Technosphere® Inhaled Human Insulin has a More Rapid Onset of Action Than Subcutaneous Insulins
- Meta Analysis of Clamp data From Three Clinical Studies -

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ABSTRACT

Inhaled Technosphere® Insulin (TI) Afrezza® is characterized by fast absorption and short half-life. It was previously reported that TI insulin has similar onset of action as subcutaneous (SC) Insulin Lispro despite its faster absorption, based on 12 patients from study MKC-TI-177. We aim to verify whether pharmacokinetic (PK) properties of TI translate into a faster onset of action compared to SC regimens. Data from 3 euglycemic clamp studies were analyzed using WinNonlin Phoenix® software. 1) MKC-TI-176 in 32 healthy volunteers at TI doses of 10, 30, 60, and 80 U versus SC RHI at 15 U; 2) MKC-TI-177 in 12 type1 diabetics at TI 20 U versus SC insulin Lispro at 8 U; 3) MKC-TI-116 in 25 type1 diabetics at TI 30 U versus SC insulin Lispro at 10 U. Area under glucose infusion rate (GIR) from time 0 till 240 min ($GIR_{AUC0-240}$) and time (T) to reach partial areas (10 and 50% $GIR_{AUC0-240}$) were estimated using the linear trapezoidal rule. GIR profiles were fitted to first order input and first order output mathematical models to estimate time to maximum GIR (T-GIR_{max}) and time to 20 and 50% GIR_{max}. PK parameters of insulin were determined using non-compartmental methods. The conclusion on onset of action of TI insulin from data of MKC-TI-177 study seems to be inconsistent with results of the pooled analysis using larger sample sizes. This pooled analysis demonstrated faster onset of action for TI than SC insulins based on all GIR_{max} and $GIR_{AUC0-240}$ parameters. Time to 20% GIR_{max} ranged from 2.5 to 18 min for TI and from 13 to 34 min for SC insulin. Time to 10% $GIR_{AUC0-240}$ ranged from 25 to 34 min for TI and from 53 to 60 min for SC insulin. The faster onset of action of TI compared to SC insulin can be relevant for optimal dosing of TI with respect to meals.

INTRODUCTION

Afrezza (Technosphere Insulin, TI)

- Recently approved by FDA to control high blood sugar in adults with type 1 and type 2 diabetes mellitus
- Characterized by fast absorption with a peak serum concentration at T_{max} ~ 15 min and return to near-baseline in about 3 hours [1].

Insulin pharmacodynamics (PD)

- No official definition of "onset of insulin action"
- Various parameters has been reported in literature [3-7].
- Parameters typically reported in glucose clamp studies:
  - $GIR_{AUC,0-t}$ – area under glucose infusion rate curve from time of dosing to time t
  - GIR_{max} – maximum smoothed glucose infusion rate
  - T_{GIRmax} – time of GIR_{max}

Possible measures of "onset of action"

- $T_{X\%}$-GIR_{max} – time for GIR to increase to X% of GIR_{max}
- $T_{X\%}$-$GIR_{AUC,0-t}$ – time to reach X% of the total insulin effect over interval t

METHODS

Data from three hyperinsulinemic-euglycemic clamp PKPD studies were obtained. All these studies were open-label, randomized, cross-over design.

Table 1. Design of PKPD clamp studies

Study code	MKC-TI-176	MKC-TI-177	MKC-TI-116
NCT number	NCT01490762	NCT01544881	NCT0062857
Population	Healthy volunteers	T1DM	T1DM
Sample size	32	12	25
Body weight (kg)	49 - 99	68 - 96	53 - 113
Age (year)	18 - 53	25 - 55	19 - 61
Doses of TI	10, 30, 60 & 80 U	20 U	30 U
Doses of SC insulin	15 IU (RHI)	8 U (Lispro)	10 U (Lispro)
GIR monitoring time	240 min (TI), 600 min (SC)	360 min	360 min

Pharmacokinetics

- Serum insulin measured by radioimmunoassay (RIA) with a lower limit of quantification (LLOQ) of 8 µU/mL
- Insulin concentration corrected by C-peptide to account for endogenous insulin (MKC-TI-176 only)
- Noncompartmental PK analysis by WinNonlin Phoenix® software (Certara, Princeton, NJ 08540 USA)

Pharmacodynamics

- Mean glucose infusion rate (GIR) profiles were smoothed and corrected for baseline
- GIR_{AUC0-t} calculated by linear trapezoidal integration.
- $T_{X\%}$-$GIR_{AUC,0-t}$ was estimated from the cumulative GIR_{AUC} over time
- T-GIR_{max} and $T_{X\%}$-GIR_{max} were estimated from exponential fits to smoothed GIR
- In study MKC-TI-176, $GIR_{AUC,0-600}$ of TI was extrapolated from $GIR_{AUC,0-240}$.

RESULTS

Pharmacokinetics and GIR profiles (Table 2):

- TI showed a much faster absorption than SC insulin in all 3 studies (Figure 1)
- Time to Peak response (T-GIR_{max}) was also shorter than for SC administration (Figure 2)
- Onset of action parameters, $T_{20\%}$-GIR_{max} and $T_{50\%}$-GIR_{max}, were much shorter for TI than SC insulin, consistently across studies and irrespective of dose level of administered insulin (Table 2).
- GIR profile from Study MKC-TI-177 was not similar to those from other studies (Figure 2, Figure 3).

RESULTS

Figure 1. Baseline corrected Insulin (PK) profiles

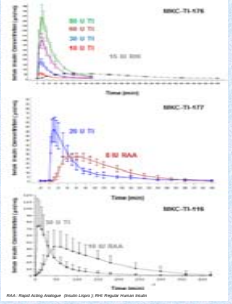


Figure 2. Baseline corrected GIR (PD) profiles

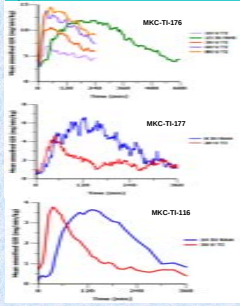


Figure 3. Model fitted GIR profiles for TI vs SC insulins

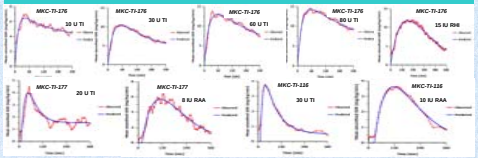


Table 2. Onset of action parameters of TI versus SC insulins

Study	TI / SC	Dose	T-GIR_{max} (min)	$T_{20\%}$-GIR_{max} (min)	$T_{50\%}$-GIR_{max} (min)	$T_{10\%}$-$GIR_{AUC,0-240}$ (min)	$T_{20\%}$-$GIR_{AUC,0-240}$ (min)	$T_{50\%}$-$GIR_{AUC0-360}$ (min)	$T_{50\%}$-$GIR_{AUC,0-360}$ (min)	Insulin $^{a}T_{max}$ (min)	Insulin $^{a}C_{max}$ (µU/mL)
MKC-TI-176	TI	10 U	41	2.5	7.7	30	112	-	-	10	53
		30 U	54	3.6	11	30	106	-	-	15	178
		60 U	57	3.5	11	34	112	-	-	15	435
		80 U	57	3.4	10	33	112	-	-	15	672
	SC	15 IU	184	13	41	53	143	-	-	120	54
MKC-TI-177	TI	20 U	45	18	13	33	94	40	135	7.5	61
	SC	8 U	111	26	40	55	132	62	155	50	36
MKC-TI-116	TI	30 U	37	13	16	25	75	27	90	10	78
	SC	10U	116	34	47	60	135	67	156	60	49

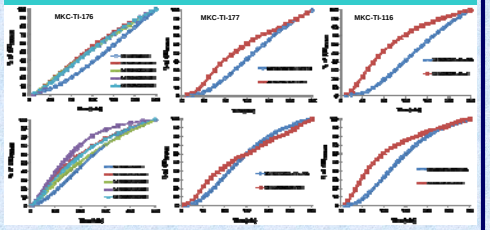
[a]Median for T_{max}, mean for C_{max}; [b]In MKC-TI-176 study SC, T-10% and T-50% $GIR_{AUC0-600}$ were 85 and 261 min respectively

RESULTS

Cumulative AUC profiles:

- Timing of TI effect is "front-loaded" - early portions of TI curves lie above curve for SC insulin
- TI has shorter duration of action – steeper curves indicate TI effect ends sooner
- MKC-TI-177 study deviates from pattern

Figure 4. Cumulative GIR_{AUC} profiles TI vs SC



CONCLUSIONS

- This meta analysis demonstrated faster onset of action for TI than SC insulins based on all derived GIR_{max} and $GIR_{AUC,0-240}$ parameters.
- Time to 20% GIR_{max} ranged from 2.5 to 18 min for TI and from 13 to 34 min for SC insulin across studies.
- Time to 50% GIR_{max} ranged from 7.7 to 16 min for TI and from 41 to 47 min for SC insulin across studies.
- Time to 10% $GIR_{AUC,0-240}$ ranged from 25 to 34 min for TI and from 53 to 60 min for SC insulin across studies.
- Study MKC-TI-177 showed an outlier GIR profile after TI administration
- The faster onset of action of TI compared to SC insulins is relevant for optimal dosing of TI.

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Disclosures: All authors are employees of MannKind or Sanofi.

American Diabetes Association • 76th Scientific Sessions • June 10 - 14, 2016, New Orleans, Louisiana

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Poster 931-P