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

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Introduction

- Cost effectiveness (CE) of dose individualization strategies (DIS) is rarely considered in early drug development decision making.
- The intersection of pharmacometrics (PM) and pharmacoeconomics (PE) should lead to a more comprehensive understanding of the probability of success for new therapeutics.
- We studied the CE of a 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).

Methods

- Literature metadata for DU were digitized and assembled for analysis.
- The PM model described longitudinal eczema area and severity index (EASI) score as a fractional decrease from baseline, and included placebo response, topical corticosteroids (TCS) and drug effects.
- A DIS was emulated as a reduction in interindividual variability (IIV) of DX efficacy response and as a reduction in therapy discontinuation rate (TDR) relative to DU.
- The PE model (from a published PE analysis of dupilumab in AD) was a Markov model with three health states: non-responder, EASI response, and death, linked to state-specific quality-adjusted life years (QALYs).
- Simulation scenarios included variations of DX properties relative to DU (increased Emax, reduced IIV, and decreased TDR).
- Replicate simulations were implemented in an interactive tool developed on the Metworx platform using R and Shiny.
- A cost utility analysis (CUA) was applied to each scenario and summarized as the difference in (DX - DU) QALYs and probability of CE versus willingness to pay (WTP).

Results

Table 1. CUA: Probability of CE for DX and DU at a WTP threshold of $100,000.

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

- Improved TDR (Scenarios 4 and 5), or reduction in Price (Scenario 7), resulted in meaningful increase in CE of DX relative to DU.

Conclusions

- In AD, DIS focused on reducing side effects and decreasing TDR may lead to improved CE for new therapeutics relative to DU.
- TPP characteristics improving efficacy do not necessarily translate to increased QALYs or improved probability of CE.
- PM-PE modeling based approaches may be useful in generating insights about CE for early drug development decision making.
- Further evaluation and assessment of sensitivity to assumptions is necessary for specific modalities and DIS methods.

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Individualized dosing may improve the **cost effectiveness** of new therapeutics in atopic dermatitis.

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Supporting Content

PM (left) and PE (right) Models

$$\mathrm{EASI}(t_{ij}|\mathrm{drug}_i) = \frac{E0_i}{1 + g_{\mathrm{Pbo}}(t_{ij}) + g_{\mathrm{TCS}}(t_{ij}) + g_{\mathrm{Drug}}(t_{ij})}$$

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

$$g_{\mathrm{TCS}}(t_i) = \frac{\mathrm{Emax}_{\mathrm{TCS},i} \times t_i}{\mathrm{ET50}_{\mathrm{TCS}} + t_i} \times e^{-k_{\mathrm{decTCS}} \cdot (t_i - p_{\mathrm{TCS}})}$$

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

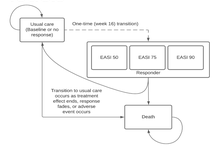
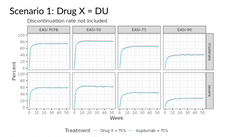


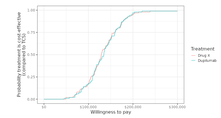
Table 2. Simulation Scenarios

Scenario	Drug X Model Parameters Relative to Dupilumab			
	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

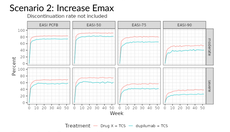
Typical Efficacy Response (left) and CUA (right) by Scenario

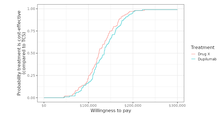
Scenario 1: Drug X = DU



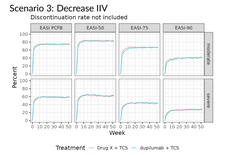


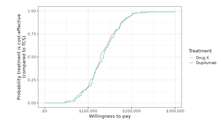
Scenario 2: Increase Emax



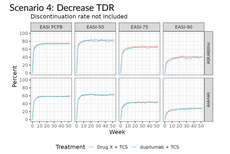


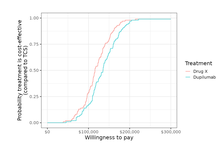
Scenario 3: Decrease IIV



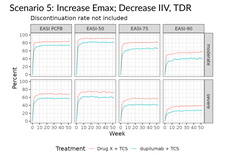


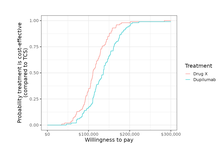
Scenario 4: Decrease TDR



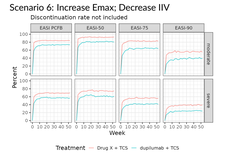


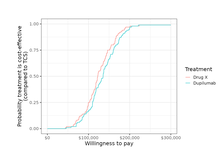
Scenario 5: Increase Emax; Decrease IIV, TDR





Scenario 6: Increase Emax; Decrease IIV





Scenario 7: Increase Emax; Decrease IIV, Price