The use of meta-analysis to improve decision-making from first-in-patient trials in psoriasis

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http://www.pasiphic.calpoly.edu/
How can meta-analysis help facilitate early clinical development?

• Q: *how do we design small, Phase 1 trials to facilitate decision-making?*

• We want to know:
  • Do we proceed to Phase 2?
  • How should we proceed in Phase 2?

• Model-based meta-analysis (MBMA) part of the toolkit to probe the fitness of trial designs to answer these questions.
  • i.e. “is this trial design adequate for our purpose?”
Motivating example

• What’s the drug?
  • Fully human monoclonal antibody, binds soluble target (linear pharmacokinetics)
  • Seeking indication for the treatment of psoriasis

• What do we know?
  • Volunteer studies established multiple, high doses in volunteers (700 mg IV) safe and well-tolerated (no safety issue)
  • Drug under consideration has no biomarker or clinical response in healthy volunteers (no efficacy or surrogate information)

• What do we do now?
  • Establish proof-of-concept in patient population

• How do we do this?
  • Test highest dose vs placebo in patient population
Tools to provide answers to these questions

Model-based meta-analysis
- Model for expected trial outcomes
- Benchmarking information

Clinical Trial Simulation
- ‘What-if’ framework for candidate drug

Back-Estimation
- Trial design quality by
  - ability to address questions
  - risk of being misled
Model-based meta-analysis database

- Characterize the dose-response relationship for mean PASI change, PASI50/75/90 for all treatment options in patients with PsA and Psoriasis.

- Database
  - Data from 301 treatment arms in 94 trials, representing 38,460 patients
  - 13 drugs, 3 of which are like our drug under consideration: adalimumab, golimumab, ustekinumab
  - Trials: Active RA (59), recent onset RA (8), Psoriatic RA (8), Psoriasis (19)

- Allows us to understand if differences in potency exist across treatments, etc.
Model-based meta-analysis model structure

\[ \text{logit}(P(\text{event})_{ijk}) = E_{0i} + \frac{E_{\text{max}} \cdot \text{Dose}}{\text{Dose} + ED_{50}} + \eta_{i,k} \]

The number of events, \( n_{ijk} \), is assumed to be multinomially distributed with parameters \( P(\text{event})_{ijk} \) and \( N_{ij} \).

- \( P(\text{event})_{ijk} \) represents the probability of a patient having an event for the \( k^{\text{th}} \) endpoint in the \( j^{\text{th}} \) treatment arm of the \( i^{\text{th}} \) trial.
  - The number of events are assumed to be multinomially distributed.
  - The correlation between repeated observations (multiple endpoints) for a specific group of patients (treatment arm) within a trial is estimated.
- \( E_{0i} \) is the response to background treatment (placebo) in the \( i^{\text{th}} \) trial.
  - A different background treatment response is estimated for every trial.
- \( E_{\text{max}} \) is the maximal drug effect, reflecting the maximal difference in response between placebo and active treatment.
- \( \text{Dose} \) is the total daily/weekly/monthly dose.
  - Different regimens are corrected for total daily/weekly/monthly dose.
- \( ED_{50} \) is the dose to achieve 50% of \( E_{\text{max}} \).
- \( \eta_{i,k} \) is a trial specific random effect with mean 0 and variance \( \omega_{k}^{2} \).

Mandema 2011, CPT
Results of the model-based meta-analysis for psoriasis

PASI Response

Dose ED

Dose EE PASI

\[ \text{PASI Response} = \frac{E_{\text{max}} \cdot \text{Dose}}{ED_{50} + \text{Dose}} \]

fully human mAbs with linear PK
i.e. like our drug under consideration

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<th>Compound</th>
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<th>ED50 (mg)</th>
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\( E_0 = 9.98\% \) for all compounds

Dodds, ASCPT meeting 2011
Tools to provide answers to these questions

- Model-based meta-analysis
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  - ‘What-if’ framework for candidate drug

- Back-Estimation
  - Trial design quality by ability to address questions • risk of being misled

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PASI\% = E_0 + \frac{E_{max} \cdot Dose}{ED_{50} + Dose}
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Define successful trial qualities

• A successful trial gives a clear and correct evaluation of maximum drug potency relative to placebo
  • Marketed cases: $E_{\text{max}} - E_0 = 84.2\% - 9.98\% = 74.2\%$
  • The “go / no-go” (G/NG) criteria:
    • maximal drug effect over placebo $(E_{\text{max}} - E_0) > 50\%$.
  • Set a reasonable bar for progression, with the understanding that small trials can be misleading

• A successful trial gives an accurate understanding of the drug’s dose-response relationship, informing dose levels to be tested in future Phase 2 dose-ranging study
  • Adequate dose-response information was defined as an $ED_{50}$ estimate within 2-fold of true
  • Unlikely to select arms in a subsequent Phase 2 that are too high or low
  • Set a reasonable bar, with the understanding that subsequent Phase 2 will refine this estimate.
Clinical trial simulation drug test cases

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</tr>
<tr>
<td>discontinumab</td>
<td>23.1%</td>
<td>11.8</td>
</tr>
<tr>
<td>mehmimab</td>
<td>45.0%</td>
<td>32.1</td>
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E0 = 9.98% for all compounds; N=1000 simulated trials; N=16 subjects for each trial; Intersubject variability for E_max (maximum drug effect), E0 (placebo effect) and ED50 (dose of ½ E_max) were 71, 71 and 100%.

Marketed monoclonal antibody test cases and (similar) hypothetical test case in the psoriasis space examined.
Tools to provide answers to these questions

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Clinical trial simulation trial design test cases

Know:
- Placebo response
  - \((E_0) = ~10\%\)
- Standard-of-care maximal response
  - \((E_{\text{max}}) = ~85\%\)
- Half-maximally efficacious dose
  - \((ED_{50}) = [10, 100] \text{ mg}\)
- N=16 patients
- Patients allocated to
  - “Concentrated” design:
    - placebo (N=4)
    - 700 mg (N=12)
  - “Distributed” design:
    - placebo (N=4)
    - 21 mg (N=3)
    - 70 mg (N=3)
    - 210 mg (N=3)
    - 700 mg (N=3)

Learn:
- the portfolio value of our candidate drug (i.e. *does our candidate have a worse, same or better* \(E_{\text{max}}\)?)
- our dose-response profile to help us design an efficient Phase 2 (i.e. *what is our candidate’s* \(ED_{50}\)?)
Clinical trial simulation and back-estimation

• Stochastic simulation and estimation

• Simulation
  • Individual PASI% responses simulated 1000 times for:
    • True drug parameters and variability (5 drugs)
    • Dose level allocation (2 designs) for 16 subjects

• Estimation
  • Concentrated designs:
    • Placebo patients: \( PASI\% = E_0 \)
    • High dose patients: \( PASI\% = E_0 + E_{\text{max}} \)
  • Distributed designs:
    • All patients: \( PASI\% = E_0 + \frac{E_{\text{max}} \cdot \text{Dose}}{ED_{50} + \text{Dose}} \)
Design performance for Go/No-Go decision-making

Only a minor (0-10%) advantage with Concentrated designs
Design performance for dose-selection decision-making

- Adalimumab
- Golimumab
- Ustekinumab
- Discontinumab
- Mehmimab

Good dose-response information available from Distributed design
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Summary in the larger context of drug development

- Approach can be applied to programs where more meaningful development decisions from Phase 1 are desired

- A number of tools are at our disposal:
  - Model-based meta-analysis: benchmarking / context
  - Clinical trial simulations: “what-if”
  - Back-estimation: design quality

Distributed designs trade minor (0-10%) Go/No-Go performance to gain valuable dose-response information needed to guide Phase 2 design

Other studies may conclude differently… make it quantitative!
Acknowledgements

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