Nearly Pain-Free Self-Administration of Methotrexate Using an Investigational Auto-Injector: Results of a Phase 2 Clinical Trial in Rheumatoid Arthritis Patients With Mild-to-Severe Functional Limitations

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ABSTRACT

Title: Nearly Pain-Free Self-Administration of Methotrexate (MTX) Using an Investigational Auto-Injector: Results of a Phase 2 Clinical Trial in Rheumatoid Arthritis (RA) Patients With Mild-to-Severe Functional Limitations

Background: MTX is the cornerstone of RA treatment. Limitations of systemic exposure of oral MTX can affect its efficacy. Subcutaneous (SC) MTX improves bioavailability, which may result in better efficacy and tolerability. Self-administration of SC MTX via conventional vial and syringe is challenging for some patients due to injection-associated anxiety, functional limitations, injection-site adverse events (AEs), and especially pain. An investigational auto-injector that delivers SC MTX was tested with the intention of addressing these patient concerns.

Methods: 108 RA patients were enrolled in this phase 2, multi-center, open-label, single-dose, single-arm, in-clinic study to evaluate the actual human use of SC MTX administered via a developmental MTX auto-injector (MTXAI). MTX dose (10, 15, 20, 25 mg) was determined by investigators based on patient MTX regimen and disease status (controlled or uncontrolled) at time of enrollment.

Results: 101 patients completed the study; 99 were evaluable for pain (79.2% female, mean age 60.9 yrs, [SDs 10.1], mean disease duration 13.3 yrs, [SDs 11.0], 84.7% ACR Class II or III, 89.1% Functional Class II or III). All patients had been taking MTX for ≥3 months prior to study enrollment; 25% had used SC MTX. Safety was assessed by recording AEs and evaluating administration sites before and 0.25, 1, 6, and 24 hours after self-administration. Administration site pain (measured on a 100-mm visual analog scale [VAS]) is summarized in **Table 2**. Mean administration site pain was 3.6 mm/100 mm (SDs 9.1 on Day 1 with a median 1.0 mm/100 mm (0–72) and a mean of 1.4 mm (SDs 3.2) with a median of 0.0 mm (0–21) on Day 2. 93/99 patients (94%) reported VAS scores of ≤10 on Day 1; 86/99 patients (87%) reported scores of ≤5 on Day 1. Of 404 post-administration evaluations, 92.3% found no erythema. The remainder indicated "very slight, barely perceptible" erythema. 3 patients had AEs (sick sinus syndrome, exostosis, and headache) not considered related to the study drug by the investigators. 100% of patients, including those with moderate-to-severe functional limitations in dexterity, successfully used the auto-injector.

Conclusions: The MTXAI was well tolerated with almost no administration site pain and minimal erythema. Limitations in functional status did not affect patients' ability to self-administer. Improving the delivery of SC MTX with this developmental, first-in-class auto-injector may increase patient tolerance of self-administration, thereby improving adherence to SC MTX treatment regimens in patients with RA.

BACKGROUND

- Although MTX is the recognized cornerstone of RA therapy,[1] its use as an orally administered agent is limited by variations in bioavailability[2,3] and tolerability[4]
- SC MTX is an alternative treatment option with improved bioavailability,[5,6] which may result in better efficacy and tolerability[5,6,8]
  - However, in the United States, SC MTX is only used by <5% of patients[7]
  - Its acceptance is limited by injection-associated pain and anxiety, injection site AEs, and the functional limitations of RA patients
- A self-administered SC MTXAI was developed to provide a delivery system that may facilitate greater ease of use (**Figure 1**) and that may improve access to SC MTX in patients who could benefit from its use

Figure 1. The Methotrexate Auto-Injector

OBJECTIVE

- To demonstrate the ease of use and safety of the MTXAI in adult patients with RA

METHODS

Study Design and Patients

- This was a phase 2, open-label, single-dose, single-arm, dose-ranging, in-clinic study conducted at 8 sites in the United States (ClinicalTrials.gov identifier: NCT01618955)
- MTX doses were determined by the investigator based on patient's current MTX regimen and disease status (controlled or uncontrolled) at time of enrollment
  - MTX doses: 10, 15, 20, and 25 mg

Inclusion Criteria

- ≥18 years of age
- Diagnosed with adult RA[9] and treated with MTX for ≥3 months
- Concomitant medications stable for ≥3 months before screening and continued throughout treatment
- Willing and able to give written informed consent, comply with the protocol, adhere to the study visit schedule, and follow instructions

Exclusion Criteria

- Pregnant or lactating women
- History of malignancy or neoplastic disease
- Acute illness within 7 days or major illness/hospitalization within 1 month of study drug administration
- Inability to understand verbal or written English

Injection and Safety Assessments

- Patients received standardized training on the use of the MTXAI by site healthcare personnel, were given written instructions for use, and were required to demonstrate the correct self-injection technique using the written instructions
- After patient training, investigators completed the 5-item training confirmation questionnaire
- Patients performed 2 evaluations following self-injection
  - 5-item ease of use questionnaire
  - Pain (100-mm VAS) and erythema (0–4 scale) at the site of administration
- Investigators performed 2 additional evaluations following patient self-injection
  - Assessment of essential tasks questionnaire
  - Assessment of injection site erythema on a scale of 0–4 (0 = none; 1 = very slight, barely perceptible; 2 = obvious, but well defined; 3 = moderate to severe; 4 = severe), measured predose and at 0.25, 1, 6 and 24 hours postdose
- Safety assessments
  - Treatment-emergent AEs (TEAEs)
  - Serious AEs
  - Study discontinuations
- Primary end point: successful SC self-administration with the MTXAI
  1) SC self-administration was intentional
  2) SC dose was administered by the patient
  3) SC self-administration was in the appropriate location on the abdomen
  4) The device functioned appropriately
- All analyses were performed on the safety population (all patients who received study drug and carried out a successful or an unsuccessful self-administration)

RESULTS

Study Population

- Demographic and clinical characteristics are presented in **Table 1**

Table 1. Demographics and Clinical Characteristics

	Methotrexate				
	10 mg (n=20)	15 mg (n=30)	20 mg (n=31)	25 mg (n=20)	Overall (N=101)
Mean (SD) age, y	63.5 (11.5)	62.8 (9.0)	59.5 (10.5)	59.1 (9.9)	60.9 (10.1)
Women, n (%)	16 (80.0)	20 (66.7)	26 (83.9)	16 (80.0)	80 (79.2)
Race, n (%)					
White	18 (90.0)	29 (96.7)	27 (87.1)	19 (95.0)	93 (92.1)
Black	2 (10.0)	1 (3.3)	3 (9.7)	1 (5.0)	7 (6.9)
Mean (SD) duration of RA,* y	18.5 (12.8)	11.5 (11.1)	12.6 (9.4)	11.8 (10.4)	13.3 (11.0)
ACR RA classification,† n (%)					
Stage I	3 (15.0)	2 (6.7)	1 (3.2)	4 (20.0)	12 (11.9)
Stage II	8 (40.0)	17 (56.7)	30 (64.5)	9 (45.0)	54 (53.5)
Stage III	7 (35.0)	9 (30.0)	8 (25.8)	7 (35.0)	31 (30.7)
Stage IV	2 (10.0)	2 (6.7)	0	0	4 (4.0)
Functional status,‡ n (%)					
Class I	0 (0.0)	2 (6.7)	3 (9.7)	3 (15.0)	10 (9.9)
Class II	10 (50.0)	21 (70.0)	19 (61.3)	9 (45.0)	59 (58.4)
Class III	8 (40.0)	7 (23.3)	8 (25.8)	8 (40.0)	31 (30.7)
Class IV	0	0	1 (3.2)	0	1 (1.0)

*At informed consent
†ACR=American College of Rheumatology; RA=rheumatoid arthritis

- 101 patients were enrolled; all completed the study
- Mean patient age was 60.9 years (range, 37–80 years)
- At screening, the mean (SD) body mass index was 30.9 (6.64) kg/m^2
- 90.1% of patients had moderate to severe functional limitations (functional status of class II–IV)[9]
  - Class I: Completely able to perform usual activities of daily living
  - Class II: Able to perform usual self-care and work activities, but limited in activities outside of work (eg, household chores, sports)
  - Class III: Able to perform usual self-care activities, but limited in work and other activities
  - Class IV: Limited in ability to perform usual self-care, work, and other activities
- Most patients were assigned to an MTX study dose group that was the same dose as their previously MTX treatment
- 77% of patients were receiving oral MTX at enrollment
- 80.2% of patients had previous experience with SC administration of any drug
  - 31 had used an auto-injector
  - 24 had used a pen device
  - 53 had used a needle and syringe with a vial
- 20% of patients had used SC MTX previously

Injection and Safety Outcomes

- 100% of patients successfully performed self-administration with the MTXAI
- No self-administration issues were reported by the investigators
- Minimal patient-reported pain at the injection site (**Table 2**)

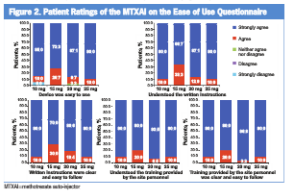
Table 2. Administration Site Pain (Safety Population)

	Methotrexate				
Administration Site Pain*	10 mg (n=20)	15 mg (n=30)	20 mg (n=31)	25 mg (n=20)	Overall (N=101)
Day 1					
Mean (SD)	1.0 (1.0)†	7.6 (15.6)	2.2 (2.9)	2.4 (2.6)‡	3.6 (9.1)§
Median	1.0	2.0	1.0	2.0	1.0
Day 2					
Mean (SD)	1.7 (4.5)	2.0 (4.1)	1.0 (1.6)	1.0 (1.2)	1.4 (3.2)
Median	0	0	0	0.5	0

*Pain was rated on a 100-mm visual analog scale, with 0 = no pain and 100 = worst pain imaginable
†n=19
‡n=20
§n=99

- Positive patient responses on the ease of use questionnaire (**Figure 2**)

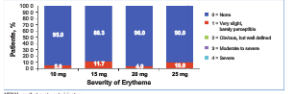
Figure 2. Patient Ratings of the MTXAI on the Ease of Use Questionnaire



MTXAI=methotrexate auto-injector

- Minimal erythema at the injection site as assessed by the investigators (**Figure 3**)

Figure 3. Investigator Ratings of Erythema Following Injection With the MTXAI



MTXAI=methotrexate auto-injector

- No patient experienced bleeding, ecchymosis, or hematoma at the injection site or required countermeasures for injection site reaction at any assessment time point

Adverse Events

- No discontinuations due to a TEAE, serious AE, or protocol deviation were reported
- TEAEs were reported by 3 patients (sick sinus syndrome, exostosis, and headache); only headache was considered to be related to study drug (**Table 3**)

Table 3. TEAEs by System Organ Class and Preferred Term (Safety Population)

	Methotrexate				
AE,* n (%)	10 mg (n=20)	15 mg (n=30)	20 mg (n=31)	25 mg (n=20)	Overall (N=101)
Any TEAE†	0	0	3 (9.7)	1 (5.0)	3 (3.0)
Cardiac disorders	0	0	0	1 (5.0)	1.0 (1.0)
Sick sinus syndrome	0	0	0	1 (5.0)	1.0 (1.0)
Musculoskeletal and connective tissue disorders	0	0	1 (3.2)	0	1.0 (1.0)
Exostosis	0	0	1 (3.2)	0	1.0 (1.0)
Nervous system disorders	0	0	1 (3.2)	0	1.0 (1.0)
Headache	0	0	1 (3.2)	0	1.0 (1.0)

AE=adverse event; MTX=methotrexate; TEAE=treatment-emergent adverse event
*Percentage was calculated using the number of patients in the column heading as the denominator
†Any AE was considered to be a TEAE if the AE started on or after the self-injection with the MTXAI device

CONCLUSIONS

- Self-injection with the MTXAI was pain-free, safe, and well tolerated
- Patients with RA, including those with moderate-to-severe functional limitations, were easily able to successfully self-administer drug with the MTXAI
- Improving the delivery of SC MTX with the MTXAI may increase patient tolerance of self-administration, and may ultimately improve medication adherence

DISCUSSION

- All patients performed a successful self-injection with the MTXAI and completed all essential tasks successfully
- All MTXAI devices functioned appropriately, as confirmed by observations of trained site personnel of patient self-injections and inspection of used devices
- 98% of patients found the MTXAI easy to use, and 100% of patients found the patient education tools for use of the MTXAI to be clear and easy to follow
- Almost all patients had moderate-to-severe functional limitations. The functional limitations did not appear to have an impact on ease of use of the MTXAI
- No AEs related to the use of the MTXAI were reported
  - Injection site pain and erythema were minimal
  - All patients completed the study
- For patients with RA, the MTXAI represents an alternative to oral administration and an alternative to the need for vials, needles, and syringes
- The design of the MTXAI is such that the needle is not visible to the patient, which may minimize needle anxiety; it is prefilled, which may minimize the risk of spillage and accidental exposure; and it is easy to use and nearly pain-free, which may promote treatment adherence and persistence

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