Pharmacokinetics and Pharmacodynamics of Anti-CD3 Monoclonal Antibody, Otelixizumab, in Subjects with Type 1 Diabetes and Psoriasis

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Objectives

Otelixizumab, a targeted T cell immunomodulator, is a monoclonal antibody directed against the CD3ε part of the T-cell receptor complex (CD3/TCR). Otelixizumab administration causes rapid transient redistribution of lymphocytes from blood and down-modulation of CD3/TCR from the T cell surface. Additionally, T cell modulation may induce up-regulation of T regulatory cells which may lead to long-term immunologic remission. These observed effects of otelixizumab are promising for treatment of various disorders, such as type 1 diabetes, psoriasis, or other T cell mediated autoimmune diseases. This study describes a population pharmacokinetic (PK) model to account for serum otelixizumab concentrations following intravenous administration for type 1 diabetes and psoriatic patients. It also characterizes the pharmacodynamics (PD) of otelixizumab effects on the absolute counts of CD4+ and CD8+ T cells and on the modulation and saturation of CD3/TCR receptors. The last were determined based on quantitative flow cytometry assays.

Methods

Clinical Study Design:

Table 1. Clinical studies of otelixizumab included in this analysis

Study	Group or Cohort	Doses (mg) [a]	Disease [b]	Number of subjects
I	Group A	24, 8, 8, 8, 8, 8	D	3
	Group B	8, 8, 8, 8, 8, 8	D	37
II	Cohort 1	1	P	4
	Cohort 2	2	P	4
	Cohort 3	4	P	8
III	Cohort 1	0.1, 0.1, 0.1	D	5
	Cohort 2	0.5, 0.5, 0.5	D	3
	Cohort 9	0.1, 0.3, 0.5	D	4
	Cohort 10	0.3, 0.5, 1.0	D	1
	Cohort A	0.1, 0.2, 0.3, 0.5	D	5
	Cohort A(1/2)	0.05, 0.1, 0.15, 0.25	D	1
	Cohort B	0.1, 0.2, 0.3, 0.75	D	4
	Cohort C	0.1, 0.2, 0.3, 1.0	D	1
	TTEDD CH1	0.1, 0.2, 0.3, 0.5x5	D	16
	TTEDD CH2	0.1, 0.2, 0.3, 0.75x5	D	18
	TTEDD CH3	0.1, 0.2, 0.3, 0.75, 1, 1.25, 1.5, 1.75	D	6

[a] Doses were given once daily for 1 to 8 days.
[b] D – Type 1 diabetes; P – Psoriasis.

Three clinical trials of otelixizumab were carried out as summarized in Table 1. The Belgian Diabetes Registry (BDR) study (Study I) was a multicenter, randomized, placebo-controlled, double-blind, Phase 2 trial in 80 patients with new-onset type 1 diabetes. Forty subjects received otelixizumab and 40 received placebo. The drug was given as an IV infusion over 2-4 hours on 6 consecutive days. The first 9 patients received a dose of 24 mg on the first day and 8 mg on subsequent days (or placebo). The remaining 71 patients received 8 mg on all 6 days (or placebo) [1]. The second study (Study II) was a multi-center, open-label, single-dose, dose-escalation Phase 1 study with 16 patients with moderate to severe psoriasis. Three single doses of 1, 2, and 4 mg were administered as 1-hour infusions. The third study referred to as TTEDD (Study III) was a Phase 2 non-randomized control, dose comparison, open label trial and was carried out on 62 patients with type 1 diabetes. The study was designed to optimize dosing schemes. Different doses and numbers of administrations were used as shown in Table 1 for the various groups and cohorts. The drug was given as an IV infusion over 2 hours.

PK/PD Model

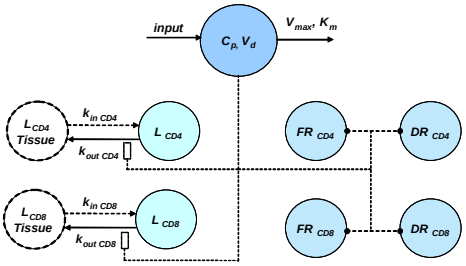

Figure 1. Diagram of PK/PD model of otelixizumab.

The schematic diagram of PK/PD model is given in Fig. 1. The serum otelixizumab concentrations (C_p) versus time were described by a one-compartment model with Michaelis-Menten (MM) saturable elimination:

$$\frac{dC_p}{dt} = Input/V_d - V_{\max}C_p/(K_m + C_p) \quad C_p(0) = 0 \tag{1}$$

where V_d is the volume of distribution, V_{max} is the capacity of the elimination process, and K_m is the affinity constant or the serum otelixizumab concentration at which the elimination rate attains one-half of V_{max}.

The lymphocyte count (L) was described by an indirect response model simplified to an inhibitory direct effect relationship:

$$\frac{dL}{dt} = k_{in} - k_{out}(1 + m \cdot C_p)L \quad L(0) = \frac{k_{in}}{k_{out}} = L_0 \Rightarrow L = \frac{k_{in}}{k_{out}(1 + m \cdot C_p)} = L_0\left(1 - \frac{C_p}{IC_{50} + C_p}\right) \tag{2}$$

where k_{in} is an apparent zero-order migration rate of lymphocytes from peripheral tissue to blood, and k_{out} is a first-order migration rate constant from blood to peripheral tissues. The drug was assumed to increase the lymphocyte migration rate in proportion (m) to the serum otelixizumab concentration. The L_0 is the pretreatment lymphocyte count and $IC_{50} = 1/m$ is the otelixizumab concentration that produces a 50% decrease from baseline lymphocyte counts.

The decrease in free CD3/TCR (FR) on the CD4+ and CD8+ lymphocytes was described by a direct inhibitory effect; the drug receptor complex (DR) was assumed to be at equilibrium with the drug concentration and the number of free receptors per cell and the total receptor number (TR) is the sum of free and otelixizumab bound receptors. Thus, the FR, DR and TR are given by:

$$FR = FR_0\left(1 - \frac{I_{\max}C_p}{IC_{50,FR} + C_p}\right) \quad DR = \frac{FR \cdot C_p}{K_D} \quad TR = FR + \frac{FR \cdot C_p}{K_D} = FR\left(1 + \frac{C_p}{K_D}\right) \cong FR \tag{3}$$

The receptor dynamic measurements (FR, DR, and TR) were done in MESF units that are proportional to the quantity measured:

$$MFR = \gamma_{FR}\, FR \qquad MDR = \gamma_{DR}\, DR \qquad MTR = \gamma_{TR}\, TR \tag{4}$$

where γ_{FR}, γ_{DR}, and γ_{TR} are proportionality constants converting FR, DR, and TR to actually measured MFR, MDR, and MTR. Combining eqs (3) with eqs (4) one obtains:

$$MFR = MFR_0\left(1 - \frac{I_{\max}C_p}{IC_{50,FR} + C_p}\right) \qquad MDR = SCL_1 \cdot MFR \cdot C_p \qquad MTR = SCL_2\, MFR \tag{5}$$

where $MFR_0 = \gamma_{FR}FR_0$ is the pretreatment value of MFR; $SCL_1 = \gamma_{DR}/\gamma_{FR}/K_D$ and $SCL_2 = \gamma_{TR}/\gamma_{FR}$ represent the proportionality constants.

Population nonlinear mixed-effect modeling was done using NONMEM (Version 6.1.0, Icon Development Solutions, Ellicott City, Maryland, USA) and the Intel Fortran Compiler 9.0. NONMEM runs were executed using Wings for NONMEM (WFN611). The first-order conditional estimation with interaction (FOCE) method was used.

Results

Table 2. Parameter estimates from population PK/PD model: fixed effects. The confidence intervals (CI) are represented as 5th – 95th percentile.

Parameter [units]	Definition	Population mean value, (SE%) [CI]
Common Parameters		
V_{max} [ng/mL/day]	Michaelis-Menten capacity constant	1.35 (37.6) [1.04 – 1.66]
K_m [ng/mL]	Michaelis-Menten affinity constant	0.968 (51.0) [0.733 – 1.25]
V_d [L]	Volume of distribution	13.9 (15.3) [12.2 – 16.8]
$L_{0,CD4}$ [10^3 cell/μL]	Initial count of CD4+ cells	0.787 (4.1) [0.745 – 0.832]
$L_{0,CD8}$ [10^3 cell/μL]	Initial count of CD8+ cells	0.386 (5.5) [0.359 – 0.415]
$IC_{50,FR,CD4}$ [ng/mL]	Concentration producing 50% decrease in FR of CD4+ cells	0.0144 (12.1) [0.0121 – 0.0177]
$IC_{50,FR,CD8}$ [ng/mL]	Concentration producing 50% decrease in FR of CD8+ cells	0.0162 (11.2) [0.0131 – 0.0198]
$IC_{50,CD4,Ps}$ [ng/mL]	Concentration producing 50% decrease of CD4+ cells in psoriasis	0.000533 (41.1) [0.000249 – 0.00105]
$IC_{50,CD8,Ps}$ [ng/mL]	Concentration producing 50% decrease of CD8+ cells in psoriasis	0.000269 (49.8) [0.0000876 – 0.000605]
$IC_{50,CD4,D}$ [ng/mL]	Concentration producing 50% decrease of CD4+ cells in diabetes	0.0187 (18.3) [0.0147 – 0.0243]
$IC_{50,CD8,D}$ [ng/mL]	Concentration producing 50% decrease of CD8+ cells in diabetes	0.0120 (19.9) [0.00918 – 0.0161]
Study II		
$MFR_{0,CD4,II}$ [10^3 MESF]	Initial MESF of TRX4+ of CD4+cells in Study II	0.901 (3.2) [0.854 – 0.954]
$MFR_{0,CD8,II}$ [10^3 MESF]	Initial MESF of TRX4+ of CD8+ cells for Study II	0.678 (3.5) [0.642 – 0.721]
$SCL_{1,II}$ [(μg/mL)$^{-1}$]	Conversion factor for settings used in Study II	138 (21.0) [94.1 – 193]
$SCL_{2,II}$ []	Conversion factor for settings used in Study II	0.988 (1.2) [0.966 – 1.01]
Study III		
$MFR_{0,CD4,III}$ [10^3 MESF]	Initial MESF of TRX4+ of CD4+cells in Study III	3.39 (2.9) [3.22 – 3.55]
$MFR_{0,CD8,III}$ [10^3 MESF]	Initial MESF of TRX4+ of CD8+ cells for Study III	2.42 (3.0) [2.30 – 2.54]
$SCL_{1,III}$ [(μg/mL)$^{-1}$]	Conversion factor for settings used in Study III	105 (11.7) [86.9 – 127]
$SCL_{2,III}$ []	Conversion factor for settings used in Study III	0.197 (2.9) [0.189 – 0.206]

Parameter [Units]	Between-subject variability (SE%) [CI]
Between subject variability, V_d [%CV]	75.90 (29.5) [62.7 – 86.4]
Between subject variability, $L_{0,CD4}$ [%CV]	28.2 (20.8) [24.1 – 31.4]
Between subject variability, $L_{0,CD8}$ [%CV]	34.4 (21.1) [29.5 – 38.6]
Between subject variability, V_{max} [%CV]	28.6 (62.7) [21.0 – 34.9]

Table 3. Between-subject variability of parameter estimates from population PK/PD model: random effects. The confidence intervals (CI) are represented as 5th – 95th percentile.

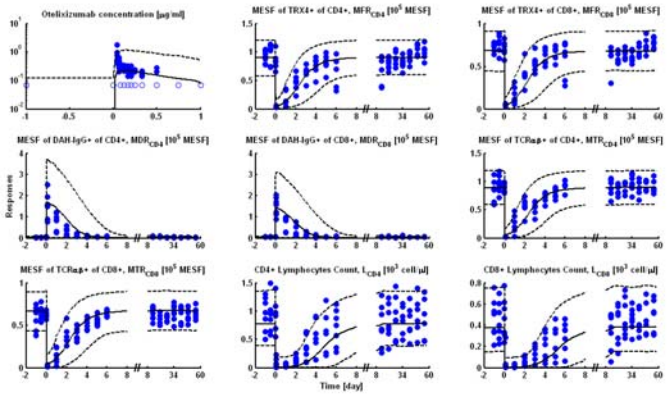

Figure 2. The time course of otelixizumab concentrations and various responses after a 4 mg dose in subjects with psoriasis (Study II: Cohort 3). The visual predictive check plots were generated from Monte Carlo simulations (n = *2000*). The simulations are represented as – 50th, -- 5th and -- 95th percentiles, • observed responses, o concentrations below the limit of quantification.

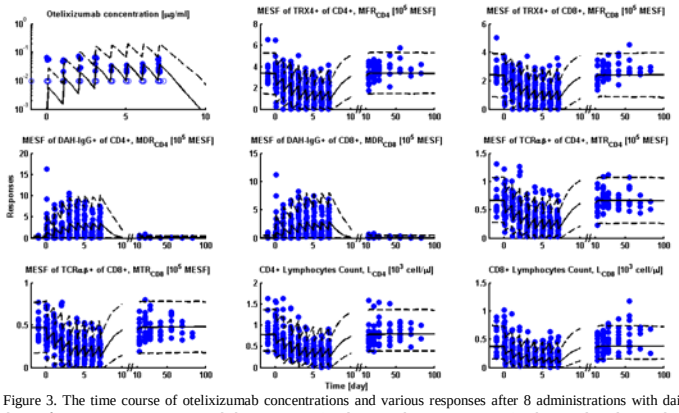

Figure 3. The time course of otelixizumab concentrations and various responses after 8 administrations with daily doses of 0.1, 0.2, 0.3, 0.5x5 mg in diabetic patients (Study III: Cohort TTEDD CH1). The visual predictive check plots were generated from Monte Carlo simulations (n = *2000*). The simulations are represented as – 50th percentile, -- 5th and 95th percentiles, • observed responses, o concentrations below the limit of quantification.

Conclusions

In conclusion, an integrated PK/PD model was proposed and successfully applied to describe otelixizumab pharmacokinetics, the time course of transient redistribution of lymphocytes in blood, and modulation and saturation of CD3/TCR at the T cell surface. The developed model describes the data reasonably well and can be used to guide dose selection in future clinical studies.

References

[1] Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med.* 2005;352:2598-2608.

[2] P. Wiczling, M. Rosenzweig, L. Vaickus, WJ. Jusko, Pharmacokinetics and Pharmacodynamics of Anti-CD3 Monoclonal Antibody, Otelixizumab (TRX4), in Patients with Psoriasis and with Type 1 Diabetes Mellitus, Journal of Clinical Pharmacology, 50: 494-506 (2010)