Pain-Related Anxiety as a Barrier to Use of Methotrexate in Rheumatoid Arthritis: Comparing Conventional Vial, Needles, and Syringe With an Investigational Auto-Injector in Healthy Volunteers

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ABSTRACT

Title: Pain-Related Anxiety as a Barrier to Use of Methotrexate in Rheumatoid Arthritis: Comparing Conventional Vial, Needles, and Syringe With an Investigational Auto-Injector in Healthy Volunteers

Background: Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment.[1] Limitations of systemic exposure of oral MTX can affect its efficacy.[2,3] Subcutaneous (SC) MTX improves bioavailability, which may result in better efficacy and tolerability.[4] Self-administration of SC MTX via conventional vial, needle, syringe (VNS) is challenging for some patients due to functional limitations, injection-site adverse events (AEs), and especially anxiety associated with pain. Use of SC MTX is limited to <5% of patients in the U.S.[5] An analysis of literature from 1982–2012 on patient perception and experiences with self-administered medication for multiple diseases (RA, diabetes, hepatitis, multiple sclerosis) also suggests that anxiety associated with pain when using conventional VNS is often a barrier to use. Improvements in the delivery of SC MTX may alleviate anxiety associated with pain. In this study, the prototype of an investigational, first-in-class auto-injector (AI) for MTX is evaluated.

Methods: This study compares administration-related pain and bleeding in healthy volunteers using conventional VNS and AI. 21 volunteers received 12 injections (6 with AI; 6 with VNS) of 1.0 mL saline administered by investigators according to a randomized schedule. Pain was measured on a 21-point scale ranging from 0 (no pain) to 20 (extremely intense pain). Injection site bleeding was also assessed.

Results: Pain was rated as none or faint for 77.8% of 126 AI administrations and 61.1% for 126 injections with VNS (Fisher exact test, $P<0.01$, **Figure 1**). In addition, no pain was reported for 55.6% of AI administrations and 35.7% with VNS ($P<0.01$). No bleeding was observed in 89.7% of auto-injector administrations vs 76.2% of those with VNS ($P<0.01$).

Conclusions: Pain-related patient anxiety often associated with SC administration of medications is a potential cause for underutilization of SC MTX in the treatment of RA. By decreasing pain associated with self-injection, an AI may address issues of needle phobia and improve rates of utilization of SC MTX in patients who may benefit from this method of delivery.

INTRODUCTION

- Although MTX is the cornerstone of treatment for RA,[1] its oral efficacy is limited by variations in bioavailability[6] and the tolerability of gastrointestinal side effects.[7]
- Compared with orally administered MTX, SC MTX has improved bioavailability,[2,6] which would be expected to improve efficacy and tolerability.[3,4,7]
- However, the functional limitations of RA patients, together with the possibility of injection-site adverse events and injection-associated pain and anxiety, preclude the use of a needle-based system in many patients.
  - This is supported by SC usage data for MTX of <5% in the United States.[5]
- A review of literature data was conducted to compare the advantages of medication delivery using an injection device to the conventional VNS method.[5]
  - Pain-associated anxiety was a major barrier to VNS use.
  - Overall, drug administration using an injection device was more patient friendly, with the potential to positively affect therapeutic outcomes **(Table 1)**.

Table 1. Advantages Associated With the Use of an Injection Device for Self-Delivery of Medication

Reduced pain, anxiety, and fear associated with self-injection
Greater ease of self-injection
Greater accuracy of dose delivery
Greater adherence to pharmacotherapy
Reduced requirement for patient training
Increased patient confidence, satisfaction, and convenience

OBJECTIVE

- To compare the pain and bleeding associated with the use of an investigational, first-in-class AI with that of conventional VNS administration in healthy subjects

METHODS

Study Design and Subjects

- Healthy volunteers aged 18–70 years of age, who were willing to adhere to study requirements, were included.
- Key exclusion criteria
  - Uncontrolled hypertension ≤2 months before enrollment
  - Current use of medications that would interfere with accurate measurement of study endpoints (eg, anticoagulants, chemotherapy, or glucocorticoids)
  - Medical conditions that would affect measurement of study end points (eg, adrenal insufficiency, hemophilia, skin disorders, recent or ongoing infection, or radiation therapy involving the injection sites)
  - Participation in an injection-related study ≤30 days before enrollment or any prior participation in an injection study sponsored by Antares Pharma
- All subjects received 12 SC injections (6 with AI; 6 with VNS) of 1.0 mL saline to the thigh and abdomen, administered by investigators according to a randomized schedule, for a total of 252 injections (126 injections per treatment group).
  - The AI was a prototypic device composed of an injector and a prefilled syringe with a capacity of 1 mL and a 27-gauge needle designed to insert ≥2.5 mm of needle.
  - VNS injection was performed with the syringe and needle component of the AI.
  - The pinch-up technique was used for SC VNS injections, but not the AI.
- Each subject was required to complete all injections and evaluations for their group for successful study completion.

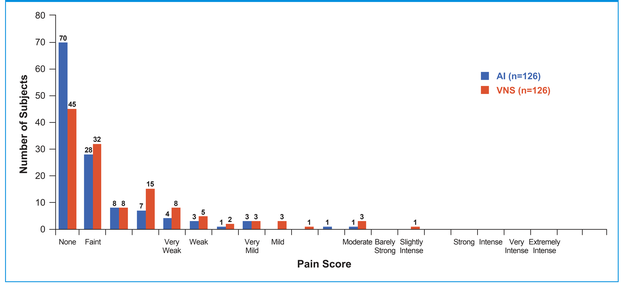
Administration Site Evaluations

- Postinjection pain was rated by the subjects using a scale ranging from 0 (no pain) to 20 (severe pain).
- Bleeding was rated by the investigator 30 seconds postinjection, using a 4-point scale based on the diameter of the bleeding area.
  - 0 = no bleeding (0–0.5 mm)
  - 1 = mild bleeding (0.5–1.5 mm)
  - 2 = moderate bleeding (1.5–4.0 mm)
  - 3 = severe bleeding (>4 mm)
- Between-group differences were measured by Fisher exact test.
- Adverse events, including hematomas and skin irritation, were documented and assessed as to severity and relationship to treatment.

RESULTS

- A total of 21 healthy volunteers (women, 76.2%) completed the study.
- The mean age of subjects was 34.5 years (range, 19–65 years) and the mean BMI was 26.2 kg/m^2 (range, 19.0–36.7).
- 10 subjects (47.6%) were Hispanic, 9 subjects (42.9%) were white, and 2 subjects (9.5%) were black.
- Pain ratings were significantly lower with the AI vs VNS **(Figure 1)**.
  - Pain was absent in 55.6% of subjects injected via the AI vs 35.7% of subjects with VNS ($P<0.01$).
- Ratings of no pain or faint pain were: AI, 77.8% of subjects; VNS, 61.1% of subjects ($P<0.01$).

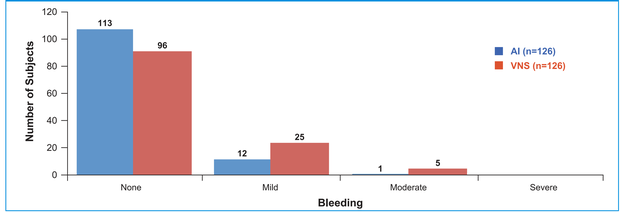
Figure 1. Pain Scores Following Subcutaneous Injection Using an AI vs a VNS



AI=auto-injector; VNS=vial, needle, and syringe.

- There was significantly less bleeding following use of the AI (89.7%) compared with VNS (76.2%; $P<0.01$; **Figure 2**).

Figure 2. Bleeding Scores Following Subcutaneous Injection Using an AI vs a VNS



AI=auto-injector; VNS=vial, needle, and syringe.

CONCLUSIONS

- SC administration of MTX may be underutilized because of patient concerns about pain and injection-associated anxiety.
- Use of the AI prototype was associated with significantly lower pain ratings and injection site bleeding vs conventional VNS.
- The AI prototype provides a SC delivery system for MTX that may increase patient acceptance of an injectable formulation for the treatment of RA.

DISCUSSION

- The use of an auto-injection device may decrease the psychological barriers associated with self-injection and provide greater convenience for the patient.
- For medications such as MTX, where oral administration is limited by bioavailability and adverse events, SC administration via an auto-injection device may be a viable treatment option in this patient population.

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