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A Double-blind, Randomized, Parallel-Group Comparison of Intraarticular Triamcinolone Acetonide Extended-Release Versus Triamcinolone Acetonide Immediate-Release on Glucose in Patients With Osteoarthritis of the Knee and Type 2 Diabetes Mellitus: a Post Hoc Analysis

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OBJECTIVE

This post hoc analysis was conducted to further characterize the clinical relevance and meaningfulness of previous phase 2 study results that demonstrated negligible effects of intraarticular injection of triamcinolone acetonide extended-release (TA-ER) on continuous glucose monitoring (CGM)–measured glucose in patients with osteoarthritis of the knee (OAK) and type 2 diabetes mellitus[1]

CONCLUSIONS

1. This post hoc analysis suggests that TA-ER was associated with a clinically meaningful reduction in hyperglycemia compared with triamcinolone acetonide immediate-release (TA-IR)
2. Relative to the TA-IR group, the TA-ER group had
   - Reduced spikes in glucose levels
   - Increased time in target blood glucose range (>70-180 mg/dL)
   - Reduced time with glucose levels >250 mg/dL
   - Decreased glucose management indicator levels (estimated glycated hemoglobin based on mean glucose)
3. TA-ER may be a safe intraarticular option for the management of OAK in patients with type 2 diabetes mellitus or prediabetes

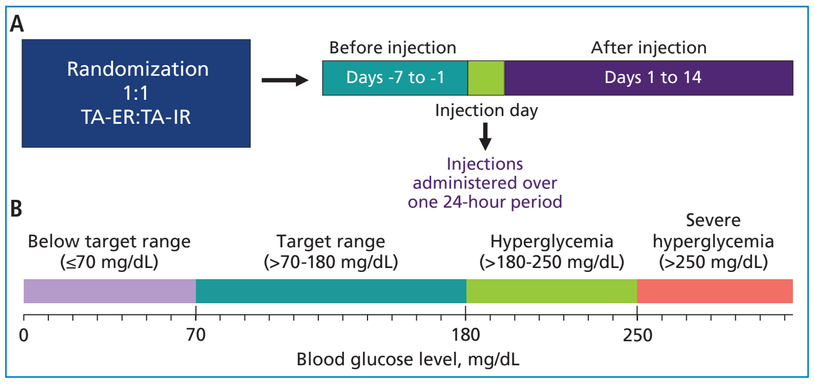
INTRODUCTION

- While intraarticular corticosteroid injections can treat pain and improve function in OAK,[2] they can be associated with hyperglycemia (blood glucose level >180 mg/dL)[3,4]
  - Intraarticular corticosteroids may result in marked hyperglycemia during the first 72 hours after injection; hyperglycemia may last up to 3 weeks after injection[3-5]
  - Severe hyperglycemia (blood glucose level >250 mg/dL) may lead to negative consequences[6-8]
- Approximately 14% of patients with osteoarthritis have diabetes, and ~30% of patients with diabetes have osteoarthritis[9]
- In a phase 2 study of patients with OAK and type 2 diabetes mellitus (n=33; NCT02762370), TA-ER showed minimal blood glucose disruption compared with TA-IR, consistent with the relatively low systemic exposure of TA-ER[1,10]

METHODS

- The study design is shown in Figure 1A
- Participants were monitored using CGM
  - An ambulatory glucose profile summarized blood glucose levels hourly 7 days before injection through 14 days after injection
- Blood glucose levels were defined as shown in Figure 1B

Figure 1. Study design (A) and blood glucose levels (B).



TA-ER, triamcinolone acetonide extended-release; TA-IR, triamcinolone acetonide immediate-release.

- Key inclusion and exclusion criteria and outcomes were as follows:

Key inclusion criteria	Key exclusion criteria
• Symptomatic OAK ≥6 months • Meet ACR clinical and radiologic criteria for OA • Type 2 diabetes ≥1 year • HbA1c ≥6.5% and <9.0%	• Systemic inflammatory joint disease • History of infection, surgical hardware, or foreign body in the index knee • IA viscosupplementation or any IA intervention in the index knee ≤6 months

Outcomes

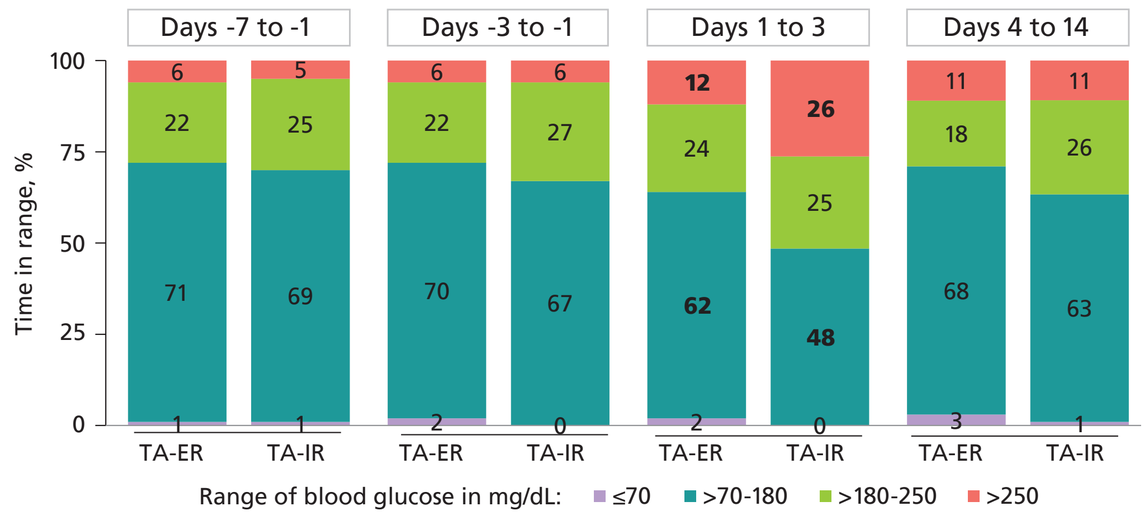
- Changes in average daily glucose levels from baseline
- Average time in or above the target range (>70-180 mg/dL)
- Time to reach 250 mg/dL
- Time to reach maximum glucose levels
- Glycemic variability
  - Estimated mean HbA1c/GMI was quantified using CGM with the following formula[11]: GMI% = 3.31 + 0.02392 × mean glucose in mg/dL

ACR, American College of Rheumatology; CGM, continuous glucose monitoring; GMI, glucose management indicator; HbA1c, glycated hemoglobin; IA, intraarticular; OAK, osteoarthritis of the knee.

RESULTS

- Baseline blood glucose levels were comparable between the TA-ER (n=18) and TA-IR (n=15) groups
- The 2 groups underwent injections at similar times on the injection day (median 12:00 PM vs 12:30 PM; range, 9:00 AM–4:00 PM for both; $P>0.2$)
- Postinjection blood glucose levels in the TA-ER group were reduced on days 1 to 3 compared with the TA-IR group
  - The median change from baseline in maximum glucose levels for days 1 to 3 was lower in the TA-ER group versus the TA-IR group (92.3 vs 169.1 mg/dL; $P=0.003$)
  - A 2-fold reduction in average time above the target range of >250 mg/dL (Figure 2; **orange** bars) was observed in the TA-ER group versus the TA-IR group (12% vs 26%; $P=0.047$) for days 1 to 3
  - A numerically larger percentage of time in the target range of >70-180 mg/dL (Figure 2; **cyan** bars) was observed in the TA-ER group versus the TA-IR group (62% vs 48%; $P=0.123$) for days 1 to 3

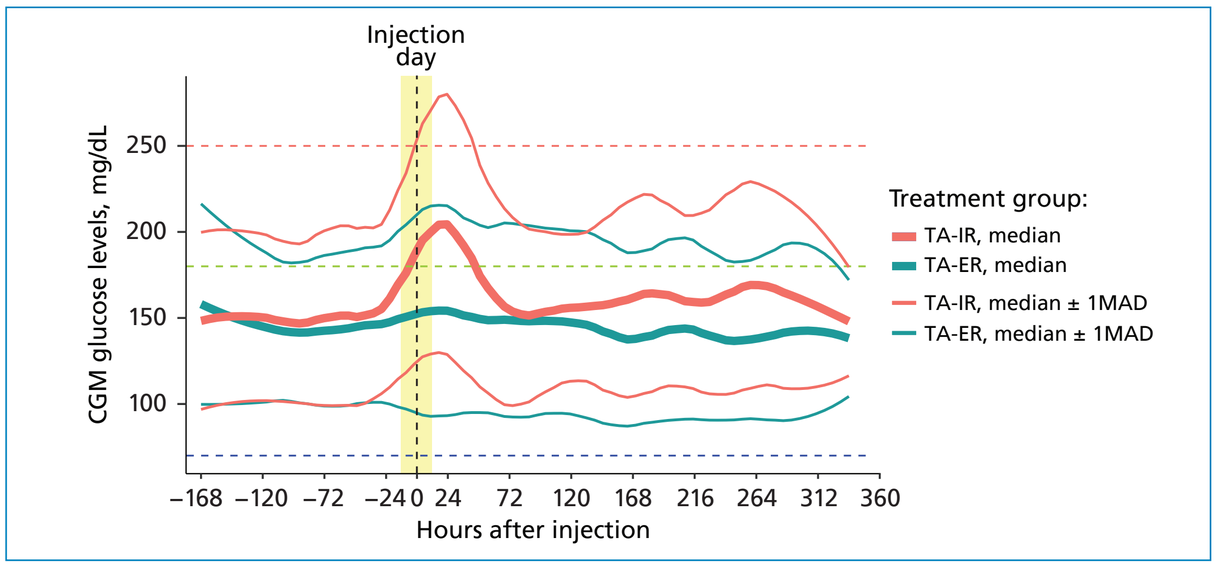
Figure 2. Percentage of time in specific blood glucose ranges by time interval and treatment group.



TA-ER, triamcinolone acetonide extended-release; TA-IR, triamcinolone acetonide immediate-release.

- Ambulatory glucose profile analyses demonstrated more consistent blood glucose levels and lower glucose spikes for the TA-ER group compared with the TA-IR group (Figure 3)
  - Similar trends were observed for 7:00 AM fasting glucose levels
- Estimated mean glucose management indicator levels were lower in the TA-ER group versus the TA-IR group for days 1 through 14 (7.1 vs 7.5; LSM difference [standard error], –0.41 [0.41]; 95% confidence interval, –1.24, 0.42), although this difference was not statistically significant ($P=0.3241$)

Figure 3. CGM levels over time.



Median glucose levels (thick lines), median glucose levels ± 1MAD (thin lines), target range limits (horizontal broken lines), and injection day (yellow shading and vertical broken line) are indicated. The red broken line indicates the severe hyperglycemia threshold, while the green and blue broken lines indicate the >180- and >70-mg/dL thresholds, respectively. CGM, continuous glucose monitoring; MAD, median absolute deviation; TA-ER, triamcinolone acetonide extended-release; TA-IR, triamcinolone acetonide immediate-release.

- The median time to glucose level 250 mg/dL and median time to maximum glucose level were significantly longer in the TA-ER group versus the TA-IR group, as follows:

Median time to glucose level 250 mg/dL		Median time to maximum glucose level		Interquartile range for maximum glucose level	
44 h	**6 h**	**34 h**	**13 h**	**114-194 mg/dL**	**131-212 mg/dL**
TA-ER	TA-IR	TA-ER	TA-IR	TA-ER	TA-IR
$P=0.003$		$P=0.007$			

DISCUSSION

- Reduced blood glucose spikes could lead to fewer short-term hyperglycemia-related adverse events
- Increased time in target range and decreased time above target range may improve glucose management in patients with OAK who have diabetes (especially in patients undergoing repeat intraarticular injections to manage OAK pain) and may also improve quality of life and reduce healthcare utilization
- Decreased glucose management indicator levels might result in reduced risk of long-term complications
- Future studies need larger sample sizes, broader patient clinical characteristics, and more clinically meaningful endpoints

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