Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate

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Abstract

Objective

Methotrexate (MTX) is recognised as the cornerstone of treatment for rheumatoid arthritis. For some patients, oral MTX demonstrates variable bioavailability, especially at higher doses. Such concerns may be mitigated by subcutaneous (SC) MTX administration. This study investigated the relative bioavailability, safety, and tolerability of MTX administered either by SC injection with a prefilled autoinjector pen (MTX pen) or orally.

Methods

This single-centre, open-label, randomised, 2-period, 2-sequence, single-dose, crossover study enrolled healthy subjects aged 18 to 55 years into 1 of 4 dose groups (7.5 mg, 15 mg, 22.5 mg, and 30 mg), where they received a single dose of SC MTX and of the oral MTX tablets. Blood samples were collected from subjects predose and at prespecified time points postdose for pharmacokinetic analyses. Adverse events (AEs) were recorded to assess differences in safety and tolerability.

Results

Bioavailability, as measured by maximum plasma concentrations (C_{max}) and area under the plasma-concentration curves (AUC_{0-t}), was generally higher with the SC MTX pen compared with oral administration for all dose groups. AUC_{0-t} ratios increased with ascending doses; C_{max} ratios did not increase. A total of 80 AEs were reported in 35/62 subjects; none were severe. Differences in the safety profiles were related to the route of administration. Single administrations with the MTX pen were well tolerated at the injection site.

Conclusion

Single-dose administration with the SC MTX pen resulted in a higher relative bioavailability compared with oral administration. SC MTX pen administration was associated with fewer gastrointestinal AEs than oral MTX.

Key words

subcutaneous methotrexate, rheumatoid arthritis, bioavailability, autoinjection.

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U. Pichlmeier and K.-U. Heuer are full-time employees of medac GmbH.

Introduction

Oral methotrexate (MTX) is widely used in the treatment of several inflammatory disorders and is the most commonly prescribed treatment for rheumatoid arthritis (RA) (1-3). Despite its exceptional efficacy and widespread use, oral MTX tablets have shown bioavailability variations at the higher doses sometimes needed to maximise outcomes (4, 5). Multiple studies have shown that these bioavailability variations are dose-dependent, with greater variability and reduced absorptions at the higher doses sometimes required to manage RA (6-12). This variability in oral MTX bioavailability is attributed to saturation of gastrointestinal (GI) transport processes and the absorption mechanism (13-15), and forms the basis of the confounding and inconsistent relationship between dose of oral MTX and treatment response.

Additionally, treatment with oral MTX tablets is commonly associated with GI disorders, such as abdominal pain, anorexia, stomatitis, nausea, vomiting, diarrhoea, and constipation (4, 16). The frequency of these GI side effects in patients using oral MTX tablets often warrants a switch to parenterally administered MTX or another therapy (4).

Given the limitations of oral MTX, there is a need for an MTX formulation that has improved bioavailability, distribution, and mitigated GI side effects. Subcutaneously (SC) administered MTX is well absorbed and well tolerated (17). Importantly, 24-week studies in patients with RA suggest that SC MTX may be more effective than oral MTX at the same dose (18, 19). Several studies have demonstrated that the bioavailability of subcutaneous (SC) MTX is greater than that of oral MTX, and data from these studies suggest that SC MTX is not associated with the saturation problem observed with oral MTX (9-11, 14). Overall, parenteral MTX appears to have consistent bioavailability (14).

A single-dose, prefilled, autoinjector pen containing MTX (SC MTX pen; medac GmbH, Wedel, Germany) has been recently developed to facilitate self-injection by patients with RA. The objective of this study was to investigate the relative bioavailability of MTX administered by SC injection with the autopen compared to oral MTX tablets. Further, this study sought to assess the overall safety and tolerability of MTX after both routes of administration (oral and SC), and the local injection-site tolerability of SC using the MTX pen.

Materials and methods

Study design

This open-label, randomised, 2-period, 2-sequence, single-dose, crossover study of 4 dose groups of MTX (7.5, 15, 22.5, and 30 mg) was conducted in healthy individuals between June 2012 and August 2012 at a single research centre in Mannheim, Germany. All subjects were randomly assigned to 1 of the 2 treatment sequences within each dose group. Each subject participated in only 1 of the 4 dose groups and received a single dose of MTX administered either with the SC MTX pen (in the abdominal wall) or orally in tablet form. After a washout phase of at least 1 week, MTX was then administered by the alternative route. All patients provided written informed consent and the protocol was approved by the Independent Ethics Committee. This study was conducted in accordance with the Declaration of Helsinki.

Study medication

Study medication consisted of a prefilled pen containing 0.15, 0.3, 0.45, or 0.6 mL of the 50-mg/mL MTX solution; corresponding to 7.5-, 15-, 22.5-, or 30-mg oral MTX tablets (2.5-mg per tablet) (Dava Pharmaceuticals Inc., Fort Lee, New Jersey, United States [US]). The prefilled autoinjector pen used in this study is designed with a removable cap that contains a small needle shield. After removal of the cap, drug administration is performed by firmly pressing the pen against the skin while pressing the injection button. Upon the initiation of injection an audible click is produced; complete injection is achieved within 5 seconds. A protective shield covers the needle after removal of the pen from the injection site. The pen can be visually inspected to determine if the MTX solution was completely injected.

The lowest dose, 7.5-mg MTX, was included in this study design because

this dose is considered to be the recommended starting dose for MTX in the US. The 30-mg MTX dose was included because this is the maximum dose typically administered to patients with RA.
In this study, subjects were also administered co-medications for safety reasons. Specifically, subjects received folinic acid (Calciumfolinat-GRY® 15-mg tablets; GRY-Pharma GmbH, Kirchzarten, Germany) to reduce the severe haematotoxic and gastrotoxic effects of MTX, and potassium-sodium-hydrogen-citrate (Uralyt-U® granulate; Madaus GmbH, Germany) to reduce the nephrotoxic effects of MTX.

Subjects
The study included men or women between 18 and 55 years of age in general good physical health and within the normal weight range (body mass index within 18.5 to 30.0 kg/m^2). Women had to have been previously surgically sterilised by hysterectomy or bilateral tubal ligation, or be postmenopausal for at least 2 years. To assure that the study subjects were healthy and in a comparable status, a comprehensive list of exclusion criteria was applied. This list included, but was not limited to, the following: heavy smoker (>10 cigarettes/day); demonstrating excess in xanthine consumption (>5 cups of coffee or equivalent per day); heavy alcohol consumption; any history of alcohol or drug abuse; demonstrating any active physical disease, acute or chronic; any history of drug hypersensitivity; laboratory values outside the reference range suggesting an unknown disease and/or requiring further clinical evaluation by the investigator; any history of, or current, malignancy; and/or pregnancy.

Blood collection and plasma preparation
Blood samples were collected predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 48 h postdose. Samples were collected in prelabeled tubes containing ethylenediaminetetraacetic acid (Monovette®, Sarstedt, Germany). Immediately after collection, the samples were cooled, protected from daylight, and centrifuged within 45 min at approximately 4°C at 2800 x g for 10 min; the plasma was then removed and stored below -20°C until evaluation.

Bioanalytics
Bioanalysis were carried out in the Department of Bioanalytics at CRS GmbH, Mannheim, Germany in accordance with the principles of Good Laboratory Practice. For the analysis of MTX in plasma, a validated, internally standardised, liquid chromatography–tandem mass spectrometry method with a lower limit of quantification of 5 ng/mL was used. The possible effect of co-medications on the selectivity of the MTX assay was investigated and ruled out.

Pharmacokinetic assessments
Pharmacokinetic characteristics were estimated based on plasma concentrations of MTX using actual time of sampling. Primary target characteristics for pharmacokinetics in this study were the area under plasma concentration curve from administration to last observed concentration at time t (AUC_{0-t}; calculated by the linear trapezoidal formula) and maximum plasma concentration (C_{max}; highest observed plasma concentration of the measured concentration-time profile) of MTX. Primary endpoints in the study were the SC MTX pen/oral MTX tablet ratios for AUC_{0-t} and C_{max}. Drug elimination, expressed as apparent terminal elimination half-life ($t_{1/2\lambda z}$), was evaluated as a secondary target characteristic.

Safety assessments
Safety assessments included recording of adverse events (AEs), vital signs, electrocardiogram (ECG), safety laboratory tests, physical examination, and overall tolerability. An AE occurring before the first administration of MTX was considered a pretreatment AE. All AEs occurring after administration of MTX were attributed to the last preceding treatment and were considered treatment-emergent adverse events (TEAEs). Safety assessments also included evaluating local injection-site tolerability (pain and itching as assessed by the subject, and redness, swelling, and haematoma as assessed by the investigator). Local tolerability was assessed immediately after injection, as well as at 2, 24, and 48 h after MTX administration in each study period. All findings of local tolerability assessments were documented as TEAEs.

Statistical analysis
Statistical analysis was performed for 2 subject populations: the pharmacokinetic analysis group consisted of all subjects that could have the primary pharmacokinetic parameters of MTX derived for all treatments and the safety analysis population consisted of all subjects that received at least 1 MTX dose. The biometrical evaluation was carried out by the Department of Clinical Data Management at CRS using SAS® software, version 9.2. The estimation of pharmacokinetic parameters was carried out applying a validated SAS® program. Individual plasma concentrations and derived pharmacokinetic parameters were recorded individually and summarised by treatment using descriptive statistics and frequency tables as appropriate. Descriptive statistics of pharmacokinetic parameters were calculated by dose group and treatment. An analysis of variance was performed on AUC_{0-t} and C_{max} of MTX. The parametric point estimates for the SC MTX pen/oral MTX tablet ratios of primary pharmacokinetic parameters and 90% confidence intervals (CIs) were calculated using the least square means from the analysis of variance of log-transformed data with subsequent exponential transformation. Thus, the assessment of bioavailability was based on the 90% CIs for the ratio of the population geometric means (SC MTX pen/oral MTX tablet) for the parameters under consideration. Safety and tolerability data were listed individually and described by descriptive statistics, when appropriate.

Results

Subject characteristics
A total of 65 subjects, 51 men and 14 women (race/ethnicity: 62 White, 1 Hispanic, 1 Asian, and 1 Black; data not shown), were randomised to treatment (Table I). After randomisation, 62 of the 65 subjects received at least

Table I. Patient demographic and baseline characteristics.

Characteristics	Methotrexate Dose							
	7.5-mg Group		15-mg Group		22.5-mg Group		30-mg Group	
	PP	SP	PP	SP	PP	SP	PP	SP
Total patients (n)	14	16	14	17	14	15	12	14
Female	3	4	5	5	4	4	1	1
Male	11	12	9	12	10	11	11	13
Age (years)*	47.93 (5.23)	47.88 (5.26)	41.21 (12.52)	41.12 (12.06)	41.64 (7.75)	42.33 (7.93)	42.25 (9.43)	39.93 (10.84)
Range	33.0–55.0	33.0–55.0	20.0–55.0	20.0–55.0	26.0–52.0	26.0–52.0	25.0–54.0	19.0–54.0
Body height (cm)*	176.07 (8.24)	175.13 (8.15)	173.64 (10.53)	173.76 (10.02)	176.50 (8.46)	176.53 (8.15)	175.17 (5.80)	176.00 (5.74)
Range	160.0–186.0	160.0–186.0	156.0–189.0	156.0–189.0	167.0–197.0	167.0–197.0	165.0–183.0	165.0–183.0
Body weight (kg)*	79.36 (10.99)	78.27 (10.81)	77.39 (12.58)	77.48 (11.90)	78.95 (6.53)	79.47 (6.60)	80.44 (10.03)	82.30 (10.42)
Range	57.6–91.1	57.6–91.1	56.3–99.3	56.3–99.3	66.0–93.6	66.0–93.6	55.6–91.0	55.6–96.2
BMI (kg/m²)*	25.51 (2.41)	25.43 (2.29)	25.69 (3.63)	25.66 (3.30)	25.40 (2.15)	25.55 (2.16)	26.15 (2.54)	26.49 (2.52)
Range	21.6–28.5	21.6–28.5	18.6–30.0	18.6–30.0	20.1–28.3	20.1–28.3	20.4–29.3	20.4–29.4

*Values are mean (SD) with the exception of all range values.
BMI: body mass index; PP: pharmacokinetic population; SD: standard deviation; SP: safety population.

1 dose of MTX, either with the MTX pen or by oral administration. The other 3 subjects were randomised by mistake and were withdrawn from the study prior to treatment. In total, 11 subjects were excluded from the pharmacokinetic data set in accordance with the statistical analysis plan. Three of these subjects were excluded because they were not treated. The other 8 subjects were excluded because only the data for 1 treatment period was available due to discontinuation after the first MTX dose. Reasons for discontinuation after the first MTX dose were as follows: private reasons (2 subjects), test result(s) (5 subjects; for at least 3 subjects, test results met removal criteria), and an adverse event making continuation of the study undesirable (1 subject).

Pharmacokinetic characteristics following SC versus oral administration of MTX

Geometric mean MTX plasma concentrations after SC and oral administration of single doses of 7.5-, 15-, 22.5-, and 30-mg MTX are shown in logarithmic concentration scales in Figure 1. Rapid absorption of MTX was observed following both SC and oral MTX adminstration. The absorption of MTX was faster after SC administration compared with oral administration. C_{max} levels were achieved between 0.5 and 2.5 hours after administration for both treatment methods. AUC_{0-t} was higher after SC MTX pen adminstration compared with oral MTX tablet administration for all dose groups (Table II). Unlike the AUC_{0-t} profile of oral MTX, which began to plateau above 22.5 mg, the AUC_{0-t} of the SC MTX pen never reached a plateau and maintained linearity at all doses tested (Fig. 2A). AUC_{0-t} ratios (90% CIs) for the SC MTX pen/oral MTX tablet were 135.00% (123.04%, 148.13%) after 7.5-mg MTX, 148.59% (132.31%, 166.87%) after 15-mg MTX, 150.57% (142.13%, 159.50%) after 22.5-mg MTX, and 168.19% (137.85%, 205.21%) after 30-mg MTX (Fig. 2B). Higher mean C_{max} values were observed after SC MTX pen adminstration compared with oral MTX tablet for all dose groups except for the 7.5-mg dose group, where no difference was observed (Table II). C_{max} ratios (90% CIs) for the SC MTX pen/oral MTX tablet were 100.12% (91.13%, 109.99%) after 7.5-mg MTX, 129.39% (115.44%, 145.02%) after 15-mg MTX, 130.91% (113.78%, 150.63%) after 22.5-mg MTX, and 128.00% (102.70%, 159.53%) after 30-mg MTX (Fig. 2B). AUC_{0-t} ratios for the SC MTX pen/oral MTX tablet increased with ascending doses, whereas the C_{max} ratios for the SC MTX pen/oral MTX tablet did not increase with ascending doses (Fig. 2B). The variability of AUC_{0-t} was higher after oral MTX tablet administration for all doses except for the 22.5-mg dose (Table II). Geometric mean $t_{1/2\,\lambda\,z}$ values were similar for all dose groups (Table II).

Safety outcomes

A total of 80 TEAEs were reported by 35 of the 62 subjects (56.5%) included in the safety analysis population (Table III). Of the 80 TEAEs reported, 63 were considered mild and 17 were moderate in severity. None of the TEAEs were serious. Most of the TEAEs (75 of 80 events) were considered to be drug related (Table III).

The overall frequency of TEAEs and the number of subjects with TEAEs was higher after oral MTX administration compared to SC MTX administration: 44 TEAEs in 27 of the 57 subjects (47.4%) *versus* 36 TEAEs in 19 of the 59 subjects (32.2%; Table III). In the 7.5-mg, 22.5-mg, and 30-mg MTX dose groups, the number of subjects with TEAEs was higher after oral MTX tablet administration compared with the SC MTX pen. In the 15-mg MTX dose group, the number of subjects with TEAEs was similar with both administration routes (Table IV).

The most frequently reported TEAEs belonged to the Medical Dictionary for Regulatory Activities system organ class GI disorders (28 TEAEs in 22 subjects) followed by nervous system disorders (14 TEAEs in 12 subjects) and general disorders and administration-site conditions (13 TEAEs in 10 subjects; Table III). GI disorders were observed more frequently after oral MTX tablet administration compared with SC MTX pen administration, occurring in 28.1% of subjects *versus*

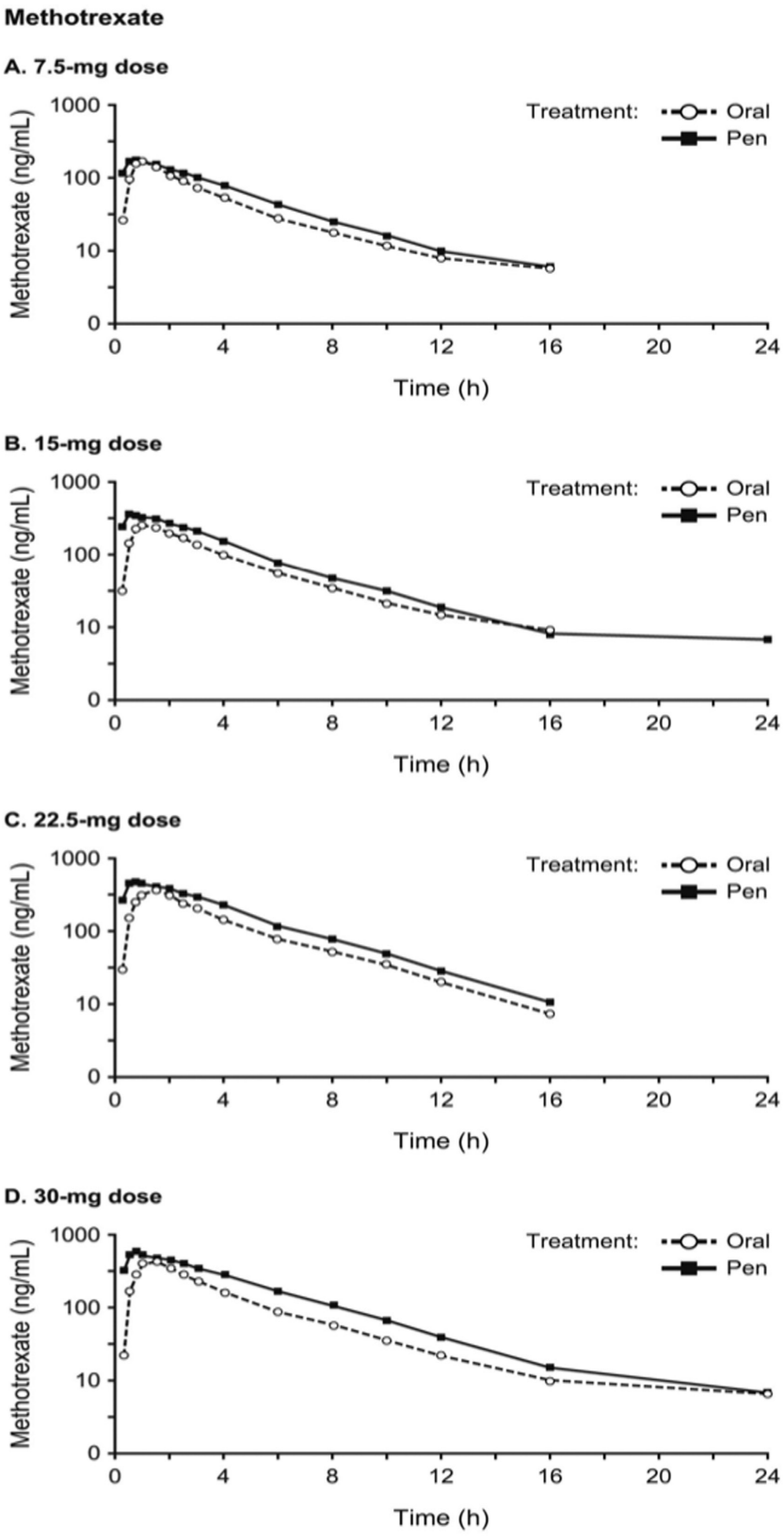

Fig. 1. Logarithmic concentration scales showing geometric mean concentrations of MTX *versus* time between SC MTX pen and oral MTX tablet groups for each of the doses used in this study (**A**: 7.5 mg, **B**: 15 mg, **C**: 22.5 mg, and **D**: 30 mg).
The MTX auto pen contained 0.15, 0.3, 0.45, or 0.6 mL of the 50-mg/mL MTX solution corresponding to 7.5-, 15-, 22.5-, or 30-mg MTX. Oral MTX tablets corresponded to 7.5-, 15-, 22.5-, or 30-mg MTX.

15.3% of subjects, respectively. The most frequently reported GI event was diarrhoea with 13 events reported in 12 subjects. The percentages of subjects reporting nervous system disorders were comparable across both administration routes (11.9%, SC MTX pen *versus* 10.5%, MTX tablet; Table III). The most frequently reported nervous system disorder TEAE was headache. General disorders and administration-site conditions were reported more frequently after SC MTX pen administration than after oral MTX tablet administration due to the number of injection-site reactions (Table III). All other TEAEs occurred in less than 5% of subjects (data not shown). None of the subjects had redness or swelling after SC administration with the MTX pen; however, 2 subjects developed a mild haematoma at the injection site. Mild pain or burning sensation at the injection site was reported by 5 of the 59 subjects. All TEAEs were of mild to moderate severity. At all dosages except 15 mg, the percentage of TEAEs was lower for the MTX pen compared with the MTX tablet. A full summary of the severity and target organ class for TEAEs by treatment group can be found in Table IV.

The results of laboratory testing showed a reversible increase in transaminases in several subjects after SC MTX pen and/or oral MTX tablet administration (data not shown). In 2 subjects from the 30-mg MTX dose group (1 subject receiving MTX pen administration and 1 subject receiving oral MTX), the increase was 2-fold the upper limit of normal or above and resulted in the discontinuation of these subjects from the study. Regarding haematology evaluations, no decreases meeting the criteria for leucopenia, thrombocytopenia, or anemia were observed. Clinically significant abnormal urinalysis results were observed in 1 subject in the 30-mg dose group after SC MTX pen administration. Bilirubin, erythrocytes and haemoglobin, protein, and urobilinogen were found in urine and recorded as AEs. Two subjects in the oral MTX tablet group (1 in the 15-mg MTX dose group and 1 in the 22.5-mg MTX dose group) had clinically significant in-

Table II. Pharmacokinetic characteristics by treatment across all dose groups.

Pharmacokinetic Characteristics	MTX Dose Group	SC MTX Pen* Geometric Mean (CV [%])	Oral MTX Tablet* Geometric Mean (CV [%])	Point Estimate SC/Oral (%) [90% CI (%)]
AUC_{0-t} (h·ng/mL)	7.5 mg	782.73 (9.78)	579.79 (21.79)	135.00 (123.04, 148.13)
	15 mg	1594.84 (11.79)	1073.32 (30.26)	148.59 (132.31, 166.87)
	22.5 mg	2272.55 (10.80)	1509.34 (13.64)	150.57 (142.13, 159.50)
	30 mg	2824.72 (12.79)	1679.47 (42.27)	168.19 (137.85, 205.21)
C_{max} (ng/mL)	7.5 mg	185.99 (15.55)	185.77 (23.43)	100.12 (91.13, 109.99)
	15 mg	392.00 (27.06)	302.96 (31.25)	129.39 (115.44, 145.02)
	22.5 mg	512.71 (21.16)	391.64 (20.46)	130.91 (113.78, 150.63)
	30 mg	576.26 (19.43)	450.20 (40.31)	128.00 (102.70, 159.53)
$t_{1/2\lambda z}$ (h)	7.5 mg	2.88 (15.40)	2.96 (20.23)	–
	15 mg	2.76 (14.22)	3.21 (32.54)	–
	22.5 mg	2.72 (8.49)	2.78 (12.37)	–
	30 mg	2.96 (22.88)	2.89 (20.50)	–
t_{max} (h)		Median	Median	
	7.5 mg	0.63	1.00	–
	15 mg	0.75	1.00	–
	22.5 mg	0.75	1.50	–
	30 mg	0.75	1.50	–

*SC MTX pen contained 0.15, 0.3, 0.45, or 0.6 mL of the 50-mg/mL MTX solution; corresponding to 7.5-, 15-, 22.5-, or 30-mg MTX tablet dose. Oral MTX tablets USP corresponded to 7.5-, 15-, 22.5-, or 30-mg MTX.
AUC_{0-t}: area under the plasma concentration curve from administration to last observed concentration at time t; C_{max}: maximum plasma concentration; CI: confidence interval; CV: coefficient of variation; MTX: methotrexate; SC: subcutaneous; $t_{1/2\lambda z}$: apparent terminal elimination half-life; t_{max}: time to C_{max}; USP: United States Pharmacopeia.

Table III. Overview of TEAEs between treatment groups for all dose groups combined (Safety Analysis Population).

TEAEs	SC MTX pen (n=59)			Oral MTX tablet (n=57)			Total (n=62)		
	#	n	%	#	n	%	#	n	%
All TEAEs	36	19	32.2	44	27	47.4	80	35	56.5
Mild	29	17	28.8	34	22	38.6	63	31	50
Moderate	7	5	8.5	10	7	12.3	17	9	14.5
Serious	0	0	0	0	0	0	0	0	0
Nonserious	36	19	32.2	44	27	47.4	80	35	56.5
Drug-related	35	19	32.2	40	25	43.9	75	34	54.8
Not drug-related	1	1	1.7	4	3	5.3	5	3	4.8
Leading to withdrawal	1	1	1.7	3	2	3.5	4	3	4.8
Most frequently (>5% of subjects) occurring drug-related TEAEs (MedDRA System organ class, preferred term)*									
Gastrointestinal disorders	9	9	15.3	19	16	28.1	28	22	35.5
Diarrhoea	5	5	8.5	8	8	14	13	12	19.4
Nausea	3	3	5.1	3	3	5.3	6	6	9.7
Abdominal pain upper	–	–	–	3	3	5.3	3	3	4.8
Nervous system disorders	8	7	11.9	6	6	10.5	14	12	19.4
Headache	7	7	11.9	6	6	10.5	13	12	19.4
General disorders and administration-site conditions	9	8	13.6	4	6	7	13	10	16.1
Fatigue	2	2	3.4	3	3	5.3	5	4	6.5
Injection-site pain	5	5	8.5	–	–	–	5	5	8.1

*System organ classes are given by frequency of TEAEs.
MedDRA: Medical Dictionary for Regulatory Activities (version 15.0); MTX: methotrexate; n: number of patients; SC: subcutaneous; TEAEs: treatment-emergent adverse events; %: percentage of patients with TEAEs; #: number of TEAEs.

creases in diastolic blood pressure; the subject from the 22.5-mg oral MTX dose group was withdrawn from the study. No safety-relevant influences of MTX treatment on ECG parameters occurred in subjects of this study.

Discussion

The primary objective of this study was to assess the relative bioavailability of 4 doses of SC MTX administered with a prefilled autoinjector pen compared to oral tablet administration. Results of our pharmacokinetic assessments showed that MTX was rapidly absorbed after both SC and oral administration; however, the absorption of MTX was faster after SC administration compared with oral administration. Additionally, administration of MTX using the SC MTX pen resulted in a higher mean C_{max} of MTX compared with oral tablet administration for all dose groups, with the exception of the lowest dose (7.5 mg). We also found that AUC_{0-t} was higher after administration with the SC MTX pen compared with oral MTX tablet administration for all dose groups. In addition, AUC_{0-t} ratios increased with ascending doses, whereas C_{max} ratios did not increase with ascending doses. The elimination of MTX was similar for both SC and oral treatments, as expected, with comparable geometric mean $t_{1/2\ \lambda\ z}$ values for all dose groups evaluated.

The pharmacokinetic findings in this study indicated that administration of SC MTX with the autopen resulted in a higher relative bioavailability of MTX compared with oral administration of MTX tablets after single doses. Our results are consistent with data from previous studies reporting higher bioavailability of MTX following SC administration *versus* oral administration (11, 14). Although similar MTX bioavailability can be achieved with parenteral MTX delivery by other mechanisms, patients with RA have been reported to prefer administration via autopen due to ease of use and convenience (20). Also, our data showed that the variability of MTX C_{max} and AUC_{0-t} was higher after oral administration than after SC administration for all doses except for the 22.5-mg dose. In a study of patients

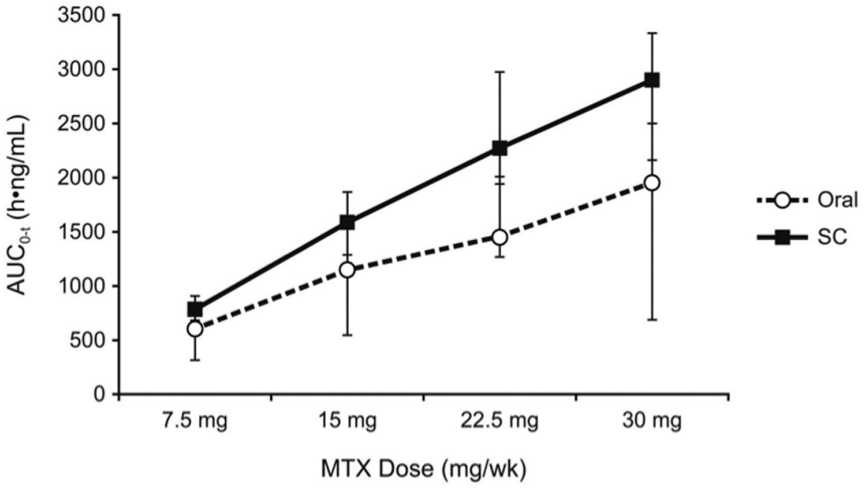

Fig. 2A. Median AUC_{0-t} of oral MTX and SC MTX pen at each dose evaluated.

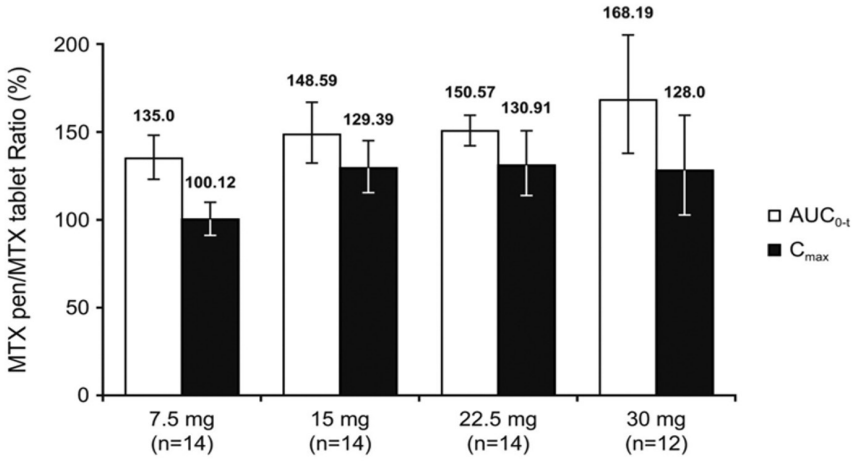

Fig. 2B. Point estimates of SC MTX autopen to oral MTX tablet ratios (%, 90% CI) of AUC_{0-t} and C_{max} at each dose evaluated.

with RA treated with low-dose oral MTX, Jundt *et al*. (14) reported 85% bioavailability with considerable variability (54% to 99%) following oral MTX and 97% bioavailability following SC MTX administration. Hoekstra et al (11) found bioavailability following oral MTX to be even lower (64%) and highly variable (21% to 96%) at doses at or greater than 25-mg weekly. AUC_{0-t} and C_{max} values in this study showed evidence of a saturation effect with increasing doses of oral MTX, and this effect occurred across a broad dose range. Multiple studies have shown that oral MTX demonstrates a saturation effect at higher doses (typically above 25 mg), such that bioavailability is actually lower at higher doses of MTX (9, 13, 15). Hamilton and Kremer (9) found reduced bioavailability of MTX following administration of increased doses of oral MTX (mean dose was 17 mg) in patients with RA, leading them to assert that practitioners should not expect consistent and complete bioavailability of oral MTX across the common dose range typically used to treat patients with RA. In contrast, SC MTX AUC_{0-t} values did not plateau across all dose ranges tested, demonstrating linear absorption with each dose and therefore higher exposure than comparable oral doses. This finding was also observed in a recent study on the bioavailability of MTX using a different auto-injector system (21), supporting our considerations that this route of administration may be preferable when higher doses of methotrexate are indicated.

Additional studies have also shown data in support of this concept. In patients intolerant of, or unresponsive, to oral MTX tablet treatment, parenteral MTX improves disease control and reduces the need for biological therapy (22-25). Therefore, if the goal is to increase bioavailability of MTX because of an insufficient clinical response, we suggest that practitioners should consider switching the route of administration of MTX from oral to SC, instead of increasing the dose of the oral formulation. The potential of MTX as a therapeutic strategy for RA may have been overshadowed by the development and successful use of biologic agents throughout the past 15 years (26). Formulations of MTX with improved bioavailability may be an appropriate strategy to reintroduce this agent as an effective therapeutic option to achieve optimal outcomes and may delay the need for patients to transition to biologic therapy.

This study also sought to assess the overall safety and tolerability of MTX after both routes of administration, and the local injection-site tolerability of the SC MTX pen. The safety profiles identified in this study were in accordance with the current knowledge regarding the safety profile of MTX (27). Single doses of MTX were well tolerated after both SC MTX pen and oral MTX tablet administration. The majority of TEAEs from both treatment groups were considered drug related, although most were nonserious or mild. There were no serious TEAEs reported after either route of MTX administration.

Incidences of TEAEs were comparable between the 2 treatment groups with the exception of GI disorders and administration-site conditions. GI disorders were the most frequently reported TEAEs and the percentage of subjects reporting GI TEAEs was almost 2-fold higher in the oral MTX tablet group compared with the SC MTX pen group. The GI safety findings are not surprising because previous studies have reported that (a) parenteral MTX produces fewer GI symptoms than oral MTX (28); (b) switching from parenteral MTX to oral MTX increases the frequency of GI AEs (29); and (c) SC MTX shows

Table IV. Summary of TEAEs by system organ class and severity across all dose groups.

	Methotrexate dose*															
	7.5-mg group				15-mg group				22.5-mg group				30-mg group			
	SC (n=16)		Oral (n=14)		SC (n=16)		Oral (n=15)		SC (n=14)		Oral (n=15)		SC (n=13)		Oral (n=13)	
Severity of TEAEs	F	%	F	%	F	%	F	%	F	%	F	%	F	%	F	%
Total TEAEs	2	12.5	8	28.6	11	37.5	7	33.3	9	35.7	16	60.0	14	46.2	13	69.2
Mild	1	6.3	8	28.6	10	37.5	7	33.3	9	35.7	13	53.3	9	38.5	6	38.5
Moderate	1	6.3	-	-	1	6.3	-	-	-	-	3	13.3	5	23.1	7	38.5
Serious	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Non-serious	2	12.5	8	28.6	11	37.5	7	33.3	9	35.7	16	60	14	46.2	13	69.2
Leading to withdrawal	-	-	-	-	-	-	-	-	-	-	1	6.7	1	7.7	2	7.7
System organ class																
Gastrointestinal disorders	1	6.3	3	21.4	3	18.8	3	13.3	2	14.3	6	33.3	3	23.1	7	46.2
General disorders and administration site conditions	-	-	-	-	3	12.5	1	6.7	2	14.3	1	6.7	4	30.8	2	15.4
Nervous system disorders	1	6.3	1	7.1	3	18.8	1	6.7	4	21.4	4	26.7	-	-	-	-
Respiratory, thoracic and mediastinal disorders	-	-	2	14.3	-	-	-	-	-	-	-	-	-	-	-	-
Infections and infestations	-	-	1	7.1	-	-	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders	-	-	1	7.1	-	-	-	-	-	-	-	-	-	-	-	-
Investigations	-	-	-	-	-	-	1	6.7	-	-	-	-	5	15.4	3	7.7
Musculoskeletal and connective tissue disorders	-	-	-	-	1	6.3	-	-	-	-	2	6.7	1	7.7	-	-
Metabolism and nutrition disorders	-	-	-	-	-	-	-	-	1	7.1	1	6.7	-	-	-	-
Renal and urinary disorders	-	-	-	-	-	-	-	-	-	-	-	-	1	7.7	-	-

*SC MTX pen contained 0.15, 0.3, 0.45, or 0.6 mL of the 50-mg/mL MTX solution; corresponding to 7.5-, 15-, 22.5-, and 30-mg oral MTX tablet dose. Oral MTX tablets USP corresponded to 7.5-, 15-, 22.5-, and 30-mg MTX.
F: frequency of adverse events; n: number of patients; SC: subcutaneous; TEAEs: treatment-emergent adverse events; %: percentage of patients with TEAEs; USP: United States Pharmacopeia.

reduced intensity of GI symptoms compared with oral MTX (30).

The results of the local injection-site tolerability assessments of SC MTX pen demonstrated that single SC administrations were generally well tolerated. There were no incidences of redness or swelling and only 2 subjects developed a mild haematoma. Mild pain or burning sensation at the injection site was reported by 8.5% of subjects who received an SC MTX pen injection. Overall, differences in the safety profiles were mainly considered to be related to the route of administration, such that GI disorders were more frequent in the oral MTX tablet group and injection-site reactions were only reported by subjects receiving the SC MTX pen injection.

Multiple subjects in this study experienced reversible increases in liver transaminases. These TEAEs occurred in subjects from both SC MTX pen and oral MTX tablet treatment groups. MTX carries a risk of potential liver toxicity; thus, it is important that patients experiencing increased transaminases be carefully monitored. Temporary increases in transaminases up to 3 times the upper limit of normal are known to be associated with MTX administration (31, 32).

Our results provide useful data regarding the bioavailability and safety of the SC MTX pen *versus* oral MTX tablet. Further, this study purposely used doses of MTX that are relevant for practical use in patients with RA, including a 30-mg dose, which is the highest dose available of the SC MTX pen. This study is limited in that it included only healthy individuals, not patients with RA, and did not test extended administration of MTX, only 2 single doses.

Conclusion

In summary, these data demonstrate that administration of MTX with the SC autopen is capable of improving bioavailability and thus maximising exposure compared with oral MTX tablets at the equivalent dose, and that this effect extends across a broad range of doses that are commonly used in treating patients with RA. Importantly, SC MTX administration eludes the saturation effect that occurs with increasing doses of oral MTX. Lastly, the safety profile of the SC MTX pen appears to exhibit diminished incidences of GI AEs. Altogether, this study supports the use of the SC MTX pen for the treatment of patients with RA who may benefit from higher drug exposure.

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