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Perspectives from EMA Scientific Committees

Pharmacovigilance Risk Assessment Committee - PRAC

Regulatory challenges and opportunities

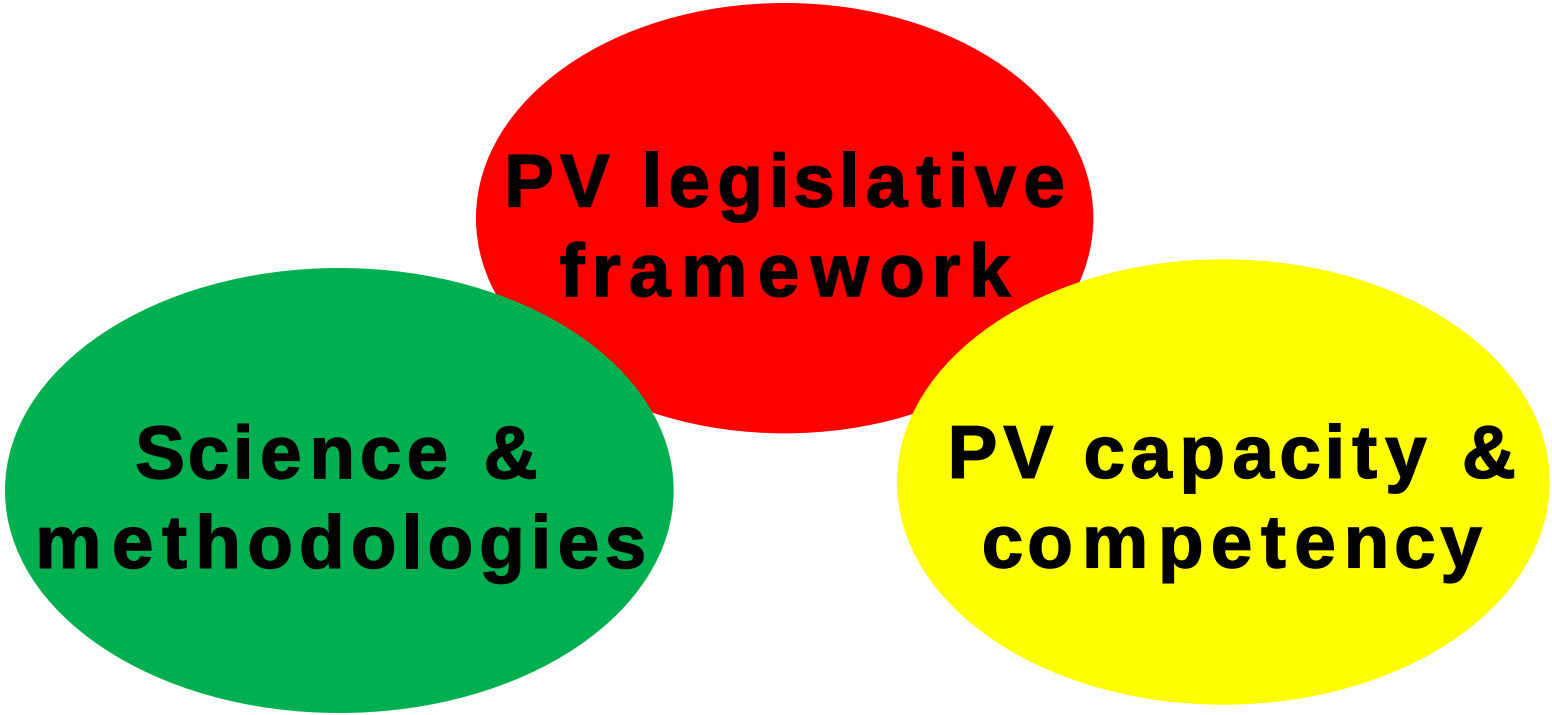
PCWP/HCPWP workshop on personalised medicines

Presented by June Raine on 14 March 2017
Chair PRAC

Pharmacovigilance Risk Assessment Committee

All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit

PRAC's aim is excellence in public health protection



PRAC's key developments shaping medicines evaluation

Proactively investigating drug safety
signal detection throughout lifecycle , wider definition of adverse reaction including error, post-authorisation studies

Responding to safety & benefit risk issues
risk-proportionate decisions to rigorous timescales, effectiveness of risk minimisation

Driving forward a new era in transparency
prompt access to information on activities

Increasing involvement of stakeholders
health professionals, patients and public

PRAC's "Road Map" to personalised drug safety

EU Guideline on pharmacogenomics in pharmacovigilance published November 2015

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10 January 2014
EMA/281371/2013
Committee for Medicinal Products for Human Use (CHMP)

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

Draft

Draft Agreed by Pharmacogenomics Working Party	April 2013
Adoption by CHMP for release for consultation	20 December 2013
Start of public consultation	30 January 2014
End of consultation (deadline for comments)	30 July 2014

What is scope of PGx in PV guideline?

Pharmacogenomics in pharmacovigilance guideline addresses influence of PGx on PhV activities:

- **how to evaluate** the PhV related issues for MPs with PGx associations
- **how to translate** results of evaluation to appropriate treatment recommendations in product information for patients and HCPs

Emphasis is on particular aspects of **PhV activities & risk minimisation measures** related to medicines in genetic subpopulations

Types of genomic biomarkers relevant for PhV are illustrated with examples…

Examples in PGx in PV guideline

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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

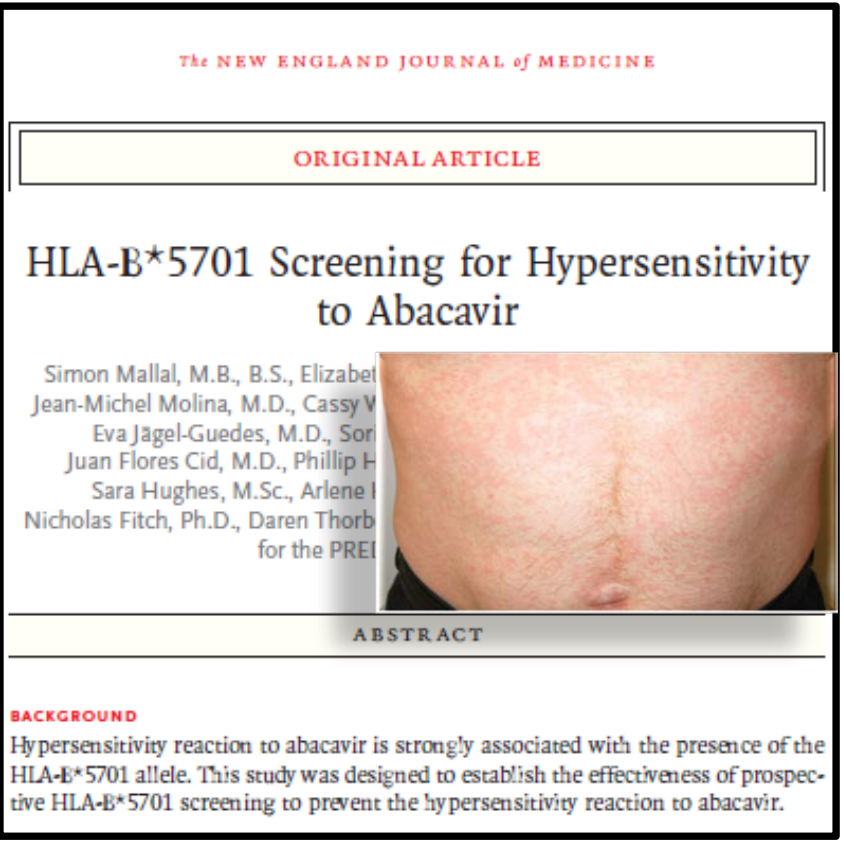
Celecoxib CYP2C9

Warfarin CYP2C9

Thiopurine TPMT

Irinotecan UGT1A1

Statin *SLCO1B1*



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabet
Jean-Michel Molina, M.D., Cassy V
Eva Jägel-Guedes, M.D., Sor
Juan Flores Cid, M.D., Phillip H
Sara Hughes, M.Sc., Arlene I
Nicholas Fitch, Ph.D., Daren Thorb
for the PREI

ABSTRACT

BACKGROUND

Hypersensitivity reaction to abacavir is strongly associated with the presence of the HLA-B*5701 allele. This study was designed to establish the effectiveness of prospective HLA-B*5701 screening to prevent the hypersensitivity reaction to abacavir.

Abacavir hypersensitivity

Evidence -double blind prospective RCT

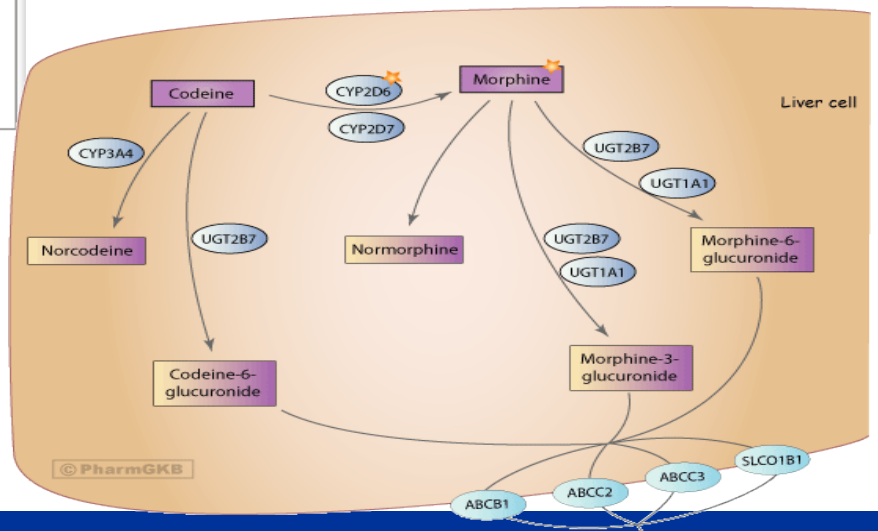
Genomic biomarker:	*HLA-B*5701* (all races)
Allele frequency (ethnicity):	6-8% in Caucasians, 1% in Asian pops, less than 1% in African populations
Issue-ADR (severity, frequency, etc):	Hypersensitivity, serious
Prevalence phenotype:	- 8%
Risk of ADR:	48% to 61% of patients with allele vs 0% to 4% of patients without allele
Data source (incl. study design, etc):	Prosp. CT and others
PPV	55 %
NPV	100%
Label (sections in SPC):	4.1

Codeine analgesia in children, serious opiate toxicity

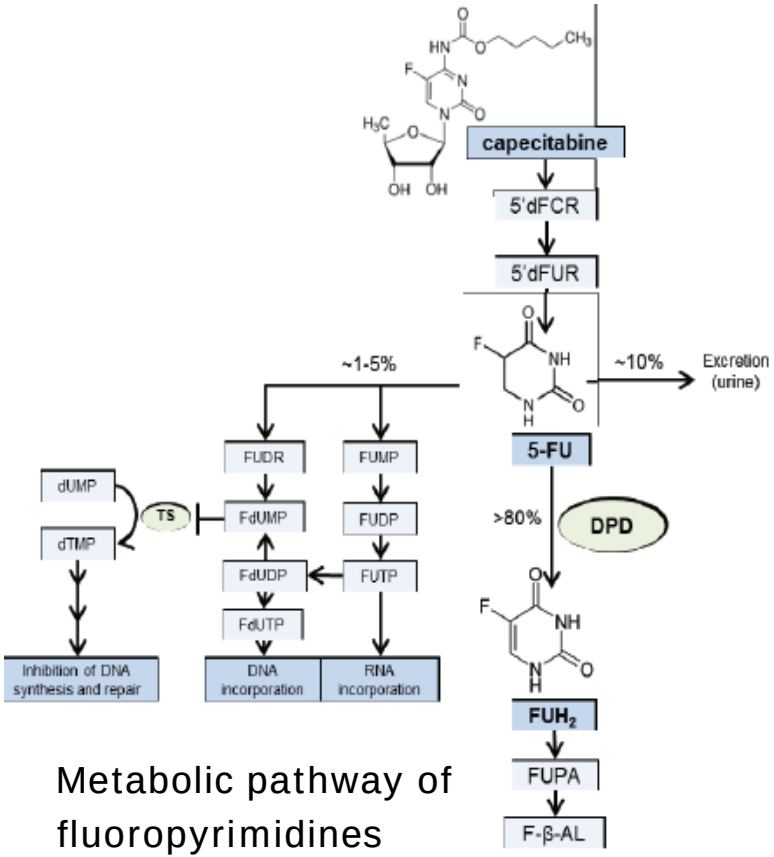
Evidence – spontaneous cases, data on prevalence of ultra-rapid metabolisers

The risk of respiratory depression outweighs the benefits of using codeine for moderate pain in children under 12 years as there are safer alternatives | SCIENCE PHOTO LIBRARY

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recommended that use of codeine-containing medicines in children be restricted to those aged over 12 years with acute moderate pain that cannot be relieved by other analgesics, for example, paracetamol or ibuprofen.



5-fluorouracil and capecitabine toxicity



Metabolic pathway of fluoropyrimidines

Evidence from 2 meta-analyses linking DPYD variants to severe toxicity, leading to recommendations for dose reduction for initiation?

Dose recommendations for DPYD variants

DPYD variant	% of standard dose
*DPYD**2A	50%
c.1679T>G	50%
c.2846A>T	75%
c.1236G>A/HapB3	75%

Regulatory challenges

Genomic data collection in post-marketing phase

Level of "certainty" on the evidence

Implementation of use of pharmacogenomic biomarkers

Measuring effectiveness of the risk minimisation activities

Understanding the perspectives and views of patients and HCPs

Opportunities for pharmacogenomics in pharmacovigilance

Use of all available data – including “big data”

Registries initiative under way at EMA

Biobanks, capability to link genetic material & electronic health records

Evaluating impact of regulatory action and activities – PRAC strategy

Engaging even more actively with patients, the public and healthcare professionals

PRAC focus on evaluating impact of regulatory action

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11 January 2016
EMA/790863/2015
Pharmacovigilance Risk Assessment Committee

PRAC strategy on measuring the impact of Pharmacovigilance activities

Adopted

Involving patients & public in decisions

Interaction with patient and health profession organisations by PRAC has so far been arranged ad hoc

EMA has consulted widely on arrangements for public hearings for safety referrals

First public hearing will be held later in 2017

Key questions

Are PRAC's activities sufficiently systematic on PGx in PV?

Are we utilising the guideline on PGx in PV optimally?

Are we setting the evidential bar too high to support making recommendations?

Could PRAC be more proactive in stimulating research in PGx?

Does current product information adequately present PGx information to support individual decisions on benefit risk?

Can PRAC collaborate more in support of personalised medicines?