CONCISE REPORT

Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥15 mg may be overcome with subcutaneous administration

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ABSTRACT
Objective To compare the relative bioavailability, safety and tolerability of oral methotrexate (MTX) and subcutaneous (SC) MTX administered via an auto-injector (MTXAI) in patients with rheumatoid arthritis (RA).
Methods In this randomised, multicenter, open-label, three-way crossover study, patients ≥18 years with adult RA undergoing treatment with MTX for ≥3 months were assigned to receive MTX 10, 15, 20 and 25 mg weekly in a random sequence of three treatments: oral, SC into the abdomen and SC into the thigh. For 24 h after administration of each treatment, blood samples were collected for pharmacokinetic analysis and injection sites were assessed.
Results Forty-seven patients completed the study. Systemic exposure of oral MTX plateaued at doses ≥15 mg/week. In contrast, SC MTX demonstrated a linear increase in systemic exposure that was greater than oral MTX at each dose. No unexpected AEs were noted for either formulation.
Conclusions Unlike oral MTX, the systemic exposure of SC MTX did not plateau over the doses studied, particularly at doses ≥15 mg/week. In this study, higher systemic MTX exposure was not associated with increases in AEs. Patients with an inadequate clinical response to oral MTX may benefit from higher drug exposure by switching to SC MTX.
Trial registration number NCT01618968.

INTRODUCTION

Methotrexate (MTX) is the disease-modifying antirheumatic drug of choice for rheumatoid arthritis (RA) worldwide.[1] [2] Gastrointestinal (GI) tract absorption limitations may compromise the bioavailability[3] of higher oral doses. Studies have shown that the bioavailability of oral MTX varies widely among patients and decreases with increasing dose.[4–6] The GI side effects of oral MTX, such as nausea and vomiting, also limit optimal use.[4] [5] [7] Doses greater than 15 mg/week are frequently used to control disease activity, but may be only partially effective in some patients and poorly tolerated by others. A previous study of oral and subcutaneous (SC) MTX in patients with RA suggested that limitations in systemic exposure of oral administration may affect efficacy. In that trial, clinical responses were significantly better in patients given SC MTX.[8]

In the current phase II study, the relative bioavailability of oral MTX and SC MTX delivered via an MTX auto-injector (MTXAI) recently approved by the US Food and Drug Administration[9] was explored in patients with RA.

METHODS
Patients

Patients with RA were ≥18 years of age and treated with MTX for ≥3 months. Concomitant medications had to be stable for ≥3 months. Women could not be pregnant or lactating. Patients with other serious medical conditions and those taking additional medications, including DMARDs, that could interfere with PK outcome measurements were excluded. Administration of non-steroidal anti-inflammatory drugs (NSAIDs) was not permitted within ±12 h of MTX administration.

Study design and treatments

This was an 8-week, open-label, randomised-sequence, three-way crossover study conducted at four clinical sites in the USA. The allocation sequence was created by Medpace using a Williams design to balance variance from potential carry-over effects. At the time of enrolment, investigators selected dose based on patient's then-current oral MTX regimen (10, 15, 20 or 25 mg weekly). Each patient received one dose of MTX via each of three routes: oral MTX (tablets), SC MTX into the abdomen and SC MTX into the thigh. Blood samples were obtained for pharmacokinetic (PK) analysis predose and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 4, 6, 8, 10, 12 and 24 h after dosing.

The study was conducted in accordance with the Declaration of Helsinki and was in compliance with Good Clinical Practice Guidelines. This trial is registered with clinicaltrials.gov (NCT01618968).

Objectives

The primary objectives were to compare the relative bioavailability of oral MTX with that of SC MTX using the MTXAI and to determine whether the two injection sites provided bioequivalent drug exposure. Secondary objectives were to compare the time of peak concentration (t_{max}), apparent terminal rate constant (λ_z) and terminal half-life ($t_{1/2}$) of MTX for the three methods of administration. PK

parameters were calculated with standard non-compartmental methods. Safety was evaluated for SC and oral MTX.

Pharmacokinetic evaluations

The PK population included patients with ≥1 postdose plasma MTX concentration value who did not have a major protocol deviation to affect data integrity. Plasma concentrations as determined by AUC from time 0 to the last measurable concentration (AUC_{0-t}), or extrapolating to infinity (AUC_{0-inf}) and the maximum observed concentration (C_{max}) for each dose level were compared. The linear trapezoidal method was used to calculate AUC when concentration data were increasing or constant, and the logarithmic trapezoidal method was used if concentration data were decreasing. Geometric mean and geometric coefficient of variation percentage (CV%) were calculated for the AUCs and C_{max}. The geometric CV% was calculated as $100 \cdot (\exp [SD^2] -1)^{0.5}$, where SD is the standard deviation of the log-transformed data. Intrasubject CV% was calculated as $100 \cdot \sqrt{(EXP (\Sigma^{**}2) - 1)}$, where $\Sigma^{**}2$ is the residual variance estimate from the SAS MIXED (SAS Institute Inc, Cary, North Carolina, USA) procedure (PROC MIXED).

Safety assessments

The safety population included randomised patients who received ≥1 dose (see table 1 for baseline demographics and clinical characteristics, and online supplementary table 1 for baseline disease characteristics). Adverse events (AEs) were monitored and severity, relationship to study drug, action taken, outcome and classification as serious or non-serious were recorded. An AE was considered to be treatment-emergent (TEAE) if it started on or after the first dose. Changes in safety laboratory parameters and vital signs were monitored, and administration sites were examined. During the MTXAI treatment periods, injection site assessments were performed predose and at 0.25, 1, 12 and 24 h postdose.

Statistical analysis

A sample size of approximately 48 patients (12 randomised patients per dose level, with no replacements) was planned to provide a sufficient number of patients to determine the relative bioavailability, safety and tolerability of MTX administered via the three methods. For comparisons among treatments, a mixed-model analysis that took into consideration sequence, treatment and treatment period as fixed effects and subjects nested within sequence as a random effect was used to compare dose-normalised logarithmically transformed values for C_{max}, AUC_{0-t} and AUC_{0-inf}. Least-squares (LS) mean for each

treatment, differences between treatment LS means and 90% CIs for differences between treatment LS means were obtained. Results were transformed back to the original scale to obtain geometric LS means, point estimates of the geometric test and LS mean ratios, and 90% CI for these ratios. Relative bioavailability comparisons were based on route and/or location of administration at each dose level using analysis of variance (ANOVA). For bioequivalence assessments of abdomen and thigh SC administration sites, the dose-normalised PK parameters were used in the ANOVA model. Bioequivalence was established if the 90% CI for point estimates of the geometric test and reference LS mean ratios were within the prespecified range of 80% to 125%. If bioequivalence was established among the SC injection sites, the data from the SC injection sites were pooled for comparison with oral administration.

RESULTS

Patients

Patients participated from May through August 2012. Of the 54 patients screened, 50 were randomised and 49 took ≥1 dose of study drug and were included in the safety and PK analyses. The study was completed by 47 patients; two patients discontinued the study after the first dose of MTX (one due to an AE and one due to death).

PK assessments

The C_{max} of MTX was comparable across routes and doses (table 2). However, the AUC from 0 to 24 h (AUC_{0-24h}) and AUC_{0-inf} values were consistently higher at all dose levels for the SC MTXAI compared with oral MTX. There was consistently greater bioavailability of SC MTX compared with oral MTX administration at all dose levels (figure 1). For oral MTX, the mean AUC plateaued at doses ≥15 mg. In contrast to the plateau in exposure seen with oral MTX, the exposure of MTX increased in a dose-proportional manner with SC MTX. Pharmacokinetic measures for SC MTX in the thigh and abdomen demonstrated bioequivalence.

Dose-normalised MTX PK parameters are presented in table 2. The ratio of the dose-normalised AUC_{0-24h} and C_{max} of the SC MTX compared with oral MTX was 127.61 (90% CI 122.30 to 133.15) and 94.88 (90% CI 87.95 to 102.37), respectively. The relative systemic bioavailability of SC MTX at 10, 15, 20 and 25 mg was 121%, 114%, 131% and 141%, respectively, of that seen with oral dosing. For the secondary analysis variables, t_{max}, λ_z and $t_{1/2}$, PK results were consistent across dose and route of administration.

Table 1 Baseline demographic and clinical characteristics of the patients in the safety population

	MTX				
	10 mg (n=13)	15 mg (n=12)	20 mg (n=12)	25 mg (n=12)	Overall (N=49)
Mean age,* y (SD)	62.9 (12.51)	63.4 (7.49)	60.0 (10.40)	59.0 (11.53)	61.4 (10.53)
Women, n (%)	11 (84.6)	5 (41.7)	8 (66.7)	7 (58.3)	31 (63.3)
White, n (%)	12 (92.3)	11 (91.7)	10 (83.3)	11 (91.7)	44 (89.9)
Black, n (%)	1 (7.7)	1 (8.3)	2 (16.7)	1 (8.3)	5 (10.2)
Mean (SD) BMI, kg/m^2	30.7 (7.64)	31.1 (5.35)	30.5 (5.54)	30.6 (7.43)	30.7 (6.39)
Mean (SD) duration of RA,* years	13.9 (9.29)	14.4 (7.33)	11.6 (8.76)	13.4 (10.32)	13.3 (8.78)

*At informed consent.
BMI, body mass index; MTX, methotrexate; RA, rheumatoid arthritis.

Table 2 Dose-normalised MTX PK parameters by treatment (PK analysis population)

	C_{max} (ng/mL)	t_{max} (h)	λ_z (L/h)	$t_{1/2}$ (h)	AUC_{0-24h} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)
Oral MTX (n=47)						
Mean (SD)	22.697 (7.4967)	1.388 (0.8378)	0.188 (0.0333)	3.804 (0.6574)	107.64 (37.732)	109.47 (39.190)
CV%	33.0	60.4	17.7	17.3	35.1	35.8
Geometric mean	21.586	–	–	–	101.73	103.23
Geometric CV%	32.7	–	–	–	34.6	35.3
SC MTXAI (abdomen and thigh, n=96)						
Mean (SD)	20.222 (7.1509)	1.523 (0.9175)	0.184 (0.0331)	3.887 (0.7017)	135.87 (44.274)	138.69 (46.477)
CV%	35.4	60.3	18.0	18.1	32.6	33.5
Geometric mean	19.081	–	–	–	129.38	131.72
Geometric CV%	35.1	–	–	–	31.9	32.8

λ_z, apparent terminal rate constant; AUC_{0-24}, area under the concentration versus time curve from 0 to 24 h; AUC_{0-inf}, area under the concentration versus time curve from time 0 to infinity; C_{max}, maximum observed concentration; CV%, coefficient of variation percentage; MTX, methotrexate; MTXAI, methotrexate auto-injector; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; t_{max}, time to reach maximum observed concentration.

Safety

Treatments in both the oral MTX and SC MTX arms were generally safe and well tolerated. No new treatment-related safety signals were identified within the study (see online supplementary table 2).

DISCUSSION

Prior PK studies comparing oral to parenteral MTX mostly tested MTX dosed in mg/m^2 and never clearly established a continuum of bioavailability over the range of commonly used doses.[4] The current study is the first to compare bioavailability across commonly prescribed doses of oral and SC MTX and raises the possibility that there is no advantage to increasing the oral MTX dose above 15 mg/week, a common clinical practice. Subcutaneous MTX exhibited a linear, dose-proportional increase in exposure with no plateau. At each dose level, SC administration achieved higher MTX exposure than the comparable oral dose and continued to increase through doses of 25 mg/week. Potential confounders of the comparison of dosage forms were minimised by the random sequence crossover design. No increases in AEs were observed with SC MTX. These findings suggest that the SC admin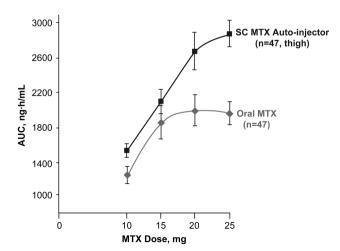istration may overcome some of the limitations of oral MTX and allow for optimisation of MTX in the treatment of RA as defined in treatment guidelines.[1] [2]

Figure 1 Mean±SEM AUC by MTX dose. Mean oral MTX exposure plateaus at doses ≥15 mg/week. AUC, area under the concentration versus time curve; MTX, methotrexate; SC, subcutaneous; SEM, SE of the mean.

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