Attainment of Minimal Disease Activity Using Methotrexate in Psoriatic Arthritis

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ABSTRACT. ***Objective.*** An international task force has recommended that disease remission or minimal disease activity (MDA) be the target of treatment for psoriatic arthritis (PsA) and that remission or MDA should be attained within 6 months of initiating medication. The aim of this study was to establish the proportion of patients with PsA who achieve MDA after 6 months of methotrexate (MTX) treatment.

Methods. Patients who initiated MTX and were naive to biologics between 2004 and 2014 were included. The primary outcome was the achievement of MDA after 6 months of MTX, defined as the presence of at least 5 out of the following 7: tender joint count ≤ 1, swollen joint count (SJC) ≤ 1, Psoriasis Area Severity Index (PASI) ≤ 1 or body surface area ≤ 3%, tender entheseal points ≤ 1, Health Assessment Questionnaire score ≤ 0.5, patient global disease activity visual analog scale (VAS) score ≤ 20, and patient pain VAS ≤ 15. Of 204 patients identified, 167 were treated with MTX for at least 3 months and had sufficient data for analysis at 6 months.

Results. At 6 months, 29 patients (17.4%) achieved MDA; 97 patients (58.1%) achieved an SJC ≤ 1 and 138 (82.6%) a PASI ≤ 1. Only 22 (13.2%) achieved the patient global disease activity criterion. Lower back pain and dactylitis were associated with a lower probability of achieving MDA.

Conclusion. MTX use achieves MDA by 6 months in < 20% of patients. This compares unfavorably with data for tumor necrosis factor inhibitor use. (First Release July 15 2016; J Rheumatol 2016;43:1718–23; doi:10.3899/jrheum.160111)

Key Indexing Terms:
PSORIATIC ARTHRITIS METHOTREXATE DISEASE ACTIVITY REMISSION

The preservation of health, employment, and functional capacity is the goal of modern treatment for inflammatory arthritis. The principles of the treat-to-target strategies developed and tested in rheumatoid arthritis (RA)[1,2] are now being applied to other rheumatic diseases, including systemic lupus erythematosus[3] and spondyloarthritis[4]. An international task force has published recommendations for treating ankylosing spondylitis and psoriatic arthritis (PsA) to target[4]. Disease remission was recommended as the preferred target, while a state of minimal disease activity, or MDA, achieved by 6 months was also deemed acceptable.

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Methotrexate (MTX) is the first-line medication used to treat PsA; however, randomized controlled trials examining the efficacy of MTX have failed to provide adequate evidence for a disease-modifying effect because the studies have either been underpowered or have used dosages considered suboptimal[5,6,7]. With the advent of efficacious biological therapies that inhibit tumor necrosis factor-α (TNFi) and disease progression[8,9,10], there is a need to establish definitively whether MTX is at least equivalent to the TNFi in preventing radiographic progression and associated deformity and disability. Further incentive to address this deficit in knowledge surrounding MTX arises from the notable risk of infection associated with TNFi use[11] and the high cost associated with their prescription[12,13].

The objective of our study was to establish the proportion of patients with PsA taking MTX who achieve MDA after 6 months of use.

MATERIALS AND METHODS

Since 1978, the University of Toronto Psoriatic Arthritis Clinic has prospectively collected clinical, radiographic, and laboratory data on patients with PsA[14,15]. Patients are followed according to a standard protocol and all data are collected on an Oracle database. Patients were eligible for inclusion in this study if MTX was commenced for the first time between January 2004 and April 2014. Patients were also eligible for inclusion even if they used other disease-modifying antirheumatic drugs (DMARD), such as leflunomide (LEF) or sulfasalazine. Patients with a history of TNFi or other biological use were excluded.

Of 1306 patients enrolled in the clinic up to April 2014, 1107 commenced a new medication on or after the first clinic visit. Of those, 525

patients initiated MTX on or after the baseline visit, while 219 initiated MTX for the first time after January 1, 2004. Of the 219, 15 patients had been prescribed biological medication at or before initiating MTX and were thus ineligible for inclusion, leaving 204 patients.

Patient assessments. At each visit, a detailed clinical history (including detailed medication history), physical examination, (including general and musculoskeletal examination), and laboratory evaluation (including erythrocyte sedimentation rate and/or C-reactive protein) are carried out. Radiographic assessments, including hands, feet, spine, and pelvic radiographs are performed at 2-year intervals. Axial involvement is defined by the presence of at least unilateral grade 2 sacroiliitis[16,17].

MDA outcome. The primary outcome was MDA at 6 months. The definition of MDA was detailed by Coates, *et al*, and developed by 60 experts in PsA[18,19]. The presence of at least 5 out of the following 7 domains are necessary to declare MDA present: tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, Psoriasis Area Severity Index (PASI) ≤ 1 or body surface area (BSA) ≤ 3%, tender entheseal points ≤ 1, Health Assessment Questionnaire (HAQ) score ≤ 0.5, patient global disease activity visual analog scale (VAS) score ≤ 20, and patient pain VAS ≤ 15.

All patients provided written informed consent at time of enrollment in the longitudinal clinic study. The study had approval from the University Health Network Research Ethics Board committee.

Statistical analysis. Descriptive statistics were used to evaluate the demographic and disease characteristics of the patients included in the study. A multivariate logistic regression analysis with backward elimination was used to identify variables independently predictive of achieving MDA. Time-dependent covariates were examined using a Cox regression analysis to assess their association with time to MDA. Significance was attached to a p value of < 0.05.

RESULTS

Of the 204 patients eligible for study inclusion, 29 (14.2%) stopped and re-started MTX frequently or took MTX an insufficient length of time (< 3 mos) to allow accurate analysis of its effect on MDA, resulting in their exclusion, leaving 175 patients. Data allowing calculation of MDA were available on 167 of these patients at 6 months (81.9% of the original 204 patients eligible for study inclusion; 95% of the 175 with MTX exposure for at least 3 mos), on 124 patients at 12 months, and 107 patients at 24 months. These descending numbers were reflective of data relating to MDA at available clinic visits and/or a decline in drug survival with time.

The disease and demographic characteristics of the 204 patients eligible for inclusion in the study are shown in Table 1. The mean swollen joint count for the group was 6.0 (7.4) while the average BSA affected was about 9%. Just over half of the study group was taking nonsteroidal antiinflammatory drugs (NSAID) at the time of MTX initiation and a small percentage was prescribed concomitant LEF.

Oral MTX was prescribed for 158 (77.5% of the 204 eligible) of the patients, with the remainder taking parenteral MTX in the form of subcutaneous or intramuscular injections.

Attainment of MDA at 6 months. Twenty-nine of the 167 patients (17.4%) who had exposure to MTX for at least 3 months (and had data available to determine MDA status) achieved MDA 6 months after commencing MTX (Table 2). Of these patients, if those who were already in MDA when treatment with MTX was initiated are excluded, only 22 (14.1% of 156 patients) achieved MDA 6 months after commencing MTX.

Table 1. Demographic and disease characteristics at the start of methotrexate use (n = 204). Data are mean (SD) unless otherwise indicated.

Variables	Values
Sex, male, n (%)	110 (53.9)
Age, yrs	47.1 (13.5)
Duration of psoriasis, yrs	17.0 (13.2)
Duration of PsA, yrs	6.2 (8.0)
Smoking status, n (%)	
None	128 (63.7)
Current	28 (13.9)
Past	45 (22.3)
PASI	5.5 (8.0)
BSA, % affected	9.1 (14.2)
ESR, mm/h	19.1 (18.5)
CRP, mg/l	14.6 (22.3)
Tender joint count	10.2 (10.7)
Swollen joint count	6.0 (7.4)
Body mass index, kg/m^2	30.5 (6.9)
Dactylitis, n (%)	53 (26.1)
Enthesitis, n (%)	48 (23.5)
NSAID, n (%)	106 (52.0)
Leflunomide, n (%)	9 (4.4)
PGA (out of 10)	2.6 (0.9)
PtGA*	2.5 (0.9)
Patient pain score*	5.3 (2.4)
HAQ	0.8 (0.7)
CASPAR criteria, n (%)	204 (100)

*These were scored out of 10 and transformed into their centile equivalent for the purposes of MDA calculation. MDA: minimal disease activity; PsA: psoriatic arthritis; PASI: Psoriasis Area Severity Index; BSA: body surface area; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drugs; HAQ: Health Assessment Questionnaire; CASPAR: Classification of Psoriatic Arthritis criteria; PGA: physician's global assessment; PtGA: patient's global assessment.

Among the 29 patients who achieved MDA, of the individual component targets that characterize MDA, 58.1% achieved the target SJC, 41.3% the TJC, 82.6% the target psoriasis measure, and 90.4% the target entheseal count. There were smaller percentages of patients achieving the patient-report outcome (PRO) measures of MDA, with < 17% achieving adequate analgesic effect and 13.2% the global disease activity target.

The average dose of MTX did not differ between those who did and did not attain the MDA target by 6 months, at 17.8 (4.2) and 17.3 (3.9) mg/week, respectively ($p > 0.05$).

Discontinuation of MTX. Of the 175 patients with sufficient data for analysis, 65 patients discontinued MTX at some point during the followup period (between 2004 and 2014). Sixteen (24.2% of the 65 patients) did so owing to lack of efficacy, 31.8% because of side effects, and 15.2% because of patient preference. Of those stopping MTX as a result of side effects, the majority did so because of intolerable nausea and/or vomiting (35.7%) or hepatic enzyme derangement

Table 2. Disease variables and the proportion of patients achieving the individual component targets of MDA at 6 months (n = 167). Data are frequency (%) unless otherwise indicated.

Variables	Values
ESR, mm/h, mean (SD)	15.8 (16.5)
CRP, mg/l, mean (SD)	8.9 (9.5)
PASI, mean (SD)	3.5 (5.6)
BSA, % affected	7.3 (14.3)
TJC, mean (SD)	8.0 (8.9)
SJC, mean (SD)	4.4 (6.4)
Dactylitis	25 (15.2)
Enthesitis	11 (6.6)
PGA, out of 10, mean (SD)	2.2 (0.9)
PtGA*, mean (SD)	2.4 (0.9)
Patient pain score*, mean (SD)	4.0 (2.5)
HAQ, mean (SD)	0.6 (0.6)
MDA, mean (SD)	29 (17.4)
Tender joint count ≤ 1	69 (41.3)
Swollen joint count ≤ 1	97 (58.1)
PASI score ≤ 1 / BSA ≤ 3%	138 (82.6)
Tender entheseal points ≤ 1	151 (90.4)
Patient pain score ≤ 15	28 (16.8)
Patient global disease activity ≤ 20	22 (13.2)
HAQ score ≤ 0.5	20 (12.0)

*These were scored out of 10 and transformed into their centile equivalent for the purposes of MDA calculation. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PASI: Psoriasis Area Severity Index; BSA: body surface area; HAQ: Health Assessment Questionnaire; MDA: minimal disease activity; TJC: tender joint count; SJC: swollen joint count; PGA: physician's global assessment; PtGA: patient's global assessment.

(19%). Mean (SD) MTX drug survival was 3.1 years (2.8), with a minimum of 0.04 and a maximum of 9.9 years.

Predictors of achieving MDA with MTX. Of 204 patients, 13 were in MDA at the start of MTX use, while 107 (52.5%) achieved MDA at some point during a followup clinic visit. The mean time to achieving MDA was 1.4 years (1.3; minimum time = 0; maximum time = 5.6 yrs). Excluding those in MDA at the time of commencing MTX, 14.1% (22 out of 156 patients) achieved MDA at 6 months, while 25.6% of 117 patients did so at 12 months, and 31% of 100 patients after 24 months of MTX therapy.

Analysis of fixed and time-dependent covariates using regression analysis revealed that the presence of inflammatory and mechanical back pain, as well as dactylitis, were independently associated with a lower probability of achieving MDA, where MDA was the outcome variable of interest (Table 3).

DISCUSSION

This analysis of an observational cohort of patients with PsA examined the frequency of achieving the target of MDA by 6 months following initiation of MTX. While over half of the patients attained a state of MDA at some point during followup, < 18% of patients reached the prespecified target by 6 months with a mean dose of 17.8 mg per week, which was a similar dose to those who did not achieve MDA. The physician-dependent components of the MDA outcome measure (TJC, SJC, PASI, and enthesitis scores) were achieved by a greater proportion of patients than the patient-reported outcome (PRO) measures (pain score, functional assessment and global disease activity). Regression analysis revealed that inflammatory and/or mechanical back pain and dactylitis were associated with a lower probability of achieving MDA. This is of interest because those particular outcomes are captured by the PRO and not by the physician's assessment in the application of the composite MDA tool.

Psoriatic disease is a heterogeneous disease affecting multiple aspects of the musculoskeletal and cutaneous systems, including the peripheral joints, the axial skeleton, entheseal attachments, skin, and nails. Measures of disease activity used in other rheumatic diseases, particularly RA, do not capture psoriatic disease activity holistically. This has led to the development of consensus on 6 core domains respective of PsA activity (peripheral joint activity, cutaneous activity, and 4 PRO: global health, pain, physical function and health-related quality of life) along with consideration given to enthesitis, dactylitis, axial disease, fatigue, physician global, radiographic change, and acute-phase reactants, as part of the OMERACT (Outcome Measures in Rheumatology Clinical Trials) agenda[20].

The ultimate goal of treatment in PsA is disease remission, which has been defined by an international task force as "the absence of clinical and laboratory evidence of significant inflammatory disease activity," with MDA or "low disease activity" an acceptable alternative treatment target, to be achieved by 6 months[4]. MDA criteria were developed by the Group for Research in Psoriasis and Psoriatic Arthritis (GRAPPA)[18] and have been used as an outcome measure in a number of studies[19,21,22,23]. Data analyzed from our PsA cohort suggested that sustained MDA for a period of at least 12 months was associated with a significant reduction in clinically assessed joint damage progression[21].

This is the first study, to our knowledge, that has applied the MDA composite measure to assess MTX response after 6 months of treatment. After 3 months of treatment with MTX, Coates and Helliwell reported that MDA was achieved by 22.4% of patients in an open-label study from the TICOPA (Tight Control of Psoriatic Arthritis) trial[24]. Our results are somewhat disappointing and compare unfavorably with previously published work pertaining to achievement of MDA with TNFi. Coates and Helliwell applied the MDA criteria to clinical trial data from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT)[25] and the Infliximab Multinational Psoriatic Arthritis Controlled Trial 2 (IMPACT 2)[19,26]. Patients in the IMPACT study had all failed at least 1 DMARD, while a subset of patients included in IMPACT 2 had never taken DMARD. Based on their analysis, the authors reported that MDA was achieved at

Table 3. Time-dependent analyses (Cox regression analysis for time to MDA); n = 204. Baseline = start of MTX treatment.

Multivariate Model Covariates	HR	95% CI	p	Reduced Model HR	95% CI	p
Fixed covariates						
Sex, males vs females	1.16	(0.94, 1.43)	0.18	—	—	—
Duration of psoriasis at start of MTX, 1-yr increase	1.01	(0.997, 1.01)	0.20	—	—	—
Duration of PsA at start of MTX, 1-yr increase	0.99	(0.98, 1.01)	0.46	—	—	—
Sacroiliitis at start of MTX	1.07	(0.83, 1.39)	0.60	—	—	—
Time-dependent covariates starting from baseline						
ESR, 1-unit increase	0.997	(0.99, 1.01)	0.51	—	—	—
Nail disease, yes vs no	0.95	(0.78, 1.17)	0.64	—	—	—
Dactylitis, yes vs no	0.62	(0.40, 0.98)	0.04	0.62	(0.39, 0.97)	0.04
Clinically damaged joints, 1-unit increase	0.99	(0.98, 1.01)	0.23	—	—	—
BMI, 1-unit increase	0.99	(0.97, 1.01)	0.32	—	—	—
Inflammatory back pain, yes vs no	0.41	(0.25, 0.67)	0.004	0.40	(0.24, 0.65)	0.002
Mechanical back pain, yes vs no	0.52	(0.37, 0.73)	0.0002	0.51	(0.36, 0.71)	< 0.0001

MDA: minimal disease activity; MTX: methotrexate; PsA: psoriatic arthritis; ESR: erythrocyte sedimentation rate; BMI: body mass index.

6 months by 52% (44 of 77 patients) of those receiving infliximab in the IMPACT 2 trial (compared with 21% on placebo), and by 48% (15 of 31 patients) at Week 16 in the IMPACT study (vs 3% on placebo)[19]. Mease and colleagues[27] retrospectively applied the MDA criteria to data from the ADalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), which included patients with an inadequate response to NSAID, while those taking MTX were allowed to continue the medication for the duration of the trial[28]. Of 62 patients with relevant data available at 6 months, 39% achieved MDA, compared with 7% receiving placebo. Examination of the percentage of responders for the individual components of MDA in the adalimumab group revealed that almost 60% achieved the target PASI score, 32% the swollen joint count target, and 38.7% the tender joint target. Of note, 50% achieved the patient's global assessment (PtGA) target and 48.4% the pain target[27]. This compares with a low proportion of 13% and 17% achieving the PtGA and pain targets, respectively, in our study. Analysis of the Go-REVEAL trial of golimumab in PsA also demonstrated a significantly higher percentage of golimumab-treated patients achieving MDA compared to those treated with placebo. Moreover, better protection against radiographic progression was noted among patients who achieved MDA[29]. It has also been reported that biological medications are associated with a greater chance of achieving sustained MDA compared with DMARD therapy (RR 1.868, CI 1.197–2.913)[21].

In contrast, 2 uncontrolled, prospective studies from Naples, Italy, examined predictors of MDA at 3 months[22] and the effect of hepatic steatosis and carotid arterial plaque on achieving MDA at 12 and 24 months[23], after commencing TNFi. Iervolino, *et al* reported that only 16.2% (n = 22) of 136 patients starting TNFi achieved MDA at 3 months and that 20 of those 22 maintained MDA at 6 months[22], while Di Minno and colleagues found that 36% of patients (98 of 270 patients) achieved MDA after 12 months of taking TNFi[23]. These findings, although from prospective studies, differ markedly from the 39%, 52%, and 28% MDA response reported from the ADEPT, IMPACT 2, and GO-REVEAL analysis[19,27,29], respectively, but are similar to the results we report here, with 17.4% achieving MDA at 6 months and 25.6% of 117 patients attaining MDA by Month 12 of MTX treatment.

An explanation for the low rate of MDA achievement in our study comes from the results of the regression analysis. Back pain, either inflammatory or mechanical, and dactylitis were significantly associated with a lower probability of achieving MDA. Of note, the physician-dependent components of the MDA measure did not account for either of these variables. GRAPPA did not include axial disease as a core domain in the components of MDA because of the noted absence of a validated disease activity measure for axial involvement in PsA, and because the Bath Ankylosing Spondylitis Disease Activity Index in PsA does not correlate with the treating physician's assessment of disease activity[30]. It was decided that axial disease activity would be captured in the PRO variables of pain, global disease activity, and physical function (HAQ)[18]. In our study, the low rate of achievement of the target PRO measures (global assessment, pain score, and physical function) might have been reflective of active axial inflammation. Unlike the TNFi, MTX is not effective in treating spondylitis[31]. Therefore, back pain would remain untreated and patient symptoms would be captured in the relevant PRO measures. Further, adverse effects from MTX may also have been indirectly reported by patients through the global assessment component of the MDA measure, resulting in lower overall achievement of MDA.

The dose of MTX associated with best efficacy in treating PsA is unknown. The Methotrexate In Psoriatic Arthritis trial had a negative result using a target dose of 15 mg/week. While specific dose targets for MTX in PsA have not been offered by GRAPPA treatment recommendations[32], The

European League Against Rheumatism advises a weekly dosage between 15 mg and 25 mg[33]. However, bioavailability of the drug may plateau at ≥ 15 mg/week in the oral form[34], and optimization of clinical effect at higher doses might be best achieved by switching to parenteral MTX[35]. In our study, the mean doses for those who did and did not achieve MDA were similar at over 17 mg/week. The majority of patients in MDA (75.9%) at 6 months were receiving oral MTX at a mean dose of 17 mg/week, while the 24% receiving parenteral MTX were prescribed an average of almost 20 mg/week. Based on the available evidence from RA, it is plausible that a greater proportion might have achieved MDA by switching to parenteral MTX; however, parenteral MTX may lead to greater frequency of intolerable adverse effects[36], resulting in discontinuation.

The limitations of our study include the retrospective nature of the analysis. However, it should be noted that the information analyzed was collected prospectively according to a standard protocol, which includes detailed information about medications. Because our PsA cohort is from a quaternary-referral research center, a more severe disease phenotype may be more prevalent and not reflective of PsA seen in either primary or secondary care. Nonetheless, in our cohort we have a spectrum of patients from very mild to very severe disease[14,37]. While the study still offers insight into the real-world effect of MTX in PsA, it must be acknowledged that evidence gleaned from the gold standard of research studies, the randomized clinical trial, suggests that MTX is inferior to the TNFi in achieving MDA. Relevant data pertaining to 18% of the cohort eligible for inclusion were not available for analysis, which could have potentially skewed the results. Further, we were unable to determine the adherence of patients to their MTX regimen.

Based on this analysis of an observational cohort with PsA, MTX use results in MDA attainment in < 20% of patients after 6 months of treatment. Based on analysis of data from randomized controlled trials with TNFi intervention, MTX appears to be considerably less effective at producing a low disease activity state. Reasons for this relate to the disease response as measured by the individual components of the composite MDA outcome measure. In our study, physician-dependent measures (active joint count, enthesitis, PASI/BSA) showed a good response to MTX use by 6 months; however, the PRO of the MDA tool were achieved by a much lower proportion of patients. Adverse effects, such as gastrointestinal intolerance, back pain, and/or dactylitis are reasons for this, as suggested by the results from a regression analysis. While a randomized controlled trial of MTX in PsA that is adequately powered and dosed remains elusive, the accumulating evidence suggests that the TNFi should replace MTX as the best first-line agent in PsA, particularly in the context of the treat-to-target agenda and the potential for disability that results from delayed initiation of effective treatment.

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