Gaps Between Biomarkers and Surrogate Endpoints: CNS

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Overview

• Definitions Biomarker, Surrogate, Clinical Endpoint
• Biomarker in Psychiatry
• Biomarker in Neurology
Definition of Biomarker

• A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

• FDA Pharmacogenomics Guidance defines possible, probable and known valid biomarker categories depending on available scientific information on the marker
Biomarker Validation

- Unintended effect
- Affected by intervention
- Not affected by intervention

Well → Biomarker → Disease

Not useful

Ideal marker

Partly useful

Confusing marker
Definition of Surrogate Endpoint

• A biomarker intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence.
Surrogates

• to increase the likelihood of providing beneficial effects on clinical efficacy endpoints

• validity for a given treatment not necessarily applicable for another treatment with different mechanism of action

• do in most cases not replace clinical efficacy endpoints in definitive trials (Phase III)
Definition of Clinical Endpoint

- A characteristic or variable that reflects how a patient feels, functions or survives

- Except for survival, all these involve intermediary measurement
Clinical Effects of Atypical Antipsychotics

• Clinical efficacy in schizophrenic patients (acute treatment of psychotic episodes and relapse prevention)
  – Positive and Negative Symptoms Scale (PANSS)
    • % patients responding by reduction in PANSS by 30%
  – Clinical Global Impression (CGI)

• Safety/Tolerability
  – ESRS, BAS, AIMS, prolactin, QTc, weight, glucose and lipid metabolism
Biomarkers for Antipsychotics

• Biomarkers in early clinical development
  – PET (« local PK in area of interest in CNS »):
    • D₂ and 5-HT₂ receptor blockade for atypicals
  – Quantitative EEG
  – prolactin

• Surrogates
  – ?
PET Study for CNS Receptor Occupancy

PET Images with 11C - Raclopride Binding to D2 Receptors in Human Brain

Before Aripiprazole

During Aripiprazole
2 mg/day, 14 days

During Aripiprazole
30mg/day, 14 days
Changes in qEEG by New Atypical

- no sedation
- long lasting action
- rapid onset
- rapid onset

Per Protocol Population (N=11)
Pharmacodynamics - EEG - Absolute Energy
Interkinetic Maps: 0.1 MG vs PLACEBO, D05, BL-D01
qEEG in Healthy Subjects and Answers to Questions

• Penetration of blood brain barrier?
• Dose response relationship, minimum CNS active dose?
• Time course of pharmacodynamic effect?
• PK/PD?
• Sedation?
• Limitations:
  – Healthy subjects very sensitive to low doses of antipsychotics
  – Applicability to patients unclear
  – Status of validation incomplete
  – Relevance of qEEG for new modes of actions beyond typical or atypical antipsychotics unclear
Prolactin: a Useful Biomarker for Antipsychotic Efficacy?

from de Visser et al. 2001
Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S. E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., and John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators*
CATIE: Antipsychotics Investigated and Doses

• Mean modal doses/day
  (total number of schizophrenic patients: 1493)
  – olanzapine 20 mg
  – perphenazine 21 mg
  – quetiapine 543 mg
  – risperidone 4 mg
  – ziprasidone 113 mg
Outcome CATIE: Time to Discontinuation of Treatment

longer for olanzapine than for quetiapine, risperidone, perphenazine, and ziprasidone regarding:

- for any cause
- for lack of efficacy
- owing to patient’s decision

no difference between the drugs:
- owing to intolerable side effects
Other AEs

• **Prolactin increase**: only with risperidone, not for other antipsychotics

• **Weight gain ≥7%**: olanzapine 30%, others 7-16%

• **Risk Metabolic Syndrome**: more with olanzapine than others, ziprasidone reduced the risk

• **QTc prolongation**: no differences
Prolactin: a Useful Biomarker for Antipsychotic Efficacy?

• Apparently not of predictive value for clinical efficacy under real life conditions of treatment with most 2nd generation antipsychotics, at best perhaps for some D2 receptor blockers

• Indicator for supramaximal doses of some antipsychotics?
NK1 Antagonists for Depression?
NK1 Antagonist in CNS
Indications

• Aprepitant (MK-0869) successfully registered and launched in US 2003 against nausea and emesis in cancer patients under emetogenic chemotherapy (Emend™)

• Aprepitant under evaluation for depression in Phase III based on a large positive Phase II trial and a small negative Phase II trial with lower dose

• Dosing in Phase III trials based on results from PET studies (determination of CNS NK1 receptor occupancy over time) and Phase II trial with positive outcome

• Expectation/hope: first new antidepressant concept/target in 10 years
NK1 Receptor Occupancy in CNS: Displacement by Aprepitant

- Frank & Hargreaves 2003
Aprepitant for Depression

- Nov. 12, 2003--Merck & Co., Inc. announced today that it is discontinuing its Phase III clinical development program for its substance P antagonist investigational product, MK-0869, for the treatment of depression.
- The Phase III clinical program was halted because the compound failed to demonstrate efficacy for the treatment of depression.
Are NK1 Antagonists Useful in Depression?

• Effect on development portfolios of a number of other pharmaceutical companies?
• Potential reasons for negative outcome of Phase III trials with aprepitant:
  – Unrelated to aprepitant and other NK1 antagonists: Antidepressant trials frequently negative (up to 50%)
  – Related to aprepitant: not effective enough or results too variable?
  – Related to all other NK1 antagonist: Will one be shown to be effective in depression in future trials?
• If not: Are CNS NK1 receptors an adequate target in depression?
Biomarkers in Neurology

- Multiple Sclerosis
  - MRI (supportive evidence of benefit for registration and labelling of interferon-1-β)
- Stroke (entry criteria for infarct size and penumbra; potential endpoints for intervention studies)
  - diffusion and perfusion MRI,
  - perfusion CT
- Alzheimer’s Disease
  - volumetric MRI,
  - MR spectroscopy,
  - FDG-PET,
  - SPECT,
  - amyloid PET,
  - microglial tracers, β-amyloid, Tau-proteins
Neuroimaging in CNS Drug Development

Uppoor et al. 2005 (CDER, FDA)

Neuroimaging studies in CNS drugs approved from 1995 to 2004

- 106 NDAs approved in Neuropharmacology Division
- 15 (out of 106) included neuroimaging studies
- 5 (out of 15) receptor occupancy
- 2 (out of 15) support POC