Rescue Analgesic Medication Use by Patients Treated with Triamcinolone Acetonide Extended-Release for Knee Osteoarthritis Pain: Pooled Analysis of Three Phase 2/3 Randomized Clinical Trials

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ABSTRACT

Introduction: In clinical trials for knee osteoarthritis (OAK), rescue medication is commonly provided to manage uncontrolled index-knee pain. The impact of treatment on rescue medication utilization provides important information on the robustness of analgesic effect. In randomized controlled OAK trials (NCT01487161, NCT02116972, NCT02357459), intra-articular (IA) triamcinolone acetonide extended-release (TA-ER) demonstrated substantial, prolonged analgesia versus saline-placebo and TA crystalline solution (TAs) as assessed by patient-reported pain scales. This pooled analysis assessed the impact of TA-ER on rescue medication use.

Methods: Patients (N = 798) with OAK (American College of Rheumatology criteria; Kellgren–Lawrence grade 2/3) and baseline average daily pain intensity score ≥ 5 to ≤ 9 (0–10 numeric rating scale) received a single IA injection of TA-ER (N = 324), saline-placebo (N = 262), or TAs (N = 212). Acetaminophen/paracetamol tablets were provided to treat uncontrolled pain (knee or otherwise). Rescue medication consumption was monitored through a daily diary; pill counts were confirmed at the clinical site. Differences in rescue medication use were measured by least-squares mean (LSM) differences, number of rescue medication tablets used per day, and in area under the effect (AUE) curves of rescue medication tablets used per week.

Results: The overall number of rescue medication tablets used per day through week 24 was significantly less (p ≤ 0.05) for TA-ER versus saline-placebo (LSM difference, -0.43) and TAs (-0.24). Rescue medication use was significantly (p ≤ 0.05) lower following TA-ER versus saline-placebo across weeks 1–12 (AUE_{weeks1–12}; LSM difference, -24.5) and weeks 1–24 (AUE_{weeks1–24}; -51.6) and versus TAs across weeks 1–12 (AUE_{weeks1–12}; -21.1).

Conclusions: In patients with painful OAK, reduced rescue medication use may be a potential benefit of TA-ER and further supports its analgesic efficacy. Additional research is needed to assess whether TA-ER impacts the use of other common oral analgesics (nonsteroidal anti-inflammatory drugs, opioids) for patients with OAK.

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Osteoarthritis of the knee (OAK) is a painful condition that contributes to reduced mobility and impaired quality of life [1, 2]. Symptomatic OAK is typically managed with analgesics, including oral agents [e.g., acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids] and standard intra-articular corticosteroid (IACS) injections [2–4]. Although oral pain-relieving agents can be effective in alleviating OAK pain, a number of associated adverse effects limit their long-term use [2, 4–7]. Conventional IACS injections reduce pain and improve function in OAK; however, the analgesic effect of standard IACS, such as triamcinolone acetonide crystalline suspension (TAc), may be of limited duration because of the rapid egress of corticosteroid from the joint space following injection [8–10]. Longer-acting IA pain relief treatments that reduce the long-term use of oral analgesics are needed for the management of patients with chronic OAK pain.

Triamcinolone acetonide extended-release (TA-ER) is a microsphere-enabled [75:25 poly(lactic-co-glycolic acid), nominal drug load of 25% (w/w)] longer-acting IA agent. Pharmacokinetic data show that TA joint residency time increased and systemic exposure decreased following TA-ER injection compared with standard TAc in patients with OAK [10]. This reduced systemic release of TA following TA-ER has been observed in several studies and may contribute to the reduced glycemic control disruption observed with TA-ER compared with TAc treatment in patients with OAK and type 2 diabetes [10–13]. The local synovial fluid TA concentration profile following TA-ER injection is in line with the prolonged, clinically meaningful efficacy observed in randomized controlled trials of patients with OAK [13–15]. In a phase 3 study, TA-ER significantly improved mean average daily pain (ADP) intensity score compared with saline-placebo at the 12-week primary endpoint ($p < 0.0001$) and provided continued significant improvements to week 16 ($p < 0.05$) [14]. TA-ER also provided significant improvements in the Western Ontario and McMaster Universities Osteoarthritis Index.
(WOMAC)-A (pain), -B (stiffness), and -C (function) and in the Knee Injury and Osteoarthritis Outcome Score-Quality of Life scores compared with both saline-placebo and TAcS at week 12 (\(p < 0.05\); prespecified exploratory endpoints) [14]. In the same study, TA-ER demonstrated an acceptable safety profile and most adverse events (AEs) were grade 1 or 2 and nonserious [14].

It is common in clinical trials of analgesic agents for rescue medication to be issued to participants for use as needed to manage uncontrolled index-knee pain [16]. Measuring rescue medication use can provide important information on the robustness of the overall analgesic effect because effective pain medications should reduce the need for rescue medication. According to guidance from the US Food and Drug Administration, rescue medication can be used to define a “responder” in clinical studies and can be used as a primary outcome measure and, furthermore, rescue medication use should be considered a secondary endpoint when pain intensity is the primary efficacy endpoint [17]. The use of rescue medication is frequently cited as a secondary endpoint or an additional efficacy measure in clinical trials evaluating the efficacy of other IA agents for OAK [18–23]. However, evidence is limited regarding the impact of conventional IACS on rescue medication use. One meta-analysis reported no difference in the proportion of rescue medication use with IA injection of conventional IACS [18]. Conversely, in a phase 3 study of TA-ER, rescue medication (acetaminophen/paracetamol) was provided to patients to manage uncontrolled index-knee pain, and use was evaluated as an additional efficacy measure in clinical trials evaluating the efficacy of other IA agents for OAK [18–23].

METHODS

Compliance with Ethics Guidelines

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Protocols of the three clinical studies (ClinicalTrials.gov identifiers: NCT01487161, NCT02116972, and NCT02357459) contributing information to the pooled analyses were approved by governing ethics bodies at the participating sites, and patients provided written informed consent before participating in any study-related procedures.

Study Design

Full details on patient eligibility, study design, and interventions in the phase 2 [13], phase 2b [15], and phase 3 [14] clinical trials included in this pooled analysis have been reported and are briefly summarized here. All studies enrolled men and women \(\geq 40\) years of age whose body mass index was \(\leq 40\) kg/m\(^2\). Participants had symptomatic OAK as defined by American College of Rheumatology OA criteria for \(\geq 6\) months [24], Kellgren–Lawrence grade 2/3 OA based on screening index-knee radiography [25], and baseline ADP intensity score \(\geq 5\) of the previous 7 days [26, 27]. Each trial used a similar multicenter, double-blind, randomized, parallel-group, controlled design. In each trial, patients were evaluated every 4 weeks following a single IA injection through 12 or 24 weeks. Data from patients treated with saline-placebo, TAcS 40 mg, and TA-ER 32 mg (delivered dose) were pooled for the purposes of this analysis.

Concomitant Medication

The following analgesics were considered restricted medications and were not to be taken or used during the studies: oral NSAIDs, aspirin (> 325 mg/day), centrally acting pain medica-
tions (e.g., pregabalin, gabapentin, duloxetine,
milnacipran), opioids, and topical therapies (e.g., topical NSAIDs, capsaicin, lidocaine patches, other local treatments) applied to the index knee. Rescue analgesic medication (acetaminophen/paracetamol 500-mg tablets) was issued to patients for use on an as-needed basis to manage uncontrolled index-knee pain or any other type of pain, and was not to be used for prophylaxis. Consumption of rescue medication was monitored through a daily diary reporting system, and pill counts were confirmed at the clinical site.

**Study Assessments**

The objective of the pooled analysis was to examine rescue medication use in three phase 2/3 clinical trials. Results from all three studies contributed to the findings for weeks 1–12 and results from the phase 2b/3 studies contributed to the findings from weeks 1–24. The mean number of rescue medication tablets used per week was computed for each patient by summing the number of tablets used in each weekly interval and dividing by the number of days of non-missing responses in the weekly interval.

Treatment-emergent AEs (TEAEs)—defined as any AE with onset after the administration of study treatment or any AE that was present at baseline but worsened in intensity through the end of the study—were analyzed.

**Statistical Analysis**

Effects of IA injection treatment on rescue medication use were measured by least-squares means (LSM) at each week through week 24 for TA-ER versus saline-placebo and TAc, analyzed with mixed effects model for repeated-measures methodology on observed data with no imputation for missing data. Area under the effect (AUE) curves of rescue medication use for TA-ER versus saline-placebo and TAc through week 12 (AUEweeks1–12) and week 24 (AUEweeks1–24) were analyzed using analysis of covariance, with study site as a covariate.

**RESULTS**

**Demographics and Baseline Disease Characteristics**

The pooled analysis included a total of 798 patients, with more patients receiving TA-ER (N = 324) than saline-placebo (N = 262) or TAc (N = 212). Across the three studies, demographic and baseline disease characteristics were well balanced for the three treatment groups, including similar baseline ADP intensity scores (Table 1). Most patients were female (58.6%) and white (84.3%). Mean body mass index at baseline was 30.55, 30.58, and 30.15 kg/m², and OAK was Kellgren–Lawrence grade 3 in 60.8, 59.5, and 58.0% of patients in the TA-ER, saline-placebo, and TAc treatment groups, respectively.

**Rescue Medication Use**

The use of rescue medication decreased following IA injection (Fig. 1a). The overall average number of rescue medication tablets used per day through 24 weeks [LSM (standard error, SE)] was 0.89 (0.090) for TA-ER compared with 1.32 (0.100) for saline-placebo, and the total LSM difference (95% CI) was –0.43 (–0.65, –0.20; p = 0.0002) for TA-ER compared with saline-placebo (Fig. 1b). Fewer rescue medication tablets were used per week by patients treated with TA-ER than saline-placebo at all time points, and the decreased use was significant (p < 0.05) at each of weeks 1–16 and 19–20 (Fig. 1a). Rescue medication use was also statistically significantly lower with TA-ER than with saline-placebo across weeks 1–12 (AUEweeks1–12; LSM difference, –24.5; p = 0.0121) and weeks 1–24 (AUEweeks1–24; LSM difference, –51.6; p = 0.0023; Table 2).

The overall average rescue medication tablets used per day through 24 weeks was lower for TA-ER with an LSM (SE) of 0.89 (0.090) compared with 1.13 (0.113) for TAc, and a total LSM difference (95% CI) through week 24 of –0.24 (–0.48, –0.01; p = 0.0433) for TA-ER compared with TAc (Fig. 1b). TA-ER treatment
reduced rescue medication use compared with TAcS at each week through week 24, with the difference reaching significance ($p < 0.05$) at weeks 6, 7, and 10 (Fig. 1a). TA-ER also significantly reduced rescue medication use across weeks 1–12 ($\text{AUE}_{\text{weeks 1–12}}$; $\text{LSM}$ difference,
21.1; \( p = 0.0424 \)) and numerically reduced medication use across weeks 1–24 (AUE\(_{\text{weeks1–24}}\); LSM difference, \(-32.2; p = 0.0731\); Table 2).

### Safety

Pooled safety data from the trials are presented in Table 3. Most TEAEs were grade 1 or 2, and there were no deaths. The incidence of TEAEs (51.9, 49.2, and 56.1%, respectively) and serious TEAEs (3.1, 1.1, and 1.9%, respectively) was similar across the TA-ER, saline-placebo, and TAc groups. Few patients discontinued because of TEAEs (1.2, 0.8, and 0.5% in the TA-ER, saline-placebo and TAc groups, respectively).

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### Table 2  Area under the effect curve of average rescue medication use

|                  | TA-ER 32 mg \( N = 324 \) | Saline-placebo \( N = 262 \) | TAc 40 mg \( N = 212 \) |
|------------------|-----------------------------|-----------------------------|--------------------------|
| AUE\(_{\text{weeks1–12}}\) |                             |                             |                          |
| LSM (SE)         | 82.6 (7.81)                 | 107.1 (8.57)                | 103.7 (9.74)             |
| LSM difference vs. saline-placebo (\( p \) value) | \(-24.5 (0.0121)\)         |                             |                          |
| LSM difference vs. TAc (\( p \) value)         | \(-21.1 (0.0424)\)         |                             |                          |
| AUE\(_{\text{weeks1–24}}\) |                             |                             |                          |
| LSM (SE)         | 135.6 (13.48)               | 187.2 (14.80)               | 167.9 (16.82)            |
| LSM difference vs. saline-placebo (\( p \) value) | \(-51.6 (0.0023)\)         |                             |                          |
| LSM difference vs. TAc (\( p \) value)         | \(-32.2 (0.0731)\)         |                             |                          |

\( AUE \) area under the effect curve, \( LSM \) least-squares mean, \( SE \) standard error, \( TAc \) triamcinolone acetonide crystalline suspension, \( TA-ER \) triamcinolone acetonide extended-release.
In this pooled analysis of three phase 2/3 clinical trials, TA-ER provided pain relief as shown by significant and sustained reductions in rescue medication use from baseline. In addition, patients treated with TA-ER required less rescue medication throughout the studies than patients treated with saline-placebo or TAc.

The safety profiles of TA-ER, saline-placebo, and TAc were similar in this pooled analysis and consistent with that in the individual studies. Providing rescue medication to patients participating in OA clinical trials can prevent dropout due to episodes of acute breakthrough pain or lack of efficacy and can provide an alternative way of measuring pain relief across treatment arms. The use of rescue medication is a clinically important indicator of analgesic efficacy and can be a secondary or an exploratory outcome measure in OA studies [16, 17].

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The current analysis is limited by its pooled retrospective nature. This led to differences in the number of patients receiving each treatment because of differences in individual study designs and durations. In addition, the allowance to use rescue medication for any worsening pain, not limited to OA knee pain, may have confounded the results; however, given the fact that these were large randomized trials, the impact of this potential confounder was considered to be minimal.

**CONCLUSIONS**

In patients with painful OAK, TA-ER treatment reduced rescue medication use compared with saline-placebo and TAc. These findings provide another indication of analgesic benefit of TA-ER.
beginning at week 1 and lasting throughout 24 weeks. Reducing concomitant analgesic medication use in this patient population may be an additional benefit of TA-ER treatment.

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**Data Availability.** The datasets generated during and/or analyzed during the current analysis are available from the corresponding author on reasonable request.

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