IMPACT OF UPPER RESPIRATORY TRACT INFECTION ON THE SAFETY OF TECHNOSPHERE® INHALED INSULIN IN PATIENTS WITH TYPE 1 OR TYPE 2 DIABETES

PAUL D. ROSENBLIT[1], ELENA NIKONOVA[2], JOHN STEWART[3], PHILIP A. LEVIN[4]

[1]DIABETES/LIPID MANAGEMENT & RESEARCH CENTER, HUNTINGTON BEACH, CA, USA; [2]ARTECH INFORMATION SYSTEMS, LLC, MORRISTOWN, NJ, USA; [3]SANOFI, LAVAL, QC, CANADA; [4]MODEL CLINICAL RESEARCH, BALTIMORE, MD, USA

INTRODUCTION

- Afrezza® (human insulin) inhalation powder, commonly cited as Technosphere® inhaled insulin (TI), is a dry-powder formulation of recombinant human insulin developed for treatment of patients with type 1 diabetes (T1D) or type 2 diabetes (T2D).[1]
- TI consists of microparticles of fumaryl diketopiperazine to which insulin is adsorbed; the resulting powder is filled into unit dose cartridges and administered via the Gen2 inhaler device (**Figure 1**).[1,2]
- Compared with subcutaneous regular human insulin, and contemporary rapid-acting insulin analogs, TI has been shown to have a more rapid absorption, reaching maximum blood concentration within 15 minutes, with a short duration of action of 2–3 hours due to its elimination profile (**Figure 2** and **Table 1**).[3,4]
- The PK/PD profile of TI is more similar to the physiological profile of insulin than currently available standard rapid-acting insulins.[2]
- Upper respiratory tract infections (URTIs) occur in patients with diabetes at a similar frequency to the general population.[5]
- It has recently been shown that URTIs have no impact upon the PK/PD properties of TI;[6] however, concerns remain regarding the safety of TI during URTIs.
- There is particular concern regarding the impact of illness, such as uncomplicated URTIs, on safety, in particular the risk of hyperglycemia, ketoacidosis, and hypoglycemia in patients with diabetes receiving TI.

OBJECTIVE

- To assess whether URTIs affect the safety of TI in patients with T1D and T2D.

METHODS

Study Design and Patient Selection

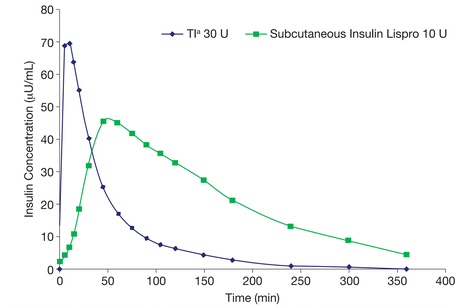
- A post hoc analysis of the TI arms of 9 clinical studies (two phase 2b, seven phase 3 randomized clinical trials) in patients with T1D or T2D who developed a symptomatic URTI while being treated with TI.
  - URTI was defined as ≥ 3 URTI symptoms from a questionnaire with a list of symptoms (runny nose, nasal stuffiness, sneezing, sore throat, scratchy throat, hoarseness, new-onset cough, sinus pain/pressure, head congestion/headache, and plugged ears/ear discomfort) in the 24 hours prior to and/or on the day of a clinic visit; symptoms were documented by each trial investigator
- Patient-level data from the safety population in the TI arms were grouped and compared based on whether patients experienced a URTI versus did not experience a URTI:
  - patients on TI who did not experience any episodes of URTI were identified, and any adverse events (AEs) they experienced were included in the no-URTI group
  - patients on TI who experienced ≥ 1 URTI were identified:
    - any AEs that occurred during a period of URTI were included in the URTI group
    - if the same patients had periods during which they were not experiencing a URTI, any AEs that occurred during these periods were included in the no-URTI group
    - patients not using TI were not included in this study

Assessments

- Demographic and clinical characteristics of patients.
- Discontinuation of TI due to URTI.
- Adverse events:
  - the incidence of AEs was given by the percentage of patients using TI who experienced AEs in URTI and no-URTI groups
  - the rate of AEs was estimated by the number of events experienced by each patient per year
  - hyperglycemia/ketoacidosis was defined by each trial investigator
  - hypoglycemia was defined as documented symptomatic hypoglycemia and/or blood glucose levels of < 70 mg/dL
  - overall AEs excluded hyperglycemia, hypoglycemia and URTIs

Figure 1. Gen2 Inhaler Device for the Delivery of TI.

Figure 2. Pharmacokinetic/Pharmacodynamic (PK/PD) Profile of Inhaled TI Versus a Subcutaneous Rapid-Acting Insulin.



[a] TI was delivered via the MedTone inhaler device, which has been shown to be equivalent to the marketed Gen2 inhaler in terms of efficacy and safety.[7]

Table 1. PK/PD Profile of Subcutaneous Insulin Versus Inhaled TI.

	Time to Maximum Insulin Concentration, min	Duration of Action, h
Regular human insulin (subcutaneous)	80-120	5-8
Insulin analogs (subcutaneous)	40-50	3-5
TI (inhaled)	12-17	2-3

Statistical Analysis

- Event rates were compared using a nonlinear model with a negative binomial distribution.

RESULTS

Patient Characteristics

- Baseline demographic and clinical characteristics of patients are shown in **Table 2**.

Discontinuation of TI

- Across the 9 studies included in this analysis, the number patients discontinuing TI due to URTIs was low (**Table 3**).
  - a total of 14 (0.5%) patients with diabetes who were treated with TI discontinued treatment due to URTIs; those values were reduced to 9 (0.3%) patients if bronchitis was excluded (**Table 3**)
- Discontinuation due to treatment-emergent adverse events (TEAEs) ranged from 0.9% to 11.3% (**Table 3**).

Table 2. Demographic and Clinical Characteristics of Patients at Baseline.

Study ID	Number of Patients	Age, Years, Mean (SD)	Female, n (%)	Race: White, n (%)	Body Mass Index, kg/m², mean (SD)
MKC-005	180	58 (8.6)	78 (43.3)	179 (99.4)	30.1 (4.7)
MKC-009	285	38 (13.0)	134 (47.0))	241 (84.6)	26.2 (4.0)
MKC-010	144	58 (8.3)	65 (45.1)	144 (100)	29.6 (4.0)
MKC-030	914	51 (11.6)	363 (39.7)	784 (85.8)	29.9 (5.3)
MKC-102	316	56 (10.7)	156 (49.4)	209 (66.1)	31.5 (4.8)
MKC-103	355	57 (8.4)	199 (56.1)	268 (75.5)	31.0 (4.3)
MKC-117	65	39 (11.8)	25 (38.5)	56 (86.2)	25.1 (3.7)
MKC-171	347	38 (12.9)	190 (54.8)	330 (95.1)	26.1 (4.1)
MKC - 175	177	57 (9.1)	95 (53.7)	151 (85.3)	31.8 (4.9)
Patients with URTIs across 9 studies	245	51 (12.9)	107 (43.7)	201 (82.0)	29.9 (4.9)
All patients across 9 studies	2,596	51 (12.0)	1,206 (46.5)	2,182 (84.1)	29.58 (5.1)

Table 3. Discontinuation of TI in the 9 Studies.

Study ID	Phase	Safety Population Total (N)	Diabetes Type	Patients who discontinued due to any TEAE, n (%)	Patients who discontinued due to URTI, n (%)
MKC-005	2	227	2	2 (0.9)	0 (0)
MKC-009	3a	293	1	16 (5.5)	3 (1.0)[a]
MKC-010	2b	144	2	16 (7.0)	0 (0)
MKC-030	3a	923	1, 2	104 (11.3)	5 (0.5)[b]
MKC-102	3	323	2	33 (10.2)	2 (0.6)[c]
MKC-103	3	355	2	(< 5.0)	0 (0)
MKC-117	3	65	1	4 (6.2)	1 (1.5)[d]
MKC-171	3	347	1	25 (7.2)	3 (0.9)[e]
MKC- 75	3	177	2	7 (4.0)	0 (0)[f]
Total across 9 studies		2,854		NA	14 (0.5) Excluding bronchitis: 9 (0.3)

[a] 1 URTI, 1 bronchitis, 1 upper respiratory tract congestion; [b] 3 URTI, 2 bronchitis; [c] 2 bronchitis; [d] 1 influenza-like illness; [e] 2 URTI, 1 viral respiratory tract infection (reported in basal insulin optimization phase); [f] 1 URTI (temporary discontinuation).
NA, not available.

Hyperglycemia/Ketoacidosis

- All identified patients experienced at least 1 episode of hyperglycemia/ketoacidosis, regardless of URTI (**Figure 3**).
- The annualized rate of hyperglycemia/ketoacidosis was significantly greater in the patients with URTIs compared with those without URTIs (**Figure 4**).
  - this corresponds to an estimated 4.58-fold increase in hyperglycemia/ketoacidosis events per patient-year for patients with URTIs (95% CI: 3.71- 5.64; $P = 0.01$)

Hypoglycemia

- Patients in the URTI group were less likely to experience hypoglycemia compared with those in the no-URTI group (**Figure 3**).
  - this corresponds to an estimated decrease of 19.1% in the incidence of hypoglycemia in patients with URTIs compared with those without URTIs (95% CI: 13.1-25.0; $P = 0.0001$)
- The annualized rates of hypoglycemia were comparable between groups (**Figure 4**).

All AEs Excluding URTIs and Hypoglycemia

- All patients in both groups experienced at least 1 AE (n = 246 patients in the URTI group; n = 2,595 patients in the no-URTI group) (**Figure 3**).
- Patients in the URTI group had significantly higher annualized rates of AEs compared with patients in the no-URTI group (**Figure 4**).
  - this corresponds to an estimated 4.06-fold increase in the occurrence of AEs per patient-year (95% CI: 3.27-5.03; $P = 0.01$) for patients with URTIs

Figure 3. Incidence of Safety Outcomes During URTI or No-URTI Periods in Patients With T1D and T2D Receiving TI.

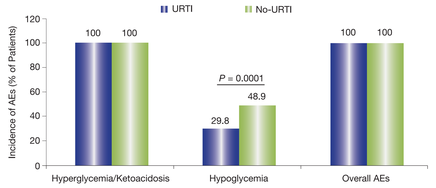
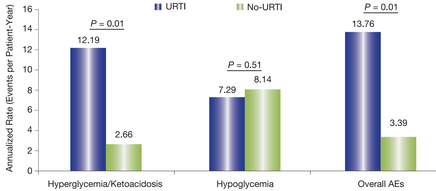


Figure 4. Annualized Rates of Safety Outcomes During URTI or No-URTI Periods in Patients With T1D and T2D Receiving TI.



DISCUSSION

- The incidence of hyperglycemia/ketoacidosis was comparable for patients with URTIs (100%) and without URTIs (100%), while the annualized rate was significantly greater in those with URTIs (12.19 events per patient-year for the URTI group versus 2.66 events per patient-year for the no-URTI group; estimated ratio 4.58, 95% CI:3.71-5.64; $P = 0.01$).
- The incidence, but not the annualized rate, of hypoglycemia was greater in the no-URTI patient group.
- The annualized rate of overall AEs was significantly greater in patients with URTIs.
- The increased rate of hyperglycemia/ketoacidosis and the decreased frequency of hypoglycemia associated with URTI periods suggest that some patients experiencing a URTI do not receive the full benefit of the glucose-lowering effect of TI; this was expected, as URTIs of varying degrees trigger a stress hormone response, leading to higher overall glycemia, which is associated with a greater rate of hyperglycemia (and possibly a greater rate of ketoacidosis).
- Additional insulin dosing may be required when patients have URTIs, whether utilizing standard fast-acting insulin therapies or TI.
- These study findings are limited to patients with URTI; patients with lower respiratory tract infection were not studied.
- The main limitation of this analysis was its post hoc nature; it does, however, provide important insights into how future studies may be structured.

CONCLUSIONS

- Therapy with TI for the management of T1D and T2D was associated with a lower incidence of hypoglycemia in patients with a URTI compared with those without a URTI, while the incidence of hyperglycemia/ketoacidosis was comparable between groups.
- The annualized rate of hyperglycemia/ketoacidosis was significantly higher during URTI periods, suggesting that some patients might need to intensify therapy to maintain normal blood glucose values at these times.

REFERENCES

1. Rave K, et al. Diabetes Care. 2007;30:2307-8.
2. Rave K, et al. J Diabetes Sci Technol. 2008;2:205-12.
3. Rave K, et al. Diabetes Obes Metab. 2009;11:715-20.
4. Boss AH, et al. J Diabetes Sci Technol. 2012;6:773-9.
5. McElduff A, et al. Br J Clin Pharmacol. 2005;59:546-51.
6. Levin P, et al. Poster presented at ADA 2015; poster 94-LB.
7. Marino MT, et al. Poster presented at Diabetes Technology Meeting 2010; poster A96.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was funded by Sanofi US, Inc. The authors received writing/editorial support in the preparation of this poster provided by Catarina Fernandes, PhD, of Excerpta Medica, funded by Sanofi US, Inc. Afrezza and Technosphere are registered trademarks of MannKind Corporation.

Rosenblit: AbbVie, Boehringer Ingelheim, Janssen, Kowa, Takeda – member of the speaker/teaching faculty; Amgen, Dexcom, Eisai, Novo Nordisk, Orexigen, Pfizer, Sanofi – clinical research trial support; AstraZeneca (Bristol-Myers Squibb), GlaxoSmithKline – member of the speaker/teaching faculty, clinical research trial support; Lilly – clinical research trial support, consultant/advisor; Merck – member of the speaker/teaching faculty, clinical research trial support, consultant/advisor; Amarin, AstraZeneca, Sanofi, Regeneron – consultant/advisor.
Nikonova: Artech Information Systems, LLC, under contract with Sanofi – employee.
Stewart: Sanofi, Canada – employee; Sanofi – stockholder.
Levin: Novo Nordisk, Inc. – advisory panel, consultant, research support, speakers bureau; Sanofi US, Inc. – advisory panel, consultant, research support, speakers bureau; Eli Lilly and Company – research support, speakers bureau; Amylin Pharmaceuticals, Inc. – research support, speakers bureau; GlaxoSmithKline – research support ; Boehringer Ingelheim – research support ; AstraZeneca – research support, speakers bureau; MannKind Corporation – speakers bureau.

Email address for presenting author: pdrosenblit@yahoo.com