Biomarkers: Physiological & Laboratory Markers of Drug Effect

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Biomarker Definition

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

BIOMARKERS DEFINITIONS WORKING GROUP:
BIOMARKERS AND SURROGATE ENDPOINTS: PREFERRED
DEFINITIONS AND CONCEPTUAL FRAMEWORK.
CLIN PHARMACOL THER 2001;69:89-95.

Biomarkers Have Many Uses in Medicine

Markers of drug effect or response (laboratory, physiological, or other) are a subset of the general class of biomarkers

Other biomarkers may include diagnostic, prognostic or physiologic status information not linked to drug response

Clinical Endpoint Definition

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

Clinical endpoints are usually acceptable as evidence of efficacy for regulatory purposes

Surrogate Endpoint Definition

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

SURROGATE ENDPOINT

A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

Robert J. Temple

SURROGATE MARKER

Use of this term is discouraged because it suggests that the substitution is for a marker rather than for a clinical endpoint

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Biomarkers in Drug Development

Use of Biomarkers in Early Drug Development and Decision Making

Evaluate activity in animal models

Bridge animal and human pharmacology via proof-of-mechanism or other observations

Evaluate safety in animal models, e.g., toxicogenomics

Evaluate human safety early in development

Examples of Biomarkers Commonly used in Drug Development

Safety biomarkers: serum creatinine and blood chemistries; CBC, CXR, ECG

Drug phamacokinetics

Pharmacodynamic (efficacy) biomarkers:
  Blood glucose
  Urine, sputum, etc cultures
  Pulmonary function tests

Use of Biomarkers in Later Drug Development and Decision Making

Evaluate dose-response and optimal regimen for desired pharmacologic effect

Use safety markers to determine dose-response for toxicity

Select or deselect patients for inclusion in trials

Determine role (if any) of differences in metabolism on above

Use of Surrogate Endpoints in Late Drug Development

Use to assess whether drug has clinically significant efficacy: this is often faster than using clinical endpoint

Surrogate endpoints may be used to support "accelerated approval" of a drug if the surrogate is deemed reasonably likely to predict a clinical endpoint of interest

A few surrogate endpoints are acceptable for full approval (e.g., are "validated")

Biomarkers used as Surrogate Endpoints

"Validated Surrogate Endpoints"
    Blood pressure
    Bone mineral density for estrogenic compounds
    Hemoglobin A1C for glycemic control

"Non-Validated Surrogates" used for accelerated approval
    HIV copy number
    Tumor shrinkage

The Most Widely Used Surrogate Endpoint*

BLOOD LEVELS AS A SURROGATE FOR CLINICAL EFFICACY AND TOXICITY IN THE EVALUATION OF GENERIC DRUGS

* Comment by Carl Peck: CDDS WORKSHOP, McLean, VA, May 13, 1998

Use of Biomarkers
in Clinical Practice

Disease and disease subtype diagnosis

Prognostic determination

Selection of appropriate therapy
        Maximize efficacy
        Minimize toxicity

Selection of correct dose

Monitoring outcomes (good and bad)

Why Are Biomarkers Important?

Diagnosis is the foundation of therapy

Biomarkers are quantitative measures that allow us to diagnose and assess the disease process and monitor response to treatment

Biomarkers are also crucial to efficient medical product development

As a consequence of scientific, economic and regulatory factors, biomarker development has lagged significantly behind therapeutic development

Biomarker Development: More is at Stake than Efficient Drug Development

Biomarkers are needed to create evidence- based medicine as well as personalized medicine: who should be treated, how and with what

Absent new markers, advances towards more targeted therapy will be limited and treatment will remain largely empirical (i.e., trial and error)

It is imperative that biomarker development be accelerated along with therapeutics

Problem: Classic Thinking about Biomarkers Inhibits New Biomarker Development

Development of biomarkers "confounded" with the surrogate endpoint issue

Near impossibility of "validating" new surrogates has created a significant barrier

I will present the classic view first (slides courtesy of Dr. Art Atkinson) and then a proposal for a new framework

Note: classic view not "wrong" as much as limiting

HIERARCHY OF BIOMARKERS   (Classic view)

Graphic illustration

↑Validity   Biomarkers → Surrogate Endpoints

HIERARCHY OF BIOMARKERS* (Classic view)

TYPE 0:   NATURAL HISTORY MARKER   (Prognosis)

TYPE I: BIOLOGICAL ACTIVITY MARKER (Responds to therapy)

TYPE II: SINGLE OR MULTIPLE MARKER(S)
          OF THERAPEUTIC EFFICACY (Surrogate endpoint, accounts fully for
clinical efficacy)

* Mildvan D, et al.: Clin Infect Dis 1997;24:764-74.

"Validation" of Biomarkers (e.g., for use as Surrogate)

BIOLOGICAL PLAUSIBILITY

    EPIDEMIOLOGIC EVIDENCE THAT MARKER IS A RISK FACTOR

    MARKER MUST BE CONSISTENT WITH PATHOPHYSIOLOGY

    MARKER MUST BE ON CAUSAL PATHWAY

    CHANGES IN MARKER REFLECT CHANGES IN PROGNOSIS

STATISTICAL CRITERIA

    CHANGES IN MARKER MUST BE CORRELATED WITH CLINICAL OUTCOME (but correlation does not equal causation)

(Not confounded by adverse drug effects)

ADDITIONAL SUPPORT FOR BIOMARKER as SURROGATE*

SUCCESS IN CLINICAL TRIALS
EFFECT ON SURROGATE HAS PREDICTED OUTCOME WITH OTHER DRUGS OF SAME PHARMACOLOGIC CLASS

EFFECT ON SURROGATE HAS PREDICTED OUTCOME FOR DRUGS IN SEVERAL PHARMACOLOGIC CLASSES

OTHER BENEFIT/RISK CONSIDERATIONS
SERIOUS OR LIFE-THREATENING ILLNESS WITH NO ALTERNATIVE THERAPY

LARGE SAFETY DATA BASE

SHORT-TERM USE

DIFFICULTY IN STUDYING CLINICAL ENDPOINT

* Temple R: JAMA 1999;282:790-5.

Limitation of Current Conceptual Framework
for Development of Surrogate Endpoints

Problems with use of surrogate endpoint identified in 1980s

CAST outcome:
Use: antiarrhymics for prevention of sudden death

Surrogate: suppression of VBP's

Mortality increased in treatment arms

Temple. "A regulatory authority's opinion about surrogate endpoints". Clinical Measurement in Drug Evaluation. Wiley and Sons. 1995

Use of Surrogates Discouraged

Surrogate EP supposed to "completely correlate with the clinical endpoint"

This is not possible and has led to serious (but I would argue, misplaced) disillusionment with the use of biomarkers

Flemming TR, DeMets DL: Surrogate endpoints in clinical trials: are we being misled?

Ann Intern Med 1996;125:605-13

Surrogate Endpoint Development: 1990s

HIV epidemic spurred the use of new surrogate endpoints for antiretroviral therapy: highly controversial at first given CAST experience

Rigorous statistical criteria for assessing correlation of candidate surrogate with clinical outcome were published*

No surrogate EP has ever met these criteria

*Prentice. Stat in Med 8: 431, 1989

Surrogate Endpoint Development: HIV

HIV RNA copy number is now used as early drug development tool, surrogate endpoint in trials, and for clinical monitoring of antiviral therapy

Lack of complete correlation with clinical outcomes has not compromised utility

Successful development of antiretrovirals and control of HIV infection

Surrogate Endpoint Use: 2000s

Controversy over use of glycemic control as efficacy endpoint: rosiglitazone

Wrong dispute

Real argument is over how much premarket cardiovascular safety data to accumulate

Controversy over use of LDL cholesterol (as assessed by another biomarker, carotid artery intimal thickness on ultrasound): Vytorin

Fundamental Problems with the
Current Conceptual Framework
for Surrogate Endpoints

There is no "gold standard" clinical outcome measurement – concept of "ultimate" clinical outcome is flawed

Survival: data show that desirability of longer survival dependent on quality of life, in many individuals' estimation.

Generalizability of any single outcome measure (e.g., mortality) can be limited by trial parameters (e.g., who was entered)

Confusion between desirability of prolonged observation (for safety and long term outcomes) and use of surrogate

Fundamental Problems with Current Conceptual Framework for Surrogate Endpoint Development

Patient outcomes are multidimensional—a single outcome measure (whether clinical or surrogate endpoint) can miss domains of interest.

Very difficult to capture both benefit and harm within a single measure—very unlikely for a biomarker.

The concept of "ultimate clinical outcome" includes parameters such as duration of observation that are important dimensions. However, knowledge about these dimensions could be acquired outside of the biomarker measurement

Additional Problems with Surrogate Endpoint Framework

Per-patient view of outcomes very different from population mean view of outcomes.

For example, "ultimate" benefit in survival of 8% over placebo not meaningful to you if you are not in the 8% who actually respond

Newer (and older, e.g., metabolizing enzymes) biomarkers provide information at the individual level

Summary:Problems with Current Biomarker Conceptual Framework

Overemphasis on "surrogacy" as single objective of biomarker development

Difficulty in achieving surrogate "validation" frustrates progress

New science and technology will contribute numerous candidate biomarkers—require path forward

Fate of Most Candidate Biomarkers

Discovered in academic laboratory

Clinical series results published

Further small academic series published

Some uptake in academic centers in clinical care

Assay may be commercialized as laboratory service

Fate of Most Candidate Biomarkers

Small number may be developed into commercially available laboratory tests

Fewer may become integrated into clinical care

Evidence base for use often remains slim/controversial

Not adopted for regulatory use because of absence of needed evidence (e.g., PSA)

Future of Drug Development and Biomarker Development Tightly Linked

Biomarkers represent bridge between mechanistic understanding of preclinical development and empirical clinical evaluation

Regulatory system has been focused on empirical testing: skewing overall clinical evaluation towards "all empirical"

Mechanistic clinical evaluation lacking

Towards the Robust Use of Biomarkers in Drug Development

Implement new biomarker use throughout preclinical and clinical development

"Qualify" biomarker for intended use: less focus on surrogacy

Goal is understanding mechanistic bases for individual response to therapy to increase *informativeness* of development process

Achieve more predictable drug development and therapeutic outcomes

Towards the Robust Use of Biomarkers in Drug Development

FDA's Critical Path Initiative: proposal to use consortia to qualify biomarkers through resource sharing

Currently such consortia are being set up in areas such as animal safety testing and overall biomarker development

Clinical safety biomarkers of great interest

Promising Safety Biomarkers

Drug Metabolizing enzyme status
    6-Mercaptopurine: enzyme TPMT

    "Strattera": enzyme CYP 2D6

    Irinotecan: enzyme UGT1A1

    Warfarin: enzyme CYP 2C9; pharmacodynamic biomarker VK0RC1)-- safety and efficacy

Genetic Basis of Rare, Serious Adverse Event
    Abacavir: HLA-B*5701 and hypersensitivity

    Carbamazepine: HLA-B*1502 and Stevens-Johnson Syndrome

    More to come, e.g., hepatic injury

Potential Imaging Biomarkers

FDA Central and Peripheral Nervous System Drug Advisory
Committee meeting: Oct 26, 2008

Three sponsors presented development plans for 3 different imaging
agents for detection of amyloid in diagnosis of Alzheimer's disease

Difficult challenge because of lack of a gold standard other than
histologic verification

Potential Genomic Efficacy Biomarkers

Metabolism of prodrugs: necessary for conversion to active drug in vivo

    Clopidogrel

    Tamoxifen

Pathway markers in cancer

    Recent Oncology Drug Advisory Committee meeting on K-RAS and 2 EGFR targeted drugs (Erbitux, Vectibix) to treat colon cancer: should treatment be restricted to those with wild type K-RAS?   (Dec 16, 2008)

Biomarker Development Consortia

Predictive Safety Consortium
C-Path Institute, Tucson AZ

Animal safety biomarkers generated as a part of animal toxicology testing

Thousands of animal tox studies done each year in US for drug development purposes

Firms had developed in-house biomarkers but not shared them

Predictive Safety Testing Consortium

Fourteen pharmaceutical companies joined consortium

Agreed to cross-validate markers for organ-specific drug injury

Have submitted first qualification package to FDA for renal injury markers

FDA and EMEA have accepted for use in animal studies

Other Biomarker Consortia

SAE consortium
> Industry consortium
> Genetic basis of serious rare adverse events

"The Biomarker Consortium"
> NIH/FDA/PhRMA/BIO/patient groups/ many others
>> Discovery and qualification of biomarkers

Cardiovascular Markers
> Duke University/FDA/others
> Research on digital ECG warehouse
> Cardiac biomarker projects

Summary

Important public health need for development of additional biomarkers to target and monitor therapy

This requires use in clinical trials during drug development

Business model/regulatory path for such markers is not clear to industry

Clarification and stimulus required

Summary

Definitions for biomarkers, clinical outcomes and surrogate endpoints have been developed

Further development of the model needed in order to increase use and utility of markers in drug development

Single measurements will rarely capture all dimensions of clinical outcomes

Summary

FDA is developing these concepts as part of its "Critical Path" Initiative.

Development will include process for refining general framework as well as individual projects on biomarker and surrogate endpoint development