STEp-down approach in MEthotrexate use for the Treatment of Rheumatoid Arthritis (STEMETRA): a pilot study demonstrating efficacy and safety of short-term, high dose methotrexate

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Abstract

Objective

Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment, showing a suitable efficacy-safety profile, relatively low-cost, and versatile dosages and routes of administration. However, there are no clear indications yet on the optimal use of MTX in RA, whereas existing recommendations disagree on relevant aspects. STEMETRA is a 16-week open-label, monocentric, pilot study aimed at evaluating the efficacy and the safety of a step-down strategy of using subcutaneous (sc) MTX in patients with RA.

Methods

The study consists of the administration of a starting dose of MTX 50 mg sc/week for 4 weeks, to be subsequently reduced to 15 mg/week in a 12-week period. Fifteen RA patients naive to any disease specific therapy were enrolled.

Results

One patient was lost to follow-up after week 12, 4 patients withdrew because of adverse events, therefore, 10 patients concluded the study. Mean DAS28(CRP) at baseline was 5.6 (±0.37 SE), whereas, at week 16, mean DAS28(CRP) was 1.6 (±0.41SE). Most patients who concluded the study achieved ACR70 response and remission (7 out of 10), whereas three still showed moderate disease activity.

Conclusion

In this study, the step-down MTX approach was effective in inducing remission in most of the patients enrolled, without increasing the risk of adverse events. Thus, short-term higher dosages of MTX could be more effective in reaching remission earlier. Nonetheless, these results should be confirmed in larger populations of patients.

Key words

rheumatoid arthritis, disease activity, remission, safety, step-down approach

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Received on September 4, 2023; accepted in revised form on December 2, 2024

Competing interests: none declared.

Introduction

Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment, showing a suitable efficacy-safety profile, relatively low-cost, and versatile dosages and routes of administration. However, there are no clear indications yet as to the optimal use of this drug in RA, whereas existing recommendations disagree on important aspects (*e.g.* route, starting and maximal dose, titration increase/decrease, and intervals to monitor toxicity) (1). Even if some systematic reviews published in the past years support a higher starting dosage and subcutaneous (sc) route over oral (OR) administration, especially for doses above 15 mg/weekly, standardised studies on efficacy and safety based on dose and route administration are still lacking, thus leading to a need for recommendations for a specific approach to follow (2-4). Moreover, suboptimal use of MTX in the early phases of the disease has been reported as an early predictive feature of difficult-to-treat RA (5). Therefore, clear indications on the best approach to use MTX are urgently needed to optimise the management of RA patients and ensure better outcomes. STEMETRA is a 16-week single arm, non-controlled, open-label, prospective, monocentric, observational pilot study aimed at evaluating as proof of concept the efficacy and safety of a step-down strategy of using MTX sc in patients with RA.

Methods

Fifteen patients diagnosed with RA according to the 2010 ACR/EULAR classification criteria and naive to any disease specific therapy were enrolled. The only baseline therapy was corticosteroids. Among the 15 patients enrolled in the study, 13 subjects had early RA (mean disease onset 6.01±3.06 months), while 2 patients had long-standing disease. The protocol treatment schedule consisted of the administration of MTX 50 mg sc/week for four consecutive weeks, followed by 25 mg/week for four weeks, and then 15 mg/week for eight weeks. All patients received oral supplementation of folinic acid (leucovorin) 12 mg, 12 hours after the injection of MTX. The study was approved by the Local Ethics Committee (May 5th 2016, Liguria Regional Ethics Committee register number 217REG2015). Demographic and clinic characteristics were collected at baseline. The patients were then evaluated at weeks 2, 4, 8, 12, and 16 for clinic and laboratory data collection. At each time point, a complete joint count was performed and patient-reported outcomes (PROs), Visual Analogue Scale (VAS) pain, Global Health (GH), Health Assessment Questionnaire (HAQ) were collected. In addition, at every assessment, disease activity scores [DAS28(ESR), DAS28(CRP)], clinical disease activity index (CDAI) and simplified disease activity index (SDAI) were calculated; full blood count, transaminases, acute phase reactants, creatinine, urinalysis were tested as well and information on related adverse events (AEs) was reported. Finally, a descriptive statistical analysis was performed.

Results

Fifteen RA patients (10 females and 5 males; mean age, 60 years (±2.76SE) were enrolled in the study. The demographic and disease characteristics at baseline are reported in Table I. At baseline, 53.3% patients were on therapy with glucocorticoids (GCs) before the the introduction of MTX (mean 4.4±2.4 mg prednisone equivalent a day). One out of 15 patients was lost to follow-up after week 12; 4 patients withdrew because of AEs; therefore, 10 out of the 15 enrolled patients concluded the study. A total of 14 AEs occurred in 7 patients; nobody of them developed serious AEs: 7 were of mild entity and tolerated by the patients, 8 resolved, whereas 6 persisted; 4 of them led to drug withdrawal (Table II). Gastrointestinal reactions were the most frequent, followed by urinary tract infections. Most of the AEs (10 out of 14) developed within the first 4 weeks of treatment. Mean DAS28(CRP) at baseline was 5.6 (±0.37SE), whereas, at week 16, mean DAS28(CRP) was 1.6(±0.41SE) (Fig. 1). Most patients who concluded the study achieved ACR70 response and remission (7 out of 10) (Fig. 2), whereas 3 still showed moderate disease activity. Among the 7

Table I. Demographic and disease characteristics at baseline.

Patients (n)	15
Age (mean ±SD; median)	60± 11; 63
F (n;%)	10
RF positive (n;%); aCCP positive (n;%)	9;8
BMI	25.8± 3.4; 25.1
Smoke	1
Alcohol	7
Early RA (n;%)	13 (86)
Long-standing RA (n, %)	2 (14)
Comorbidities	4
CVD	1
Dysthyroidism	2
COPD	1
Gastric ulcer	1
Previous GC use	8
Prednisone equivalent dose at baseline (mean ±SD; median) (mg)	4.4± 2.4;5
NSAID use	7
HAQ	1.5± 0.8;1.4
DAS28(ESR)	5.5± 1.1;5.6
DAS28(CRP)	5.6± 1.4; 5.2
SDAI	32.5± 14.2;31.6
CDAI	29.8± 12.3;29.5
ESR (mm/h)	40.4± 27.5;30
CRP (mg/L)	26.6± 12;34.3
TJC	9.6± 5.6;8.5
SJC	7.3± 5;7
VAS pain	35.2± 33.1;20
GH pt	6.3± 2.4;7
GH ph	6.8± 1.6;7
AST	19± 6;17
ALT	21± 13;14
gGT	31± 20;25
RBC	4.53± 0.47;4.50
WBC	8.97± 2.55;9.03
PLT	345± 109;349

patients in remission, 5 had maintained an average steroid dose comparable to the initial dose (mean 4.4±2.4 mg prednisone equivalent per day), while 2 patients were not taking prednisone; in addition, none of these patients required an increase in steroid dosage due to disease flares during follow-up.

Discussion

In this study, the step-down MTX approach was demonstrated to be effective and safe. According to data reported in other studies, one-third of patients showed AEs, causing withdrawal of the drug. (6, 7) Although half of the patients enrolled experienced at least one collateral effect from the drug, previous systematic reviews reported a similar percentage (49.8–72.9%) in patients using a lower dosage of MTX (8, 9). Most of the AEs that appeared within the first 4 weeks of treatment were mild and completely resolved in half of the cases. Interestingly, the increase in transaminase levels was reported only in one patient and resolved within week 8. So, overall, MTX seems to show the same incidence of adverse reactions even when used at higher doses for a short period of time. (10). It

Table II. Adverse events reported during treatment.

Adverse event	n (%)	Grade	Week of appearance	Solved	Withdrawal
Headache	1 (6.6)	Mild	4	Yes	No
Cutaneous local reaction	1 (6.6)	Mild	4	Yes	No
Nausea	2 (13.3)	Mild	4	Yes	No
Diarrhoea	1 (6.6)	Moderate	8	No	Yes
Lack of appetite	1 (6.6)	Mild	8	No	No
Dizziness	1 (6.6)	Moderate	12	No	Yes
Fatigue	2 (13.3)	Mild	16	No	No
Urinary tract infection	4 (24)	Moderate	4	Yes	No
			4	Yes	No
			12	No	Yes
			12	No	Yes
Increased transaminases	1 (6.6)	Moderate	2	Yes	No

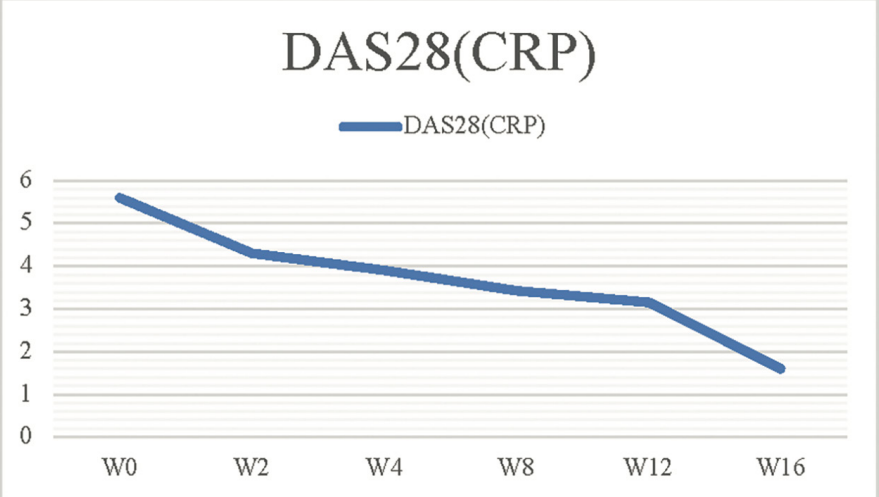

Fig. 1. DAS28(CRP) changes from baseline to week 16.

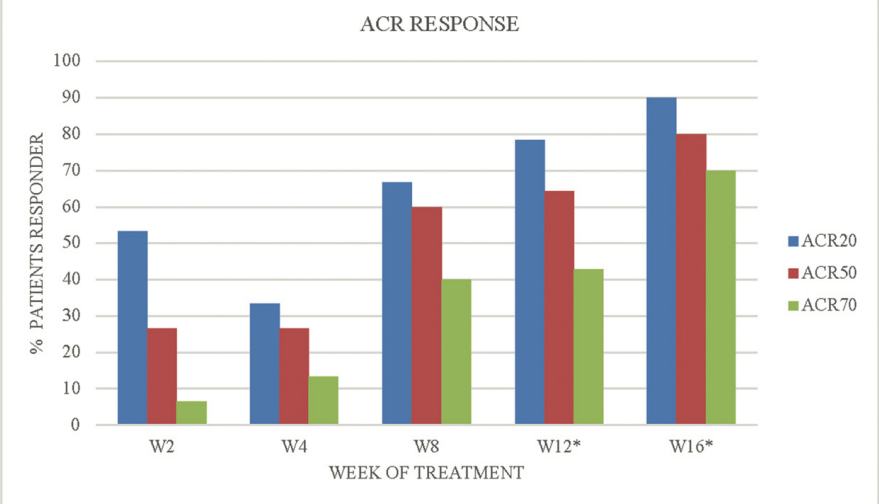

Fig. 2. ACR response across weeks of observation.
*W12: total patients: 14. *W16: total patients: 10 patients.

must be specified that these data from other researches consider the time period much longer than our follow-up, however, numerous AEs in patients receiving MTX can be detected already within the first 4 weeks of treatment (*e.g.* leukopenia, respiratory side effects) (11). In addition, according to the literature, the incidence of gastrointestinal side effects ranges from 20% to 65% and they seem to occur irrespective of treatment duration (12). Moreover, our study explored the effects of an initially higher dosage of MTX (50 mg sc/week), administered for a period of 4 weeks, followed by a reduction to more standard therapeutic doses (particularly after 8 weeks). Therefore, the rates of side effects observed after the initial weeks of higher MTX doses are likely to align with those reported in the literature.

In addition, the STEMETRA approach was highly effective in inducing remission in most of the patients enrolled, since 70% of patients who concluded the study reached ACR70 response and remission within only 16 weeks of treatment. A recent review highlights that in a subgroup of patients with early rheumatoid arthritis (RA), intensive strategy approaches, such as oral methotrexate (MTX) starting at 7.5 mg/week with an increase of 5 mg/month, resulted in a significantly higher sustained remission rate and a shorter mean time to sustained remission after 1 and 2 years. Additionally, there was an improvement in clinical disease activity parameters within the first year, compared to the conventional approach (13). On the contrary, different studies in which MTX was used in current clinical practice at lower dosages showed lower efficacy and more time was needed in order to reach the target. Additionally, the concept of "high-dosage methotrexate" is in line with the presence of a time-limited window of opportunity, which is a period in which the disease is more susceptible to disease-modifying treatment. In particular, patients who receive treatment within 3 months of symptom onset, often referred to as 'early' treatment, tend to have more favourable outcomes compared to those treated later. Studies have shown that aggressive therapy administered during this early window can significantly slow the progression of long-term structural damage (14). In the ORAL START study, considering long-standing RA (mean duration of RA 2.7 years), in the arm taking MTX monotherapy, only 12% of RA patients naive to therapy obtained ACR70 response after 6 months, whereas in the PREMIER study, only 26% of those receiving MTX monotherapy achieved ACR70 response after one year (15, 16). The effectiveness of a step-up approach MTX monotherapy was investigated in a study using data from the DREAM registry, which reported remission in 70% of patients in a mean time of 27 weeks (17) Thus, short-term higher dose with a step-down approach *of* MTX usage could be more effective to reach remission earlier. Furthermore, most studies published in which MTX was used at high dosages predominantly considered oral administration. As shown by pharmacokinetic studies, at the same dosage level, the bioavailability of sc MTX is significantly higher and less variable than that of oral route MTX. This is due to the fact that MTX OR is absorbed by the small gut through an active transport mechanism with a bioavailability ranging from 30% to 70% and which plateaus for doses >15 mg, suggesting an absorption limitation (18). Once MTX is in the cell, it is gradually and progressively polyglutamated. Longer-chain polyglutamates take 3–8 weeks to become detectable in erythrocytes, whereas polyglutamation reaches steady-state levels in a median time of 28 weeks. However, there is some variability between patients due to different polyglutamation rates that depend on age, renal function and MTX dose. Higher intracellular polyglutamated MTX (MTXGlun) levels seem to be associated with better clinical response. A recent study suggests that a loading dose regimen of methotrexate, consisting of a weekly subcutaneous injection of 50 mg followed by a weekly oral dose of 20 mg, showed improved simulated clinical outcomes compared to the standard oral dosing regimen (19).

Subcutaneous administration is associated with higher bioavailability of MTX as well as with a significant increase in long-chain MTXGlun when compared to the oral route. Actually, randomised, double-blind studies and retrospective or longitudinal analyses in real-life settings showed that MTX sc is more effective and tolerated than MTX OR (15). Since MTX dose is one of the major determinants of MTXGlun concentrations, using higher dosages of MTX SC seems to be a good strategy to reach earlier maximal benefits from the drug (21). Meta-regression analysis of studies using higher initial MTX dosage (20–30 mg/week) did not support better effectiveness of increasing the MTX dose (22). However, these studies were heterogeneous, with most of them considering OR administration and this can be a source of bias if considered the reduced bioavailability of MTX OR dosages superior to 15 mg/week (23). Moreover, starting with higher oral doses may also result in discontinuation due to AEs, such as nausea. To our knowledge, this is the first study that confirms the effectiveness and tolerability of MTX sc even when used at higher dosage in RA patients. According to the treat to target (T2T) strategy in RA, remission or LDA should be reached in the shortest possible time, optimally within the first 3–6 months, in order to avoid progression of the disease, radiographic damage and refractoriness to therapies. The TEAR study has demonstrated that remission is a reachable target in patients with early RA treated with MTX monotherapy (24). A T2Tstrategy with MTX in patients with early RA effectively decreased synovitis, osteitis, and tenosynovitis and prevented structural damage progression (25). However, MTX is still often used suboptimally in RA patients. In the MARI study, our group demonstrated that the weekly dose of MTX prescribed for the treatment of RA is suboptimal, even in conditions of inadequate control of the disease activity (52.9% of the patients still present an active form) (26). Of note, low-dose MTX use in the early phases of the disease is an early predictive feature of difficult-to-treat RA (5, 27). This last condition has a huge

impact in terms of human, social, and economic costs. Therapeutic decisions should also consider cost-effectiveness aspects. Early MTX monotherapy is more cost-effective than the early combination of MTX with bDMARDs or Jak-inhibitors. Of note, early MTX strategy has been estimated at less than $5,000/quality-adjusted life year (QALY), whereas bDMARDs and JAK-inhibitors usage ranges from ~$126,000 to $140,000 per QALY (28, 29). Further advantage (5536 US$) is obtained when switching to MTX sc in case of failure of MTX OR instead of adding bDMARD (30). In the present study we demonstrated that higher MTX sc dosages could reach better results faster than those reported in other studies using the combination with adalimumab (ADA) or tofacitinib (TOFA). In the PREMIER study, after one-year therapy, 46% of early RA patients receiving ADA in combination with MTX reached ACR70 response, while in the ORAL Standard study, a maximum of 20% of patients with inadequate response to MTX were able to reach ACR70 response after 6 months following the addition of TOFA or ADA (15, 31). In contrast, 70% of patients who concluded our study achieved ACR70 response in 16 weeks of treatment. Thus, short-term higher dose MTX usage could be a more effective and cost-saving way to reach remission earlier.

Regarding the concomitant use of GCs, it was not possible to compare the groups of subjects based on the different steroid regimens. The statistical analysis would be underpowered due to the limited number of patients. However, all patients were at most on treatment with low dose GCs during the first three months (duration of follow-up in our study) according to the EULAR RA management recommendations. Further studies with longer follow-up could be useful to analyse steroid regimens in the step-down step-down MTX approach.

However, this study has some limitations. First of all, being a pilot study, only a small number of patients were enrolled; secondly, the period of observation was limited to 16 weeks, but the effects of the treatment will be evaluated also over a longer period; thirdly, the study lack of a comparator arm treated with MTX as in current clinical practice (lower initial dosages, oral administration). These limitations make it impossible to make a proper statistical analysis that could identify significant statistical differences that can support the approach proposed in the present study. Finally, this schedule cannot be run as it is, since in the presence of renal failure, hepatic steatosis, alcohol consumption, smoking, MTHFR polymorphisms, and Asian ethnicity, patients could be exposed to higher toxicity. Thus, in these specific conditions, lower dosages should be preferred.

Despite these limitations, the STEMETRA study represents a modern proof of concept in terms of tolerability, effectiveness, and cost-saving aspects of short-term high-dose MTX SC in patients with RA. Thus, this old drug attested once again its anchor-role in the treatment of RA, more and more when its use is optimised.

In conclusion, the results of this study should be confirmed in larger populations of patients with a comparator arm and longer period of observation; although not applicable in some categories of patients, the approach proposed in the STEMETRA study could be considered a valid regimen for a more optimal use of MTX.

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