiming at remission in all patients and settling for a low disease activity only for those patients who cannot reach this target or for those with a long-standing disease. Since the population enrolled in this study was DMARD-naïve, it would have been more appropriate to select a target of remission for most cases, limiting the choice of a less stringent target to well selected patients and to those with contraindications to a step-up therapeutic approach. Moreover, the DAS28 is known to be a non-stringent parameter to define clinical remission (5, 30-32). However, physicians involved in this study claimed that the decision regarding the target was shared with patients almost every time (98.2% of cases), in line with the overarching principles of the recommendations.

The third recommendation suggests that the timing of control visits should be chosen based on disease activity and a follow up should not exceed 3 months in case of activity. Furthermore, the update of the EULAR recommendations encourages assessing patients with a high disease activity on a monthly basis (13). In our population, the timing with which follow-up visits were rescheduled were not related to the DAS28 disease activity differently from what the recommendation suggests: in 7.4% of patients in DAS28 high disease activity and in 8.4% of patients in DAS28 moderate disease activity the control visit was more than 3 months apart. Therefore, finding strategies aimed at optimising follow-up visits for patients in high and moderate disease activity could be useful in order to ensure control visits in a more appropriate time (33, 34).

The 2013 recommendations suggest that MTX should be part of the first therapeutic approach for patients with an active disease, underlining the possibility of using both monotherapy and combined therapy in DMARD-naïve patients. While in the 2013 recommendations the task force members decided to quote the combined therapy as an appropriate choice based on the evidence supporting that a combination of DMARDs may be superior to MTX monotherapy (35, 36), in the more recently published recommendations (37) this has not been confirmed, based on a systematic literature review (38). In our population, 84.9% of patients were treated with MTX both in monotherapy and in combined therapy, confirming MTX as the first choice for RA patients. In most cases the drug was prescribed as a monotherapy: this could depend on the fact than Italian rheumatologists can start a biologic treatment after the failure of a single DMARD or based on the evidence of a higher risk of toxicity during a combined DMARDs therapy (39, 40). Many countries tend to prefer an oral administration of MTX (41, 42) while in our population a subcutaneous route was selected in 94.3% of patients, in line with the evidence that a parenteral administration is more effective and better tolerated (43, 44).

In case of contraindication or early intolerance to MTX, recommendations suggest that another DMARD should be considered, in particular SSZ or LEF. HCQ is usually used in combined therapies or in case of very mild disease (45, 46). In the previous recommendations there were specific references to other DMARDs, such as CYA, azathioprine or cyclophosphamide but they were unanimously removed due to the lack of data supporting their actual efficacy, so the pool of experts suggested that their use should be limited to rare and very select cases. In our population, 22 patients had a contraindication to MTX: most of these patients were treated with HCQ, SSZ or LEF, no patient was treated with azathioprine or cyclophosphamide and a treatment with CYA in mono or combined therapy was chosen in 2 cases. HCQ prescription was not reserved only to patients with a mild disease activity, but it was also prescribed in case of active disease, mostly combined with GCs. The use of HCQ is probably related to its safety and practicality (47, 48).

The 2013 update of the EULAR recommendations concerning the use of GCs referred exclusively to an oral administration at low dosage (up to 7.5 mg/day), suggesting that GCs should be taken into account as part of an initial strategy for the treatment of RA (49-51). In our population, 69% of patients were treated with GCs, in line with data from international cohorts (52). The most prescribed dosage was up to 5 mg/day but 24.1% of patients took more than 7.5 mg/day at the beginning of the treatment.

This study has some limitations. Adherence of Italian rheumatologists was checked by using the recommendations available when the study was planned. As a matter of fact, a new set of recommendations was published in 2017 (13) and 2020 (37). However, the main recommendations remained unchanged, in particular as for MTX use, application of the treat-to-target strategy and use of glucocorticoid at the very beginning of the disease. The number of patients included in the study is limited and we have no data regarding the total amount of subjects evaluated in the same period who did not meet the inclusion criteria. Despite the limited sample size, the study provides information collected from large University Hospitals and smaller Rheumatology centres, thus offering a representative and unbiased picture of the general attitude in Italy. The data presented in this paper refer to baseline; additional aims for a following paper will include the evaluation of the adherence to a treat to target strategy,

the rate of patients starting a biologic treatment and the type of biologic drug prescribed after failure of conventional DMARDs, the assessment of the rate of patients achieving the selected target at 12 months and the rate of patients who do not start a biologic treatment despite failure to reach the target, the evaluation of the influence of different clinical settings on the treatment and the frequency of adverse events during treatment with conventional DMARDs. Another important analysis will focus on the determinants of the diagnostic delay and its impact on the clinical outcome.

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