Application of mechanism-based population PKPD modelling in the rational selection of clinical candidates: an anti-IgE antibody example

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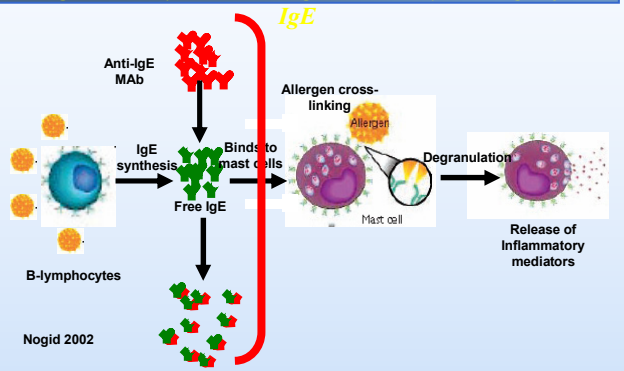
INTRODUCTION

- Lack of predictability of clinical efficacy and safety is an important problem facing pharmaceutical research today.
- Translational pharmacokinetic-pharmacodynamic (PKPD) modelling and simulation has the ability to integrate data generated on diverse test platforms during discovery and development in a mechanistic framework.
- Successful implementation of translational PKPD early in the drug development cycle could have a substantial impact on overall efficiency and success of pharmaceutical research and development (R&D).
- Conventional, empirical PKPD approaches have limited predictive capabilities and therefore, a mechanism-based approach is required for predictive translational PKPD.
- Mechanism-based PKPD is particularly attractive in the area of biologics, which have certain tractable PKPD properties that make them amenable to translation across the preclinical-clinical interface.

BACKGROUND

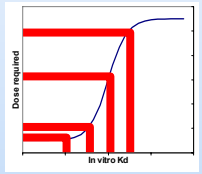
Anti-IgE antibody arrests allergic cascade by binding to free IgE



Treatment success defined by reduction of free IgE levels to < 25 ng/mL

Objective of PKPD analysis

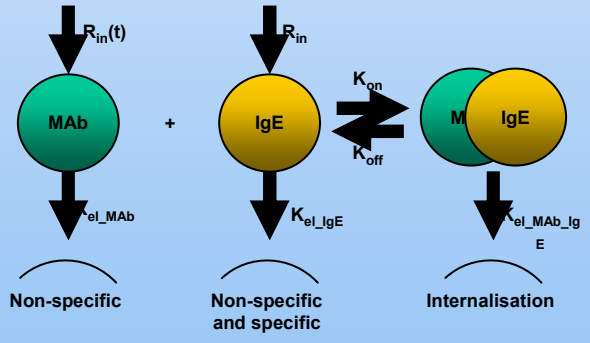
- Clinically precedented mechanism – omalizumab (Xolair™) – an IgG-1 monoclonal antibody is available on the market
- Omalizumab dosed at every-2-week (q2w) or every-4-week (q4w) intervals
- Maximum administered dose of 375mg q2w – dosing limitation possibly due to cost/convenience of therapy[2]
- Would increasing affinity of antibody to IgE result in reduced dose requirements?
- What other *in vitro* properties can be changed to provide better dosing benefits *in vivo*?



Objective:
To characterise the relationship between *in vitro* affinity and *in vivo* efficacy profile of anti-IgE antibody omalizumab
To evaluate alternative *in vitro* changes to the molecule to improve its *in vivo* profile

METHODS

Objective of PKPD analysis



Rin(t): input rate into the blood compartment of antibody, Kel_mAb: non-specific elimination of antibody, Rin: Endogenous systhesis rate of IgE, Kel_IgE: First order elimination rate constant of IgE, Kon/Koff: On/Off rates of mAb at IgE, Kel_mAb_IgE: Internalisation rate of antibody-antigen complex

Features of the PKPD model

- Model accounts for IgE synthesis and catabolism through non-specific and specific means, antibody absorption and distribution, clearance of antibody through non-specific means (reticuloendothelial system), binding of antibody to IgE and elimination of complex
- Model can be easily modified to account for different disease states (e.g. moderate/severe asthma, allergic rhinitis, etc.)
- Cyclical changes in IgE kinetics can also be easily accommodated
- By specifically accounting for IgE/antibody/complex kinetics, model can account for accumulation or depletion of total antigen for assessment of any potential risks
- Measure of IgE (or any other antigen) levels constitutes a mechanism-based translatable biomarker with a potentially high degree of linkage to efficacy
- (See Mager 2001, Meno-Tetang 2005 for model details)

PKPD parameters

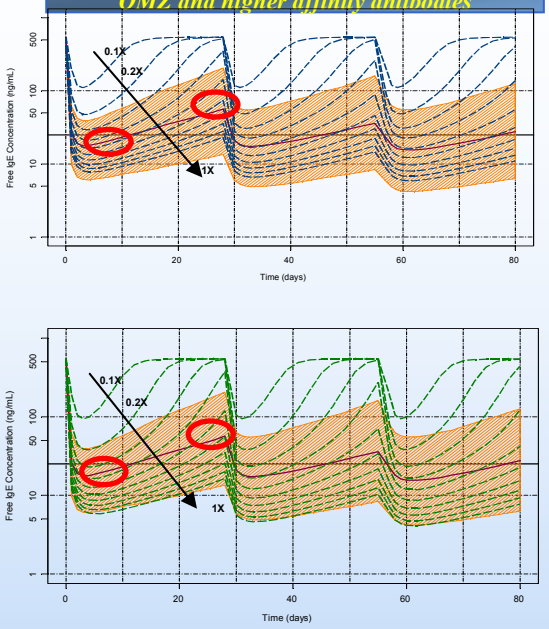
- PKPD properties of antibodies are relatively uniform but are different from other small molecules[5]
- PKPD parameters for omalizumab were gathered from literature[6,7]

Parameter	Assumed estimate
Absorption rate constant (day^{-1})	0.5
Bioavailability (%)	50
Volume of distribution (mL/kg)	60
Non specific elimination rate constant of antibody (day^{-1})	0.02
On-rate at IgE ($nM^{-1}day^{-1}$)	0.6
Off-rate at IgE (day^{-1})	0.8
Baseline IgE levels (ng/mL)	500
Non specific elimination rate constant of IgE (day^{-1})	0.8
Non specific elimination rate constant of IgE-antibody complex (day^{-1})	0.2

10-30% uncertainty was assumed on all PKPD parameters for simulation

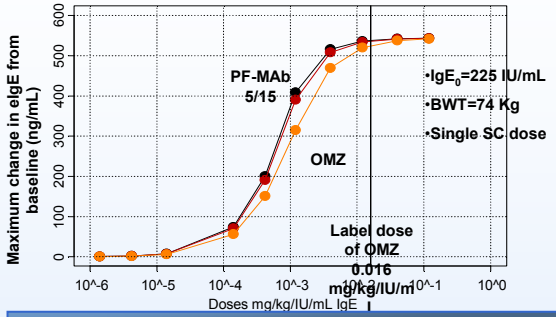
RESULTS AND DISCUSSION

Predicted (mean 90%CI) free reduction with OMZ and higher affinity antibodies

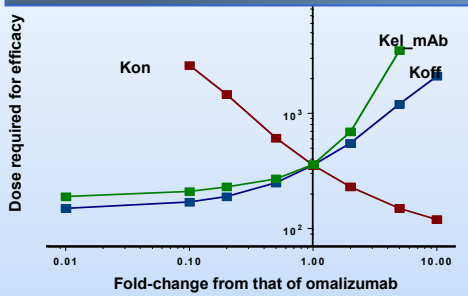


Mean (90%CI) free IgE reduction after label Xolair dose shown (red/brown) along with predicted mean IgE reduction of 5X and 15X more potent antibodies at doses 0.1X – 1X that of Xolair.

Dose-response (dose vs maximum change in free IgE)



Summary of sensitivity analysis



Efficacy is defined as the duration of mean free IgE level below 25 ng/mL

Nominal patient weight of 74 kg and baseline IgE level of 300 IU/mL assumed

Discussion

- Predicted free IgE reduction for omalizumab shown (left) along with confidence intervals
- Two higher affinity antibodyies (10X and 15X affinity to IgE) are also shown
- Comparision of mean profiles reveals that approximately half the dose required for efficacy in both cases
- Increasing affinity results in lower dose requirement, however, lower dose leads to shorter half-life and hence slightly shorter duration of IgE reduction
- Limited increase in dosing efficiency seen between 5 and 15X affinity increase
- Dose vs peak IgE reduction plot shown (top right) for different affinities
- Limited dose-respons seen at affinities lower than that of omalizumab – a maximum of 2-fold reduction in doses can be expected at affinity increase beyond 10-15-fold
- Local sensitivity analysis to Kon, Koff, and Kel_mAb summarised (bottom right)
- Similar to affinity, reduction in non-specific clearance of mAb could lead to 2-fold dose reduction
- Increased affinity to IgE should be carefully balanced with changes in on-rate to the receptor, which could counterbalance slower off-rates
- Global sensitivity analysis required to obtain joint confidence intervals

CONCLUSIONS

- Translational PKPD using mechanism-based modelling and simulation can be used to guide selection of clinical candidates by providing clear guidelines for discovery colleagues based on previous clinical experience
- A maximum reduction of 2-fold in dose can be expected with a ~10-fold increase in affinity or reduction in non-specific clearance, so long as on-rate at the receptor is not compromised. Further increase in affinity is not predicted to translate into clinical dosing benefit, hence expensive affinity maturation steps can be avoided
- Increasing maximum reduction in IgE should be balanced with shorter duration of effect due to dose-dependant half-life
- Other more empirical models have also been reported for this system, but the mechanism-based approach provides the flexibility to evaluate sensitivity in response of the system to different components. Also, model is adaptable for follow-on compounds and different disease states
- Biologics present a convenient treatment modality for the successful implementation of mechanism-based models in translational research
- This approach is likely to take on more importance in the context of increased investment in second generation antibodies[8]

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