Personalisierte Pharmakotherapie

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Klinik für Klinische Pharmakologie und Toxikologie
Universitätsspital Zürich
Pharmacotherapy success rates

Bronchial asthma: 60%
Cardiac arrythmia: 60%
  Depression: 70%
  Diabetes type II: 60%
  Migraine: 50%
  ACE inhibitors: 70%
  β-blocking agents: 70%
Inflammatory bowel disease: 60%

Why do so many patients not respond? Can we predict responders and non-responders? Can we „personalize“ medicine?
Pharmacotherapy: Current situation

Clearly, we need to improve. Will „personalized medicine“ help us?
Pharmacogenomics: Hype or hope?

- **Genome wide approach**
- **Gene-Expression GWA approach**
- **Next generation sequencing**

- **Single gene approach**
- **Candidate-pathway approach**

*Schwab et al. DMW 2011*
All patients with same diagnosis

1

Remove non-responders and toxic responders

2

Treat

Responders and Patients Not Predisposed to Toxicity
Determinanten der Arzneimittelantwort

- Alter
- Geschlecht
- Genetische Faktoren
- Polypharmazie
- Krankheiten
- Alkohol
- Ernährung
Genetische Determinanten der Arzneimittelantwort

Pharmakokinetik

Pharmakodynamik

Krankheits-Genotyp

Komorbidität
Pharmakokinetische Determinanten der Arzneimittelantwort

Absorption

Verteilung

Metabolismus

Ausscheidung
Arzneimittelmetabolismus

Phase I-Reaktionen: Arzneistoff → Phase-I-Metabolit

Phase II-Reaktionen: Phase-I-Metabolit → Phase-II-Metabolit

Cytochrom P450 (CYP) Enzyme
Genetischer Polymorphismus im Arzneimittelabbau
Arzneimittelmetabolisierende Enzyme

Evans WE and Relling MV. Science 1999;286:487-91
Pharmakogenetik von CYP2D6

- > 70 Allele; 5 verantwortlich für 95% der Variabilität
- Substrate: u.a. Betablocker, Tamoxifen, Antidepressiva, Antipsychotika, Kodein
- PM Frequenz bei Kaukasiern: 7-10%
- PM Frequenz bei Asiaten: < 1%
Pharmakogenetik von CYP2D6

- multiple aktive Genkopiien
- kein Enzym

CYP2D6 und Betablocker

<table>
<thead>
<tr>
<th>Drug</th>
<th>% metabolized by CYP2D6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>75</td>
</tr>
<tr>
<td>Timolol</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Propranolol</td>
<td>40</td>
</tr>
<tr>
<td>Atenolol</td>
<td>0</td>
</tr>
</tbody>
</table>

Lennard 1989
CYP2D6 und Kodein

Kodein \(\xrightarrow{\text{antitussiv}}\) Morphin \(\xrightarrow{\text{analgetisch}}\) M-3-Glukuronid \(\xrightarrow{\text{inaktiv}}\)

Morphin \(\xrightarrow{\text{analgetisch}}\) M-6-Glukuronid \(\xrightarrow{\text{aktiv}}\)

\(\text{CYP2D6}\)

\(\text{UGT}\)
CYP2D6 und Tamoxifen

Tamoxifen → CYP2D6 → 4-OH-Tamoxifen ↔ Endoxifen

CYP2D6 Langsammetabolisierer

→ niedrigere Endoxifen-Plasmaspiegel

→ ungünstigerer klinischer Verlauf bei Mamma-Ca
CYP2D6-basierte Dosisanpassungen für Antidepressiva und Neuroleptika

Kirchheiner et al., Mol Psychiatry 2004
CYP2C19 Substrate

Protonenpumpeninhibitoren

Cyclophosphamid

- bei Schnellmetabolisierern: - Ovariale Insuffizienz
  - Urotoxizität

Clopidogrel

- Prodrug, muss über CYP2C19 aktiviert werden
- 25% zeigen ein geringes Ansprechen, dadurch erhöhtes Risiko für ischämische Ereignisse!
Wirkmechanismus der Protonenpumpeninhibitoren

Schubert-Zsilavecz und Stark, Pharm. unserer Zeit 2005; 3: 194
Abhängigkeit des pH im Magen (24 h) vom CYP2C19 Genotyp unter 20 mg Omeprazol

T. Furuta et al., Drug Metab. Pharmocokinet. 2005; 20: 153
Clopidogrel is Converted to its Active Metabolite by CYP Enzymes in the Liver

Clopidogrel is converted to its active metabolite by CYP enzymes in the liver. The active metabolite irreversibly inhibits the ADP receptor on platelets, leading to inhibition of platelet aggregation.

Clopidogrel Resistance

- Clopidogrel resistance 8-40%* (300 mg loading dose)
  - Extrinsic
    - Failure to prescribe
    - Poor compliance
    - Variability in absorption
    - Body mass index
    - Under dosing
    - Drug-drug interaction
  - Intrinsic
    - Cellular factors
      - Number of P2Y12 receptors
      - Varying level of responsiveness
      - Platelet activation via alternate pathways
    - Genetic
      - Polymorphism of P2Y12 receptor gene
      - Polymorphism of CYP3A
      - Polymorphism of CYP2C19

Gurbel PA. Cardiovascular Medicine 2006
Clopidogrel Resistance

Clopidogrel resistance 8-40%* (300 mg loading dose)

Extrinsic
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  - Polymorphism of CYP3A
  - Polymorphism of CYP2C19

Gurbel PA. Cardiovascular Medicine 2006
Clopidogrel Exposure in Correlation to Genotype

PMs = Poor metabolizers; heteroEMs = Heterozygous extensive metabolizers; homoEMs = Homozygous extensive metabolizers

Kim KA. Clin Pharmacol Ther 2008;84:236-42
Platelet Inhibition in Correlation to Genotype

Inhibition of platelet aggregation (%)

PMs = Poor metabolizers; heteroEMs = Heterozygous extensive metabolizers; homoEMs = Homozygous extensive metabolizers

Kim KA. Clin Pharmacol Ther 2008;84:236-42
Association between Status as a Carrier of a CYP2C19 Reduced-Function Allele and the Primary Efficacy Outcome in Subjects Receiving Clopidogrel

Mega JL et al., NEJM 2009;360:354

hazard ratio for carriers: 1.53
Pharmakogenetik-basierte Dosisanpassungen aufgrund von pharmakokinetischen Unterschieden

## Medikamentöse Therapie bei IBD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genes associated with drug response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine 6-mercaptopurine</td>
<td>Thiopurine methyltransferase (TPMT)</td>
</tr>
<tr>
<td>5-aminosalicylates sulfasalazopyridin</td>
<td>N-acetyltransferase 1 (NAT1)</td>
</tr>
<tr>
<td></td>
<td>N-acetyltransferase 2 (NAT2)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Glucocorticoid receptor β (hGRβ)</td>
</tr>
<tr>
<td></td>
<td>Multidrug resistance gene product 1 (MDR1)</td>
</tr>
<tr>
<td></td>
<td>Transporter of antigenic peptide 2 (TAP2)</td>
</tr>
<tr>
<td>Infliximab (anti-TNFα)</td>
<td>Fc gamma receptor IIIa (V/V ➔ better response than F/F)</td>
</tr>
</tbody>
</table>
Pharmakologie von Azathioprin

- **TPMT:**
  - homozygot mutiert: 0.3% von Kaukasiern
  - heterozygot: ~11%
  - homozygot Wildtyp: 89%
Frequency of TPMT activity distribution in IBD patients

TPMT deficiency leads to higher TGN levels

Krynetski and Evans, Pharm Res 1999;16:342
Pharmakogenetik der TPMT

niedrige TPMT Akt. 1/300
intermediäre TPMT Akt. 11%
hohe TPMT Akt. 89%
? Sehr hohe TPMT Akt.

Schwere Toxizität
Hohes Risiko für Toxizität
Niedriges Risiko für Toxizität
Niedriges Risiko ?

Klinische Antwort

+ ← -
HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S.,
for the PREDICT-1 Study Team*

Hypersensitivity to abacavir

- An immunologically mediated hypersensitivity reaction affecting 5 to 8% of patients during the first 6 weeks of treatment
- Symptoms include combinations of fever, rash, constitutional symptoms, gastrointestinal tract symptoms, and respiratory symptoms that become more severe with continued dosing
- Immediate and permanent discontinuation of abacavir is mandated, resulting in a rapid reversal of symptoms
- Subsequent rechallenge with abacavir is contraindicated, since it can result in a more severe, rapid, and potentially life-threatening reaction
Study design

1956 patients infected with HIV1, not previously treated with abacavir

980 underwent screening for HLA-B*5701:
  55 positive => did not receive abacavir
  925 negative => 858 received abacavir => 803 could be evaluated for hypersensitivity reaction

976 were assigned to the control group:
  913 received abacavir => 847 could be evaluated for hypersensitivity reaction
Screening eliminated immunologically confirmed hypersensitivity reaction, with a negative predictive value of 100% and a positive predictive value of 47.9%.
Conclusion

HLA-B*5701 carriage clearly demarcated a high-risk group of patients, accounting for approximately 6% of the population, from the remaining 94% who were at low risk for a hypersensitivity reaction to abacavir
Drug Induced Liver Injury (DILI)

Parent drug

Reactive metabolite

Direct cell stress

Mitochondrial inhibition

Initiation of immune response

Bak

Bax

Bad

Cytochrome c release

Inhibition of respiratory chain

Caspases-8, -10

Apaf-1

Caspases-9

Caspases-3, -6, -7

Apoptosis

Russmann, Jetter, Kullak-Ublick, Hepatology 2010; 52: 748-61
Mechanisms of drug-induced liver disease

- Induction of apoptosis
- Direct toxicity to cholangiocytes
- Interference with transporters
- Sinusoidal obstruction syndrome
- Direct toxicity to hepatocytes
- Mitochondrial injury
- Immune-mediated

adapted from Russmann and Reichen: "Drug-induced and toxic liver disease"; in Weinstein, Hawkey, Bosch: Clinical Gastroenterology and Hepatology, Elsevier, 2005; 677-686
Flucloxacillin liver injury: HLA-B*5701 genotype is a major determinant

- 51 DILI cases vs. 282 population controls
- Odds ratio 80.6 (22.8-284.9)
- the absolute risk to develop DILI with this genotype is only 1 in 500-1000

Daly AK et al., *Nature Genetics* 2009; 41: 816-819
## HLA associations with hepatotoxicity

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated allele</th>
<th>Drug</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-A</td>
<td>*3303</td>
<td>Ticlopidine</td>
<td>Candidate gene</td>
</tr>
<tr>
<td>HLA-B</td>
<td>*5701</td>
<td>Flucloxacillin</td>
<td>GWA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lapatinib</td>
<td></td>
</tr>
<tr>
<td><strong>Class II</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>*1501</td>
<td>Amoxicillin-clavulanate</td>
<td>Candidate gene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*1501</td>
<td>Lumiracoxib</td>
</tr>
<tr>
<td></td>
<td>*0701</td>
<td>Ximelagatran</td>
<td>GWA / candidate gene</td>
</tr>
</tbody>
</table>

*Aithal GP & Daly AK, Nat Genet 2010; 42: 650*
Klinische Relevanz von Arzneimitteltransportern

- Intestinale Absorption
- Hepatische und renale Exkretion
- Verteilung im Zielgewebe
- Therapieansprechen
- Krankheitsempfindlichkeit
Hepatische Statin-Aufnahme erfolgt über OATP1B1

Zair ZM, Kullak-Ublick GA, Pharmacogenomics 2008; 9: 597-624
SLCO1B1 Variants and Statin-Induced Myopathy —
A Genomewide Study

The SEARCH Collaborative Group*

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
HMG CoA reductase inhibitors (statins)

Simvastatin (Zocor®)

Pravastatin (Selipran®)

Fluvastatin (Lescol®)

Rosuvastatin (Crestor®)

Atorvastatin (Sortis®)

Stark H. PharmuZ 2003
Sept. 1998 - October 2001:

12,064 participants from the UK who had had a myocardial infarction

- 80 mg simvastatin daily
- 20 mg simvastatin daily

Blood samples: 2, 4, 8 and 12 months then every 6 months

Creatine kinase (CK) and alanine aminotransferase (ALT)

Subjects were questioned about new, unexplained muscle pain or weakness
Sept. 1998 - October 2001

by Sept. 2006:

80 mg simvastatin daily

- 49 / 6031 participants had developed definite myopathy
- 49 / 6031 participants had developed incipient myopathy

20 mg simvastatin daily

- 2 / 6033 participants had developed definite myopathy
- 6 / 6033 participants had developed incipient myopathy
80 mg simvastatin daily by Sept. 2006:

- 49 / 6031 participants had developed definite myopathy
- 96 controls matched for age, sex, estimated GFR, and use/nonuse of amiodarone at baseline
- 49 / 6031 participants had developed incipient myopathy
Results of Tests for a Trend in the Association between Myopathy and Each SNP Measured in the Genomewide Association Study

P values are shown for each SNP measured among 85 participants with myopathy and 90 matched controls who were taking 80 mg of simvastatin daily. Analyses are based on 316,184 of the 318,237 SNPs (99.4%) on the Sentrix HumanHap300-Duo BeadChip (Illumina). A result above the horizontal red line indicates strong evidence of an association (P < 5 x 10^{-7}).
OATP1B1 polymorphism: pharmacokinetics of simvastatin (acid)

Pasanen et al., Pharmacogenet Genomics 2006; 16: 873-9
Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to OATP1B1 rs4149056 Genotype

Pharmakogenetik in der Onkologie

- Monoklonale Antikörper
  - Trastuzumab (Herceptin®) HER2-Ak *
  - Rituximab (MabThera®) CD20 AK
  - Cetuximab (Erbitux®) k-ras Gen (darf nicht mutiert sein)

- Arzneimittel mit Wirkung auf tumorspezifische Signalwege
  - Imatinib (Glivec®) Tyrosinkinase-Inh.

* HER2 = Human Epidermal Growth Factor Receptor 2
ca. 25% der Brustkrebs-Patientinnen exprimieren vermehrt HER2/neu auf ihrer Zelloberfläche