



Concept paper on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products

Qun-Ying Yue
Oct 8, 2012

Background

- **Large variability in drug response can be related to genomic variations.**
- **subsets of patients may have a different B/R profile.**
- **At time of MA, information may be limited for genomic sub-populations.**
- **Rare but serious ADRs may be identified late in the drug development phase or only post marketing.**
- **Available PGx related guidelines mainly on drug development phase.**

Need for guidance on PGx in PhV

- **for evaluation of PG issues in conduct of PhV in order to inform /improve clinical use of specific treatments.**
- **The concept paper aims to discuss:**
 - 1) how to give systematic consideration of the implications of GBM guided use of MPs in RM for lack of efficacy or safety concerns
 - 2) conditions when and how post-authorisation genomic data may need to be collected;
 - 3) level and type of evidence for identification/assessment of signals;
 - 4) risk minimisation measures, depending upon the possible clinical implications (including provide information in the label).
 - 5) Effectiveness of RMini measures

What are the questions for PGx /PhV?

- **Genomic biomarkers**
- **Patient selection**
- **Drug choice**
- **Drug dose (or treatment recommendation)**

Ex: Genetic testing an individual - Define

risk status for ADRs

- **Abacavir- HLA-B*5701**
- Flucloxacillin HLA-B*5701
- **CBZ HLA-B*1502**
- **CBZ HLA-A*3101**
- Phenytoin HLA-B*1502
- Allopurinol HLA-B*5801
- Warfarin-VKORC1
- QT-HERG

rate of drug metabolism

- Codeine CYP2D6
- Tamoxifen CYP2D6
- Clopidogrel CYP2C19
- Celecoxib CYP2C9
- Warfarin CYP2C9
- Thiopurine TPMT
- Irinotecan UGT1A1
- Statin *SLCO1B1*
-

(For disease diagnosis/prognosis - oncological implications, HIV, etc)

Genomic information in the labeling

- **Mandatory (clinical use)**
- **Recommendation (should when possible to perform, should/or consider...)**
- **For information (Insufficient data for recommendation)**

SPC – section 4.1 – Indication: Abacavir (Ziagen)

- Ziagen is indicated in antiretroviral combination therapy for HIV infection.
-
- Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the HLA-B*5701 allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing.
- (prospective confirmation study, clear clinical validity/utility, high NPV and PPV)

Carbamazepine SJS and cADRs – two GBM in patients with different ethnic origins (SmPC 4.2, 4.4, 4.8)

Population example	HLA-B*1502 SJS/TEN	HLA-A*3101 cutaneous hypersensitivity ADRs
Han Chinese and Thai	Testing whenever possible is recommended to <u>prevent</u> carbamazepine induced SJS	(Associated with mild cutaneous reactions such as maculopapular exanthema in Han Chinese)
Other Asian populations (e.g. Philippines and Malaysia)	Testing may be considered	
European Caucasians and Japanese		Insufficient data supporting a recommendation for screening . If known positive, consider B/R.

WS on PGx 121008

8

Testing risk status for idiosyncratic reactions (e.g. HLA alleles and CMZ cutaneous reactions)

- Identify the clinical variables
 - SJS/TEN, or all cutaneous reactions; frequency of the reactions
- Identify the genetic variants –HLA-B*1502, HLA-A*3101, what frequency (in ethnic populations)
- Risk increase – relative and absolute
- Performance of the GBM – sensitivity and specificity;
- Predictability - Positive (PPV) and negative (NPV) predictive values (In ethnic populations)
- Data sources and level of “certainty” on the evidence
- Presence of therapeutic alternatives

IPRAC 25 Sept 2012

9

Clopidogrel – CYP2C19

- 4.2 - Pharmacogenetics: CYP2C19 PM status is associated with diminished response to clopidogrel. The optimal dose regimen for PMs has yet to be determined (see section 5.2).
- 4.4 - PGx: Based on literature, patients with reduced CYP2C19 function have lower active metabolite and diminished antiplatelet responses, and higher CV event rates following MI
- 4.4, 4.5: Since clopidogrel is metabolised partly by CYP2C19, use of inhibitors expected to result in reduced active metabolite level and a reduction in clinical efficacy. Concomitant use of CYP2C19 inhibitor should be discouraged
- 4.5: interaction with PPI
- 5.2:Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity.
- There may be genetic variants of other CYP450 enzymes with effects on the ability to form the active metabolite of clopidogrel.

WS on PGx 121008

10

Tamoxifen controversy

- Association between CYP2D6 genotype or inhibitor use with breast cancer outcome;
- No association (dose, compliance, inhibitor use, alleles analysed, etc, may confound. Other metabolic pathways?)
- Different prospective studies evaluating 5 yrs of adjuvant tamoxifen (20mg/d) for CYP2D6 and breast cancer,
 - 2 with “positive” findings with significant differences, (Goetz et al 2005 HR 4.0 (1.7-9.4), Goetz et al 2008 HR 2.2 (1.06-4.55));
 - the ATAC had a HR (PM vs EM 1.06 (0.51-2.22).
 - BIG study HR 0.58 (0.28-1.21) (tumor derived DNA, CYP2D6*5 not analysed)
- The controversy is unlikely resolved through retrospective analyses (CYP2D6 partially explains variability in endoxifen PK)

Tamoxifen and CYP2D6 – SmPC (4.4, 4.5, 5.1, 5.2; Sept 2010)

- **CYP2D6 PMs have a lowered plasma level of endoxifen, one of the most important active metabolites of tamoxifen**
- **Potent inhibitors of CYP2D6 should whenever possible be avoided during tamoxifen treatment.**
- **The PM status may be associated with reduced response. The consequences have not been fully elucidated.**
- **The available studies have mainly been performed in postmenopausal women.**

Biomarkers related to Pharmacokinetics (e.g. codeine and CYP2D6)

- Identify the clinical variables – lack of efficacy or particular toxicity (level of exposure)
- Identify the genetic variants –CYP2D6 (about 80 variants), what frequency (in ethnic populations)
- Risk increase – (gene) dose effect
- Performance of the GBM – sensitivity and specificity;
- Predictability – for exposure? for clinical outcome? (In ethnic populations)
- Therapeutic drug monitoring /phenotyping possibility
- Data sources and level of “certainty” on the evidence
- Presence of therapeutic alternatives

IPRAC 25 Sept 2012

13

1) How to give systematic consideration of the implications of GBM guided use of MPs in RM for lack of efficacy or safety concerns?

- For a new medicinal product, it is generally expected to have data available at approval on relevant PG issues relating to efficacy or safety (e.g. dose for genomic subpopulations).
- It should be discussed in the RMP:
 - Extent of PG effects and implications on PGBM use in target population.
 - whether use in patients with unknown or different genotype could be a safety concern or requires additional data to be generated
 - If important genomic polymorphism identified but not fully studied, this should be reflected in safety specification and PhV plan.
 - Whether it is a safety concern for risk minimisation will depend upon the possible clinical implications.

2) When and how post-authorisation genomic data may need to be collected?

- Efforts for PG evaluation should be based on prior knowledge (literature, class effect) or on observations within the development programme.
- In case of medically important ADRs or lack of effectiveness noted post authorisation, the collection and storage of genomic material (e.g. blood, saliva, tissue), may prove essential.
- Collecting genomic samples from every patient receiving medication and experiencing medically important ADR or lack of effectiveness in the initial post-launch period, is encouraged. DNA from such patients could be compared with DNA from patients without these safety or efficacy concerns.

Exposure dependent (Type A)

Perhexiline neuropathy and CYP2D6 activity

Shah RR et al. BMJ 1982; 284: 295-9

Debrisoquine MR	Neuropathic group (N=20)	Non- neuropathic group (N=14)	Not on perhexiline (N=38)
Median	14.4	0.65	0.55
> 12.6	50%	None	8%
≤ 1.0	15%	64%	66%
Perhexiline (g/week)	1.99±0.48	2.39±0.90	-

3) Level and type of evidence for identification/assessment of signals

- **Ideally, data from well conducted RCT(s)**
 - **Retrospective data analysis**
 - Biological sample or BM status availability from all or majority of the subjects from RCT
 - Prospectively stated hypothesis & appropriate analysis plan
 - Replication
 - Biological plausibility
 - Difference between [BM+] vs [BM-] is large
- (Data collected during post authorisation studies on abacavir and carbamazepine based on clinical observations - example of successful PGx data collection influencing the RM measures.)

CDC ACCE Criteria for evaluating a genetic test

- ***Analytic validity:***
 - How accurately and reliably the test measures the genotype of interest.
- ***Clinical validity:***
 - How consistently and accurately the test detects or predicts the intermediate or final outcomes of interest.
- ***Clinical utility:***
 - How likely the test is to significantly improve patient outcomes.
- ***Ethical, legal, and social issues***
 - May arise in the context of using the test.
- **<http://www.cdc.gov/genomics/gtesting/ACCE/index.htm>**

WS on PGx 121008

18

4) Risk minimisation measures, depending upon the possible clinical implications (including provide information in the label).

- The Impact of the BM will depend on the level of clinical evidence, PPV and NPV of the BM in the population.
- level of “certainty” on the evidence should be taken into consideration.
- importance of contextual factors should be considered, such as:
 - the severity of the disorder, presence of therapeutic or diagnostic alternatives, ethnicity, etc.
- Routine RM – based on SPC guideline
- Additional RM - may be needed, such as:
 - restricted access to the medicinal products based on specific (genotypic or phenotypic) tests, a patient registry, or additional educational materials to the prescribers or patients regarding important PGx information

WS on PGx 121008

19

Recommendations of SmPC guideline – PGx (1)

- 4.1- If the product's indication depends on a particular genotype or the expression of a gene or a particular phenotype, this should be stated in the indication.
- 4.2- Special populations: patients with a particular genotype; with cross-reference to other relevant sections for further detail as appropriate; Where necessary, dosage adjustments in patients with a particular genotype should be stated (with cross-reference to other relevant sections for further detail as appropriate).
- 4.3- Situations where the medicinal product must not be given for safety reasons to individuals with a particular genotype or phenotype, should be stated in the contraindication
- 4.4- Subjects with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced pharmacodynamic effect or adverse reaction. This should be described as warnings or precautions.
- 4.5- **Additional information on special populations** If there are patient groups in which the impact of an interaction is more severe, or the magnitude of an interaction is expected to be larger e.g., patients with decreased renal function (parallel pathway is renal excretion), paediatric patients, elderly etc, this information should be given here.

Recommendations of SmPC guideline – PGx (2)

- 4.8- **e. <Other special populations>** may include information on clinically relevant differences (i.e. in nature, frequency, seriousness or reversibility of ADRs, or need for monitoring) specifically observed in other special populations such as elderly, patients with renal impairment, hepatic impairment, other diseases or a specific genotype. Cross-reference to other sections such as 4.3, 4.4 or 4.5 may be added as appropriate
- 4.9- If applicable, counteractive measures based on genetic factors should be described.
- 5.1- Any relevant pharmacogenetic information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk depending on a particular genotype or phenotype.
- 5.2- Variations with respect to polymorphic metabolism should be described, if clinically relevant, in quantitative terms (with cross-reference to 4.2 when applicable). The frequencies of the alleles of interest affecting pharmacokinetics in ethnic populations should be presented.

5) Effectiveness of RMini measures

- Awareness and knowledge on the recommendations on PGBM use?
- Are the recommendations followed? Why or why not?
- How to measure the effectiveness of the risk minimization measures?
 - when concerned PG testing is mandatory/recommended/for information: usage data? Uptake on testing at national level?
 - when recommendation concerns interactions - measure impact on co-prescribing interacting drugs
- (GVP XVI – tools and methodologies for this topic is under development)

HLA-B*1502 Screening before CBZ in Taiwan

- Chen et al: B*1502 screening to **prospectively** identify subjects at risk.
- 23 hospitals in Taiwan, 4877 candidate
- DNA was genotyped for HLA-B*1502 allele.
- those HLA-B*1502 positive (7.7%) were advised not to take CBZ
- those testing negative (92.3%) were advised to take CBZ.
- The subjects were interviewed by telephone once a week for 2 months to monitor for symptoms. The estimated historical incidence of SJS–TEN was used as a control.
- Mild, transient rash 4.3%; more widespread rash 0.1% hospitalized. No SJS–TEN. (estimated historical incidence 0.23% =approx. 10 cases $P<0.001$).
- Conclusion: **identification** HLA-B*1502 carriers and **avoidance** of CBZ in these subjects was strongly associated with a **decrease in the incidence of CBZ induced SJS–TEN.**

Challenges

- **Post-marketing genomic data collection**
- **Level of “certainty” on the evidence**
- **Implementation of the PGBM use**
- **Measure the effectiveness of the risk minimisation activities**