ESTABLISHING CLAIMS FOR LONG-TERM THERAPEUTIC BENEFIT FOR ALZHEIMER'S DISEASE, INCLUDING DISEASE PROGRESSION: A US REGULATORY PERSPECTIVE

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Drugs Approved For The Treatment of Alzheimer's Disease

"Treatment of mild to moderate dementia of the Alzheimer's type"

Tacrine
Rivastigmine
Galantamine

Drugs Approved For The Treatment of Alzheimer's Disease (Continued)

"Treatment of moderate to severe dementia of the Alzheimer's type"

Memantine

Drugs Approved For The Treatment of Alzheimer's Disease (continued)

"Treatment of dementia of the Alzheimer's type"

(i.e., dementia of the Alzheimer's type, regardless of severity)

Donepezil

Clinical trials on which approval of drugs for Alzheimer's Disease have been based so far are NOT designed to distinguish between

- A purely symptomatic effect of the drug

And

- A disease-modifying effect of the drug

Labeling states: "There is no evidence that ---------- alters the course of the underlying dementing process"

Design of clinical trials on which approval of drugs for Alzheimer's Disease has been based:

Randomized, double-blind, placebo-controlled,

parallel-arm studies of at least 3-6 months' duration

Approval of drugs for Alzheimer's Disease has been based on demonstrating statistically significant ($p < 0.05$) superiority of such drugs over placebo on <u>each</u> of 2 co-primary clinical outcome measures:

- A cognitive rating scale
- A global or functional assessment

All drugs approved for the treatment of Alzheimer's Disease are approved for long-term treatment

Demonstration of Long-Term Efficacy of Drugs for Alzheimer's Disease

- Randomized withdrawal after prolonged open-label treatment?
- Longer-term (e.g., 12 or 18 month) randomized, controlled trials?

Significant limitations with either approach

DISEASE MODIFICATION

An effect of the drug on the pathology and/or pathophysiology of the disease

Effect on “progression” (“slowing the progression”)

= Disease modification

PROPOSED METHODS OF DEMONSTRATING DISEASE-MODIFYING EFFECTS OF DRUGS IN ALZHEIMER'S DISEASE

Using Clinical Outcome Measures

Randomized withdrawal study design

Randomized start study design

Using Biochemical Markers

Beta-amyloid peptides

Tau protein

Others

Using Brain Imaging Modalities

Volumetric magnetic resonance imaging

Magnetic resonance spectroscopy

Positron emission tomography

Single-photon emission computerized tomography

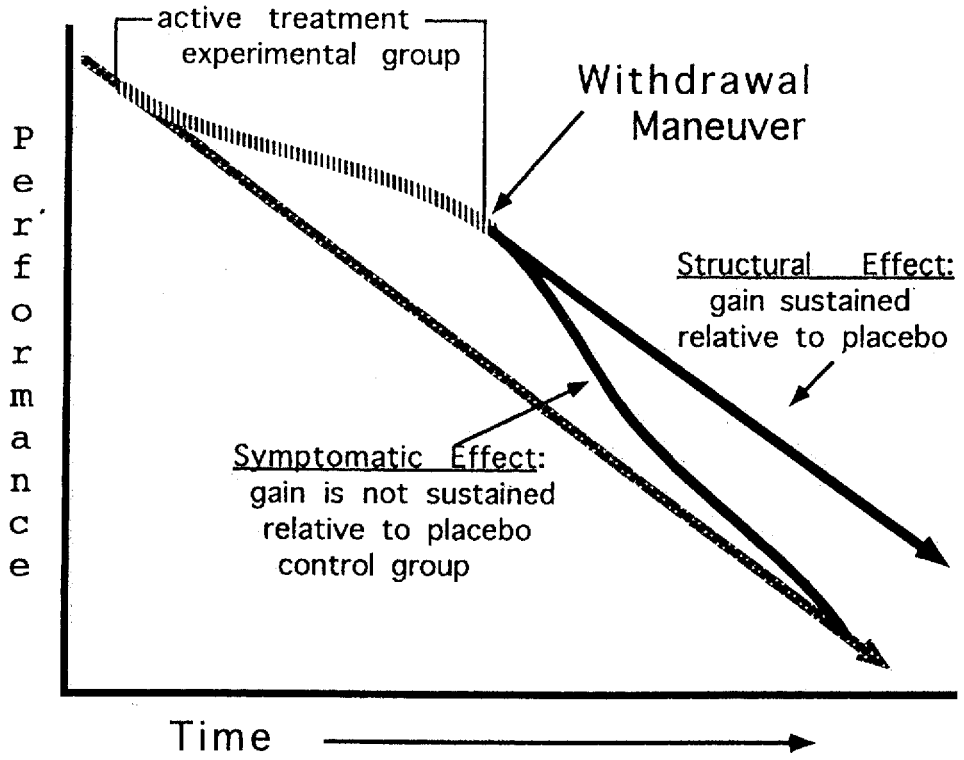
Others

Clinical study designs proposed for detecting a disease-modifying effect of a drug for Alzheimer's Disease

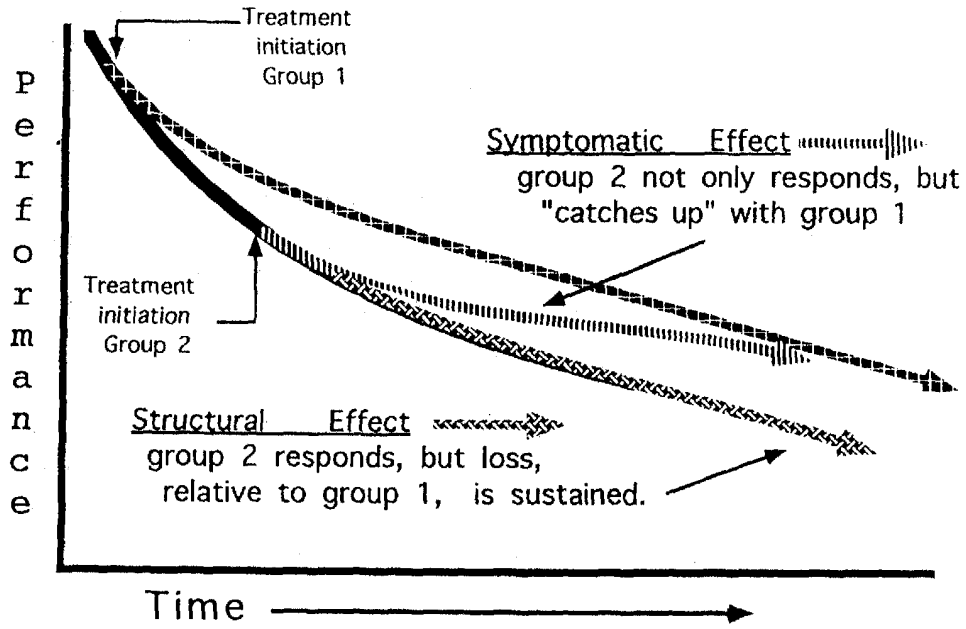
- Randomized withdrawal
- Randomized start

These designs have been based upon clinical outcome measures

RANDOMIZED WITHDRAWAL DESIGN (Leber, 1997)



RANDOMIZED START DESIGN (Leber, 1997)



Specific biochemical measures and brain imaging modalities have been proposed as surrogate markers for disease-modifying effects of drugs intended for the treatment of Alzheimer's Disease

DEFINITION OF A SURROGATE ENDPOINT (Temple, 1995)

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.

Examples Of Surrogate Endpoints

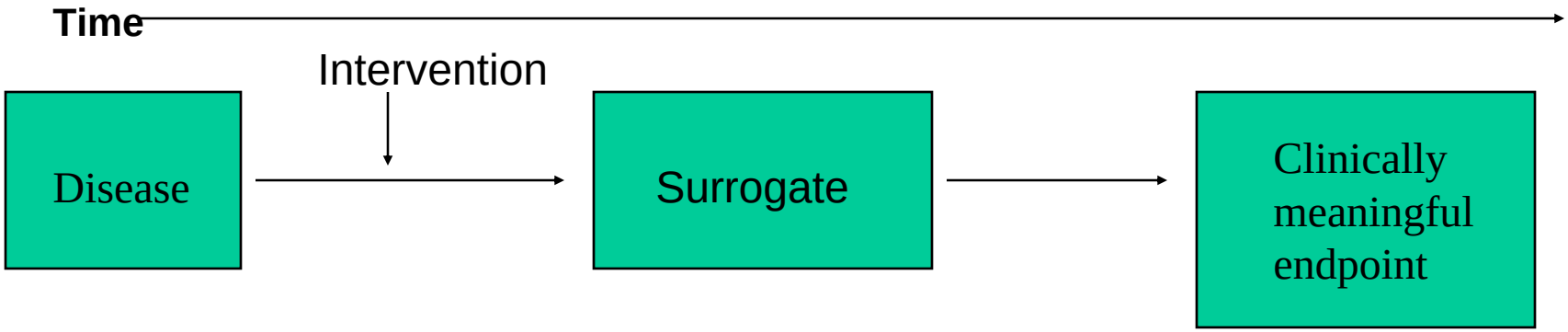
Surrogate Endpoint	Clinical Outcome
Reduction in serum lipid levels	Reduction in cardiovascular mortality
Reduction in tumor volume	Increased survival
Improved bone mineral density	Reduced fracture rate
Increased CD4 cell count	Reduced mortality

PROPERTIES OF A SURROGATE ENDPOINT

- **A proposed surrogate endpoint must not merely be a correlate of the true clinical outcome.**
- **The effect of an intervention on a valid surrogate endpoint must reliably predict the effect on the clinical outcome of interest**
- **The treatment effect on the clinical outcome should be explained by its effect on the surrogate marker**

(Fleming TR, DeMets DL. Ann Intern Med. 1996;125:605-613)

IDEAL SURROGATE ENDPOINT



- Surrogate is in the only causal pathway for the disease

- Intervention's entire effect on clinical endpoint is mediated through surrogate

Problems

- Surrogate is sensitive out of proportion to clinically meaningful outcome
- Surrogate is insensitive on account of "noise"

A number of proposed surrogate endpoints have failed their intended purpose

CODE OF FEDERAL REGULATIONS: SURROGATE MARKERS

- Surrogate markers are subsumed under the Accelerated Approval regulations

- Accelerated Approval regulations are for drugs studied in serious or life-threatening illnesses and which produce meaningful therapeutic benefit to patients over existing treatments

ACCELERATED APPROVAL REGULATIONS (1992)

(21 CFR Sec. §314.510)

- **FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has its effect on a surrogate endpoint that is reasonably likely, based on epidemiological, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit**

- **Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit**

SURROGATE MARKERS IN INTERVENTIONAL TRIALS FOR ALZHEIMER'S DISEASE

Suggested Questions To Establish Validity

- **What clinical outcome is the marker a surrogate for?**
- **Does the marker reliably predict the clinical outcome?**
- **Is the desired clinical outcome based on the effect of the intervention on the surrogate?**
- **Assuming that the surrogate marker is to be used to support a claim that the intervention has a disease-modifying effect, to what extent does the drug effect on the marker reflect a drug effect on the pathology and/or pathophysiology of the disease?**
- **Is the effect of the intervention on the surrogate marker clinically meaningful, and of sufficient importance to outweigh the risks of the intervention?**

VALIDATION OF SURROGATE MARKERS FOR INTERVENTIONAL STUDIES IN ALZHEIMER'S DISEASE

- **The biological basis for the intervention-induced change in the surrogate marker should be understood.**

- **Correlation with a concurrent clinical outcome is insufficient, by itself, to establish the "surrogacy" of the marker, and/or that an intervention-induced effect on the marker is indicative of the desired effect, e.g., disease-modification.**

SUGGESTED PRACTICAL STEPS TO VALIDATE SURROGATE MARKERS FOR CLINICAL TRIALS IN ALZHEIMER'S DISEASE

- **Compare the surrogate marker with the desired clinical outcome across multiple products and clinical trials**

- **Explain the biological basis for the intervention-induced change in the surrogate marker**

SLOPE-BASED ANALYSIS FOR ESTABLISHING DISEASE MODIFICATION

It is unlikely that a comparison of the rate of change in key clinical efficacy parameters (based on slopes) between active treatment and control groups, using a standard parallel-arm study design, could support a claim for disease modification.

An increasing divergence over time of the slopes for the active treatment and control groups has been seen for several drugs not usually considered to be disease-modifying

Key Pre-Approval Donepezil Efficacy Trial

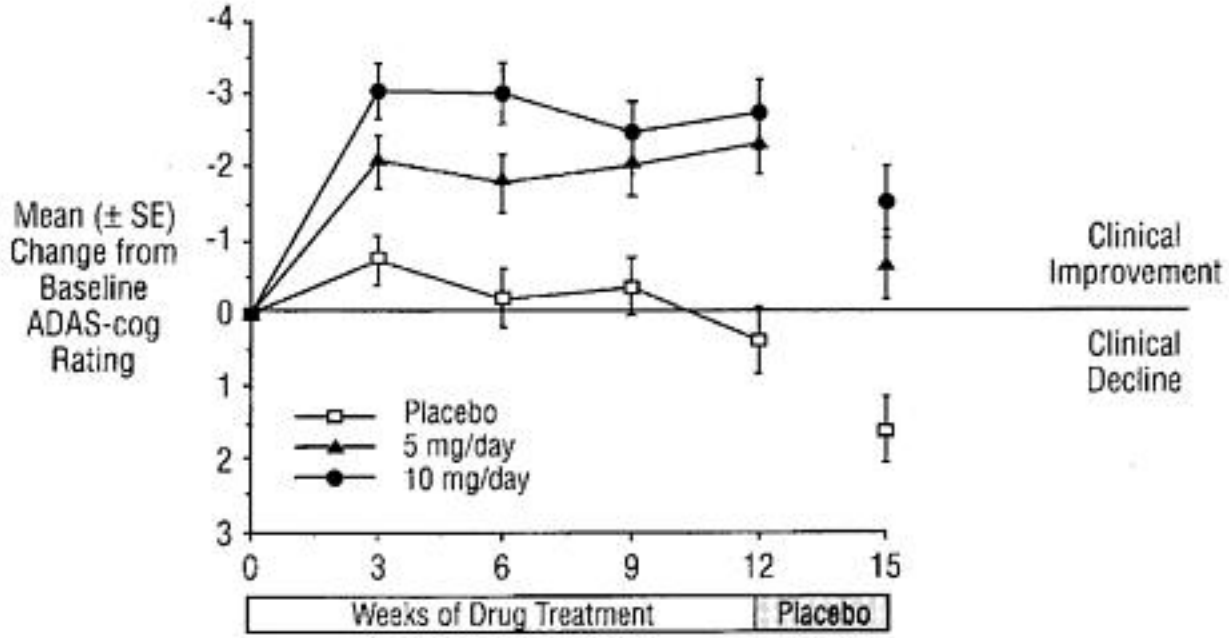


Figure 4. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing the 15-week Study.

Current FDA View

- **No specific study designs or instruments have been endorsed by us as methods of demonstrating disease-modification in Alzheimer's Disease.**

- **Imaging or biochemical measures alone are unlikely to suffice as a means of establishing a disease-modifying effect of putative treatments for Alzheimer's Disease. They will need to be used for that purpose in combination with clinical measures.**

Current FDA View (cont'd)

- **A randomized start or randomized withdrawal study design (with clinical outcome measures) appears in form to be a more convincing means of demonstrating a disease-modifying effect than the use of surrogate markers in combination with standard clinical designs.**

- **We do not know what criteria will be applied in determining that a drug has a disease-modifying effect in Alzheimer's Disease when an application seeking such a claim is submitted. Accordingly, the first such application will be presented to our Advisory Committee for their opinion.**

Question For Consideration

From a clinician or patient perspective, how important is it that an intervention for Alzheimer's Disease be demonstrated to have a disease-modifying effect?

Would not a substantial and sustained clinical benefit alone be of greater significance?