The Experimental Therapeutics of Rare Diseases

Robert C. Griggs, M.D., FAAN

Professor of Neurology, Medicine, Pediatrics, Pathology and Laboratory Medicine, Center for Human Experimental Therapeutics

University of Rochester School of Medicine & Dentistry

Department of Neurology

Outcome Measures and Infrastructure for Phase III Studies in Batten Disease (JNCL)

December 6, 2013

Conflicts of Interest…and Biases

- Pharma support:
  - Consultant – PTC Therapeutics; Marathon, Novartis
  - Muscle Study Group: Meeting Support from Pharma
  - Drug supply – Taro; Acorda
- NIH – clinical trials; training grant
- FDA – orphan product designations; grants
- Muscular Dystrophy Association; Parent Project for Muscular Dystrophy: grants
- American Academy of Neurology – editorial stipend
- American Brain Foundation – Board member (non-compensated)

The Experimental Therapeutics of Rare Neurological Diseases

- The reason
- The goals
- The challenges
- The strategy
- Study design
- Recruitment
- Paying for the treatment

Rare Disease Research: The Goals (1)

- Translational research: T-1, T-2, T-3, T-4, T-5
- To identify the causes, pathogenesis and courses
- To improve the outcome of all patients, everywhere
  - Outcome measures
  - Successful treatments
  - Treating the universe of patients
  - Standards of care

Rare Disease Research: The Goals (2)

- T-1 Discovery of the cause
- T-2 Model(s) of disease; fixing the model; designing the treatment for human subjects
- T-3 Randomized clinical trials
- T-4 Real world implementation: economic issues; co-morbidity, personalized medicine
- T-5 Global availability

Rare Diseases: A Common Challenge

The 7000+ rare diseases (defined as <200,000 U.S. residents) affect ~30 million people in the U.S. alone.

Rare Disease Research: The Challenges (Partial List)

- Are all neurological diseases rare?
- Are there 10,000 (or more) rare neurological diseases?
- Are there any successes?: FDA-approved treatments <200 --- and there are problems with the treatments

The Strategy (1)

Patient referrals: A major problem in the U.S.

- “Leakage” from one system to another
- No central diagnostic facilities
- Molecular testing often “not covered”
- Travel costs

ISSUES & OPINIONS

RARE DISEASE CENTERS FOR PERIODIC PARALYSIS: CHINA VERSUS THE UNITED STATES AND UNITED KINGDOM

QING KE, MD, PhD,[1,2] MING QI, PhD, FACMG,[1,2] WEIPING WU, MD, PhD,[3] BENYAN LUO, MD, PhD,[1] MICHAEL HANNA, MD,[4] BARBARA HERR, MS,[2] ROBERT C. GRIGGS, MD,[2] and the Consortium for Investigation of Neurological Channelopathies (CINCH)

[1] Department of Neurology, The First Affiliated Hospital of School of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, 310003, China
[2] University of Rochester Medical Center, Rochester, New York, USA
[3] General Hospital of the People's Liberation Army, Beijing, China
[4] MRC Centre for Neuromuscular Diseases, Institute of Neurology, University College London, London, UK

Muscle and Nerve, in press, 2013

How do Patients Get to an Appropriate Expert in "Their" Disease?

China: Self-referred to a major hospital

U.S.: Referred to a well-known expert

U.K.: A single NHS-designated center for many diseases

Teleneurology for Rare Disease Research

- Telephone reporting of outcomes
- Skype for examination of patients?
- Or for “personal contact”

The Strategy (2)

Defining patient outcomes: "A developing counter culture"

- Patient-centric vs physician-centric: "The physicians global impression of change" vs a clinically-meaningful patient-reported outcome
- Validation

Validation of An Outcome Measure

- Assessing in another group of patients with the same disease?
- Demonstrating benefit in a clinical trial?
- Using the outcome for registration of a treatment
- Changing practice; practice guidelines
- Supported by third party coverage

The Strategy (3)

- Patient registries
- Defining patient outcomes: requires patient input
- Longitudinal study of the outcomes: test/retest reliability; rate of progression (and variation)
- Statistical analyses: Powering a study to detect improvement of the outcome
- Validating the outcome in a clinical trial

PRELIMINARY COMMUNICATION

Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia

A Randomized Controlled Trial

Jeffrey M. Statland, MD
Brian N. Bundy, PhD
Yunxia Wang, MD
Dipa Raja Rayan, MRCP
Jaya R. Trivedi, MD
Valeria A. Sansone, MD
Mohammad K. Salajegheh, MD
Shannon L. Venance, MD
Emma Ciafaloni, MD
Emma Matthews, MRCP
Giovanni Meola, MD
Laura Herbelin, BS
Robert C. Griggs, MD
Richard J. Barohn, MD
Michael G. Hanna, FRCP
for the Consortium for Clinical Investigation of Neurologic Channelopathies

JAMA 2012;308(13):1357-1365

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

Mexiletine for Treatment of Myotonia

A Trial Triumph for Rare Disease Networks

Eric P. Hoffman, PhD

Henry J. Kaminski, MD

JAMA 2012;308(13):1377

Study Design

- Reverse the disease: Lazarus effect
- Stop the disease = cure
- Slow the disease = cure?

Most rare diseases can be diagnosed early in their course

or

- Improve a biomarker?

The Importance of Subpart H

- Validated biomarker
- Establishing the “benefit” of treatment of the biomarker
- Sufficient for registration of a new treatment?

Pivotal Studies of Orphan Drugs Approved for Neurological Diseases

Jun Mitsumoto, MPH,[1] E. Ray Dorsey, MD, MBA,[2] Christopher A. Beck, PhD,[3] Karl Kieburtz, MD,[2] and Robert C. Griggs, MD[2]

Objective: To identify design elements of clinical trials leading to US Food and Drug Administration approval of drugs for neurological diseases with and without orphan indications.

Methods: We used publicly available information to identify approvals for drugs for neurological diseases with an orphan indication (n = 19) and compared them with recent approvals for drugs for neurological diseases without an orphan indication (n = 20). We identified "pivotal trials" from drug labels and drug approval packages, and assessed them on four elements of clinical trial design: control, blinding, randomization, and size.

Results: All drugs for neurological diseases (100%) approved without an orphan indication included at least two randomized, double-blind, placebo-controlled trials. In comparison, 32% of drugs with an orphan indication had at least two such trials ($p < 0.001$) and 74% had at least one ($p = 0.02$). Thirty-three pivotal trials were conducted for the 19 drugs approved with an orphan indication. Of the 33 trials, 11 (33%) did not use a placebo control, 9 (27%) were not double blind, and 4 (12%) were not randomized. Drugs approved without an orphan indication had more pivotal trials per drug (3.8 vs 1.7 trials; $p < 0.001$) and a larger mean trial size (506 vs 164 trial participants; $p < 0.001$).

Interpretation: The US Food and Drug Administration has approved orphan drugs for neurological diseases without randomized, doubled-blind, placebo-controlled pivotal trials. As orphan drug development grows, demand will likely increase for alternative designs for conducting adequate and well-controlled studies to demonstrate drug efficacy.

Ann Neurol 2009;66:184–190

Pivotal Studies of Orphan Drugs Approved for Neurological Diseases

- All drugs approved for disease without orphan designation: 2 large randomized controlled trials (RCT)
- For orphan diseases
  - Only 32% had 2 RCTs (placebo controlled)
  - Only 74% had 1 RCTs (placebo controlled)
  - 33% not placebo controlled
  - 27% not double blind
  - 12% not randomized

Clinical Trials in Rare Diseases

Study design: randomized, placebo-controlled trials preferred.

- Large, multicenter
- N of 1 trials

Problems with the Large, Multicenter Trial

- Ethical: Therapeutic misconception
- Excludes co-morbidity; atypical cases; selected populations
- Selects a single or small number of outcomes
- Ignores subsets
  - That benefit
  - That worsen

The n of 1 Trial

- For chronic diseases --- “predictable course”
- Placebo-controlled, randomized
- Tailored to the patient (outcome, benefit, side effects, biomarker)
- Arguably essential for many long-term treatments that do not have a Lazarus effect

POINT OF VIEW

Unintended Effects of Orphan Product Designation for Rare Neurological Diseases

Sinéad M. Murphy, MB, BCh, MRCPI,[1,2] Araya Puwanant, MD,[3] Robert C. Griggs, MD,[3] and the Consortium for Clinical Investigations of Neurological Channelopathies (CINCH) and Inherited Neuropathies Consortium (INC) Consortia of the Rare Disease Clinical Research Network

ANN NEUROL 2012;72:481–490

NEWSPAPER OF THE YEAR

THE TIMES

Monday May 27 2013 | thetimes.co.uk | No 70895

Max 18C Min 0

Only £1

Weekend of winners

See Sport and the game

STEFAN ROUSSEAU / PA

Health chiefs refuse to pay for lifesaving treatment

Martin Barrow Health Editor

Patients with a rare and potentially fatal disease are being denied the only drug that will save their lives because it is too expensive.

The Department of Health has overruled experts who recommended that the drug, Soliris, should be given to all patients with a rare blood disease that causes irreversible kidney failure.

Experts said that the decision had far-reaching consequences for the health service because personalised medicines, such as Soliris, are to become more common. There are fears that the ruling could deter the develop-

Conclusions

- **Our patients are counting on us**
- Goal: Arrest of disease?
- Surrogate marker needed

Conclusions

- Our patients are counting on us
- **Goal: Arrest of disease?**
- **Surrogate markers needed?**