European Federation of Pharmaceutical Industries and Associations

Modeling & Simulation to support evaluation of Safety and Efficacy of Drugs in Older Patients

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EMA Geriatrics Workshop
London, March 22-23, 2012

Outline

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Introduction

- The goal for any drug development is to understand the benefit of a new drug in the general population.
- The challenge is to understand all subpopulations, particularly those that may potentially be more at risk in terms of safety and efficacy.
- Potential for increased risk can be due to alterations in PK or PD
  - PK: eg change in organ capacity (eg renal failure) or co-medication leading to DDI risks
  - PD: loss of reserve capacity eg CNS receptors, increased sensitivity eg increased bleeding risk with anticoagulants, co-morbidity
- Age is rarely an independent source of variability but confounded by other factors and may not be a significant factor or the best factor to guide dose adjustment

Strategic considerations in drug development

- In order to quantitatively assess drug benefit/risk in older patient population, necessary PK/PD data need be collected from older patients in the clinical trials
    - Often an arm of older healthy volunteers is included early on or a separate PK study is performed in various age groups.
- Data are collected through the development but key information is generated from the later stages (Phase II/III)
- Multiple covariate /confounding effects may exist to complicate evaluation of drug PK/PD in older patients
- Population PK/PD modeling and simulation can be useful to evaluate drug PK/PD in older patients
- Adequate assessment of exposure-response is needed in older patients

What value can M&S provide?

- Population PK ➔ covariate effects and variability in PK parameters ➔ quantify any age related effect on exposure
  - Pop PK can integrate various patient factors important for the exposure
- Population PK/PD (exposure-response) ➔ covariate effects and variability in PD (responses) ➔ quantify any age related effect on response
  - both in intensity (E_{max}) and sensitivity (EC_{50}) for both desired and adverse effects

Inferences from Population PK/PD M&S for Older Patients

Dosing recommendation need to consider all identified individual factors rather than any single individual factors

- Often renal clearance is a better predictor than age (example: dose adjustment for decreased creatinine clearance, CLcr).
- Combination of factors could be guiding the dose: eg patients with CLcr<30 and BW<50 kg should only receive half the dose.
- Due to greater drug utilization (co-medications) the probability of a drug-drug interaction might be higher in older patients and can hence lead to need for dose reduction, secondary to age.
- Highly heterogeneous older patients (with diverse or wide covariate distributions) should be on individualized therapy, especially when the therapeutic window of a compound is narrow.

The EFPIA survey – 15 answers

Can Pharmacokinetics and Modelling help?

In which patients? Examples?

- Already used in some cases
- For dosing recommendations
- To describe the impact of age on PK (e.g. by a modelling approach using sparse Phase III data or by a dedicated clinical pharmacology study) it is a pre-requisite and subsequent simulations can be used to determine the appropriate dosing regimen if a dosing adjustment is needed.
- There are age related effects, e.g. on renal function, but the variability added by disease is much greater due to the greater chance for co-morbidity
- To assess combined risks of impaired renal function and DDI
- Pharmacodynamic modelling is also an important tool

The EFPIA survey

- Population PK analysis could be helpful if a sufficient number of patients in different age ranges are included in the clinical trials
- When there is a particular PD effect that is linked to efficacy/safety, especially in case you have a biomarker.
- Multicompartment modellisation for anticipating effect on specific organ with high drug-tissue concentration.
- Population PK/PD has potential for detecting - while accounting for random inter- and intra-variability - fixed covariate effects like age and PK and/or PD genetic polymorphism on clearance particularly in clinical situations where blood concentration values are sparse.
- In Phase III specific programs where PK information would not be available, modelling could help bridging exposure data from Phase I/II studies to Phase III response data via genotyping of a pooled subset of the patient population enrolled in the Phase III program.

Case 1 (Drug X) - Clinical Pharmacology in Older Healthy Volunteers

Clinical pharmacology knowledge potentially relevant to Drug X PK in older patients

- ADME: mainly eliminated via metabolism by CYP3A, with urinary excretion <1%.
- Age/gender study (older/young, male/female design) results: AUC and C_{max} increase by 52% and 63%, respectively, in older as (≥ 65 yrs) compared to young (16-45) ➔ no dose adjustment is necessary (based on the flat exposure-efficacy/safety relationship).
- No dose adjustment is needed in patients with renal impairment

Case 1 - Population PK from Phase II/III

- Altogether, ~7 000 patients (Phase II + Phase III studies) were included in a population PK analysis. The population was 20-97 years old, with an average of 63. About 43% were ≥ 65 years and 15% ≥ 75.

- Covariate effects potentially relevant to Drug X PK in the older population:
  - Concomitant moderate CYP3A inhibitors/inducers increase/decrease AUC by about 2-fold/half but need no dose adjustment; concomitant use of strong CYP3A inhibitors/inducers should be avoided.
  - Age and renal impairment were found to not significantly impact Drug X

Case 1 - Exposure-Response

- The exposure-efficacy relationship for drug X is flat with the pre-specified key efficacy endpoints.
- The exposure-safety relationship for drug X is flat with the pre-specified key safety endpoints.
- Risk analyses with the pre-specified efficacy/ safety endpoints were conducted to evaluate the potential risk factors.

➔Overall, the difference, if any, between young and older patients is minimal.

Case 1 - Geriatic Use and Summary

Labeling: 8.5 Geriatric Use

- In Phase III, 43% of patients were ≥65 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups.
- No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the older and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Summary and lessons learned:

- Population M&S was useful to evaluate PK/PD in the overall population and allowed comparisons to be made between young and older patients
- Consistent conclusions were reached between population PK in older patients and the observations in the older healthy volunteers

Case 2 – PK and Exposure-response for prediction of clinical utility

- Ximelagatran - an oral thrombin inhibitor in recurrent venous thromboembolism (VTE)

- Phase III Study
  - 1200 patients with a previous VTE treated with ximelagatran 24 mg bid or placebo for 18 months
  - 3600 PK samples from 600 patients evaluated by Population PK

- Exposure response evaluated by logistic regression
  - Recurrent VTE, Bleeding, ALAT-elevation

- Patient covariates tested for influence of PK or Exposure - Response relationships
  - Gender, Weight, Smoking, Age, CLcr

Case 2 – Covariate effects on PK

- Renal function the most important factor for CL_{po}
  - Explains ~50% of the variability
- Gender, age and weight less important, but significant

Patient co-variate(s)	OFV	p-value	Estimated effect of covariate (CL_{po} at extreme covariate values)	Random inter-patient variability (CV)	Explained fraction of inter-patient variance by covariate(s)
No covariates	-14084	NA	NA	43%	NA
CrCL	-14326	<0.001	0.95% per unit CrCL (10.4; 37.2)	32%	46%
Gender	-14167	<0.001	Females -30%	40%	16%
Weight	-14162	<0.001	+1.1% per kg (16.8; 48.0)	40%	15%
Age	-14148	<0.001	-0.6% per yr (38.2; 22.6)	40%	13%
CrCL & gender	-14405	Gender<0.001	Females -24%	29%	55%
CrCL & weight	-14329	Weight >0.05	+0.2% per kg (26.6, 32.8)	32%	46%
CrCL & age	-14326	Age >0.05	+0.07%.per yr (28.2, 29.6)	32%	46%

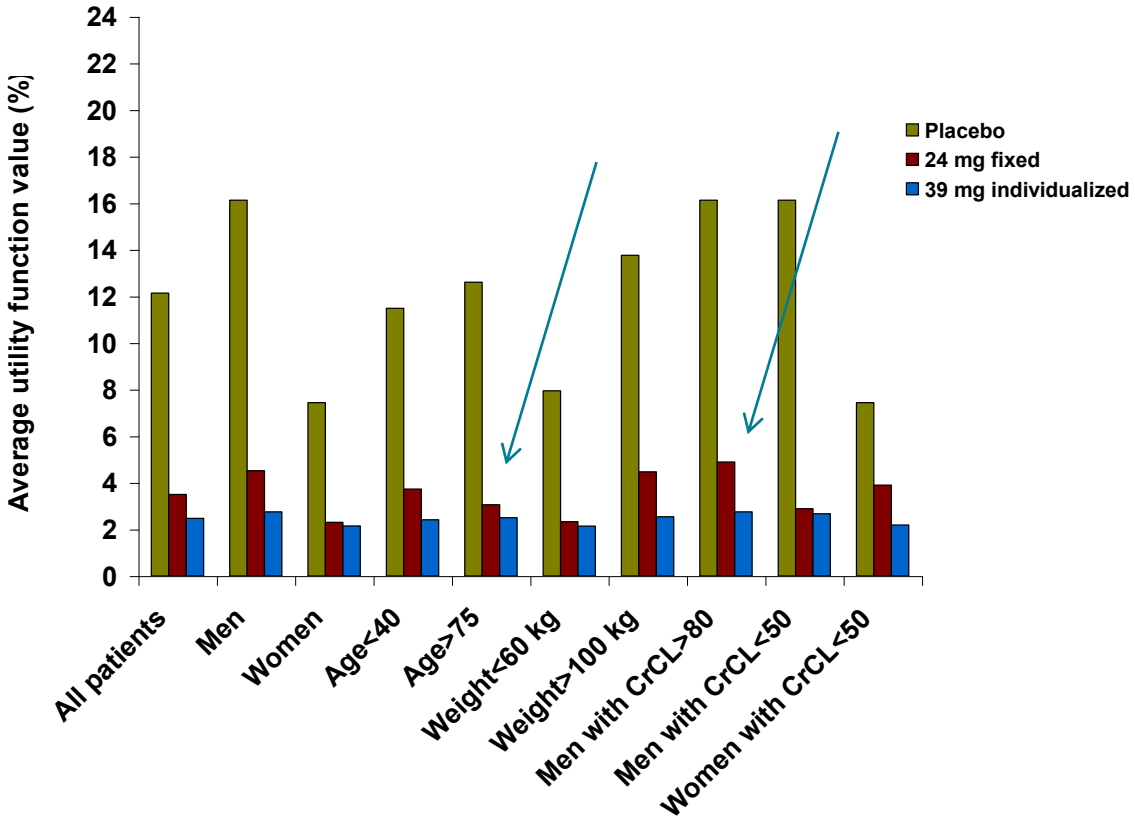
No covariate effects on any other PK parameter were included in these models.

Median age 58 years (range 18-87)

Marie Cullberg , 2006

Case 2 – Clinical utility function in subgroups

Marie Cullberg , 2006



- No dose adjustment suggested in older or any other subgroup of patients
- Models useful to support the studied dosage and prediction of clinical utility of alternative dosing strategies

- Predicted clinical utility better with ximelagatran than placebo in all subgroups
- At a fixed dose of 24 mg bid the predicted clinical utility is
  - Similar or better in older patients (bleeding risk ~2-fold higher, but VTE-risk ~1/3 of that in young)
  - Poorest in men with good renal function (higher gender-related risk of recurrent VTE and lower exposure due to high CLcr)
- Completely individualized dosing is not predicted to improve clinical utility significantly

Summary and Lessons Learned

- Traditional statistical analysis can tell if there is a difference in this subpopulation of older patients
- M&S is powerful to quantitatively evaluate PK/PD and recommend dosing regimens in older patients
  - M&S can integrate information regarding PK, efficacy and safety to guide dose recommendations
  - Modeling can identify individual factors and overall variability in PK/PD and hence increase the understanding of underlying factors
  - Simulations can help to quantify any dose adjustments needed
  - Temporal information during the study can strengthen the information available in this subpopulation
  - Clinical pharmacology study results can support the M&S and be helpful if it is difficult to recruit older patients, but the population PK/PD results in the older patient population will be more informative
- We need to improve our understanding as how to evaluate risk/benefit in the older patients.

THANK YOU!

Acknowledgement:

Alan Xiao; **Senior Pharmacometrician, AZ Wilmington**

Marie Cullberg**; Senior Clinical Pharmacology Scientist, AZ Mölndal**

Solange Rohou**; Director European Regulatory Affairs, AZ**

Disclaimer

The view and opinions expressed in these slides are my own and do not necessarily represent the views of AstraZeneca