Meta-analysis to compare combination therapies: A case study in kidney transplantation

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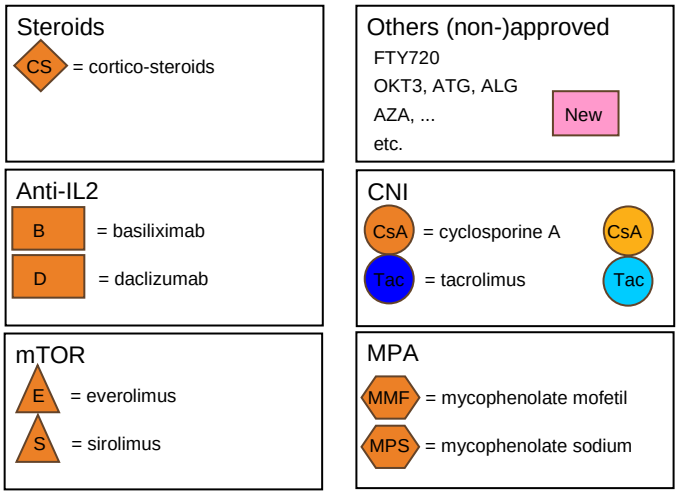
Outline

- Introduction
- Methods
  - Search – selection – extraction
  - Limitations of literature
  - Statistical model
  - Margin derivation
- Health authority interactions
- References
- Results
  - Control effect
  - Model assumptions
  - Derived NI margin
- Conclusion

Introduction

Current immunosuppressive drugs for kidney transplantation



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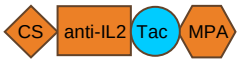
Introduction

typical standard regimens & new experimental regimen

- Control:
- CS+Anti-IL2+Tac(r)+MPA



- Control:
- CS+Anti-IL2+CsA(s)+MPA

- Experimental:
- CS+Anti-IL2+Tac(r)+STN

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Introduction

typical standard regimens & new experimental regimen

- Control (C):
- CS+Anti-IL2+CsA(s)+MPA

- Experimental (E):
- CS+Anti-IL2+Tac(r)+STN

- Putative placebo (P):
- CS+Anti-IL2+Tac(r)

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Introduction

treatments for Phase III and objectives

- The treatment arms
  - Experimental = E = (CS+B+reduced Tac+STN)
  - Control = C = (CS+B+standard CsA+EC-MPS)
- ... and 2 objectives:
  - 1st E is non-inferior compared to C: $(E-C)<\delta$
    This is directly studied
  - 2nd E is better than P: $(E-P)<0$
    This is indirectly studied
  - where P = putative placebo = (CS+B+reduced Tac)

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Introduction

treatments for Phase III and control effect

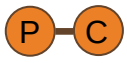
- The treatment arms
  - Experimental = E = (CS+B+reduced Tac+STN)
  - Control = C = (CS+B+standard CsA+EC-MPS)
- The statistical justification of the NI margin is based on
  - Control effect = (P-C)
  - where P = putative placebo = (CS+B+reduced Tac)
  - In order to show indirectly that NEW is better than placebo
  - Therefore: estimate the control effect using historical data

If $\delta \leq (P-C)$ then: $(E-C) < \delta \Rightarrow (E-P) + (P-C) - \delta < 0 \Rightarrow (E-P) \leq \delta - (P-C) < 0 \Rightarrow (E-P) < 0$

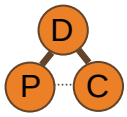
Methods

How to estimate (P-C) as a basis for δ

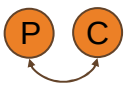
- Estimate (P-C) directly:
  - Do a meta-analysis of studies comparing P and C (or use data from single trial)



- If not available:
  - Do a meta-analysis using indirect comparisons (or use data from single trials)



- If not available:
  - Estimate both failure rates seperately combining evidence from a systematic literature search and combine them (such as historical control)



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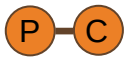

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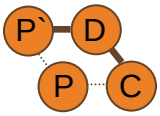

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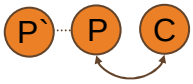

- ... with P`similar to P ...

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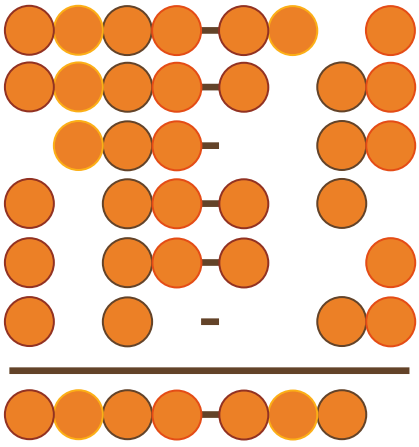
Methods

Estimate (P-C) based on historical regimens

- Here: treatments consists of several components:
  - J
  - K
  - L
  - M

- Estimate control effect
  - (P-C)=(JKL-JKLM) never studied
  - Use meta-analysis to estimate effect of each component; extrapolate the control effect



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Methods

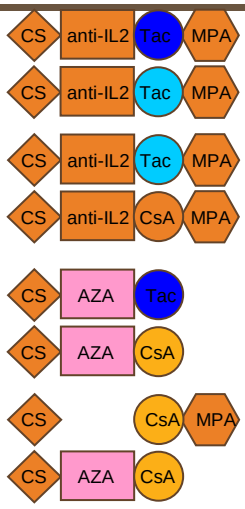
historical information: search – selection – extraction

- Sensitive literature search based on ...
  - ... MEDLINE: RCTs, Meta-analyses
  - ... internal information and experts
  - Result: 1125 publications
- Selection with defined criteria for studies with high quality
  - Main reason for exclusion: trial design (not de novo, withdrawal therapy, not in kidney Tx only, monocenter, ...)
  - Selected 47 multicenter RCTs
  - With more than 15000 patients
- Extraction by physicians
  - Should be double extraction (not fully reached)

Results

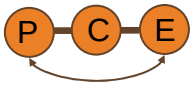
We found a variety of treatment regimens

- Study 1 CS+B+Tac(s)+MPS
  vs. CS+B+Tac(low)+MPS
- Study 2 CS+D+Tac(low)+MMF
  vs. CS+D+CsA(s)+MMF
- ...
- Study 46 CS+AZA+Tac(s)
  vs. CS+AZA+CsA(low)
- Study 47 CS+CsA(low)+MMF
  vs. CS+AZA+CsA(low)



Results

Data limitations and solutions



- Putative placebo not studied (B+CS+reduced Tac)
  - Solution: flexible meta-analysis were each treatment component contributes to the overall effect (additive on log-odds scale)
- 6M results instead of 12M results and BPAR only instead of composite endpoint
  - Solution: two covariates in the statistical analysis
- regimens used variety of dosing schemes
  - Solution: CNIs were categorized into reduced/standard; all others not to keep the model simple & estimation possible; dose effects contribute to random study effect δ_i

Methods: Statistical Model

random effects logistic regression

- $Y_{ij} \sim$ Binomial(N_{ij} , π_{ij})
- logit(π_{ij}) = $\mu + \delta_i + x_{ij} \beta$
  - with parameters μ (intercept) and β (effects of the immunosuppressant drugs and of covariates), and random study effect $\delta_i \sim N(0, \sigma^2)$.
  - The vector x_{ij} contains information on the presence or absence of each of the immunosuppressive drugs, and on covariate values.
  - The following immunosuppressive drugs/drug classes were considered: CS, anti-IL2, low CsA, standard CsA, low Tac, standard Tac, MPA, mTOR, AZA, FTY720.
  - Two covariates were included to reflect the slight difference of the endpoint: M12 (6M/12M data); CEP (BPAR alone/composite endpoint)
  - Estimation: maximum-likelihood method (PROC NLMIXED)

Methods: Statistical Model

Sensitivity analyses

- $Y_{ij} \sim$ Binomial(N_{ij} , π_{ij})
- logit(π_{ij}) = $\mu + \delta_i + x_{ij} \beta$

- Selection of trials: without mTOR inhibitors (potential interaction with CNIs); 37 studies (instead of 47)
- Bayesian analysis with non-informative priors (WinBUGS 1.4.3)

Results

Main result: estimated control effect

- Estimated failure rates (12M, composite endpoint)
  - control group: 19.3%
  - putative placebo: 29.0%

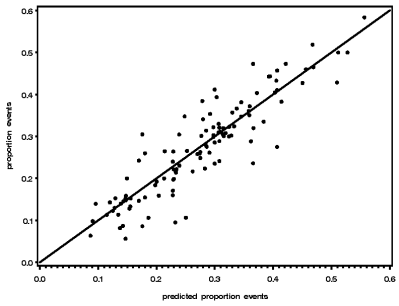
- Control effect (P-C) was estimated: 9.7% [2.6%, 16.8%]
- Sensitivity analysis without mTOR: 13.2% [5.2%, 21.3%]
- Sensitivity analysis with Bayes: 8.4% [1.8%, 15.6%]

- If the control arm would contain low Tac instead of standard CsA, the control effect (P-C‘): 16.9% [12.0%, 21.7%]

Results: Assumptions of the model

success is additive on log-odds scale

- Contribution of a single treatment component is additive on a log-odds scale ; independent of the other components
  - How to check: not testable; plot observed versus predicted
  - Result: model predicts the observed rates well



Results: Assumptions of the model

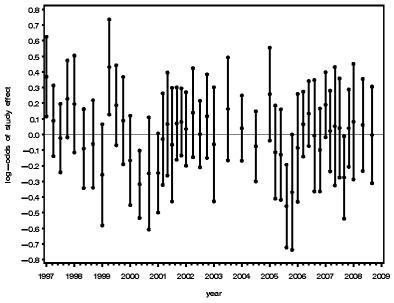
No interactions

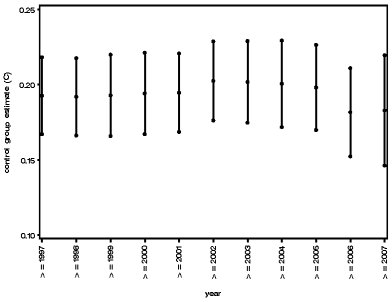
- No interactions
  - But: mTOR(E,S) * CNI(red Tac, st Tac, red CsA st CsA) expected
  - How to check: interaction could not be modeled; sensitivity analysis done without mTOR
  - Result: estimate of the control effect stable
    Main analysis with 47 studies: 9.7% (SE=3.53%)
    Sensitivity analysis with 37 studies: 13.2% (SE=3.96%)

Results: Assumptions of the model

constancy over time

- Assumption: the effects are constant over time; ‚time' is not part of the model (could not be fitted)
  - How to check: (unspecific) random effect over time (left figure)
  - failure rate of the control group over time (right figure)
  - But not: control <u>effect</u> over time (reduced Tac only in 2007/2008)





Methods

Using a delta just small enough to show efficacy

- EMEA guideline (T=test, R=reference, P=placebo):
  - Delta can be defined as the lower bound of 'T minus R' that ensures that the lower bound of the indirect confidence interval of 'T minus P' will be above zero. As the comparison is indirect it might be wise to be conservative and select some value smaller than that suggested by this indirect calculation.
  - In a submission the applicant should present both the direct confidence interval T minus R and the indirect interval T minus P.
- It can be shown that this is fulfilled using the 95% lower confidence limit of ‚R minus P' ... but its over-conservative

Hauck&Anderson / Wang&Hung / Rothmann

Methods

from control effect to a non-inferiority margin

- 95-95 approach: use the lower confidence limit of a 95% confidence interval to estimate the control effect
- Synthesis approach: no fixed margin: use meta-analysis including historical data AND acual trial to estimate the effect of E over P indirectly.
- Fixed margin synthesis approach: use the margin from the systesis approach and plug in worst case parameters for (SE_{EC}) to generate a conservative fixed margin.

$$\delta = (1-\lambda)\,\theta_{PC} - \left(\sqrt{(1-\lambda)^2 + SE_{EC}^2 / SE_{PC}^2} - SE_{EC} / SE_{PC}\right) z_{1-\alpha} SE_{PC}$$

- Preservations approaches: preserve control effects (1-λ)

Results

from control effect to a non-inferiority margin

- Results were:
  - Main analysis with 47 studies: 9.7% (SE=3.53%) [2.6%, 16.8%]
  - Sensitivity a. with 37 studies: 13.2% (SE=3.96%) [5.2%, 21.3%]
- 95-95 approach: use the lower confidence limit of a 95% confidence interval: (e.g) 5.2%
- Fixed margin synthesis approach: (based on 16% to 20% failure rate and 300 patients/arm, λ=0): 8.6%
- Fixed margin synthesis approach with 20% preservation: (based on 16% to 20% failure rate and 300 patients/arm, λ=0.2): 7.3%

Health authority interactions

FDA & EMEA (Oct 2008 to Feb 2009)

- Setting 1: (anti-IL2+CS+Tac)-(anti-IL2+CS+CsA+MPA) [5.2%, 21.3%]
- Setting 2: (anti-IL2+CS+Tac)-(anti-IL2+CS+Tac+MPA) [12%, 21.7%]

- FDA
  - Setting 1: FDA did not accept the ‚fixed margin synthesis approach'; did not accept the (clinically) proposed margin of 10% (RD)
  - Setting 2: FDA accepted the proposed margin of 10% (RD); FDA accepted therefore also implicitly the methodology

  FDA appreciates the new & innovative approach.

- EMEA/CHMP
  - Setting 1: not applicable
  - Setting 2: CHMP accepted the proposed margin of 10% (RD); CHMP accepted therefore also implicitly the methodology

Conclusion

take home message

- Solid justification of NI margin is needed, scientifically and in order to support the submission dossier.
- Estimation of the ‚control effect' is needed and may require sophisticated statistical methods and long preparation time.
- Using the lower confidence bound of the control effect seems to be standard and quite accepted however, other and less conservative methods are available but were not accepted by the FDA so far (to our knowledge).

References

- Guideline
  - Points to consider on the choice of NI margin (2006) CPMP/EWP/2158
- Papers
  - Hauck WW, Anderson S (2002) Some issues in the design and analysis of equivalence trials. Drug Information Journal;33:109-118.
  - Rothmann M. et al. Design and analysis of non-inferiority mortality trials in oncology. Stat Meth 2003;22:239-264
  - Wang SJ, Hung HMJ. Assessing treatment efficacy in noninferiority trials. Controlled Clinical Trials 2003;24:147-155