Cost Effectiveness of Individualized Dosing for a Hypothetical New Drug in Atopic Dermatitis: A Pharmacometric-Pharmacoeconomic Simulation Study

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Introduction

Model based strategies for individualized dosing of narrow therapeutic index drugs have been routinely implemented with the goal of improving therapeutic outcomes. The cost effectiveness (CE) of such approaches, however, is rarely considered in early drug development decision making.

The disciplines of pharmacometrics (PM) and pharmacoeconomics (PE) are closely aligned and intersect at the goal of a quantitative understanding of the system. Connection of these two disciplines is a logical extension of typical PM objectives and should lead to a more comprehensive understanding of the probability of success for new therapeutics.

This study investigated the CE of implementing a dose individualization strategy (DIS), along with key target product profile (TPP) characteristics for a hypothetical new drug, Drug X (DX), in atopic dermatitis (AD) relative to a reference treatment, dupilumab (DU).

The analyses exemplify assessments payors use to drive discussions about CE of new therapeutics in context of early development decision making. The specific target criterion was a two-fold increase in the probability of CE at a willingness to pay (WTP) threshold of $100,000, relative to DU.

Methods

A PM-PE model was developed for DU. The PM-PE model for DX was based on the same structure, with modifications of PM model parameters, relative to DU. Literature meta-data were digitized from published studies, and the PM model described longitudinal eczema area and severity index (EASI) score as a fractional decrease from baseline EASI score, including effects for placebo response, topical corticosteroids (TCS), and drug effects (Equation 1). An effective DIS was emulated as a reduction in DX efficacy response interindividual variability (IIV) and as a reduction in therapy discontinuation rate (TDR), which was assumed to be related to a decrease in side effects, relative to DU.

$$\mathrm{EASI}(t_{ij}|\mathrm{drug}_i) = \frac{\mathrm{E0}_i}{1 + g_{\mathrm{Pbo}}(t_{ij}) + g_{\mathrm{TCS}}(t_{ij}) + g_{\mathrm{Drug}}(t_{ij})}$$

$$g_{\mathrm{Pbo}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{Pbo}} \times t_i}{\mathrm{ET50}_{\mathrm{Pbo}} + t_i}$$

$$g_{\mathrm{TCS}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{TCSi},i} \times t_i}{\mathrm{ET50}_{\mathrm{TCS}} + t_i} \times e^{-k_{\mathrm{dT,TCS}}\ (t_i - \mu_{\mathrm{TCS}})}$$

$$g_{\mathrm{Drug}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{Drug},i} \times t_i}{\mathrm{ET50}_{\mathrm{Drug}} + t_i}$$

Equation 1. Longitudinal pharmacometric model for drug effects on the EASI endpoint in atopic dermatitis

The PE model was derived from a published PE analysis of dupilumab in AD and was characterized as a Markov model with transition probabilities between health states: non-responder, EASI response, and death, linked to state-specific quality-adjusted life years (QALYs). The cost of implementing the DIS was assumed to be negligible. Monte Carlo simulations varied DX properties relative to DU parameters: maximum fractional efficacy (Emax), IIV, and TDR (Figure 1).

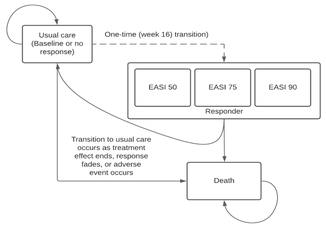

Figure 1. Pharmacoeconomic model structure for atopic dermatitis (Zimmerman *et al.*)

Simulation scenarios included variations of DX properties relative to DU: increased Emax, reduced IIV, and decreased TDR, for a population of mixed moderate/severe disease phenotypes (Table 1). All parameter modifications were relative to the DU reference. The real-world discontinuation rate for DU (which informed simulations) was 17% (~83% TDR) at 1 year (Silverberg *et al.*). Replicate simulations were implemented in an interactive tool developed in R and Shiny, running on the Metworx platform. Results were summarized for each scenario as the difference in (Drug X - DU) QALYs and probability of CE versus WTP.

	Drug X Model Parameters Relative to Dupilumab			
Scenario	Emax	IIV	TDR	Price
1	1	1	1	1
2	5	1	1	1
3	1	0.5	1	1
4	1	1	0.5	1
5	5	0.5	0.5	1
6	5	0.5	1	1
7	5	0.5	1	0.9

Table 1. PM-PE model simulation scenarios

Results

Population efficacy (typical EASI percent change and EASI 50/75/90 over time) and cost-utility (price-per-QALY relative to TCS) were projected (Figure 2). Incremental CE ratios (ICER = Δcost/ΔQALY) were compared for DX and DU to TCS. PM-PE model simulations assessed the impact of TPP characteristics on CE probability across a range of WTP thresholds. At a $100,000 WTP threshold for DX and DU, the CU Ratio for DX to DU, and the ΔQALY (90% prediction interval) were summarized (Table 2). Relative to DU, improvements in DX Emax improved mean efficacy but did not affect QALYs or CE probability (at any WTP level). Reduced IIV had no impact on CE. Decreased TDR that might result from a DIS added ~1 QALY and raised CE probability for DX relative to DU (30% versus 15%, respectively); without the decreased TDR, a CE DX would require a ~10% price reduction relative to DU.

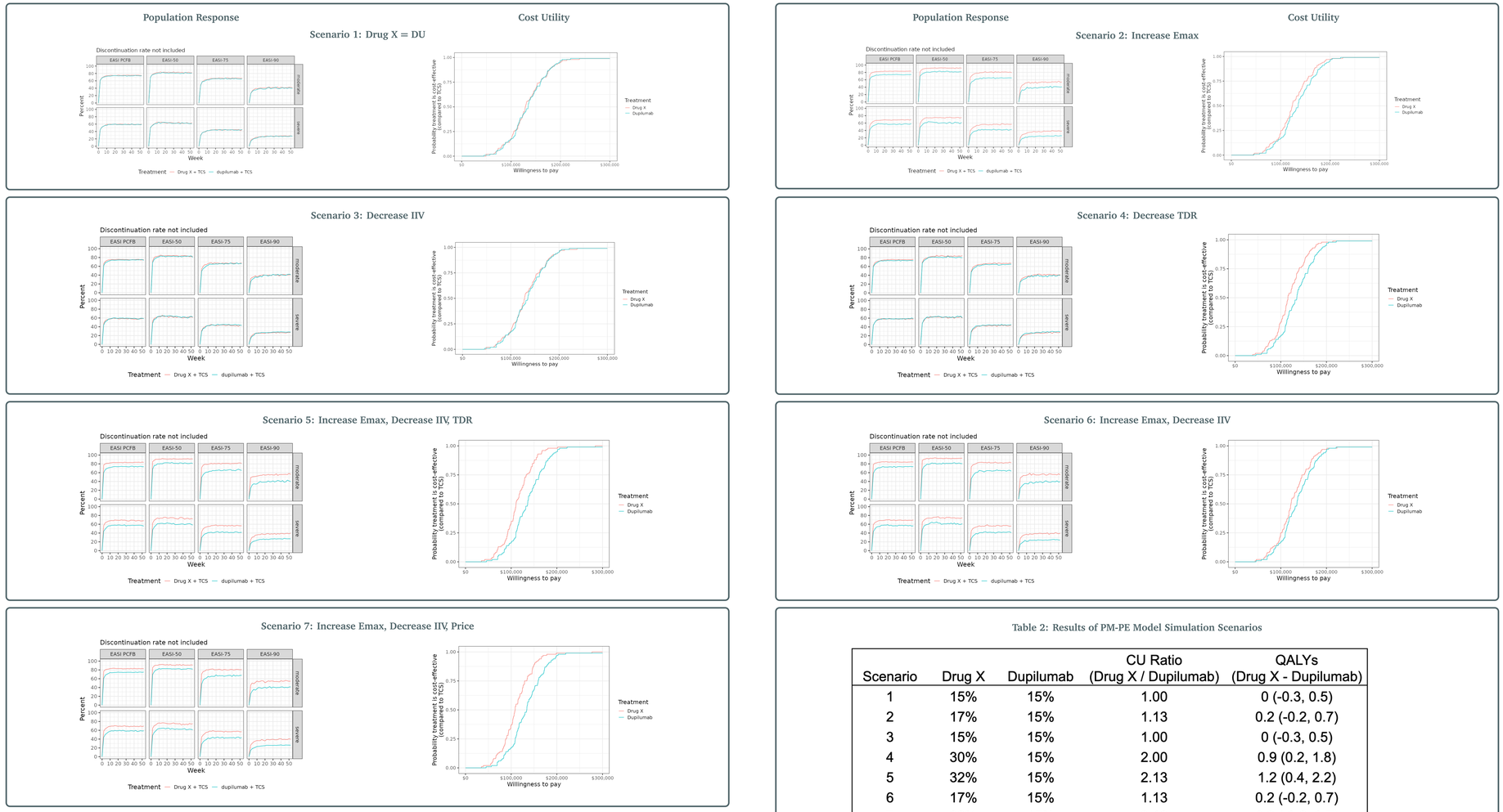

Figure 2. Expected population EASI responses over time and probability of cost-effectiveness versus willingness to pay, presented for Drug X (red) and dupilumab (blue) across simulation scenarios.

Table 2: Results of PM-PE Model Simulation Scenarios

Scenario	Drug X	Dupilumab	CU Ratio (Drug X / Dupilumab)	QALYs (Drug X - Dupilumab)
1	15%	15%	1.00	0 (-0.3, 0.5)
2	17%	15%	1.13	0.2 (-0.2, 0.7)
3	15%	15%	1.00	0 (-0.3, 0.5)
4	30%	15%	2.00	0.9 (0.2, 1.8)
5	32%	15%	2.13	1.2 (0.4, 2.2)
6	17%	15%	1.13	0.2 (-0.2, 0.7)
7	32%	15%	2.13	0.2 (-0.2, 0.7)

Conclusions

In AD, DIS focused on reducing side effects may be more impactful than those aimed at reducing IIV. TPP characteristics improving efficacy do not necessarily translate to increased QALYs or probability of CE for DX relative to DU.

References

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